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Calcium phosphate bioceramics research in Latvia

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Abstract

Calcium phosphate bioceramics including glass-ceramics and hydroxyapatite have been manufactured and investigated for implantation purposes. Three glass systems were selected based on CaO and P_2O_5 and an inert metal oxide (either Ta_2O_5, TiO_2 or Nb_2O_5). Different compositions were found giving crystal phases in a glassy matrix. These glass-ceramics were tested for strength with 4-point bending, and the biocompatibility ascertained using in vitro and in vivo tests. The Nb_2O_5 containing glass-ceramic showed bone apposition and was found to be a suitable material for implantation. Hydroxyapatite was produced using the wet method and it was found that the pH during the reaction and the dispersivity of the $Ca(OH)_2$ influence the purity of the powder. The pH was controlled by addition of ammonium hydroxide to the precipitate. Hydroxyapatite sprayed onto grit blasted titanium showed low strengths of 20–30 MPa with adhesive failure but was increased to 60–70 MPa with an intermediate glass layer. Composites of glass-ceramic with hydroxyapatite exhibited a higher strength than hydroxyapatite with a value of 100–120 MPa.

1. Introduction

Bioceramic research emerged as a response to the search for more applications of glass technology. Riga Technical University in Latvia commenced research of bioceramics in the early 1980's. At that period of time, conventional ceramics such as alumina were used for prosthetic applications but they were restricted to only a few functions in the human body [1–4]. Reports on Bioglass appeared in various journals, suggesting the promise of this new material [5,6]. Meanwhile, at Riga Technical University, work was being carried out on the synthesis, production and use of bioactive ceramics.

Bioceramic research began in Latvia with the synthesis and investigation of calcium phosphate glasses and glass-ceramics in The Department of Silicate Technology [7]. This was the first known scientific study on bioactive ceramics in the former Soviet Union [8]. Biocompatibility studies were performed in collaboration with The Latvian Institute of Traumatology and Orthopaedics and the mechanical properties were investigated together with The Biomechanics Laboratory at Riga Technical University. The Biomechanics group was also actively involved with mechanical testing of polymeric based materials in addition to glass-ceramics [9,10]. Recent collaboration has been established between The Department of Dentistry and The Department of Otolaryngology. While Latvia was part of the Soviet Union, contact was maintained with major material research centres in Eastern Europe, Moscow and Kiev. When Latvia regained independence, collaboration was established with Australia, Germany and Finland. A Biomaterials Research and Development Laboratory has recently been formed within The Department of Silicate Technology which now offers a Master's degree in biomaterials by coursework.

The aim of this paper is to provide familiarization in the area of research. The four main areas of investigation to be reported, include:

1. Glass-ceramics based on the CaO-x-P_2O_5, where x is TiO_2, Ta_2O_5 or Nb_2O_5.
2. Hydroxyapatite synthesis and production.

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3. Composites of glass-ceramic and hydroxyapatite.
4. Glass-ceramic and hydroxyapatite coatings on titanium alloys.

2. Method

2.1. Glass synthesis

The rationale for choosing the components of the glass system was based both on naturally occurring elements in bone [11] and oxides of metals which were known to be inert [12–14]. Thus, both CaO and P_2O_5 were combined with either titanium, tantalum or niobium oxides. High purity $CaCO_3$, TiO_2, $NH_4H_2PO_4$, Nb_2O_5 and Ta_2O_5 were used as source materials. The metal oxide together with $NH_4H_2PO_4$ and $CaCO_3$ were homogeneously mixed and placed in alumina crucibles for heating at 1100–1400°C in furnaces with SiC heating elements. The glass was quenched in water to produce a frit and then milled in a rotary mill. The fine powder was mixed with less than 0.5 wt% of polyvinyl alcohol and pressed at 200 MPa. Sintering and crystallization of the glass was carried out at 800–1000°C. Glass ceramic samples were then machined and polished for further testing. Bend strength was determined by 4-point bending. Chemical composition and structure analysis were determined by X-ray diffraction, infra-red spectroscopy, scanning electron microscopy, X-ray microanalysis and X-ray fluorescence.

2.2. In-vitro and in-vivo testing

Samples were immersed in solutions of different pH to determine the chemical stability of the various glass compositions. Glass-ceramic samples were then subjected to in-vitro and in-vivo studies. In-vitro tests were performed in distilled water at 70°C. This temperature was chosen to accelerate changes that otherwise may occur slowly at body temperature. A small volume of water was removed every week and the composition analysed to ascertain any compositional changes in the water. Atomic absorption spectroscopy was used to detect the dissolution products.

