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(54) **Title**: MULTICOMPONENT GLASSES

(57) **Abstract**: The present invention relates to multicomponent glasses comprising at least six components of the system SiO_2-Na_2O-CaO-K_2O-SrO-MgO-ZnO-P_2O_5-B_2O_3-MF_x, (where M is a monovalent or divalent cation and x is 1 or 2), and their use as coatings.

Multicomponent Glasses

The present invention relates to multicomponent glasses comprising at least six components of the system SiO_2-Na_2O-CaO-K_2O-SrO-MgO-ZnO-P_2O_5-B_2O_3-MF_x (where M is a monovalent or divalent cation and x is 1 or 2), and their use as coatings.

A biologically active (or bioactive) material is one which, when implanted into living tissue, induces formation of an interfacial bond between the material and the surrounding tissue. Bioactive glasses are a group of surface-reactive glasses and glass-ceramics designed to induce biological activity that results in the formation of a strong bond between the bioactive glass and living tissue such as bone. The bioactivity of bioactive glass is the result of a series of complex physiochemical reactions on the surface of the glass under physiological conditions, which results in precipitation and crystallisation of a carbonated hydroxyapatite (HCA) phase.

Because of the ability of bioactive glasses to interact with living tissue they have found use in a number of medical applications, one of which is in providing a coating for medical prostheses, including orthopaedic implants.

Metallic prosthetics are typically made of metals or metal alloys, such as titanium (Ti), Ti-alloy (Ti6Al4V), Cr-Co alloys and stainless steel (316L). These have good mechanical properties and are non-toxic, but are biologically inert. Following implantation, due to the bio-inert nature of the implant, the body encapsulates the implant in a dense fibrous tissue layer. This can result in poor stress distribution and can ultimately lead to failure of the bone-implant interface requiring additional surgical procedures.

Coating the implant with a bioactive layer has the potential of improving the bone-implant interface by eliminating the formation of the fibrous tissue and resulting in a direct bond to the bone. This also eliminates the need for PMMA-based cements, which have been used to improve implant fixation, but have caused some controversy in Japan due to a number of deaths resulting from PMMA-cement fixated implants.

Hydroxyapatite (HA) is a bioactive ceramic similar to inorganic mineralised bone. HA-based coatings have been plasma sprayed onto metal implants, however the plasma spraying process results in a mixture of amorphous and crystalline phases and complex shapes are difficult to coat. This compositional uncertainty can result in unstable degradation conditions in the body. In addition, there is a large thermal expansion mismatch between HA and the metal substrate which can lead to interfacial failure.

The FDA approved 45S5 Bioglass®, developed by Hench *et al.* in the 1970s induces HCA formation *in vitro* and *in vivo* by a multi-stage dissolution process. However, 45S5 has a tendency to crystallise readily when heated above the glass transition temperature (T_g). The thermal expansion coefficient (TEC) of this material is also larger than that of metals generally used to make biomedical implants. This large thermal expansion mismatch and tendency towards devitrification rules out the use of Bioglass® as a coating produced by enamelling, where the glass powder is applied to the metal substrate and sintered above T_g to form a homogeneous solid coating.

Work has been carried out on modifying the 45S5 glass composition to increase thermal stability and lower TEC by Tomsia *et al* (US2002/0076528). Typically the silica content of the glass is raised, the alkali metal (e.g. Na and K) content is lowered and other components are added such as magnesium oxide and boron trioxide. These modifications have a tendency to lower the bioactivity of the coating relative to 45S5, with the increase in the silica content dominating and reducing the bioactive response as the glass structure moves away from the metasilicate structure (50 mol. % SiO_2, linear silicate chains). Two compositions are identified which coat titanium well: 6P57 and 6P61 containing 57 and 61 wt. % SiO_2 respectively. However, the former glass takes 1 month to form HCA in simulated body fluid (SBF) and the later does not form HCA at all over a 2 month period in SBF. As a result, the surface of coated substrates are loaded with hydroxyapatite (HA) or 45S5 particles to increase the bioactive response.

By tailoring glass compositions, in particular by incorporating a phosphate content over 3 mol % and tailoring the content of other oxides within multi-component glass systems, glass compositions have been shown to have thermal properties making the glasses suitable for successful use as a coating by stabilisation with respect to devitrification and controlling thermal expansion coefficient (TEC) as well as exhibiting good bioactivity. It has also been determined that certain multi-component glass compositions show anti-bacterial, biocompatible and bioactive properties rendering them beneficial for use as active ingredients in personal care products such as toothpastes.

Accordingly, in a first aspect, the present invention provides an aluminium-free glass having the composition:
35-55.9 mol % SiO_2;
a combined content of Na_2O and K_2O of 4-34 mol %;
0.5-9 mol % MgO;
0.5-4 mol % ZnO;
3.1-10 mol % P_2O_5;
0-5 mol. % B_2O_3;
0-5 mol % of a metal fluoride; and
a combined mol % of CaO and SrO of 8-37 mol %,
wherein at least 2 mol % of each of Na_2O and K_2O is present.

In the glass composition of the invention the SiO_2 content may be 40-50 mol%, preferably 43.5-47 mol%, more preferably 44-46 mol%, 44-45.5 mol% or even more preferably 44.5-45 mol%.

The combined mol % content of Na_2O and K_2O may be from 5 to 31 mol %.

The Na_2O and K_2O content of a glass of the invention may each be, independently, 2-17 mol%, preferably 2.5-15.5 mol%. In certain embodiments, the mol% content of Na_2O and K_2O is equivalent, although this is not necessarily the case. Increasing the number of components within the glass composition is beneficial for thermal stability.

Therefore, even though as a general principle, increasing alkali metal content lowers thermal stability, the inclusion of both Na_2O and K_2O is beneficial.

The combined mol % content of CaO +SrO in a glass of the invention may be 10-35.5 mol %. For glasses of the invention, the CaO + SrO content may be made up entirely of CaO, entirely SrO or by a combination of CaO and SrO. Preferably, both CaO and SrO are present at a content of at least 0.5 mol %, preferably at least 1 mol%. In some embodiments, on a molar basis, up to half of the total CaO +SrO content is SrO.

In a glass of the invention, MgO may be present at 2 to 9 mol %, preferably 3 to 8.5 mol. %, preferably 3 to 8.25 mmol%.

In a glass of the invention, ZnO may be present at 0.5 to 4 mol. %, preferably 2 to 4 mol%.

