

# Electrochemical Deposition of Calcium Phosphate for Implant Osseointegration and Drug Release

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## Abstract

This study is about a modification of a previously described method for electrochemical deposition of Calcium Phosphate (Ca/P) coatings on Titanium-based devices. A one pot process for ion doping of coatings and co-deposition of drugs was exploited, with the aim to trigger specific biological responses.

Ca/P coatings were performed on Ti specimens via cathodic polarization route in an electrochemical bath originally proposed by Redepenning. For this study, the original solution was modified by adding  $Mg_3O_8P_2 \cdot 8H_2O$ ,  $MgHPO_4 \cdot 3H_2O$  or  $Ag_3PO_4$ . The obtained coatings were evaluated in terms of morphological properties, crystallographic phases and solubility. Results showed an effective incorporation of Mg or Ag ions in brushite coatings, without any major effects on morphology or cristallinity of the coatings. On the contrary, some effect on deposition kinetic was noticed. Moreover, dissolution kinetic behaviour was also studied in physiological-like environments for both as deposited and converted coatings, showing a different dissolution rate depending on crystallographic phase.

Cathodic polarization was found a simple and powerful method to obtain bone contact surface tailored coatings.

## 1. Introduction

Titanium and Ti alloys have gradually replaced other metallic biomaterials in direct bone-contact prostheses design and realization: their mechanical properties, together with the ability of a direct adhesion to bone tissue, represent the main reasons of such a success. In long term applications, moreover, titanium based devices show no allergic or immunogenic reactions and a good biostability [1]. Although all these properties make Ti and Ti alloys the preferred materials for bone contact devices manufacturing, these materials show some lack concerning the bioactivity, i.e., the ability to induce *in vivo* chemical and biological integration processes. According to the Osborn and Newesely classification, titanium and its alloys can be considered bioinert materials [2] and do not show osteoconductive properties: in the last 20 years many attempts were made to fabricate materials actively promoting bone growth [3]. Such studies were mainly directed to reduce the healing time and to contribute to improve clinical

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performance of implanted devices. Calcium phosphates (Ca/P) are a class of materials which clearly show osteoconductive ability [2], Hydroxyapatite (HA) being the most used materials among calcium phosphates [4]. The poor mechanical properties of calcium phosphates limited the use of bulk material to low loaded implantable devices [5]. For this reason, many different methods were studied and used to coat metallic implants, in particular titanium, with calcium phosphate layers: the main goal was overcome mechanical limitations of Ca/P by combining their osteoconductive ability with the mechanical properties of metals. Thermal spray techniques, and plasma spray in particular (PS), are currently the most used commercially available methods for coating implant devices with HA [3]. The PS HA coatings, although exhibiting good osteoconductive properties, present some disadvantages, that may affect the long term stability of the implant and, consequently, its lifetime. Among these drawbacks, the most significant is represented by a poor coating-substrate adhesion during the device lifetime. Moreover, a lack of uniformity of the coating in morphology and crystallinity has been noticed by several authors [6-8].

Because of these drawbacks, several techniques have been proposed to apply HA coatings on metallic substrates, such as the magnetron sputtering deposition, ion-beam deposition, electrophoretic deposition, pulsed-laser deposition and electrochemical deposition techniques [3].

Electrochemical methods possess manifold advantages in biomedical coating production and have been the subject of several studies in the last years: among them, cathodic polarization represents one of the most powerful because of the mild operating conditions. This technique was first investigated by Redepenning [9, 10] and Shirkhazadeh [11, 12]. Their studies showed that deposited phase properties were dependent on a series of parameters such as: electrolyte concentration and pH, applied voltage, ionic strength of the electrolyte, electrolyte temperature, cathode surface state, solution agitation and ionic species in the electrolyte. Several authors, since preliminary studies [9-12], have worked on the comprehension of the deposition process mechanisms and on chemical post treatments for phase conversion.

More recently, Redepenning et al. showed that deposition through cathodic polarization can be used with Ca/P phases coupled with organic molecules [13], paving the road for one pot approach in complex calcium phosphate coating realization.

In this work we propose a simple modification of the method originally developed by Redepenning [9, 10], with the aim of combining the deposition of Ca/P on complex titanium devices with a selective ion substitution. In particular, Mg and Ag ions have been selected because of their ability in promoting specific osteoblast response and antibacterial properties, respectively. The influence of these substitutions on crystalline phase formation, composition and structure of the coatings, have been evaluated in terms of chemico-physical and morphological properties. Moreover, we studied the transformation of deposited phases via a chemical conversion method, studying the influence on dissolution behaviour in physiological-like environments.