Twelve cylindrical samples of each composition were sterilised in an oven by heating at 120°C for 45 min and implanted into the soft tissue of white rats and the femur of rabbits. Implants were removed after time periods of 3, 4, 6 and 7 months, inspected and then histologically analysed.

2.3. Hydroxyapatite production

Hydroxyapatite (HAp) was synthesised using $Ca(OH)_2$ and H_3PO_4 solutions at 40°C and pH greater than 9 according to Tagai and Aoki [15]. The precipitate was repeatedly washed in NH_4OH, filtered, dried at 150°C and calcined at 800°C for 1 h. The dried hydroxyapatite cake was then milled for sintering or crushed for plasma spraying. The milled hydroxyapatite was combined with 0.5 wt% polyvinyl alcohol solution, pressed at 200 MPa and sintered for 1 h at 1100–1150°C. Machined and polished specimens prepared to dimensions of 4 x 5 x 32 mm were subjected to 4-point bending. Powder for plasma spraying was crushed and classified until the particle size was within the range of 20–80 μm.

Composites of glass-ceramic and hydroxyapatite were prepared by a similar method. Hydroxyapatite and glass powder were mixed together after milling and placed in a rotary mill to obtain a homogeneous mixture. A glass binder was then added and the resulting mass was subjected to the procedure used for glass-ceramics.

2.4. Coating manufacture

Glass-ceramic and hydroxyapatite coatings were produced with a glass bond-coat. The glass was molten in an electric furnace, quenched in water, ball milled to a surface area of 0.8–1.0 m^2/g and dispersed in isopropanol which was then atomized onto the metal to produce a uniform layer. This glass powder deposit was dried at room temperature and heated to 900–950°C in a vacuum of 1 kPa to form a uniform glass coating. The precoated metal was then further coated with hydroxyapatite or glass-ceramic by plasma spraying. The coating conditions employed argon and helium as plasma gases, a power level of 25 kW and a torch to substrate distance of 10–12 cm. Powder was fed to the gun with a fluidized bed powder feeder. The overall quality of the coatings was determined by light microscopy, profilometry and X-ray diffraction and the bond strength to the metal base was tested by tensile adhesion tests (samples 25 mm diameter, 10 cm long).

3. Results and discussion

3.1. Synthesis of glass and its properties

Several glass forming regions were found at 1400°C. The CaO–Nb_2O_5–P_2O_5 system showed the largest flexibility in composition. The capacity of forming higher metal oxide content glasses is partly attributed to the similarity in processing temperature to the melting temperature of Nb_2O_5. The glass forming field is indicated by a continuous line in Fig. 1. Two open boxes show the compositions chosen for further investigation. The higher Nb_2O_5 content glass is 11Nb, whereas 2Nb contains less Nb_2O_5. Other glass forming compositions in the niobium oxide containing system also produced a glass but were not investigated further, Fig. 2.

Two glass-forming regions, marked with a dashed line in Fig. 1, were found for the $CaO–TiO_2–P_2O_5$ system. The biocompatibility of titanium and its oxide has been well documented in biomaterial applications [16] and so a higher titanium containing glass was chosen for further investigation, marked by an open triangle in Fig. 1.

Of the three oxides, Ta_2O_5 indicated the largest restriction in composition flexibility. Only very small oxide contents permitted the formation of glass as indicated by the dotted line in Fig. 1. Higher concentrations preferably crystallized. The compositions chosen with decreasing CaO content are 21Ta and 23Ta respectively. They are marked with open circles.

Surrounding each glass-forming region is an area representing crystallized glass, Fig. 2. The phase composition of the crystallized glass was examined and found to vary depending on the system, Table 1. In general, the phases included a calcium phosphate and a phosphate containing metallic oxide. Chemical phases were identified using the JCPDs powder diffraction file.

Glasses consisting of different metal oxides were immersed in different pH solutions and the dissolved species were examined, to establish the resorbability. Resorption is important since it may affect the structural integrity of the glass-ceramic. Glass based on the titanium oxide and tantalum oxide systems exhibited less dissolution with smaller amounts of P_2O_5 and more inert oxide, respectively. These metal oxide systems exhibited a decrease of 0.2–1.3 wt.% with 0.3–0.5 mm diameter particles after immersion, whereas the tantalum oxide containing glass displayed a 0.8-1.5% weight loss. This infers that the Ta containing glasses dissolve more readily than the other glasses and could degrade at a faster rate.