The content of P_2O_5 in a glass of the invention may be 3.1 to 7 mol %, or 3.1 to 6 mol %. In certain embodiments, the P_2O_5 is at least 3.5 mol %. Accordingly, the P_2O_5 content may be 3.5 to 10 mol %, 3.5 to 7 mol % or 3.5 to 6 mole %.

A glass of the invention may also comprise 0 to 3 mol% B_2O_3, preferably 0 to 2 mol% and/or 0 to 3 mol. %, preferably 0 to 2 mol% of a metal fluoride, for example CaF_2, SrF_2, ZnF_2, NgF_2, KF or NaF, preferably CaF_2.

In one embodiment, a glass of the invention may have the composition: 40-50 mol % SiO_2; a combined content of Na_2O and K_2O of 4-16 mol%; 2-9 mol % MgO; 0.5-4 mol % ZnO; 3.1-10 mol % P_2O_5; 0-5 mol. % B_2O_3; 0-5 mol % of a metal fluoride; and a combined content of CaO and SrO of 26-37 mol %. A glass of this composition may comprise 2-8 mol % Na_2O and 2-8 mol % K_2O. A glass of this composition is particularly suited for use as a coating for Ti or a Ti alloy.

The glass composition may be 40-50 mol % SiO_2; a combined content of Na_2O and K_2O of 4-16 mol%; 2-9 mol % MgO; 2-3.5 mol % ZnO; 3.5-6 mol % P_2O_5; 0-2 mol.

% B_2O_3; 0-2 mol % of a metal fluoride; and a combined mol % of CaO and SrO of 29-36 mol %. In certain embodiments, the content of SiO_2 is 44-46 mol%, preferably 44-45.5 mol%, more preferably 44.5-45 mol%. The content of K_2O and Na_2O may independently be 2-8 mol%, preferably 2.5-6.85 mol%. The MgO content may be 3-9 mol %, preferably 3.25-8.25 mol%. The ZnO content may be 2.5-3 mol%. In certain embodiments, the combined mol % of CaO and SrO is 29.25-35.5 mol %.

In another embodiment, a glass of the invention may have the composition: 40-50 mol % SiO_2; a combined content of Na_2O and K_2O of 16-34 mol%; 2-9 mol % MgO; 0.5-4 mol % ZnO; 3.1-10 mol % P_2O_5; 0-5 mol. % B_2O_3; 0-5 mol % of a metal fluoride; and a combined content of CaO and SrO of 8-26 mol %. A glass of this composition may comprise 8-17 mol % Na_2O and 8-17 mol % K_2O. A glass of this composition is particularly suited for use as a coating for chrome-cobalt alloy or stainless steel (e.g. 316L).

Preferably, the glass composition may be 40-50 mol % SiO_2; a combined content of Na_2O and K_2O of 16-34 mol%; 2-9 mol % MgO; 2-3.5 mol % ZnO; 3.5-6 mol % P_2O_5; 0-2 mol. % B_2O_3; 0-2 mol % of a metal fluoride; and a combined mol % of CaO and SrO of 9-24 mol %. In certain embodiments, the content of SiO_2 is 44-46 mol%, preferably 44-45.5 mol%, more preferably 44.5-45 mol%. The content of K_2O and Na_2O may independently be 9.75-15.5 mol %. The MgO content may be 3-8 mol %, preferably 3-7.5 mol %. The ZnO content may be 2.5-3.5 mol%, preferably 3 mol %. The combined mol % of CaO and SrO may be 10-23 mol %.

In certain embodiments, the glass has the composition: 44-46 mol % SiO_2 (preferably 44.5-45.5, more preferably 45 mol%); a combined content of Na_2O and K_2O of 18-22 mol%; 1-6 mol % P_2O_5 (preferably 4-5 mol%, more preferably 4.5 mol%); 0-5 mol. % B_2O_3; 0-5 mol % of a metal fluoride; and a combined mol % of CaO and SrO of 19-26 mol % (preferably 20-23 mol%). A glass of this composition may comprise, independently, 9-11 mol % of each of Na_2O and K_2O (preferably 9.5-10.5 mol %, more preferably 9.75-10 mol%). A glass of this composition is particularly suited for use as a coating for a chrome-cobalt alloy.

In certain embodiments, the glass has the composition: 44-46 mol % SiO_2 (preferably 44.5-45.5, more preferably 45 mol%); a combined content of Na_2O and K_2O of 28-34 mol%;; 2-8 mol % MgO (preferably 3-7 mol%); 2-4 mol % ZnO (preferably 3mol%); 3.1-6 mol % P_2O_5 (preferably 4-5 mol%, more preferably 4.5); 0-5 mol. % B_2O_3; 0-5 mol % of a metal fluoride; and a combined mol % of CaO and SrO of 8-15 mol % (preferably 10-14.5 mol%). A glass of this composition may comprise, independently, 14-17 mol % of each of Na_2O and K_2O (preferably 15-16 mol %, more preferably, 15.25-15.5 mol%). A glass of this composition is particularly suited for use as a coating for stainless steel (e.g. 316L).

Glasses of the first aspect of the invention preferably have a MgO content of 8.25 mol% or less, preferably 7.5 mol% or less and a combined Na_2O and K_2O content of at least 8. For glasses of the embodiments described as being particularly suited for coating Cr-Co alloys or 316L, the combined Na_2O and K_2O content is at least 18 mol%, preferably at least 28 mol% for the glasses described as being particularly suited for coating 316L.

The glass may be provided in particulate form, i.e. as a glass powder.

Glasses of the first aspect of the invention can be used to coat a metal or metal alloy substrate. Accordingly, in a second aspect the invention provides a coating composition comprising a glass of the first aspect of the invention. The coating composition may be for use in coating a metal or metal alloy substrate, which is preferably a medical or dental implant and may be formed from, for example, Ti, Ti-alloy, Cr-Co alloy or stainless steel.

Preferably, a glass of the invention has thermal properties enabling it to be coated onto a substrate and sintered. A coating may be formed by applying glass powder to a substrate and sintering above Tg to form a solid coating. The sintering temperature can be, for example 600-900°C, preferably 700-800°C. The glass composition may be formulated such that crystallisation during the sintering process is avoided.

In addition to coatings the glasses of the invention can be used in powder form (e.g. as a bone graft substitute), to form fibres (homogeneous or with a core-clad structure), porous scaffolds, bulk monoliths, a composite structure with a biodegradable polymer or utilised as a component in a cement, with the inorganic ions coordinating acidic functional groups in polymer (e.g. carboxylate groups in PMMA) during the setting reaction. Glasses of the invention can be used to form a porous material in a process comprising forming a slurry of melt-derived glass particles, a polymerisable monomer, a cross-linker and an initiator in a solvent; adding a surfactant and a catalyst to the slurry; agitating a slurry in the presence of a gas to generate a foam; drying a foam; and sintering the dried foam to produce a porous scaffold. This production process is described in WO 2009/144455.

