Bioactive nanocrystalline sol-gel hydroxyapatite coatings

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Sol-gel technology offers an alternative technique for producing bioactive surfaces for improved bone attachment. Previous work indicated that monophasic hydroxyapatite coatings were difficult to produce. In the present work hydroxyapatite was synthesized using the sol-gel technique with alkoxide precursors and the solution was allowed to age up to seven days prior to coating. It was found that, similar to the wet-chemical method of hydroxyapatite powder synthesis, an aging time is required to produce a pure hydroxyapatite phase. A methodology that has been successfully used to produce nanocrystalline hydroxyapatite thin film coatings via the sol-gel route on various substrates including alumina, Vycor glass, partially stabilized zirconia, Ti–6Al–4V alloy and single crystal MgO is described. Coatings produced on MgO substrates were characterized by X-ray diffraction and atomic force microscopy, while the analogous gels were examined with thermogravimetric and differential thermal analyses. The coatings were crack free and the surface was covered with small grains, of approximately 200 nm in size for samples fired to 1000 °C. Coating thickness varied between 70 and 1000 nm depending on the number of applied layers.

1. Introduction

Calcium phosphate ceramics were first proposed by Albee and Morrison [1] in 1920 for biomedical applications. They observed that tricalcium phosphate, injected into defects, demonstrated more rapid bone growth and union than the untreated defects. Hydroxyapatite (HAp) was first identified as being the mineral component of bone in 1926 by DeJong [2]. However, it was not until about 25 years ago that synthetic hydroxyapatite $[Ca_{10}(PO_4)_6(OH)_2]$ was accepted as a potential biomaterial for use in orthopaedics, bone grafts and dentistry. It is one of a limited number of materials that will form strong chemical bonds with bone *in vivo*, while remaining stable under the harsh conditions encountered in the human body. These properties place hydroxyapatite into the class of biomaterials known as surface active or bioactive materials. The only other materials that fall into this highly specialized classification are the biocompatible glasses and glass ceramics [3].

Most metallic orthopaedic and dental implants are bioinert and do not bond chemically to bone as does hydroxyapatite. Consequently they can become encapsulated by fibrous tissue. Thus, the only means of biofixation is mechanical interlock, whereby the implant must be manufactured in such a way that it possesses surface porosity with interconnections of 100 μm and pore sizes of 250 μm or larger in diameter [4], or be suitably surface macrotextured [5] so that hard tissue can grow into the implant and anchor it in place. Other methods available at present to fix implants firmly in place are the use of screws or bone cements [6]. If the implant does not integrate well with the surrounding bone, or is not held rigidly with a fastening device, the implant will be subjected to micromovement, and surrounding bone will remodel. This may lead to implant loosening over a period of time.

Brittleness, poor fatigue resistance and strength precludes monolithic HAp from use in load bearing situations. It is presently restricted to applications that involve non-weight-bearing conditions in service, such as bone fillers and bone graft substitutes in orthopaedics as well as ossicular bone replacements and materials for maxillofacial reconstruction [7]. Coating a load bearing substrate, such as titanium metal, with HAp overcomes the physical inadequacies of HAp. At the same time it combines the beneficial properties of both materials.

During the last two decades various coating methods were proposed to increase the bioactivity and hence accelerate and improve early bone–implant bonding. Methods that have been used to apply HAp coatings include: dip coating into a powder suspension [8], pulsed-laser deposition, electron beam evaporation combined with ion beam mixing, electrophoretic deposition [9], sputter coating [10] and plasma spraying [11]. Of these processes, only plasma spraying is used commercially.

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One of the most promising alternative coating methods is the thin bioactive layers produced by the sol-gel deposition techniques. The term sol-gel is currently used to describe any chemical procedure or process capable of producing ceramic oxides, non-oxides and mixed oxides from solutions. The overall process has been explained in various excellent review papers [12–16]. While commonly being used for producing glasses and oxides, it has more recently been utilized to produce other more complex materials as well as non-oxide ceramics.

The advantages of the sol-gel technique include: increased homogeneity due to mixing on the molecular scale; reduced firing temperatures due to small particle sizes with high surface areas, ability to produce uniform fine-grained structures; use of different chemical routes (alkoxide or aqueous based) and their ease of application to complex shapes with range of coating techniques, e.g. dip, spin and spray coating.