## 2. Materials and methods

### 2.1. Materials

In this study titanium specimens were used (Ti grade 2 C.P., diameter = 15.0 mm, thickness = 0.5 mm.): samples were pickled by acid etched (HF 3%, HNO<sub>3</sub> 20%), washed with deionized water in ultra sound bath, and dried in oven overnight before using.

### 2.2. Cathodic deposition

#### 2.2.1. Preparation of the electrolytic baths

All the chemical compounds were purchased at Sigma Aldrich and used without any further purification. According to the method developed by Redepenning *et al.* [10], saturated solutions of Ca(H<sub>2</sub>PO<sub>4</sub>)<sub>2</sub> were prepared ([Ca(H<sub>2</sub>PO<sub>4</sub>)<sub>2</sub>] = 3% (w/v) in deionized water): solutions were stirred vigorously for 30 min and then filtered with a paper sieve. The obtained electrolytic solution is indicated **RED**. This electrolytic solution has been modified by adding to the solution previously described 0.26% (w/v) of Mg<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub>·8H<sub>2</sub>O (solution **REDMg1**), 0.11% (w/v) MgHPO<sub>4</sub>·3H<sub>2</sub>O (solution **REDMg2**), and 2.1% (w/v) of Ag<sub>3</sub>PO<sub>4</sub> (solution **REDAg**) respectively.

#### 2.2.2. Cathodic polarization

Specimens were used as cathode in an electrochemical cell containing electrolytic baths (RED, REDMg1, REDMg2, REDAg) and a titanium net properly shaped was used as counterelectrode. Deposition of Ca/P was performed in galvanostatic condition ( $J = 20 \text{ mA/cm}^2$ ) and specimens were collected at different time points, up to 8 min. Specimens were then collected and rinsed in deionized water. Test were performed in triplicate.

### 2.3. Coating conversion

Conversion of brushite coatings to hydroxyapatite was studied after cathodic deposition via immersion of specimens in one of the following aqueous solutions: NaOH (pH 11); Ca(OH)<sub>2</sub>, (pH 11.5); Mg(OH)<sub>2</sub>, (pH 10.2). The immersion of the coated specimens was performed at 80°C for 2 h, with a surface/volume ratio of 4 ml/cm<sup>2</sup>. Tests were performed in triplicate.

### 2.4. Chemico-Physical characterization

#### 2.4.1. Analysis methods

Coating morphology was observed using Extended Pressure Scanning Electron Microscopy (SEM, EP Zeiss Evo 50) and a stereo-microscope (WILD 1X).

Crystallographic phases of the coating were evaluated via X-ray diffractometer (XRD Philips equipped with generator PV 1830, source Cu K $\alpha$ 1  $\lambda = 1.5406 \text{ \AA}$ ). Their composition was studied using spectrometry EDS (Oxford INCA Energy 200) and ICP-OES analysis (samples were acid etched in 10 ml 1M HNO<sub>3</sub>). The thickness of the coatings was calculated from their weight and density of the corresponding calcium-phosphate phase.

#### 2.4.2. Release kinetic

Coating dissolution kinetic behaviour was evaluated in PBS up to 21 days: at each time point the weight variation of the specimens was measured and related to the initial weight of the specimen, according to the equation (1):

$$\text{weightloss}(\%) = 100 \frac{P(t) - P_0}{P_0} \quad (1)$$

where  $P(t)$  are weights of coatings at each time point  $t$ , and  $P_0$  represent the weights after cathodic deposition and subsequent post treatments.

### 3. Results and discussion

#### 3.1. Influence of deposition parameters on Ca/P coatings

In Figure 1 SEM micrographs of Calcium Phosphate coatings obtained via cathodic polarization using RED, REDMg1, REDMg2 and REDAg electrolytic solutions are presented for 4 min of polarization treatment. Similar results have been obtained at different cathodic polarization time points (up to 8 min of polarization, data not shown).