In a third aspect, the invention comprises a coated substrate comprising a metal or metal alloy substrate and a coating formed from a glass of the first aspect of the invention. The coating will be formed from a glass of the first aspect of the invention which has been applied to the surface of the substrate and then sintered to give a sintered glass coating. The coating may be a mono-layer coating, a bi-layer coating or a multi-layer coating, wherein at least one layer is formed from a composition comprising a glass of the first aspect of the invention.

The coating will typically have an overall thickness of 10-500 μm with around 100 μm being preferred (i.e. 50-150 μm, preferably 80-120 μm).

The substrate may comprise titanium metal, a titanium alloy (e.g. Ti6Al4V), a chrome-cobalt alloy or stainless steel (e.g. 316L).

The coated substrate may be a medical implant, for example an orthopaedic or dental implant. The substrate may have an external surface completely covered by the coating or alternatively the substrate may be partially coated. For example, if the substrate is a screw, coating may be present in the grooves, but not on the thread.

In a fourth aspect, the invention provides a method of coating a substrate, wherein the substrate is as defined in respect of the third aspect of the invention, with a coating comprising a glass of the first aspect of the invention. The coating process involves applying powdered glass (or a composition comprising the glass) to the substrate and then sintering the glass. The method of coating may be dip coating, sedimentation or plasma spraying, use of a spray gun, electrostatic dry spraying, electrophoretic deposition or any combination thereof. The coated substrate is heat treated to sinter the glass. Heat treatment is preferably carried out under vacuum to ensure any bubbles formed by interfacial reactions in the heating process will float to the coating surface.

Aluminium is a neurotoxin and inhibitor of *in vivo* bone mineralisation even at very low levels and the glass of any aspect of the invention is therefore aluminium-free.

Preferred features of each of the aspect of the invention may be present in combination and apply to all other aspects *mutatis mutandis.*

The invention may be put into practice in various ways and a number of specific embodiments will be described by way of example to illustrate the invention with reference to the accompanying examples and figures, in which:

Figure 1 shows differential scanning calorimetry (DSC) traces of glasses HP1, HP2, HP3, HP5, HP7, BPS1, FPS1, 6P57, 6P61 and 45S5.

Figures 2(a), (b) and (c) show Raman spectra of glass powder of the invention and sintered coatings comprising these glasses. Figure 2(a) shows spectra for glass HP3 in powdered form and coated on Ti-alloy, sintered at 700°C, 725°C and 750°C. Figure 2(b) shows spectra for glass BPS1 in powdered form and coated on Ti-alloy, sintered at 700°C, 725°C and 750°C. Figure 2(c) shows spectra for a sintered glass, FPS1, in powdered form and heat treated at 600°C, 700°C, 750°C and 800°C.

Figure 3(a) and (b) show Raman spectra of: (a) glass HP2 after one day, one week and two weeks in SBF with crystalline Ca-hydroxy apatite for comparison; (b) glass 6P57 after one day, one week and two weeks in SBF.

Figure 4 shows the results of an ALP assay carried out with 45S5, HP1, HP2 and HP5 glasses.

The glasses of all aspects of the present invention may be bioactive glasses. A bioactive glass is one which, when implanted into living tissue, can induce formation of an interfacial bond between the material and the surrounding living tissue. The bioactivity of the glasses of the invention is a result of ion release from the glass composition and, therefore, the glasses of the invention should provide ion release under physiological conditions. Accordingly, glasses of the invention are at least partially resorbable under physiological conditions.

In the context of the present invention, a metal (II) fluoride such as SrF_2, CaF_2, ZnF_2, or MgF_2 or a metal (I) fluoride such as KF or NaF.

As used herein, 'titanium' relates to medical grade titanium, for example unalloyed titanium CP grades 1-4 (ASTM-F67). A 'Ti-alloy' or 'Ti6Al4V' refers to titanium alloyed with 6 wt. % aluminium and 4 wt. % vanadium (with the balance, 90 wt. %, being titanium) as detailed in ASTM F136.

As used herein, a 'chrome-cobalt alloy' or 'Cr-Co alloy' refers to an alloy of Chromium and Cobalt, optionally also comprising additional elements such as Molybdenum (for example the alloys specified in ASTM-F75, F799 F90 or F562).

As used herein, '316L' refers to a low-carbon stainless steel alloy of composition <0.03 C, <2 Mn, <0.75 Si, <0.045 P, <0.03 S, 16-18 Cr, 2-3 Mo, 10-14 Ni, <0.1 N and the balance Fe, all in wt. % (e.g. ASTM A240 / A240M).

The terms '45S5' and 'Bioglass®' are interchangeable and refer to the soda-lime-phosphosilicate composition: 46.1SiO_2-24.4Na_2O-26.9CaO-2.6P_2O_5, in mol. % (45 SiO_2-24.5Na_2O-24.5CaO-6P_2O_5, in wt%).

In the context of the invention, and crystalline structure, a 'glass' is an amorphous solid and a 'glass-ceramic' is a glass that, following sintering, has partially crystallised and therefore has a mixed amorphous and crystalline structure.

Throughout the application, where a glass of the invention is described as having or being formed from a composition of certain oxides/fluorides it will be appreciated that the glass composition comprises the oxides/fluorides in the proportions listed, but that other components may be present. However, in each instance where a glass composition is listed the invention also encompasses a glass formed from a composition consisting essentially of the oxides and fluorides listed, i.e. without other components. The components are given on a batch composition basis, i.e. in the proportions in which they are provided in the mixture which is melted to form the glass.

Glass Preparation

Glasses of the invention can be produced by conventional melt-cast techniques. The reagents use to make the glasses may be the oxides of the glass composition and/or other compounds that decompose with heat to form the oxides, for example carbonates. Melt-derived glasses can be prepared by mixing the appropriate carbonates or oxides, melting and homogenising the mixture at temperatures of approximately 1250°C to 1500°C, cooling the mixture, for example by pouring the molten mixture into water, to produce a glass frit which can be dried, milled and sieved to form a glass powder.