In general, the alkoxide method used involves the formulation of a homogeneous solution containing all of the component metals in the correct stoichiometry. Mixtures of metal alkoxides and/or metal alkanoates in organic solvents, which have been stabilized against precipitation by chemical additives (amines, glycols, acetylacetone, etc.), have proven the most successful. There is increasing evidence that these solutions contain heteronuclear metal complexes, in which the metal center may be linked by oxo, alkoxo or alkoxoate bridges, namely $M-O-M'$; $M-O(R)-M'$ and $M-O_2C(R)-M'$.

Dip coating or spin coating techniques can be used to apply a film of these solutions to a substrate, which is then brought into contact with water vapor. Several chemical processes may then take place in mixed oxide systems commencing with hydrolysis of some alkoxide groups, followed by oligomerization reactions, which further link the metal centers through the formation of oxo- or hydroxy- bridges. This ultimately results in the formation of a sol, which is converted to a gel on heating. Drying and firing of the gel generates the films, which are generally less than 0.1 μm thick. Control of the many processes that occur at this stage is important if good quality films are to be obtained [16]. It is also thought that coatings as thin as those produced by sol-gel may not suffer from thermal expansion mismatch, as do thicker coatings, such as those produced by dip coating into a powder suspension. The application of sol-gel processes in the preparation of single and mixed metal oxides, both in bulk powders and thin films, has increased dramatically over the last 25 years and is currently gaining popularity within the biomedical field.

During the last two decades three general concepts were adopted for the production of bioactive coatings: the first, developed by Ducheyne *et al.* [17], encompassing relatively thick (100 μm–2 mm) calcium phosphate coatings for bony ingrowth, and was based on the very innovative earlier work on porous monolithic ceramics by Hulbert *et al.* [18]; the second, thick bioglass coatings, initiated and developed by Hench *et al.* [19], for surface bioactivity and bioresorption; and a third method, developed by Kokubo *et al.* [20], based on biomimetics for thin layer hydroxyapatite growth from a simulated body fluid (SBF). Although all of these methods are very effective, full-scale commercialization has not eventuated.

In 1993, Chai *et al.* presented [21, 22] a new method of producing thin film hydroxyapatite and mixed calcium phosphate coatings via the sol-gel alkoxide route in two meetings. This was later reported in various papers [23–25]. The current paper summarizes the results of the research since its inception and the successful production of monophasic HAp thin films. These thin films offer an alternative solution for increased bioactivity. A nanometer-size bioactive coating approximately 70–1000 nm (depending on the number of coating layers) can generate an early and accelerated attachment of the bone to the implant similar to the relatively thicker coatings. This increased osteoconductivity is due to the nanocrystalline apatite growth from the coated surface, which interacts and bonds with the randomly oriented collagen fibers and the matrix [26]. In thick porous coatings gaps of up to 1 mm between HAp coating and the bone have been shown to be bridged by the healing process, leading to an early fixation [26]. The attachment to bone in HAp coated implants in three weeks was reported, which is half the time required for the uncoated implants [27]. This increased bond strength associated with accelerated osteoconductivity is very important in clinical applications where initial bone attachment determines the success rate of an implant.

Various sol-gel techniques have been used to synthesize hydroxyapatite powder [28–37]. Work by Matsuda *et al.* [31] is noteworthy on preparing powders from calcium phosphate precursors via the sol-gel processing route using metal alkoxides as the starting materials. Several other ultrafine chemical processing methods (not specifically the alkoxide route) have been reported and have proved to be attractive in refining precursor characteristics for hydroxyapatite and calcium phosphate ceramics. Unfortunately, the powder precursors prepared by some of these methods exhibit a low sinterability, due to the formation of agglomerates, although the individual crystallite sizes were nanocystalline. Brendel *et al.* [32] reported that various investigators also encountered difficulty achieving exact stoichiometry due to the volatility of the alkoxy phosphorous compounds used.

Previous work [23, 24, 34] has shown that the same difficulties were observed in achieving pure hydroxyapatite coatings. In this current report a preliminary review of successful synthesis, production and characterization of alkoxide derived pure monophasic nanocystalline hydroxyapatite coatings is given.

2. Materials and methods

The sol-gel methodology used in this investigation is similar to the conventional alkoxide method used to produce various oxides and mixed powders and is based on the work of Matsuda *et al.* [31] who successfully synthesized HAp powders.