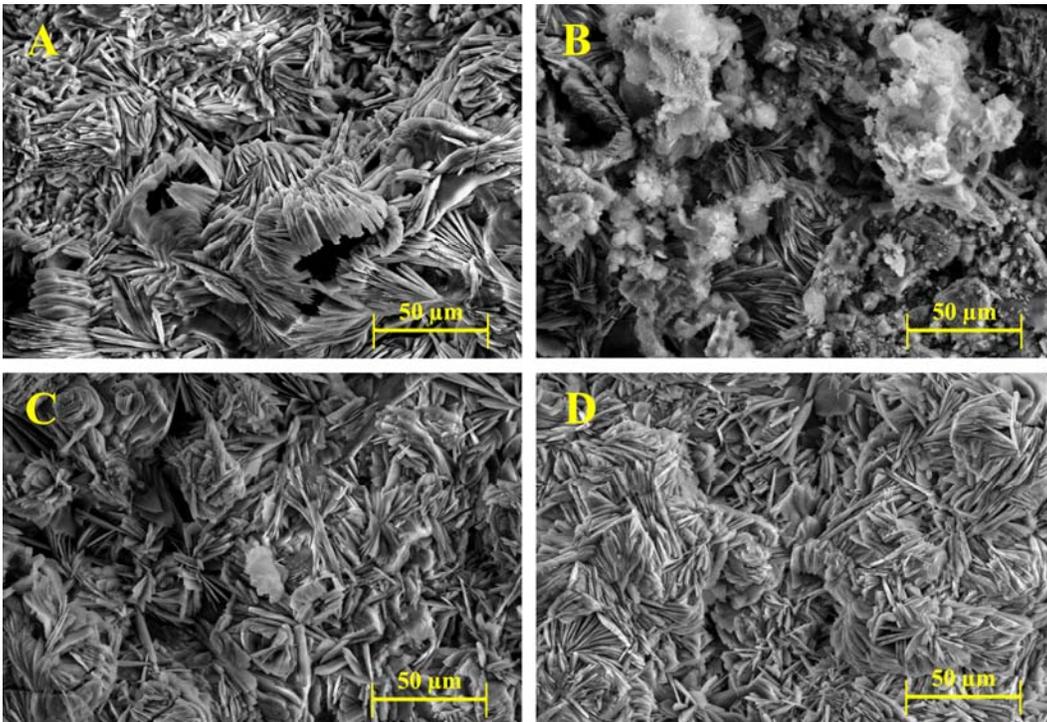


Figure 1. SEM micrographs of Calcium Phosphate coatings obtained via cathodic polarization in (A) RED, (B) , (C) and (D) electrolytic solutions ( $t = 4$  min)

Coatings appeared homogeneous, in terms of distribution and morphology, at each time point ( $t = 2, 4$  and  $8$  min), and completely covered the metal surface of the specimens also with 2 min polarization time. At a micrometric scale (Figure 1), coatings show a plate-like crystal aggregates morphology: this result is independent either on the solution used than on the time of polarization. RedMg1

specimens (Figure 1B) show also some micrometric roundshaped crystal aggregates laying over the plate-like crystal structure.

This result is consistent with the XRD analysis of coatings (Figure 2): the observed Ca/P phases are not dependant on the electrolytic bath composition: the resulting crystallographic phase is mainly brushite, a calcium phosphate precursor of the hydroxyapatite.

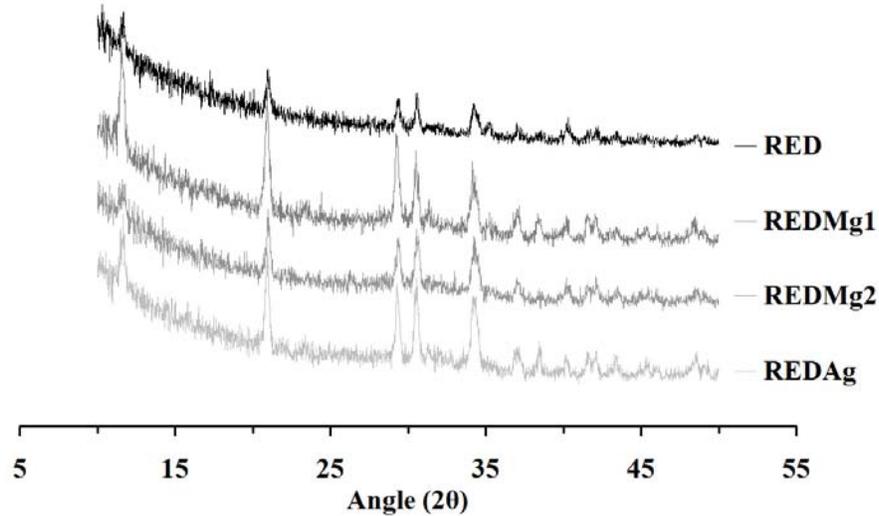


Figure 2. XRD spectra of RED, REDMg1, REDMg2 and REDAg coatings on Titanium substrates after 4 min of cathodic polarization deposition process

The weight of the Ca/P coatings are proportional to the duration of the polarization process, as shown in Figure 3. By increasing the time of treatment a general increase in the weight can be noticed, regardless of the used electrolytic solution.