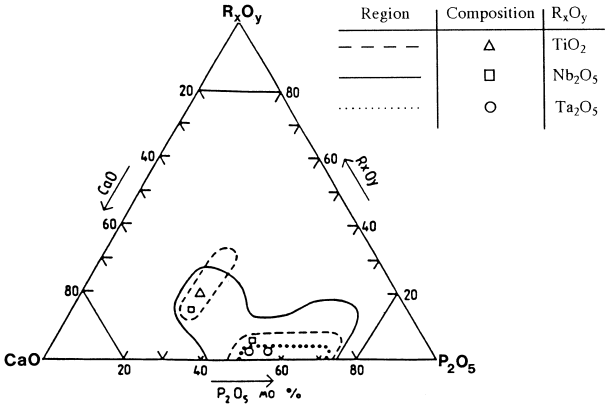

Fig. 1. Glass-forming regions of three metal oxide containing systems. The respective metallic oxide, R_xO_y, that produces a glass forming region is indicated by a dotted line for Ta_2O_5, a continuous line for Nb_2O_5 and a dashed line for TiO_2. Specific compositions marked with symbols are referred to in the text.

3.2. Glass-ceramic synthesis and properties

The TiO_2 and Nb_2O_5 containing glass systems show a large tendency to form crystallization products. The

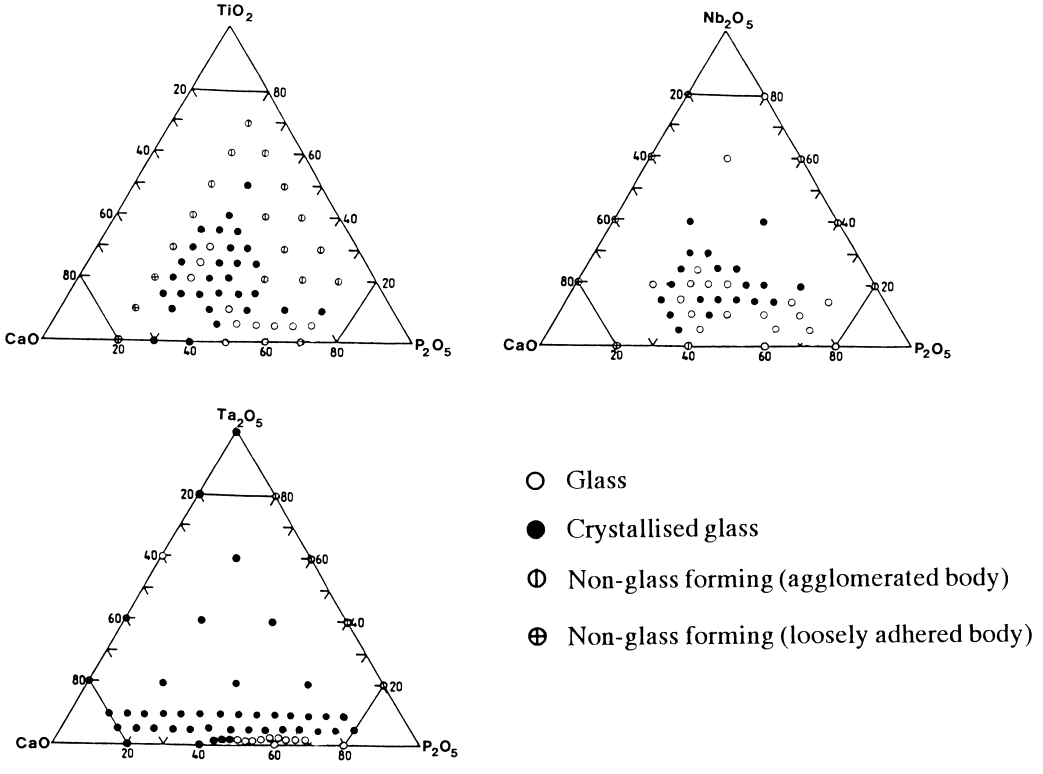

Fig. 2. Compositions investigated for the ability to form a glass. The physical condition of the composition after firing at 1400°C is shown.

