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Control of phase composition in hydroxyapatite/tetracalcium phosphate biphasic thin coatings for biomedical applications

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Biphasic calcium phosphates comprising well-controlled mixtures of nonresorbable hydroxyapatite and other resorbable calcium phosphate phases often exhibit a combination of enhanced bioactivity and mechanical stability that is difficult to achieve in single-phase materials. This makes these biphasic bioceramics promising substrate materials for applications in bone tissue regeneration and repair. In this paper we report the synthesis of highly crystalline, biphasic coatings of hydroxyapatite/tetracalcium phosphate with control over the weight fraction of the constituent phases. The coatings were produced by pulsed laser deposition using ablation targets of pure crystalline hydroxyapatite. The fraction of tetracalcium phosphate phase in the coatings was controlled by varying the substrate temperature and the partial pressure of water vapor in the deposition chamber. A systematic study of phase composition in the hydroxyapatite/tetracalcium phosphate biphasic coatings was performed with X-ray diffraction. Tetracalcium phosphate in the coatings obtained at high substrate temperature is not formed by partial conversion of previously deposited hydroxyapatite. Instead, it is produced by nucleation and growth of tetracalcium phosphate itself from the ablation products of the hydroxyapatite target or by accretion of tetracalcium phosphate grains formed during ablation. This finding was confirmed by formation of calcium oxide, *not* tetracalcium phosphate, after annealing of pure hydroxyapatite coatings at high temperatures of 700–850 °C.

1. Introduction

Owing to their excellent biocompatibility and bioactivity, calcium phosphate bioceramics have been used for biomedical applications in a variety of forms and shapes, such as dense or porous bulk materials, coatings, and cements [1–4]. One of the most important clinical applications of calcium phosphates is in the form of coatings, particularly for dentistry and orthopedics. Calcium phosphate coatings on metallic implants combine mechanical strength of metal with excellent biocompatibility and bioactivity of calcium phosphates. They stimulate stronger bonding between the bone and the metallic implant as well as promote more rapid and stable fixation of the implant. In addition, the coatings reduce the release of the metallic ions from the implant into the body and shield the metal surface from the physiological environment [5–11]. Calcium phosphates have been commonly coated on metallic implants by plasma spraying [12–16]. Numerous studies in the past decade have demonstrated, however, that another physical vapor deposition technique known as pulsed laser deposition (PLD) may be the most suitable means to placing thin calcium phosphate coatings on these implants. This is because despite some similarities with plasma spraying, PLD offers superior control over critical parameters that determine the bioactivity and mechanical properties of calcium phosphate coatings such as their chemical composition, structure, and crystallinity [17–20].

Among the calcium phosphate compounds, hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$, HA] is the most stable phase in the body fluid and is very similar to the calcium phosphate crystals that comprise hard tissues such as bone and teeth. Since HA melts incongruently, tricalcium phosphate [$Ca_3(PO_4)_2$, TCP], tetracalcium phosphate [$Ca_4(PO_4)_2O$, TTCP] and CaO can be easily formed during deposition under dehydroxylation conditions. These decomposition products are reported to

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dissolve more rapidly in the body fluid than crystalline HA, in the following order: CaO $\gg$ TTCP $>$ TCP $\gg$ HA [21]. An important thrust of current research associated with calcium phosphate bioceramics is focused on biphasic coatings composed of nonresorbable HA and resorbable TCP [22–25]. The partial dissolution of the bioresorbable phase in biphasic calcium phosphate coatings is considered beneficial because it may stimulate bone apatite formation at the interface between implant and bone [26–28]. However, if the dissolution of the bioresorbable phase is too rapid it can deteriorate the coatings. Hence, it is very important to find the optimum amount of the highly resorbable phases in the coatings so that they can enhance bioactivity at the bone-implant interface, which should ultimately improve interfacial bonding, while avoiding mechanical failure of the coatings in the short term. The HA/TCP combination has been widely studied because it can be prepared by simple methods involving the sintering of calcium-deficient apatites at or above 700 °C [24, 25]. Biphasic samples of HA and TCP prepared by these methods have been the object of frequent investigations also because of its anticipated compatibility with large-scale production of bone substitute systems such as scaffolds and grafts. Although this concept has been applied mainly to the HA/TCP combination because of the convenient, well-established methods of materials preparation, it can evidently be extended to biphasic coatings composed of nonresorbable HA and other bioresorbable phases. In fact, it is not known whether HA/TCP offers the best phase combination for simultaneously satisfying the stringent bioactivity and mechanical stability criteria for clinical applications. The main limiting factor in the exploration of other biphasic configurations is the difficulty in identifying coating deposition methods capable of generating high quality biphasic coatings with good reproducibility. In this paper, we report the synthesis of biphasic coatings made of HA and bioresorbable TTCP by PLD and the systematic control of the phase composition in the coatings with varying deposition parameters. Also, we discuss the mechanism of TTCP phase formation in the HA/TTCP biphasic coatings during deposition and their dissolution behavior in relation to pure HA coatings.