The glasses described in the following examples were prepared by mixing some or all of the reagents SiO_2, Na_2CO_3, $CaCO_3$, K_2CO_3, MgO, ZnO, B_2O_3, P_2O_5, $Ca_3(PO_4)_2$, $NaPO_3$, Na_3PO_4 and MgF_2 in amounts calculated to give the desired mol% of the various oxides making up the glass composition. Sodium phosphate and calcium triphosphate were preferred as the source of phosphate. It should also be noted that SrF_2, CaF_2, ZnF_2, NaF or KF can be used in place of MgF_2. The reagent mixture was melted at 1350-1400°C in a platinum crucible, frit cast into water, collected in a sieve and then dried for 1 hour at 150°C. The glass frits were milled in a rotary ball mill for 30 min to produce a glass powder and then sieved to produce a glass powder having a maximum particle size of <38 microns. The average particle size was around 20 microns.

As is well recognised in the art, glass compositions are defined in terms of the proportions (mol%) of the oxide (or fluoride) components in the melt mixture from which the glass is formed.

Glass Compositions - Coatings

Preferred glass compositions of the invention are set out in Tables 1A, 1B, 2A and 2B. The glass compositions shown in Tables 1A and 1B are particularly useful for coating Ti and Ti-alloy. The glass compositions shown in Tables 2A and 2B are particularly useful for coating Chrome-cobalt alloys (HP14-19) and 316L stainless steel (HP20-25). The glasses were prepared according to the melt-cast technique described above, with the respective amounts of the reagents used in the melt mixture calculated to give the mol% oxide compositions indicated in the table. For example, 200g of glass HP1 was prepared from 75.54g SiO_2, 11.98g Na_2CO_3, 45.95g $CaCO_3$, 67.78g $SrCO_3$, 15.62g K_2CO_3, 8.54g MgO, 6.90g ZnO and 18.05g P_2O_5.

Important properties taken into account when designing glasses for coating applications included thermal stability, thermal expansion coefficient matching with the substrate and bioactivity. By tailoring the glass composition, the necessary thermal characteristics to give a good coating material can be combined with a glass that exhibits good bioactivity. Specifically, improvements in properties were achieved by increasing the phosphate content (the majority of previously known glasses have either no phosphate or a very low phosphate content) and decreasing the SiO_2 content.

In addition, improved properties were achieved by inclusion of magnesium and zinc, but at a low content. Mg and Zn are attractive components as they are non-toxic and zinc is bacteriocidal. This is beneficial in a coating to reduce the risk of wound infection, speed healing and reduce the need for painful revisional surgery. Moreover, Mg and Zn (as well as silica) stabilise the glass thermally, allowing it to be sintered into a coating.

To achieve good bioactivity, it is desirable to have super-saturation of the physiological environment with calcium, strontium and phosphate ions, by dissolution of ions from a glass. This drives the chemical equilibrium towards apatite precipitation, but will not be seen in glasses which do not degrade rapidly. Mg and Zn are known to block apatite crystal growth due to their poor solubility in the apatite lattice. Thus, too high a magnesium and zinc content will prevent a glass that mineralises *in vivo* in an acceptable time period. Accordingly, a balance must be found between sinterability and chemical solubility of the glass and by having magnesium and zinc present at the amounts specified in the glasses of the invention a balance between the thermal properties required for successful coating and bioactivity is achieved.

Table 1A (Compositions in mol%):

ID	**HP1**	**HP2**	**HP3**	**HP4**	**HP5**	**HP7**	**HP8**
SiO_2	45.00	45.00	44.50	44.50	45.00	45.00	45.00
Na_2O	4.00	5.00	4.00	2.50	5.00	5.00	5.85
CaO	16.25	30.00	16.00	17.75	27.00	31.00	30.00
SrO	16.25	0.00	16.00	17.75	3.00	0.00	0.00
K_2O	4.00	5.00	4.00	2.50	5.00	5.00	5.85
MgO	7.50	7.50	7.00	7.50	7.50	7.50	5.80
B_2O_3	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MF_2	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ZnO	3.00	3.00	2.50	3.00	3.00	3.00	3.00
P_2O_5	4.50	4.50	6.00	4.50	4.50	3.50	4.50
ID	**HP9**	**HP10**	**HP11**	**HP12**	**HP13**	**BPS1**	**FPS1**
SiO_2	45.00	45.00	45.00	45.00	45.00	45.00	45.00
Na_2O	6.35	6.85	5.00	5.00	5.00	4.50	4.50
CaO	30.00	30.00	29.25	31.75	34.25	15.75	15.50
SrO	0.00	0.00	0.00	0.00	0.00	15.75	15.50
K_2O	6.35	6.85	5.00	5.00	5.00	4.50	4.50

MgO	4.80	3.80	8.25	5.75	3.25	5.00	5.50
B_2O_3	0.00	0.00	0.00	0.00	0.00	2.00	0.00
MF_2	0.00	0.00	0.00	0.00	0.00	0.00	2.00
ZnO	3.00	3.00	3.00	3.00	3.00	3.00	3.00
P_2O_5	4.50	4.50	4.50	4.50	4.50	4.50	4.50

Table 1B (Compositions in wt%):

Oxide	HP1	HP2	HP3	HP4	HP5	HP7	HP8	HP9
SiO_2	37.77	42.56	37.18	37.74	41.63	43.15	42.14	41.89
Na_2O	3.50	4.88	3.45	2.19	4.77	4.95	5.65	6.10
CaO	12.87	26.48	12.48	14.05	23.31	27.74	26.22	26.07
SrO	23.79	0.00	23.06	25.96	4.79	0.00	0.00	0.00
K_2O	5.32	7.41	5.24	3.32	7.25	7.52	8.59	9.27
MgO	4.27	4.76	3.92	4.27	4.65	4.82	3.64	3.00
B_2O_3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MgF_2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ZnO	3.45	3.84	2.83	3.45	3.76	3.90	3.81	3.78
P_2O_5	9.02	10.06	11.84	9.02	9.83	7.93	9.95	9.90
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Oxide	HP10	HP11	HP12	HP13	BPS1	FPS1
SiO_2	41.65	42.64	42.38	42.12	37.84	38.02
Na_2O	6.54	4.89	4.86	4.83	3.90	3.92
CaO	25.91	25.87	27.91	29.92	12.36	12.22
SrO	0.00	0.00	0.00	0.00	22.84	22.59
K_2O	9.94	7.43	7.38	7.34	5.93	5.96
MgO	2.36	5.24	3.63	2.04	2.82	3.12
B_2O_3	0.00	0.00	0.00	0.00	1.95	0.00
MgF_2	0.00	0.00	0.00	0.00	0.00	1.75
ZnO	3.76	3.85	3.83	3.80	3.42	3.43
P_2O_5	9.84	10.07	10.01	9.95	8.94	8.98
Total	100.00	100.00	100.00	100.00	100.00	100.00