Table 1
Major crystallized glass phases of the three metal oxide ternary systems

Glass system	Crystalline chases
$CaO\text{-}TiO_2\text{-}P_2O_5$	α and β $Ca_2P_2O_7$, $CaTiO_3$, TiP_2O_7
$CaO\text{-}Nb_2O_5\text{-}P_2O_5$	α and β $Ca_2P_2O_7$, $(CaP_2O_6)_x$, $NbPO_5$
$CaO\text{-}Ta_2O_5\text{-}P_2O_5$	$Ca(PO_3)_2$, $TaO{\cdot}PO_4$

Table 2
The Ca/P molar ratio of the various glass ceramics

Glass ceramic	Ca/P molar ratio
11Nb	0.92
2Nb	0.45
19Ti	0.83
21Ta	0.48
23Ta	0.39

Ca/P molar ratio of the glass-ceramics compositions are provided in Table 2.

Samples of glass-ceramics were manufactured by firing at 50°C intervals within the range of 800–1050°C. All samples from each glass system experienced a non-uniform dimensional change corresponding to crystallization. The most deformation resistant was the TiO_2 containing glass which could be fired up to 1050°C. All the remaining samples displayed an unsatisfactory dimensional change at a temperature of 1000°C. The strength of the glass-ceramics also increased with firing. Bending strengths of 40–75 MPa were reported for 19Ti and 11Nb. Samples 2Nb, 21Ta and 23Ta had lower bending strengths in the range of 45–60 MPa. The higher strength for the 19Ti and 1INb could be attributed to the higher metal oxide content. These compositions formed $Ca_2P_2O_7$ as the major phase as opposed to $Ca(PO_3)_2$ found in other samples.

All glass ceramic compositions appeared white. Glass-ceramic 11Nb was microcrystalline with an average grain size less than 1 μm, whereas 19Ti consisted of larger grains (10–20 μm). The bend strength of these compositions could be increased with $A1_2O_3$, Na_2O or CaF_2. For example, 19Ti fired at 950°C exhibited an increase from 40 to 80 MPa after addition of 2 mol% Na_2O [17]. Adding 5 mol% $A1_2O_3$ to 11Nb and firing at 1050°C increased the bend strength to well over 100 MPa. Modification of 11Nb with Na_2O (up to 10 mol%) facilitated an increase in strength at lower firing temperatures and would impart a higher solubility to the glass ceramic thus imparting dissolution more similar to bioactive ceramics. The addition of 8 mol% Na_2O to 11Nb (labelled as 4N) produced a bend strength of 120 MPa at a firing temperature of 800°C. By adding Na_2O, $A1_2O_3$ and CaF_2 and optimizing the production parameters, a stronger glass ceramic can thus be produced at lower temperatures.

3.3. In vitro and in vivo performance of glass ceramics

The distilled water became more acidic after soaking 2Nb, 21Ta and 23Ta for a period of one month. The resulting pH change from 7.0 in distilled water is for 21Ta shown in Fig. 3. A lower pH within the human body would promote bone resorption and a corresponding increase in the material dissolution. Any material causing a lowering of the pH in the body is thus unfavourable. It is advantageous if the material can withstand an acidic environment but it should not produce a decrease in pH. Rather, it is desirable for materials in the body to form a neutral or alkaline environment as is the case with synthetic hydroxyapatite, producing favourable conditions for bone growth. Samples 11Nb and 19Ti displayed significantly smaller pH changes for the same immersion time. Chemical analysis of the solution after immersion indicated a presence of calcium and phosphorous ions up to 40 mg/l. Heavy metals were not detected greater than the limit of detectability.

In vivo investigations indicate that glass ceramics 21Ta and 23Ta did not cause any irritation and remained attached to the surrounding tissue. An initial 30-100 μm fibrous capsule decreased with implantation time. The 19Ti glass ceramic also showed signs of a fibrous capsule up to 50 μm with a tendency to increase with time leading to aseptic irritation. Niobium oxide based glass ceramics showed the most promising results. The initial 50 μm thick fibrous layer diminished with time. No giant body cells were formed around the 11Nb implant [18]. Aseptic irritation occurred with 2Nb after 2 months.