2. Experimental procedure

We have obtained biphasic calcium phosphate coatings of thickness 1–3 μm in Ar/H_2O atmosphere by PLD using a KrF excimer laser (248 nm) with an energy density of 4–7 J/cm^2 and a pulse repetition rate of 30 Hz. The experimental setup used in our depositions closely mirrors the standard PLD configuration reported in previous studies of calcium phosphate coatings, which is described in detail elsewhere [17–20]. The base pressure of our vacuum processing system was typically below 5.0×10^{-7} Torr. Deposition was carried out in an Ar/H_2O atmosphere at various pressures in the 300–600 mTorr range. The Ar/H_2O atmosphere was obtained by efficiently bubbling a constant flow rate of 2000 sccm of Ar gas (99.999% purity) through deionized water kept at a fixed temperature of 100 °C as measured by a thermocouple probe. This was just below the boiling point of water for the pressure conditions in our bubbler. After bubbling, a small fraction of the water-containing flow was introduced into the vacuum chamber while the rest was sent to an exhaust line. In all our deposition experiments the ratio of Ar:H_2O species in the Ar/H_2O gas mixture was maintained constant by using the same bubbling conditions specified above and a fixed chamber inlet flow rate of 80 sccm. The pressure in the deposition chamber was controlled by adjusting the pumping rate of a variable-speed turbomolecular pump. This enabled good control over the partial pressure of water vapor during deposition. The ablation targets consisting of pure crystalline HA were made by compressing a commercial HA powder (97.5% purity, Plasma Biotal Ltd.) at a pressure of 2500 psi and sintering at 1200 °C in Ar/H_2O atmosphere for 1.5 h. Coatings were deposited on titanium alloy substrates (Ti-6Al-4V) in the form of 1-cm diameter disks polished with SiC paper of 180 grit, 600 grit, 1200 grit, and polycrystalline diamond suspensions of 6 and 1 μm, followed by cleaning with trichlorethylene, acetone, methanol, and deionized water in an ultrasonic bath. The crystalline structure and the phase composition of the coatings were determined using thin film X-ray diffraction (XRD) with Cu Kα radiation of 1.5418 Å wavelength at the scan speed of 0.0001–0.008 °/s. In order to estimate the weight fraction of the TTCP phase in the coatings using XRD, mixtures of pure, fine-grained TTCP (95% purity, Clarkson Chromatography Products, Inc.) and HA powders (97.5% purity, Plasma Biotal Ltd.) with different known composition were used as standards to calibrate the integrated intensity ratios of the diffraction peaks from the coatings. The integrated diffraction intensity was determined by fitting the peaks with the Pearson function [29].

3. Results and discussion

Since hydroxyl groups (OH$^-$) play a major role in the crystal quality and phase of calcium phosphate materials, a good strategy to synthesize controlled biphasic layers is to manipulate the OH$^-$ availability and rate of incorporation into the coatings. This can be achieved in PLD by varying the ambient pressure, which impacts the OH$^-$ concentration, or changing the substrate temperature, which controls the efficiency of incorporation as well as bulk and surface diffusion of OH$^-$.