Table 2A (compositions in mol%):

ID	**HP14**	**HP15**	**HP16**	**HP17**	**HP18**	**HP19**
SiO_2	45.00	45.00	45.00	45.00	45.00	45.00
Na_2O	9.75	9.75	9.75	10.00	10.00	10.00
CaO	23.00	20.70	11.50	20.00	18.00	10.00
SrO	0.00	2.30	11.50	0.00	2.00	10.00
K_2O	9.75	9.75	9.75	10.00	10.00	10.00
MgO	5.00	5.00	5.00	7.50	7.50	7.50
B_2O_3	0.00	0.00	0.00	0.00	0.00	0.00
MF_2	0.00	0.00	0.00	0.00	0.00	0.00
ZnO	3.00	3.00	3.00	3.00	3.00	3.00

P_2O_5	4.50	4.50	4.50	4.50	4.50	4.50
ID	**HP20**	**HP21**	**HP22**	**HP23**	**HP24**	**HP25**
SiO_2	44.50	44.50	44.50	44.50	44.50	44.50
Na_2O	15.25	15.25	15.25	15.50	15.50	15.50
CaO	14.50	13.05	7.25	10.00	9.00	5.00
SrO	0.00	1.45	7.25	0.00	1.00	5.00
K_2O	15.25	15.25	15.25	15.50	15.50	15.50
MgO	3.00	3.00	3.00	7.00	7.00	7.00
B_2O_3	0.00	0.00	0.00	0.00	0.00	0.00
MF_2	0.00	0.00	0.00	0.00	0.00	0.00
ZnO	3.00	3.00	3.00	3.00	3.00	3.00
P_2O_5	4.50	4.50	4.50	4.50	4.50	4.50

Table 2B (compositions in wt%):

Oxide	HP14	HP15	HP16	HP17	HP18	HP19	HP20	HP21
SiO_2	40.96	40.29	37.83	41.14	40.55	38.36	38.91	38.52
Na_2O	9.16	9.01	8.45	9.43	9.30	8.79	13.75	13.62
CaO	19.54	17.30	9.02	17.06	15.14	7.96	11.83	10.54
SrO	0.00	3.55	16.67	0.00	3.11	14.70	0.00	2.16
K_2O	13.91	13.69	12.85	14.33	14.13	13.37	20.90	20.69
MgO	3.05	3.00	2.82	4.60	4.53	4.29	1.76	1.74
B_2O_3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
MgF_2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
ZnO	3.70	3.64	3.42	3.72	3.66	3.46	3.55	3.52
P_2O_5	9.68	9.52	8.94	9.72	9.58	9.06	9.29	9.20
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Oxide	HP22	HP23	HP24	HP25
SiO_2	37.05	39.20	38.93	37.88
Na_2O	13.10	14.09	13.99	13.61
CaO	5.63	8.22	7.35	3.97
SrO	10.41	0.00	1.51	7.34
K_2O	19.90	21.41	21.26	20.69
MgO	1.68	4.14	4.11	4.00
B_2O_3	0.00	0.00	0.00	0.00
MgF_2	0.00	0.00	0.00	0.00
ZnO	3.38	3.58	3.56	3.46
P_2O_5	8.85	9.37	9.30	9.05
Total	100.00	100.00	100.00	100.00

As the major component of the glasses is silica, the silica content tends to dominate the properties. As the silica content increases the non-bridging oxygen content decreases and there are more network linkages. This is associated with a more rigid glass network so chemical reactivity decreases (dissolution and bioactivity) and thermomechanical properties increase (crystallisation resistance, softening point, mechanical strength).

As phosphate content is increased the glasses also become less thermally stable as you are increasing the size of the phosphate phase which increases the surface area of heterogeneous nucleation sites (phosphate droplets) for the silicate phase to nucleate and crystallise on.

As a comparison of the compositional design of the glasses of this invention to the glasses of Tomsia *et al* (US2002/0076528) and also those disclosed in WO2007/144662, taking 45S5 as a starting point, Tomsia increases SiO_2 significantly, keeps P_2O_5 the same, drops Na_2O and CaO and adds K_2O and MgO. In WO2007/144662, SiO_2 increases slightly, P_2O_5 Na_2O and CaO drop, and K_2O, SrO, ZnO and MgO are added.

To arrive at the glasses of this invention a different approach is taken, in which SiO_2 content is dropped, and phosphate content is increased. This approach has obtained good bioactive responses coupled with good thermal stability. This can be attributed to (a) the large number of components in the glass that increases the entropy of mixing which is a barrier to crystallisation due to the energy barrier needed to rearrange at the atomic level and form a critical size nuclei; and (b) as the phosphate phase forms $[PO_4]^{3-}$ complexes, these need modifier ions to charge balance. This takes non-bridging oxygens out of the silicate phase, so the glass is slightly more polymerised than it initially appears from the composition. This will thermally stabilise the glass but not affect the dissolution behaviour significantly. Accordingly, increases in phosphate content play a major role in obtaining thermal stability without diminishing solubility and consequently bioactivity.

As bioactivity and crystallisation resistance change rapidly around the metasilicate (50% SiO_2) composition the glasses of this invention are just on the right side of the transition in properties.

In summary, bioactivity has a structural dependence but it is also element dependent (Ca, P, Sr in particular, so a lead-metasilicate glass would not form HA *in vivo*); the silicate content and hence structure does not directly cause HA deposition, it controls the rate other ions are released into solution to form HA.

Thermal Properties

The glass compositions of the invention have been designed to have a thermal expansion coefficient that either matches or is slightly higher than the thermal explanation coefficient of a metal substrate (for example, titanium, Ti-alloy, Cr-Co alloy or 316L). This will ensure that in the coated substrate there are either minimal thermal stresses or compressive thermal stresses. As an example of this, glass HP1 was coated onto a strip of Ti6Al4V. A concave curve on the metal strip was observed, indicating the glass to have a slightly higher TFC than the metal and consequently putting the object in compression. This is desirable for brittle material such as glass.

Different short scanning (DSC) was carried out on selected glass powders in order to obtain the thermal data set out above, namely the onset of the glass transition temperature (T_g), onset of crystallisation (T_x) and peak crystallisation (T_p) of the glasses. Glass samples were run between 200 and 1000°C at a heating rate of 10°C/min.