This current method involves the dissolution of metal alkoxides in organic solvents and the subsequent combination of these solutions. The resultant solution can then be used to coat substrates using either dip or spin coating techniques, or alternatively used to produce

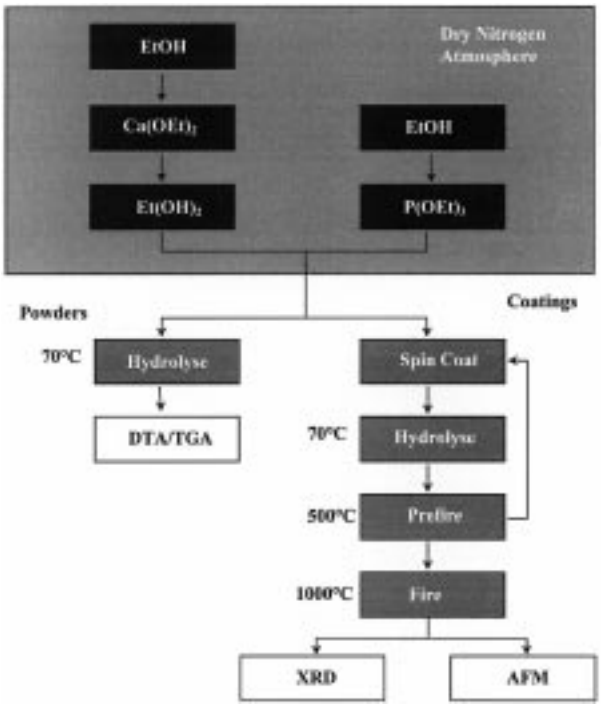

Figure 1 Schematic representation of the procedure used for the synthesis of the solutions, sample production and analysis techniques.

powders. The procedure used for the preparation of samples is shown schematically in Fig. 1.

2.1. Solution preparation

Some 1.5×10^{-3} moles of calcium diethoxide (Kojundo Ltd, Japan) were suspended in ethanol and then dissolved in ethanediol (BDH Chemicals, Australia) with the aid of vigorous stirring in a glove box containing a dry nitrogen atmosphere. A second solution consisting of a stoichiometric amount of triethyl phosphite (Aldrich, USA), diluted in ethanol, was prepared and added dropwise to the calcium bearing solution to minimize concentration gradients. Stirring was maintained for a period of 10 min. Solutions were allowed to mature for up to seven days before being used to deposit coatings. The use of a dry nitrogen atmosphere was necessary because the reactants were both air and moisture sensitive.

2.2. Coating procedure

During the various stages of this investigation Vycor glass (Crown Scientific, Australia), polycrystalline alumina (Coors, USA), partially stabilized zirconia (ICI, Australia), Ti–6Al–4V (Goodfellow, UK) and single crystal MgO (Zirmat, USA) were used as substrate materials. To minimize the surface interactions between coating and the substrate, magnesia single crystal substrates, $10 \times 10 \times 0.5$ mm in size were chosen. Substrates were ultrasonically cleaned in acetone and ethanol and then coated using a Headway Research (USA) spin coater. A volume of 0.5 ml of solution was applied to the substrate and spun at 2500 r.p.m. for 10 s to remove excess solution.

Coated substrates were hydrolyzed in an air oven (Labec, Australia) at 70 °C for 10 min, followed by prefiring at 500 °C in a muffle furnace (Ceramic Engineering, Australia) for 15 min. The coating–hydrolysis–prefiring procedure was repeated until five layers were deposited. After the final layer had been prefired, the coated substrates were heated at 200 °C h^{-1} up to 1000 °C and soaked for 15 min followed by cooling in the furnace.

2.3. Characterization techniques

Powders were analyzed using thermogravimetric and differential thermal analyses (DTA–TGA), while X-ray diffraction (XRD), scanning electron microscopy (SEM) and atomic force microscopy (AFM) techniques were employed to characterize coatings.

DTA–TGA were performed using a SDT 2960 simultaneous thermal analyzer (TA Instruments, USA). Gels for thermal analysis were produced by the direct hydrolysis of sol-gel solution at 70 °C in an air oven. During thermal analysis samples were heated at 10 °C min^{-1} to 500 °C, held for 15 min and then heated to 1200 °C at 200 °C h^{-1} (3.33 °C min^{-1}). This heating rate was chosen to replicate the heating schedule that coatings were subjected to.

XRD (Siemens D5000, Germany) was conducted on coated substrates using CuK_α radiation and a grazing angle geometry. This configuration was used to reduce X-ray penetration, hence achieving a maximum coating signal while minimizing substrate interference. Scan parameters included a scan range of 28–40° 2θ, a step size of 0.02°, a step time of 5 s and an X-ray incident angle of 1°.