Fig. 1 shows XRD scans of calcium phosphate coatings deposited at 670 °C at various Ar/H_2O ambient pressures. At 300 mTorr, three crystalline materials are identified in the coatings, namely HA, TTCP, and CaO. The HA crystalline phase manifests itself through several XRD peaks well indexed to the HA hexagonal structure ($a = 9.418$ Å, $c = 6.884$ Å) of the $P6_3/m$ symmetry group. Several prominent peaks ascribed to the TTCP phase are also observed at 300 mTorr. TTCP, which has the monoclinic structure ($a = 7.018$ Å, $b = 11.980$ Å, $c = 9.469$ Å) of $P2_1$ symmetry group, is one of the dehydrated calcium phosphate compounds. The XRD scans for these coatings also show peaks for CaO. The low-intensity and relatively broad peaks, as well as the presence of a broad amorphous-like

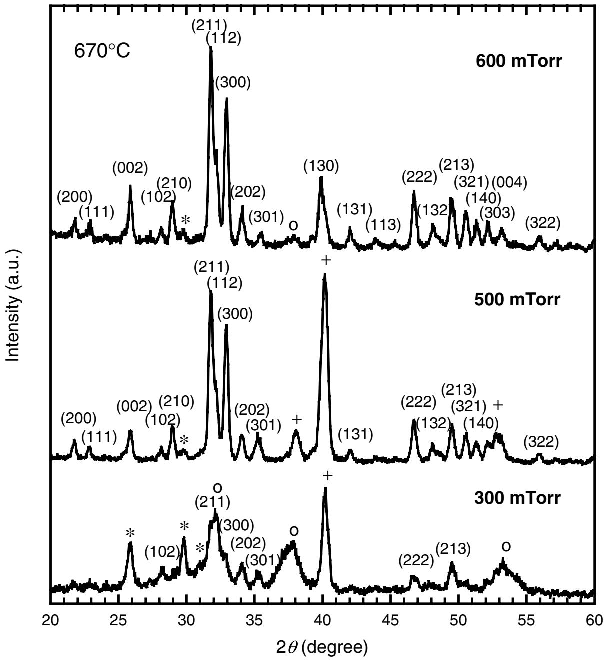


Figure 1 X-ray diffraction scans for calcium phosphate coatings deposited at different Ar/H_2O ambient pressures at 670 °C with a laser energy density of 4 J/cm^2 (Indexed peaks: hydroxyapatite; $*$ tetracalcium phosphate; ○ CaO; + Ti-6Al-4V substrate).