The X-ray microanalysis of 11Nb indicated preferential dissolution of the calcium and phosphorus constituents. The release of calcium and phosphorous

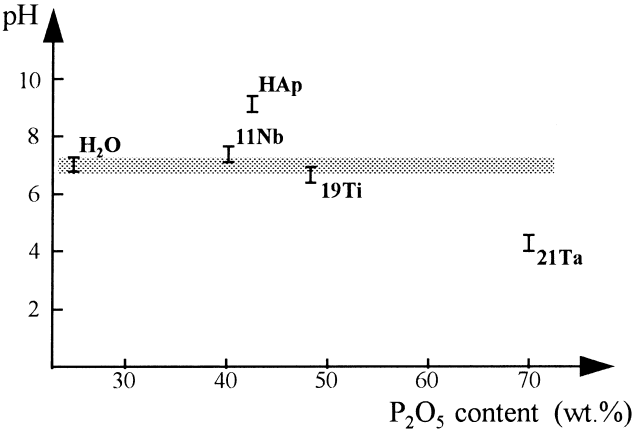

Fig. 3. The pH of physiological solutions after 1 month immersion at 70°C of HAp, 11Nb, 19Ti and 21Ta. Concentrations of calcium and phosphorus were evaluated in all solutions. Heavy metal ions were not present within the limit of detection (10 mg/l for $Ti^{3+,4+}$; 50mg/l for Nb^{5+} and 50 mg/l for Ta^{5+}).

species signifies dissolution of the phases and subsequent ion exchange with the physiological medium. This is a general observation for calcium phosphate materials [19,20] and may also occur with metallic phosphates present. Elimination of the fibrous capsule and direct apposition of bone indicates biocompatibility of the glass ceramic. X-ray diffraction and infra-red spectroscopy did not show any change in the bonding, structure and chemical phases. An infra-red spectra is shown in Fig. 4. This suggests that the structure and phase content of the glass ceramic is not altered after initial dissolution. Taking into account the mechanical properties of this ceramic, it is recommended as a material suitable for prosthetic applications. Further animal tests in rabbits are being conducted to determine the bone apposition to the improved composition, 4N.

3.4. Hydroxyapatite synthesis

Hydroxyapatite was synthesized using $Ca(OH)_2$ and H_3PO_4 as reactants. It was found that the formation rate of hydroxyapatite is dependent upon the $Ca(OH)_2$ dispersivity and the temperature of the solutions. Formation of the hydroxyapatite gel occurs faster at a higher temperature but is delayed when the dispersivity of the calcium hydroxyxide is low. Both reactant purity and dispersivity could be improved by beginning with calcium carbonate and heating to 1000°C for 12 h followed by addition to water to produce calcium hydroxide. The large exothermic reaction ensures a fine dispersion.

A faster production rate requires strict control of the reaction parameters. The pH plays an important role during the course of the reaction. It has been established that a fast reaction rate increases the acidity of the reaction mixture and the resulting pH will decrease below the level necessary for hydroxyapatite stability. The pH can be maintained above 8 with the use of a finely dispersed calcium hydroxide solution, at slightly increased addition rates of H_3PO_4.

During maturation, a separation occurs between the gel and the liquid introducing a pH difference at this interface. A contribution of any unreacted H_3PO_4 could increase the acidity in the clear layer. The pH difference can affect the stoichiometry and stability of hydroxyapatite. For example, a gelatinous precipitate with a low pH can lead to the formation of monetite or brushite. It is possible to stabilize the hydroxyapatite gel if the precipitate is placed in an alkaline environment. The pH of the precipitate can be controlled by washing with ammonium hydroxide which increases the yield of hydroxyapatite [21]. This produces favourable conditions for monophasic hydroxyapatite. A high purity (>99.5%) can thus be obtained (Table 3). This has been determined by X-ray diffraction (Fig. 5), X-ray fluorescence and infra-red spectroscopy of the calcined powder. The infra-red spectra illustrates the presence of carbonate in the hydroxyapatite, Fig. 6. The impurity levels are comparable to commercial hydroxyapatite powders and the carbonate ion within the hydroxyapatite is typical for powders made by the wet method in aerated water [22]. The presence of carbonate is also found in bone but may be removed by heating above 850°C [23]. After the washed hydroxyapatite is dried and calcined, the powder can be further processed by sintering. Bend strength tests of hydroxyapatite fired at 1150°C and for 3 h produced the best results.