The morphology of the coated substrates were examined using AFM and SEM. The Autoprobe LS AFM (Park Scientific Instruments, USA) was operated with a four quadrant 100 μm scan tube with silicon tip used in contact mode. A chromium coating of approximately 4 nm thick layer was deposited with a Xenosput (Dynavac, USA) sputter coater. The sample was viewed at 5 kV with a Jeol 6300F SEM operated with a field emission gun as an electron source.

3. Results and discussion

The use of a prefiring stage at 500 °C was found to be necessary to facilitate coating build-up. Without the prefiring stage subsequent coatings were found to partially dissolve the previous layer hence retarding successful coating thickness build-up. The prefiring stage removes volatile species allowing a rapid heating rate to the sintering temperature. Thermal shock is minimized due to the small coating thickness and the relatively small amount of material deposited. Hence, the thin coatings have a low susceptibility to thermal shock cracking and facilitate the ease of gas (including alcohol) removal. In addition, the thermal gradient within the coating is very small and the sintering conditions in all locations of the coating are similar.

Fired coatings appeared quite uniform under optical microscopy except towards the edges where they were thinner (observed as interference fringes). This is attributed to thinning of the coating due to the edge effect. Substrate coverage is thus dependent upon factors such as the solution chemistry, wettability, coating parameters and geometry of the object.

3.1. Thermal analysis

Thermal analysis of the hydrolyzed gel produced after a maturing time of seven days exhibited an endothermic peak at 110 °C and three exothermic peaks at 216, 430 and 550 °C (Fig. 2a). The large endotherm corresponds to the evolution of residual solvent and adsorbed moisture. This is followed by two large exothermic reactions at 216 and 430 °C, respectively. These reactions correspond to the formation of chemical bonds through condensation and polymerization as well as the evolution of residual water and/or alcohol. This behavior has also been reported with zirconia gels [38, 39]. A smaller exothermic reaction was observed at 550 °C and it is believed that this reaction represents the crystallization of hydroxyapatite. The vertical translation observed on the DTA–TGA curve at 500 °C represents the 15-min soak replicating the prefiring heat treatment (Fig. 2b).

3.2. X-ray diffraction

The XRD patterns for coatings produced after no aging and seven-day aging periods are shown in Fig. 3. Although hydroxyapatite (JCPDS 9-0432) is evident in solutions without aging, the presence of CaO (JCPDS 4-777) suggest that reactants have not had sufficient opportunity to react with each other.

Coatings produced after aging periods of one–seven days appear to consist solely of hydroxyapatite. Thus, it is evident that an aging period is necessary to allow the different species present in the coating solution to mix thoroughly. Given the complex kinetics of this system, and other similar processes reported in sol-gel phosphates [35, 36, 40], it is possible that various chemical reactions may take place during this maturing period. This aging phenomenon is similar to the ripening procedure used in the ''wet powder method'' to produce a stoichiometric hydroxyapatite [41].

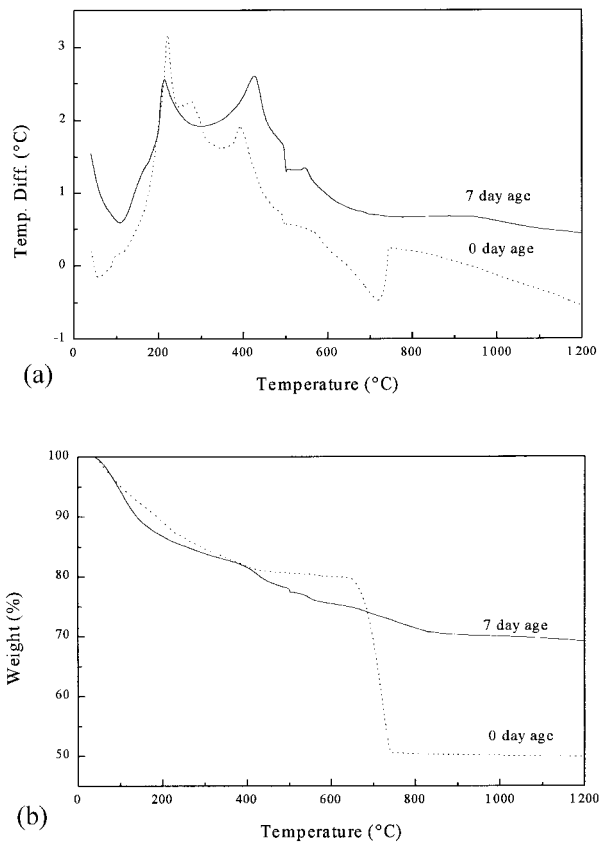

Figure 2 (a) Thermogravimetric (TGA) and (b) differential thermal (DTA) analyses plots for non-aged and seven-day matured gels.