The glass transition temperature (T_g) of the glasses of the invention is sufficiently low and the T_x-T_g is maximised to ensure that viscous flow sintering will occur below the alpha to beta phase transition of the metal substrate, which is accompanied by a large volume change.

The thermal expansion coefficients for some common biomedical material are: Pure titanium and Ti6Al4V - 9.2 x 10^{-6}°C^{-1}, CrCo (Vitallium – ASTM F75) - 14.0 x 10^{-6}°C^{-1}, 45S5 - 15.1 x 10^{-6}°C^{-1} and 316L – 17.5 x 10^{-6}°C^{-1}.

Taking titanium and Ti-alloy as a specific example, as mentioned above the thermal expansion coefficient for pure titanium and Ti6Al4V is 9.2 x 10^{-6}°C^{-1}. The thermal properties of various glasses of the invention are set out in Table 3:

Table 3:

ID	T_g (°C)	T_x (°C)	T_p (°C)	T_x-T_g (°C)	TEC (×10^{-6} °C)
HP1	606	756	909	150	11.1
HP2	599	722	767	123	11.1
HP3	606	751	772	145	11.2
HP4	641	775	804	134	11.2
HP5	599	842	914	243	11.2
HP6	603	904	946	301	11.1
HP7	597	928	968	331	11.1
FPS1	575	701	731	126	11.2
BPS1	583	706	729	123	11.2

As can be seen from the data set out above, the glasses shown in Table 3 have a TEC slightly above that of Ti and Ti-alloy. The working range (Tx-Tg) of all glasses of the first aspect of the invention is >100°C. Moreover, the optimum firing temperature for these glasses is in the 700-800°C range. This is well below the alpha to beta phase transition of titanium which occurs in the range of 955 to 1010°C (for Ti6Al4V). At 750°C, the glass powders can be fired for 30 minutes onto titanium or Ti-alloy without significant interfacial reactions occurring. Diffusion of metal ions from the metal or metal alloy substrate (e.g. Ti, V, Al) is limited to around a 5 micron interfacial region when fired at 750°C.

Glasses of the invention which are described as particularly suited for coating Ti or Ti-alloy preferably have a TEC in the range of 9-11.5 (x10^{-6}°C), glasses described as particularly suited for coating a Cr-Co alloy preferably have a TEC in the range of 13.5-16 (x10^{-6}°C) and glasses described as particularly suited for coating stainless steel, preferably have a TEC in the range of 17-19.5 (x10^{-6}°C).

Preparation of Coated Substrates

Glass powders prepared as described above were used to coat substrates by dip coating (using a suspension in a chloroform-PMMA solution or an ethanol-glass slurry) and sedimentation (from a suspension in ethanol). The coatings were fired in a dental porcelain furnace (Jelrus V.I.P. Universal) which was preheated to 420°C at which point vacuum was applied and held for 30 minutes. The furnace was then heated at 60°C/minute to 750°C and held for 30 minutes. The vacuum was then removed and the sample cooled slowly to 120°C at which point the sample was removed from the furnace. This firing schedule does not produce any grain growth of the titanium or Ti-alloy and hence no reduction of fatigue strength of the metal would be expected. In one experiment, a dental screw was successfully coated with glass HP5. The thickness of the glass layer could be controlled and a screw produced comprising a coating in the grooves, where bone would not typically osseointegrate and an un-coated thread to preserve the cutting edge of the screw.

The amorphous nature of the glasses and coatings was assessed using Raman micro-spectrometry between 200 and 1200 cm^{-1}. Samples were visually inspected for cracks and other defects. Samples which bonded well were selected for further study by cross-sectioning in epoxy resin and examining with scanning electron microscopy and energy dispersive x-ray analysis (SEM-EDX). This allows assessment of the quality and chemistry of the interfacial region between the glass coated and the metal substrate.

Glass-ceramic coatings were prepared from borate and fluorine containing glasses, with minor crystalline components forming during heat treatment. Generally crystallisation in glass coatings should be avoided as it can have negative effects on bioactivity. Accordingly, within a sintered coating of the invention the glass amorphous structure is preferably retained. However, some crystallisation of an orthophosphate phase in the borate and fluorine glasses did not adversely affect coating properties, provided the crystalline components do not induce any negative cellular response, do not hinder glass degradability and occur only within the glass orthophosphate phase. In fact, apatite-like fluoroapatite crystals which can form with fluorine containing glasses present at minor levels with nano-scale orthophosphate phase toughened the coating and provided epitaxial growth sites for HA crystals.

Raman spectra were carried on the powdered glasses as well as on sintered glass coatings. These are shown in Figures 2(a), (b) and (c). It can be seen from these spectra that the sintered glass coatings exhibit identical Raman spectra to the unsintered glass powders, indicating that no structural changes have occurred on processing. Small changes are seen in coatings comprising borate or chloride. The main v_1 orthophosphate (Q^0) phosphate vibrational band at 960 cm^{-1} sharpens and shifts slightly to a higher wave number, indicating nanocrystallites of a phosphate phase close in structure to apatite. This band is a result of the nondegenerate P-O symmetric stretching mode.

Measurement of bioactivity

The rate of development of a hydroxycarbonated apatite (HCA) layer on the surface of glass exposed to simulated body fluid (SBF) provides an *in vitro* index of bioactivity. In the context of the present invention, a glass is considered to be bioactive if, on exposure to SBF in accordance with the following procedure, deposition of a crystalline HCA layer occurs. Following this procedure for glass HP2, HCA formation was seen *in vitro* in 2 weeks, which is comparable to Bioglass®.

Preparation of Simulated Body Fluid (SBF)

The preparation of SBF was carried out according to the method of Kokubo and Takadama, Biomaterials 27 (2006): 2907-2915 with one litre of SBF containing the following reagents dissolved in distilled water:

Order	**Reagent**	**Amount**
1	NaCl	8.035g
2	$NaHCO_3$	0.355g
3	KCl	0.225g
4	$K_2HPO_4.3H_2O$	0.231g
5	$MgCl_2.6H_2O$	0.311g
6	1.0m-HCl	39ml
7	$CaCl_2$	0.292g
8	Na_2SO_4	0.072g
9	Tris	6.118g
10	1.0m-HCl	0-5ml

Assay to determine bioactivity:

Glass powders were analysed using the standard (ISO23317) simulated body fluid (SBF) test to determine *in vitro* apatite forming ability, an indicator of *in vivo* behaviour. In the analysis, glass powder was used rather than a solid disk specimen. The amount of glass powder used was calculated to give a surface area ratio of the powder to the SBF volume corresponding to the ratio given in the standard, which was 67.5 mg of 225 micron diameter glass powder to 60 ml of SBF.