3.5. Composites of glass-ceramic and hydroxyapatite

The rationale for making a composite was to produce a stronger material including hydroxyapatite as the more bioactive component, which could be fired at much lower temperature than hydroxyapatite. The 11Nb composition was thus modified with Na_2O and 20–40 vol% hydroxyapatite and fired at 900°C to produce a bend strength of 100–120 MPa.

X-ray diffraction and microanalysis indicated that hydroxyapatite was present as well as other calcium phosphate phases with varying Ca/P ratio, depending upon the particular region of the glass ceramic. The

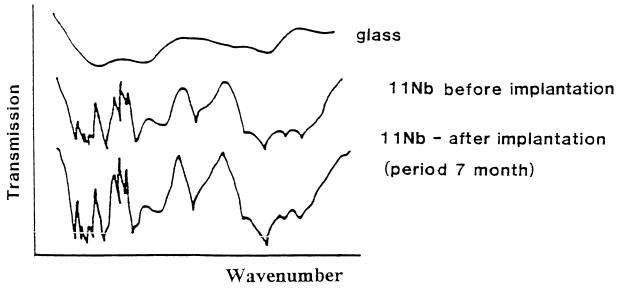

Fig. 4. Similarity of infra-red spectra for glass-ceramic 11Nb before and after implantation.

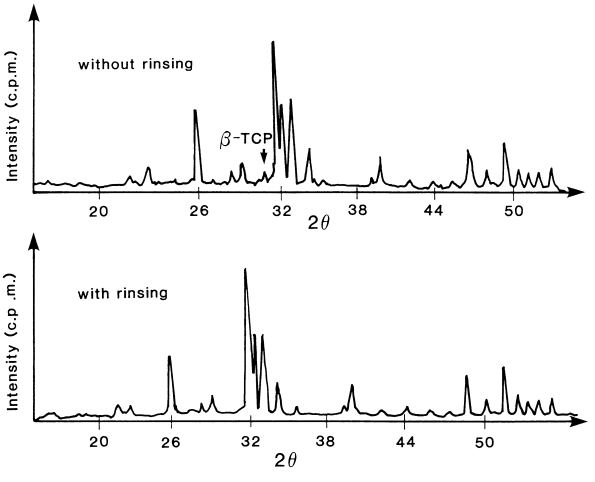

Fig. 5. Effect of rinsing on the phase composition of hydroxyapatite powder.

microstructure can be described to consist of three phase regions—the first with Ca/P between 1.56 and 1.67; the second very close to the Ca/P of the glass-ceramic and the third with Ca/P values in between. Macroscopically, the first region is very close to the size of the HAp grains with a niobium rich intermediate layer. This suggests partial dissolution of the hydroxyapatite during sintering. Similar results were obtained with the 21Ta composition and are shown in Fig. 7.

3.6. Bioceramic and glass coatings on titanium alloys

Plasma sprayed coatings with a thickness of 200 μm and a surface roughness of 10 μm have been manufactured. As sprayed coatings were characterized with X-ray diffraction. Results indicate an 8 wt% α-tricalcium phosphate in the hydroxyapatite coating, however, no change in the glass ceramic coating was observed. It is believed that the appearance of the secondary calcium phosphate, in addition to hydroxyapatite in coatings consisting of fully molten particles, is partially due to the large particle size distribution and the angular particle morphology arising from the crushing process.

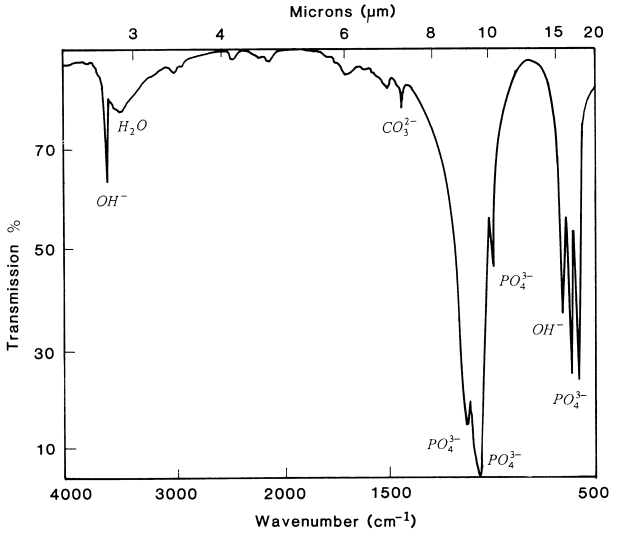

Fig. 6. Infra-red spectra of hydroxyapatite powder.