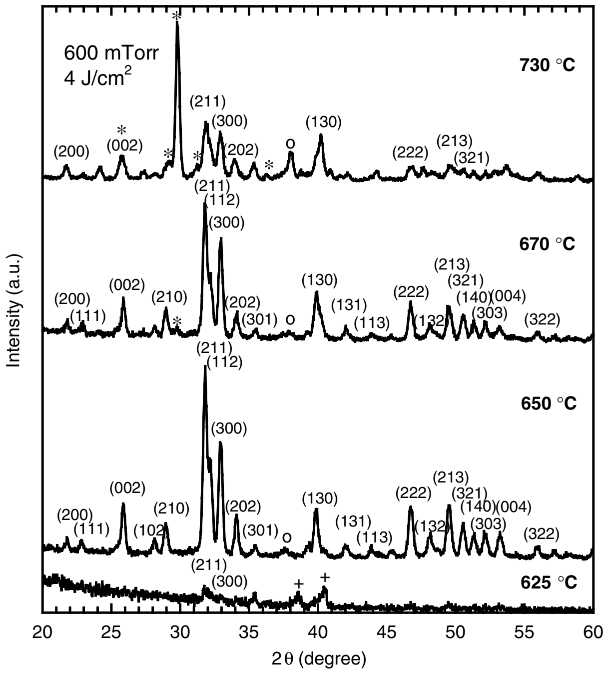
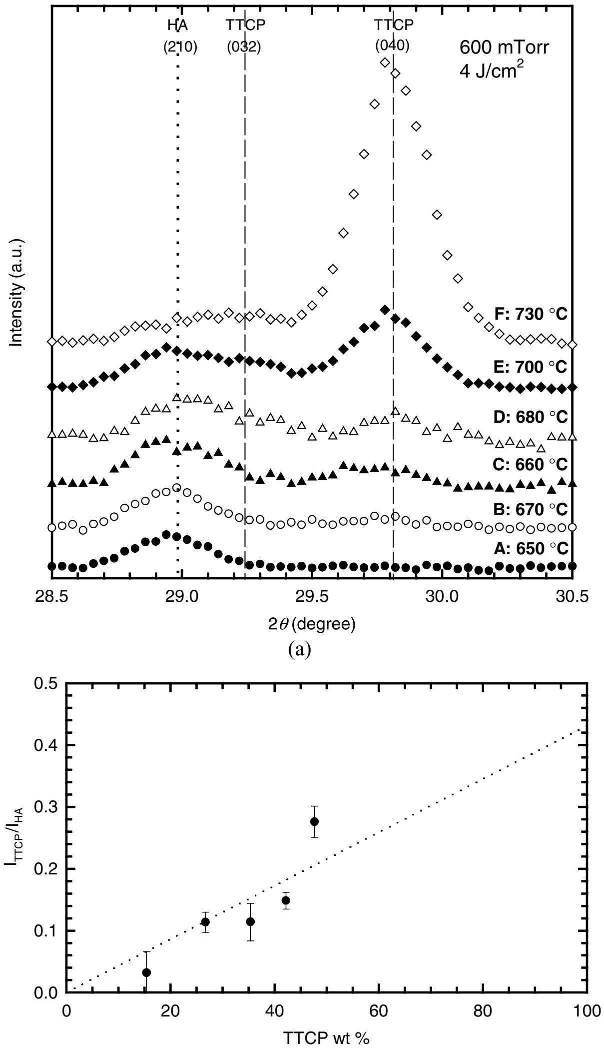


Figure 2 X-ray diffraction scans for calcium phosphate coatings deposited at different substrate temperatures with a laser energy density of 4 J/cm^2 (Indexed peaks: hydroxyapatite; $*$ tetracalcium phosphate, ○ CaO; + Ti-6Al-4V substrate). All coatings were obtained at the Ar/H_2O pressure of 600 mTorr, except 625 °C coating, which was deposited at 500 mTorr.

background feature centered at $2\theta \approx 32^\circ$ suggest a significant amount of amorphous material in the coatings deposited at 300 mTorr. This is most likely due to the low availability of OH^- groups at this pressure. Although the thermal energy provided by the substrate temperature enables crystallization of other equilibrium phases such as TTCP and CaO, the low OH^- concentration limits HA crystallization, apparently leaving a fraction of the calcium phosphate material in an amorphous state. As the Ar/H_2O ambient pressure is increased to 500 mTorr, all TTCP and CaO peaks are obviously reduced in the coatings. At 500 mTorr and 600 mTorr, the coatings consist mainly of HA crystalline phase exhibiting XRD peaks well indexed to the HA hexagonal structure. Very small amounts of TTCP and CaO can still be identified in these coatings deposited at higher ambient pressure and 670 °C. Noteworthy, however, is the fact that coatings grown at the pressure of 600 mTorr show better crystallinity of HA than the one grown at the pressure of 500 mTorr, as indicated by the higher intensity of the peaks and lower amorphous bands. These experiments suggest that a pressure of 600 mTorr may be optimal for attempting the fabrication of biphasic HA/TTCP coatings by controlling the substrate temperature and thus tuning the incorporation of OH into the layers.