The formation of HCA can be measured by micro-Raman spectroscopy. After soaking in SBF for 1 day, 1 week, 2 weeks, 3 weeks and 4 weeks, the dried powders were analysed using micro-Raman spectroscopy to observe the development of the characteristic HCA phosphate ν_1 vibrational band at around 960 cm^{-1}.

ALP Assay

Bioactivity can also be measured in an *in vitro* human osteoblast ALP assay as described below, in which alkaline phosphatase (ALP) is a marker for bone mineralisation. In this assay, human osteoblast cells are cultured in glass dissolution products.

Culture media preparation: Glass powder was sterilised (3mg in 6 well plate) by UV light. Glass-conditioned medium was prepared by incubation of 1 g glass particulate in 100ml of DMEM/F-12 NUT medium containing 1% A/A at 378C, 5% CO_2 overnight. Following filtration, the elemental concentrations were determined using Inductively Coupled Plasma (ICP) Spectroscopy.

Cell culture: SAOS2 cells were cultured in RPMI 1640+10%FBS+2mM L-glutamine. 30,000 cells were seeded per cm^2 on tissue culture plastic in well with sample. Cells were allowed to attach for 30 minutes. The wells were topped up with media and changed every other day.

Assays:

MTT: Add 50μl of 5mg/ml MTT (Sigma M2128) to each well, incubate 1h at 37C. Remove all media, add 500μl DMSO, transfer 100μl of it to a new well and read at 620 nm. (This assay shows metabolic activity).

ALP: Remove all media, add 500μl ddH_2O, freeze-thaw, mix 50μl cell lysates with 50μl ALP solution (0.1M Glycin,0.1M $ZnCl_2$, 0.1M $MgCl_2$,1 tablet nitrophenyl phosphate tablet per 5 ml). Stop reaction with 1M NaOH for 50μl per well. Read at 405nm.

Total DNA: From same cell lysates; mix 50μl cell lysates with 50μl Hoechst Dye(20μg/ml in TNE Buffer-10 mM Tris 1mM EDTA 2M NaCl pH 7.4). Read at exc. 360nm em. 460 nm. (Rago R, Mitchell J, Wilding G, Analytical Biochemistry 191, 31-34,1990.)

Results of the ALP assay (normalised to DNA) are shown in Figure 4. In Figure 4 the glasses are plotted, from left to right, in order of Sr content, i.e. 45S5, HP2, HP5 and HP1. ALP is generally higher for glasses of the invention and increases with Sr content.

Additional Cell Assay Results

Glasses HP5, HP2 and HP1 were produced by a melt-quench route. 1.5 g/L of glass powder (<38μm) was added to the RPMI 1640 culture medium and incubated on a roller at 37°C for 4 hours and then excess glass was filtered. The dissolved ion concentrations were confirmed via inductively coupled plasma-mass spectrometry (ICP-MS). The culture media enriched was supplemented with 10% (w/v) FBS, 2mM L-glutamine, 1% (w/v) penicillin-streptomycin and bone mineralizing agents (5 mM β-glycerophosphate and 50 μg/mL ascorbic acid). Sa Os-2 human osteosarcoma cells were plated at 30,000/cm^2 for metabolic activity (MTT) and alkaline phosphatase (ALP) analyses, whereas for tetracycline staining a density of 34,400/cm^2 was used. 45S5 was used a control in all experiments. MTT activity based on reduction of a tetrazolim salt was measured on days 1,7,14 and 21 post-plating. ALP activity was measured using p-nitrophenyl phosphate as a substrate and normalized to cell number against lactate dehydrogenase (LDH) enzyme activity which measures the conversion of tetrazolium salt (INT) to red formazan. 10 μg/mL of tetracycline HCl was added to cultures after 20 days to visualize newly formed mineral fluorescence images were taken after 24 hours. A semi-quantitative analysis of images was performed.

All of HP1, HP2 and HP5 showed a similar level of metabolic activity to 45S5. ALP activity after 7 days in culture was enhanced in all coting glasses compared to 45S5. SaOs-2 exposed to HP1, HP2 and HP5 showed greater ALP activity compared to 45S5 after 14 days in culture. SaOs-2 treated with dissolution ions displayed bright staining for tetracycline staining compared to all groups including 45S5 after 21 days. A positive correlation between Sr substitution and tetracycline staining was confirmed by semi-quantitative analysis of stain area.

ALP activity per cell, a marker of actively mineralizing cells was higher in cultures treated with HP1, HP2 and HP5 compared to Bioglass® 45S5. The increasing addition of Sr resulted in proportional increases in ALP activity. This is in agreement with results from tetracycline staining which show the brightest staining for bone nodule formation in cultures treated with HP1.

Claims

1. An aluminium-free glass formed from the components:

35-55.9 mol % SiO_2;

a combined content of Na_2O and K_2O of 4-34 mol %;

0.5-9 mol % MgO;

0.5-4 mol % ZnO;

3.1-10 mol % P_2O_5;

0-5 mol. % B_2O_3;

0-5 mol % of a metal fluoride; and

a combined mol % of CaO and SrO of 8-37 mol %,

wherein at least 2 mol % of each of Na_2O and K_2O is present.

2. The glass of claim 2, wherein the SiO_2 content is 40-50 mol%, preferably 43.5-47 mol%, more preferably 44-46 mol%, 44-45.5 mol% or even more preferably 44.5-45 mol%.

3. The glass of claim 1 or claim 2, wherein the content are each independently, 2-17 mol%, preferably 2.5-15.5 mol%.

4. The glass of any preceding claim, wherein both CaO and SrO are present at a content of at least 0.5 mol %, preferably at least 1 mol%.

5. The glass of any preceding claim, wherein the glass comprises one, more than one or all of the following:

a) an MgO content of 2 to 9 mol%, preferably 3 to 8.5 mol%, preferably 3 to 8.25 mol%;

b) a ZnO content of 2 to 4 mol%;

c) a minimum P_2O_5 content of 3.5 mol% and/or a maximum P_2O_5 content of 10 mol%, 7 mol% or 6 mol%;

d) a B_2O_3 content of 0 to 3 mol%, preferably 0 to 2 mol%; and

e) a metal fluoride content of 0 to 3 mol%, preferably 0 to 2 mol%.