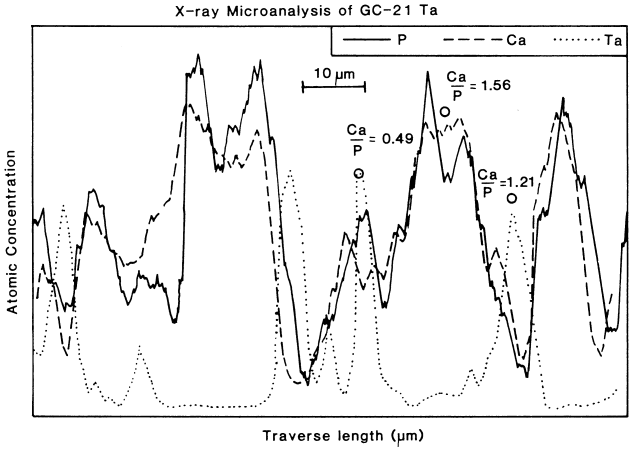

Fig. 7. X-ray microanalysis of a 21Ta and hydroxyapatite composite.

The tensile adhesion strength, measured according to ASTM 633 testing specifications, was 18–25 MPa for hydroxyapatite but 22–30 MPa for glass-ceramic. Adhesive failure occured for both coating types. The lower strength of the hydroxyapatite coating was attributed to the porosity in the feedstock powder used for thermal spraying. This porosity transferred to the coating provides a site for crack initiation within the coating. Calcination and sintering conditions are thus important to minimize the pore content of powders used for thermal spraying.

An intermediate 20 μm thick layer can be applied to increase the bond strength and encapsulate the titanium metal, thus preventing possible leaching of the titanium into the body. A glass coating from the $CaO–B_2O_3–P_2O_5$ system modified with SiO_2, $A1_2O_3$ and MgO was finely dispersed on the titanium and heated in a vacuum furnace at 800°C and 1 kPa. The resulting coating is dense and exhibits a bond strength of 70–80 MPa with the metal, leading to failure of the adhesive in all cases. Hydroxyapatite or glass-ceramic applied to the glass coating by plasma spraying produced an increase in strength compared to hydroxyapatite directly on titanium. The bond strength was raised to 30–50 MPa. The final coating assembly is shown in Fig. 8.

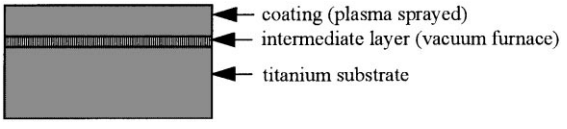

Fig. 8. Use of an intermediate bonding layer to increase adhesion of the coating to titanium.

Table 3
Comparison of the purity of hydroxyapatite powder.

Element	This work (%)	Plasma Biotal (%)	Merck (%)
Cd	0.001	0.0001	0.0005
Ba	0.01	–	–
Pb	0.002	0.001	0.002
Zn	0.0002	–	–
Cu	0.0001	0.0001	–
Mn	0.001	–	–
Mo	0.002	–	–
Sn	0.02	–	–
Fe	0.005	0.05	0.04
Cl	–	0.02	0.1
F	–	0.005	0.005
SO_4	–	0.01	0.5
Hg	–	–	0.0005
Mg	–	0.3	–
As	–	0.0001	0.0003.

4. Concluding remarks

1. Numerous compositions from the CaO–(Nb_2O_5, TiO_2 or Ta_2O_5)–P_2O_5 system were synthesized to establish glass-forming regions for production of glass-ceramics. Selected compositions were then chosen and assessed both in vitro and in vivo. The most favourable glass-ceramic from the Nb_2O_5 containing system designated as 11Nb has a bending strength greater than 100 MPa and exhibited good bone adaption to the implant with time.
2. Hydroxyapatite has been successfully synthesized with a purity greater than 99.5% which can be used both for production of monolithic materials and coatings. Hydroxyapatite plasma sprayed onto titanium exhibited tricalcium phosphate at a concentration of 8 wt%. The cohesion within these coatings is limited by the porosity within the feedstock powder. Adhesion to the substrate was found to be improved by using an intermediate glass coating.
3. Improving the performance of bioceramics has been addressed from a mechanical perspective by producing composites. Further work is addressing other macroscopic features such as porosity for bone ingrowth which is important for osseointegrated materials.

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