Fig. 2 shows XRD scans of coatings deposited at different substrate temperatures in an Ar/H_2O atmosphere of 600 mTorr. It shows a significant change of phase composition in the temperature range of 625–730 °C. Coatings deposited at 625 °C exhibit a lack of long range order, suggesting that the film is very finely crystalline, contains a large concentration of defects or is amorphous. Evidence for the presence of at least some HA crystalline phase is provided by the weak (211), (300), and (301) reflections of HA. Coatings deposited at 650 °C, however, appear to be fully crystalline exhibiting all peaks associated with the HA hexagonal structure. This change from an essentially disordered phase to crystalline HA as the temperature is increased from 625 to 650 °C has also been observed in amorphous calcium phosphates present in HA coatings obtained by plasma spray as reported by Gross *et al.* [30]. In that case some crystallization of the amorphous phase into HA occurs at temperatures as low as 500 °C for hydroxyl-rich regions of the sample, while full HA crystallization takes place only after OH^- diffusion has been enabled, which takes place at temperatures in the 600–650 °C range. This is consistent with our observations in Fig. 2. For coatings grown at 670 °C, crystalline HA is still the dominant phase, while the TTCP crystalline phase starts appearing. At the higher temperature of 730 °C, a major increase in the TTCP crystalline phase content is observed accompanied by a reduction of the HA crystalline phase. These results show that within a relatively narrow temperature range (around 100 °C), the coatings go from an essentially disordered phase to fully crystalline and then to a well-controlled biphasic system. In fact, the temperature onset for highly crystalline HA seems to be quite abrupt as the coatings change from a disordered phase to fully crystalline by a small temperature increment of just 25 °C.

The transition from a pure HA coating (650 °C) to a HA/TTCP biphasic system (∼700 °C) observed in Fig. 2 prompted more careful investigations within that temperature range that could establish to what extent the relative composition of these phases can be controlled. Fig. 3(a) demonstrates the smooth transition in the phase composition of the HA/TTCP biphasic



(a)

(b)

Figure 3 (a) X-ray diffraction scans showing control of tetracalcium phosphate (TTCP) phase content in HA/TTCP biphasic coatings. TTCP phase content of A: 0 wt%, B: 9 wt%, C: 22 wt%, D: 24 wt%, E: 84 wt% (F: TTCP content unknown due to preferential orientation) [Dotted line: (210) HA reflection; dashed lines: (032) and (040) TTCP reflections]. (b) Calibration curve of integrated intensity ratios of (040) TTCP peak to (211) HA peak in standard powder mixtures of known HA and TTCP composition (Dotted line: best fit to available data).

coatings by identifying the X-ray reflections in the scan range of $28.5^\circ \leq 2\theta \leq 30.5^\circ$. The weight fraction of the TTCP and HA phases in the films were estimated from the integrated intensity ratio of the major TTCP peak (040) and the major HA peak (211) [not shown in Fig. 3(a)] in the coatings. The weight fraction estimates were based on a calibration of the integrated intensity ratio of these major peaks against powder mixture standards of known HA/TTCP concentrations. The data points and the linear fit used as a calibration curve in these estimates are seen in Fig. 3(b).

Fig. 3(a) shows that a monotonic increase in the TTCP content in the films is observed with increasing substrate temperature in experiments carried out at 600 mTorr with a laser energy density of approximately 4 J/cm^2. One noted exception to this trend is the coating deposited at 670 °C (labeled B) which has a lower TTCP content than that obtained at 660 °C (labeled C). This temperature reversal in the otherwise monotonic increase of TTCP content with temperature is probably caused by small changes in laser energy density and is discussed in detail in the next paragraph. The detection of this minor deviation in the temperature trend as well as the general behavior of the data observed in Fig. 3(a) show that XRD analysis provides good sensitivity for probing the phase composition of our biphasic coatings. The (210) reflection from HA gradually decreases while both, the (040) and the (032) reflections from TTCP rise with increasing TTCP phase fraction in the coatings (labeled A through E). An interesting effect occurs, however, for coatings deposited above 700 °C (labeled F). At these high temperatures the (040)-to-(032) TTCP peak ratio is significantly higher than the typical ratio of randomly oriented polycrystalline TTCP, which is approximately 1.25. This indicates that the TTCP crystals in the coatings deposited above 700 °C are preferentially oriented along the *b*-axis of the monoclinic structure. For coatings deposited at these high temperatures, the TTCP phase content could not be determined using the XRD data because our calibration is based on randomly oriented powder standards. Preferential orientation effects such as the one observed in Fig. 3(a) are common in PLD-deposited materials and may enhance the mechanical properties of the coatings [31].