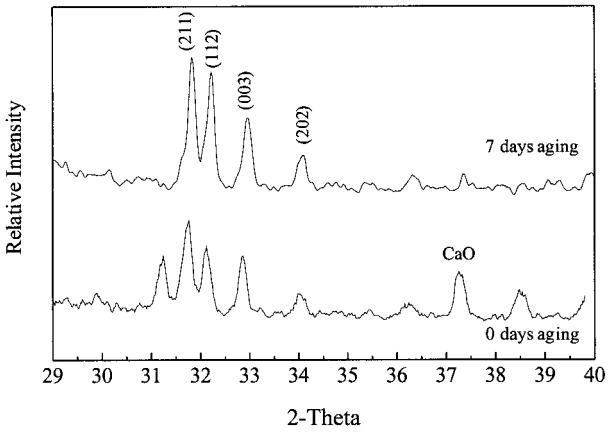

Figure 3 XRD patterns of coatings fired to 1000 °C for non-aged and seven-day matured samples.

3.3. Surface morphology

The coatings surfaces were examined using AFM and SEM. The coatings were crack free and consisted of two distinct regions: the surface was covered with small grains, approximately 200 nm in size. These smaller grains exhibited a ''cauliflower-like'' surface, which was broken up by larger grains, approximately 800 nm in diameter. These were observed at random separations across the coating surface and can be identified as peaks in Fig. 4a and lighter regions in Fig. 4b. It is possible that the larger grains had formed as a result of exaggerated grain growth.

4. Conclusions

Nanocrystalline thin film hydroxyapatite coatings have been produced via the sol-gel route. Coating thickness varied between 70 and 1000 nm dependent on the number of applied layers. Solutions were observed to wet substrates well and produced crystalline calcium phosphate coatings with some CaO also present when used immediately after solution preparation. It was found that to induce the formation of a coating that is monophasic hydroxyapatite, solutions should be aged for one–seven days prior to application. SEM and AFM examination revealed the presence of two distinct regions consisting of grains 200 and 800 nm in size, respectively, after being sintered at 1000 °C.

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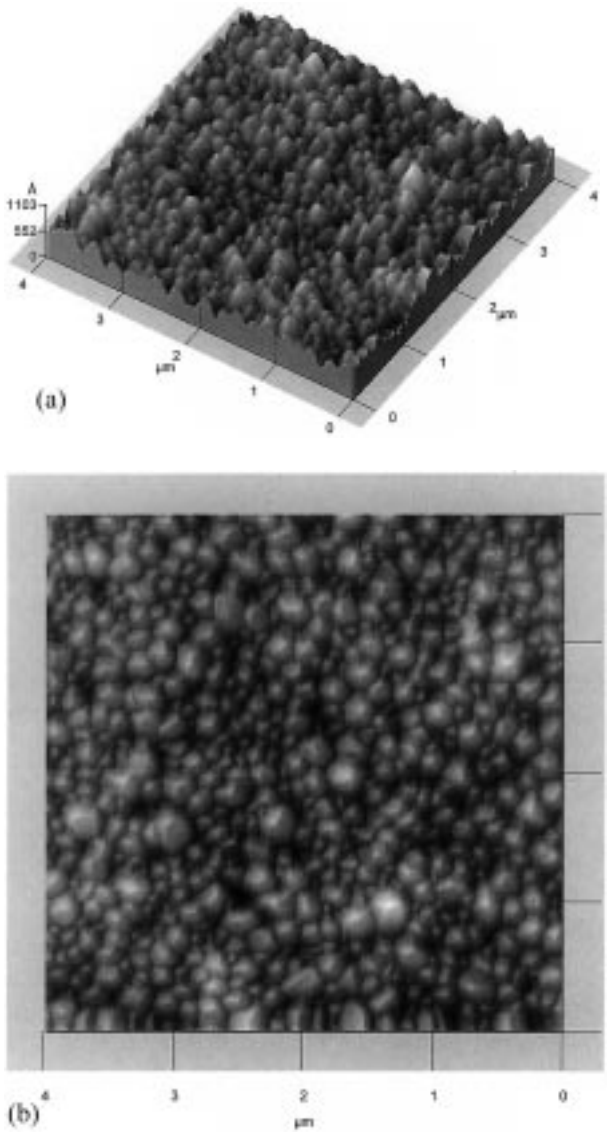

Figure 4 AFM scan of coatings, using solutions matured for seven days on an MgO substrate: (a) three-dimensional topographic view, (b) two-dimensional top view.

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