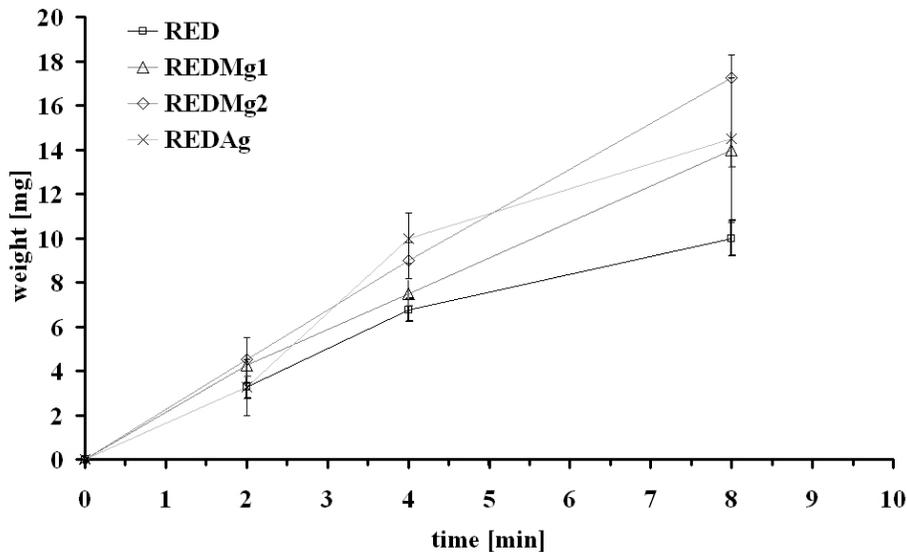


Figure 3. Weight of coating vs. time of cathodic polarization for RED, REDMg1, REDMg2 and REDAg specimens

The modification of the RED electrolytic solution seems to have a direct influence, at each time point, on the final weight of Ca/P coatings. As shown in Figure 3, Mg<sup>++</sup> ions enriched coatings resulted in the higher deposit weight. Modifications of RED solutions have been proposed with the aim of partially substitute calcium ions with magnesium and silver ions. The ICP-OES analysis of the 4 min polarization coatings show the presence of Mg<sup>2+</sup> and Ag<sup>+</sup> ions in the calcium phosphate coatings (Table 1).

**Table 1. Atomic ratios of RED, REDMg1, REDMg2 and REDAg dissolved coatings obtained via ICP-OES analysis**

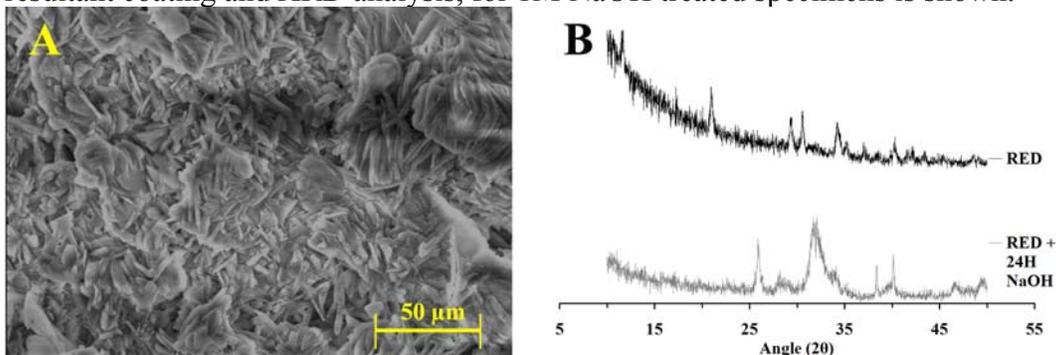
	<b>Ca/P</b>	<b>Mg/Ca</b>	<b>Ag/Ca</b>
	<b>[w/w]</b>	<b>% [w/w]</b>	<b>% [w/w]</b>
<b>RED</b>	1.42	0.00	0.00
<b>REDMg1</b>	1.32	5.22	0.00
<b>REDMg2</b>	1.43	1.51	0.00
<b>REDAg</b>	1.47	0.00	1.35

The Mg<sup>2+</sup> and Ag<sup>+</sup> cations of the solutions (Mg<sup>2+</sup> and Ag<sup>+</sup> in REDMg1/2 and REDAg respectively) were effectively detected in the corresponding coatings (Table 1). The mechanism of this incorporation, needs further investigation, and at the present time it is not clear if during the polarization takes place a selective substitution or a co-deposition of the different species. However, insertion through modification of the electrolytic bath composition is possible as an effective way to incorporate specific cationic species via a single polarization process.