A summary of the deposition parameters employed to control the phase composition of our biphasic coatings is presented in Table I. For the laser energy density and ambient pressure given, the table shows how the substrate temperature can be adjusted to synthesize biphasic coatings with controlled TTCP content in the 0–84 wt% range. As discussed previously, the TTCP crystalline phase can be obtained in water-deficient conditions induced by either low partial pressure of water vapor or high substrate temperature during deposition. These dynamic parameters (partial pressure of water and substrate temperature) are coupled. Change in one of them leads to a shift in the other if the same phase composition is to be achieved. It has been our observation that the same type of coupling occurs between substrate temperature and laser energy density. In other words, minor changes in laser energy density may lead to shifts in the substrate temperature necessary to produce the same phase composition. This effect is probably the cause for the temperature reversal for the coatings deposited at 670 and 660 °C [also labeled B and C, respectively, in Fig. 3(a)]. In this case, the coating deposited at 670 °C led to a lower weight fraction of TTCP (9 wt%) than the one produced at 660 °C (22 wt%). This reversal may be associated with the small, but significant difference in the laser energy density used for depositions, as shown in Table I. The higher laser energy density of 4.3 J/cm^2 used for the sample deposited at 660 °C (compared to 3.7 J/cm^2 for 670 °C sample) led to a large enough increase in dehydroxylation conditions that enabled more efficient formation of TTCP than in the deposition carried out at 670 °C. This observation underscores the importance of careful control of experimental conditions during PLD of calcium phosphate coatings.

Several possible hypotheses can be considered for the formation of the TTCP phase in the coatings. One

TABLE I Summary of deposition parameters used to control the phase composition of the hydroxyapatite/tetracalcium phosphate biphasic coatings produced by pulsed laser deposition. Randomly oriented polycrystalline tetracalcium phosphate exhibits (040)/(032) intensity ratio of approximately 1.25

Substrate temperature (°C)	Laser energy density (J/cm^2)	Ar/H_2O Pressure (mTorr)	$I_{TTCP(040)}/I_{HA(211)}$	TTCP (wt%)	$I_{TTCP(040)}/I_{TTCP(032)}$	TTCP orientation
650	3.7	600	0	0	NA	NA
670	3.7	600	0.04	9	NA	Random
660	4.3	600	0.10	22	1.30	Random
680	4.0	600	0.11	24	1.15	Random
700	4.0	600	0.38	84	1.25	Random
705	4.0	600	0.32	NA	2.84	*b*-axis
730	4.0	600	1.82	NA	8.50	*b*-axis
730	6.6	600	1.42	NA	3.18	*b*-axis
730	6.8	600	2.85	NA	3.82	*b*-axis

possibility is that TTCP forms during deposition by nucleation and subsequent growth of crystallites directly from the plume species. This process would take place on the surface of the growing calcium phosphate coating and by necessity be dependent on the substrate temperature. A similar scenario would involve TTCP growth from nano- and/or microscale HA particulates that upon ejection from the target (or during flight toward the substrate) undergo dehydroxylation and are converted to TTCP nano- or microcrystals. Yet another conceivable mechanism would include conversion of part of the HA crystallites into the TTCP phase after deposition. In this case dehydroxylation at the high substrate temperatures used would also be part of the process. This conversion might be particularly favored in the case of Ca-rich coatings where excess Ca^{2+} ions are available for formation of TTCP, which has a higher Ca/P ratio than HA. It is also possible that some remaining nonstoichiometric amorphous calcium phosphate phase could turn into TTCP.

In order to shed some light on the TTCP growth mechanism, a pure HA coating was annealed under vacuum for 2 h at high temperatures of 700–850 °C. Since these environments represent dehydroxylation conditions even more severe than those present during our depositions, one would expect significant formation of TTCP during annealing if TTCP originates through partial conversion of HA. The XRD scans for the coating annealed at different temperatures are shown in Fig. 4. When annealing is carried out at a substrate temperature below 700 °C, pure HA crystalline phase is maintained in the coating. However, at 750 °C signs of HA decomposition become evident with the concurrent formation of crystalline CaO. At 850 °C, crystallization of large quantities of CaO is observed, accompanied by a decrease in the HA phase. In the entire temperature range investigated, however, no other calcium phosphate phases were observed to form in the coating. Hence, it is safe to conclude that under severe dehydroxylation conditions, thermal energy alone leads to partial conversion of HA into crystalline CaO. This process is consistent with the following reaction:

$$Ca_{10}(PO_4)_6(OH)_2 \text{ (HA)} \rightarrow 10CaO + 3P_2O_5 + H_2O$$

Since P_2O_5 sublimes at 300 °C, there is no presence of P_2O_5 crystalline phase in the coating at the temperatures above 300 °C. According to this result, substrate temperatures as high as 850 °C did not lead to conversion of HA into TTCP. It is therefore appropriate to conclude that TTCP in the coatings deposited at high substrate temperature are not formed by partial decomposition of HA but by local nucleation of TTCP during the deposition or accretion of TTCP grains generated upon ablation or plume transport.

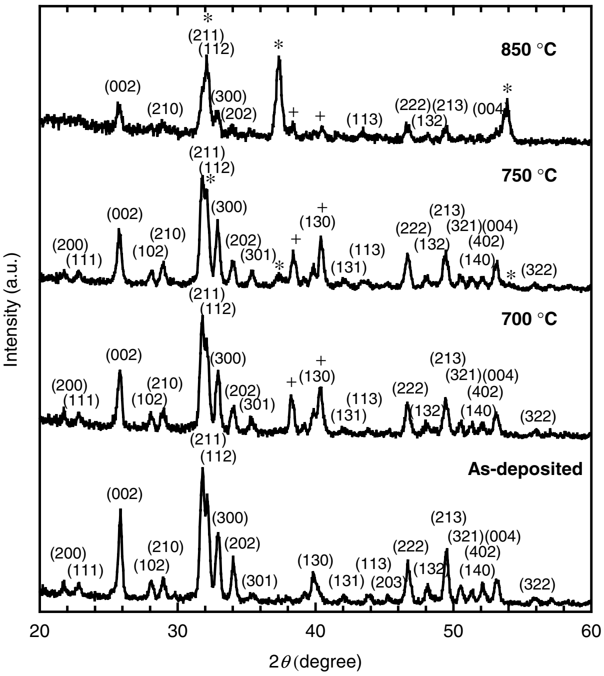


Figure 4 X-ray diffraction scans for a hydroxyapatite coating annealed under vacuum at different temperatures (∗ CaO, + Ti-6Al-4V). No conversion to tetracalcium phosphate is observed.

We have conducted dissolution experiments on HA/TTCP biphasic coatings obtained through our protocol and found that they exhibit dramatically different behavior when compared to pure HA films. XRD analysis reveals that all of the TTCP phase in the biphasic coatings dissolves quickly within 12 h in a simulated body fluid solution, while the HA phase in the coatings remains essentially unaltered for periods in excess of one month [28]. This may represent a route for triggering optimized biological response shortly after implant insertion, followed by a period of strong bone growth on a still robust nonresorbable coating.

4. Conclusion

We could systematically control the phase composition of HA/TTCP biphasic thin coatings deposited by pulsed laser deposition, by adjusting either the substrate temperature or the partial pressure of water vapor in the vacuum chamber during deposition. Tetracalcium phosphate in the coatings deposited at high substrate temperature seems to be formed *either* by nucleation and growth of TTCP crystallites directly from plume species during the deposition *or* by incorporation of TTCP particulates generated upon target ablation or during flight. Partial conversion of HA into TTCP seems to be ruled out as a mechanism of TTCP formation because annealing of pure HA coatings at high temperatures of 700–850 °C led to formation of calcium oxide in the coating, *not* tetracalcium phosphate. This finding suggests new possibilities for non-equilibrium synthesis of multi-phase calcium phosphate coatings whose phase make-up, and resulting dissolution behavior, can be engineered by controlled incorporation of individual phase constituents rather than by thermal decomposition from a single phase.

Acknowledgments

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