The cations species considered in this study may play a positive role in modulating the osteoblast cell metabolism [14], in the case of Mg<sup>2+</sup> ions, or in providing antibacterial properties (Ag<sup>+</sup> ions) [15].

### 3.2. Phase conversion and dissolution kinetic

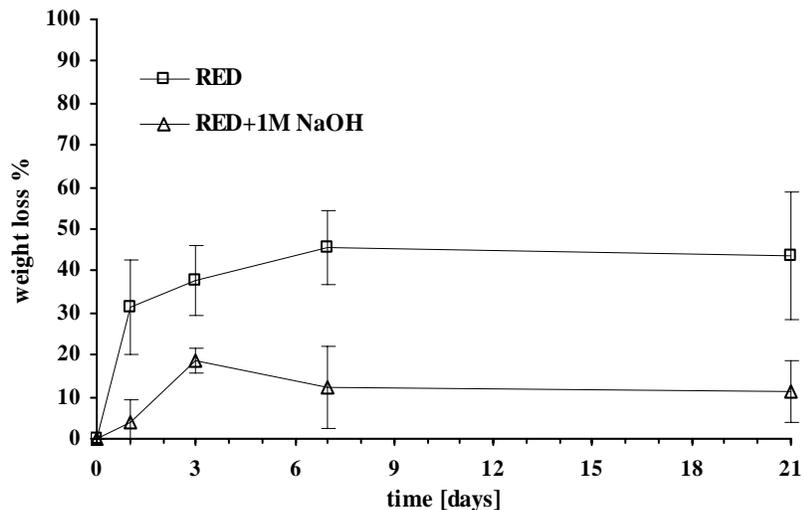
Phase conversion of the brushite coating in hydroxyapatite is possible via simple chemical treatment in basic media. As an example, in Figure 4 morphology of resultant coating and XRD analysis, for 1M NaOH treated specimens is shown.



**Figure 4. A) SEM micrograph and B) XRD analysis of RED specimens after conversion to hydroxyapatite using 1M NaOH (T = 80°C, t = 2H)**

After chemical conversion, a variation in morphology was observed (Figure 4A vs. Figure 1A): plate-like crystals dimensions decreased. Similar results were obtained by using different alkaline solutions and are independent on the deposit (RED, REDMg1, REDMg2 and REDAg). Moreover, via ICP analysis, it was possible to detect Mg and Ag ions, regardless the phase conversion (study performed on NaOH 1M solution).

The dissolution kinetics in PBS solution up to 21 days showed that the main weight loss takes place immediately after PBS immersion. For longer time, both materials reach a stable state.



**Figure 5. Kinetic dissolution behaviour of RED and RED+1M NaOH conversion coatings in PBS solution**

Moreover, from XRD analysis performed on specimens after PBS immersions, a phase transformation from brushite to HA was noticed also for RED specimens. Such transformation occurred during the PBS soaking at pH 7.4 and 37 C, became complete after 3 days of immersion.

#### 4. Conclusions

In this study, the process of cathodic electrodeposition of calcium phosphate on titanium surfaces has been analyzed. On the basis of previously reported works of Redepinning, we successfully investigated the possibility of  $Mg^{2+}$  and  $Ag^+$  ions inclusion on deposited Ca/P films. Such class of coatings may show potential advantages in mediating osteoinductive processes when incorporating Mg ions and may effectively induce antibacterial properties, when incorporating Ag ions. Transformation to HA resulted to be a pH-dependent process, and it was easily obtained through immersion in a strongly basic solution. The converted HA-coatings show a slower dissolution kinetic behaviour in physiological-like fluid, when compared to non converted brushite. The modulation of the crystalline structure of the coating may be a useful tool to trigger the *in vivo* coating

dissolution and host response. Moreover, it was observed that the PBS soaking process induced itself a coating transformation from brushite to hydroxyapatite. Future studies include a more detailed kinetic behaviour analysis and *in vitro* cytocompatibility and cytotoxicity tests. Moreover, mechanisms of ionic substitution have to be extensively studied, in order to obtain a more uniform cations doping and inclusion.

### **Acknowledgements**

Authors would like to acknowledge IIT for founding the research Grant XXX and Eurocoating (Pergine, IT) for economic and scientific cooperation. Authors are also grateful to L. Ulivi and S. Ambrosio for conducting experiments on cathodic deposition and for the useful suggestions.

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