6. The glass of any preceding claim, having the composition: 40-50 mol% SiO_2; a combined content of Na_2O and K_2O of 4-16 mol%; 2-9 mol % MgO; 0.5-4 mol % ZnO; 3.1-10 mol % P_2O_5; 0-5 mol. % B_2O_3; 0-5 mol % of a metal fluoride; and a combined content of CaO and SrO of 26-37 mol %.

7. The glass of claim 6, wherein the glass comprises one, more than one or all of:

a) 2-8 mol % Na_2O;
b) 2-8 mol% K_2O;
c) 2-3.5 mol % ZnO;
d) 3.5-6 mol % P_2O_5;
e) 0-2 mol% B_2O_3;
f) 0-2 mol% of a metal fluoride;
g) a combined mol% of CaO and SrO of 29-36 mol %; and
h) a SiO_2 content of 44-46 mol%.

8. The glass of any one of claims 1 to 5, having the composition: 40-50 mol % SiO_2; a combined content of Na_2O and K_2O of 16-34 mol%; 2-9 mol % MgO; 0.5-4 mol % ZnO; 3.1-10 mol % P_2O_5; 0-5 mol. % B_2O_3; 0-5 mol % of a metal fluoride; and a combined content of CaO and SrO of 8-26 mol %.

9. The glass of claim 8, wherein the glass comprises one, more than one or all of:

a) 8-17 mol% Na_2O;
b) 8-17 mol% K_2O;
c) 2-3.5 mol % ZnO;
d) 3.5-6 mol% P_2O_5;
e) 0-2 mol% B_2O_3;
f) 0-2 mol% of a metal fluoride;
g) a combined mol% of CaO and SrO of 9-24 mol %; and
h) 44-46 mol%, SiO_2.

10. The glass of claim 8 or 9, having the composition: 44-46 mol % SiO_2; a combined content of Na_2O and K_2O of 18-22 mol%; 1-6 mol % P_2O_5; 0-5 mol. % B_2O_3; 0-5 mol % of a metal fluoride; and a combined mol % of CaO and SrO of 19-26 mol%.

11. The glass of claim 8 or 9, having the composition: 44-46 mol% SiO_2; a combined content of Na_2O and K_2O of 28-34 mol%;; 2-8 mol % MgO; 2-4 mol % ZnO; 3.1-6 mol % P_2O_5; 0-5 mol. % B_2O_3; 0-5 mol % of a metal fluoride; and a combined mol % of CaO and SrO of 8-15 mol % .

12. The glass of any preceding claim, having a MgO content of 8.25 mol% or less, and a combined Na_2O and K_2O content of at least 8 mol%.

13. The glass of any preceding claim, wherein the glass is in particulate form.

14. A coating composition comprising a glass as defined in any one of claims 1 to 13.

15. A coated substrate comprising a metal or metal alloy substrate and a sintered coating formed from a glass as defined in any one of claims 1 to 13.

16. The coated substrate of claim 15, wherein the substrate comprises titanium metal, a titanium alloy, a chrome-cobalt alloy or stainless steel.

17. The coated substrate of claim 15 or 16, which is a medical or dental implant, for example an orthopaedic or dental implant.

18. The coated substrate of any one of claims 15 to 17, wherein

a) the substrate comprises Ti or Ti alloy and the coating is formed from a glass as defined I any one of claims 1 to 7, 12 or 13;

b) the substrate comprises Cr-Co alloy and the coating is formed from a glass as defined in any one of claims 1 to 5, 8 to 10, 12 or 13;

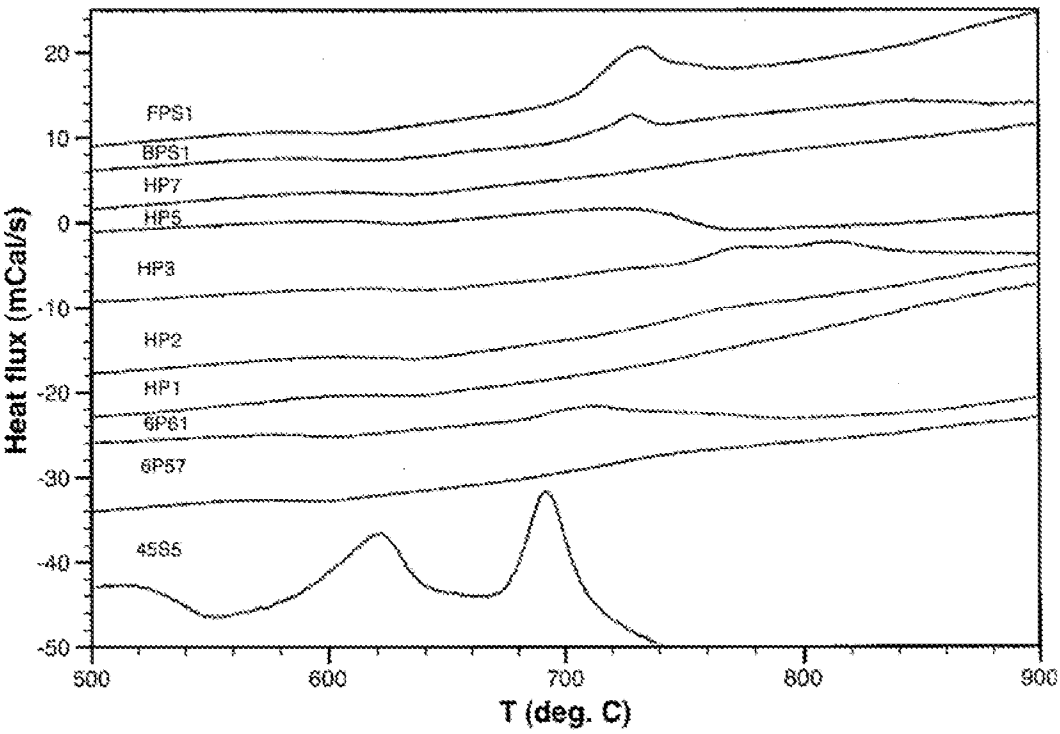
c) the substrate comprises stainless steel and the coating is formed from a glass as defined in any one of claims 1 to 5, 8, 9 or 11 to 13.

19. A method of coating a metal or metal alloy substrate, comprising applying a glass as defined in any of claims 1 to 13 to the substrate and then sintering the glass.

20. A glass as defined in any one of claims 1 to 13 or a composition of claim 14, for use in coating a metal or metal alloy substrate.

21. A porous scaffold comprising a glass as defined in any one of claims 1 to 13.

22. A glass, coating, coated substrate, glass powder or method substantially as described herein with reference to one or more of the examples and/or figures.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BPS1
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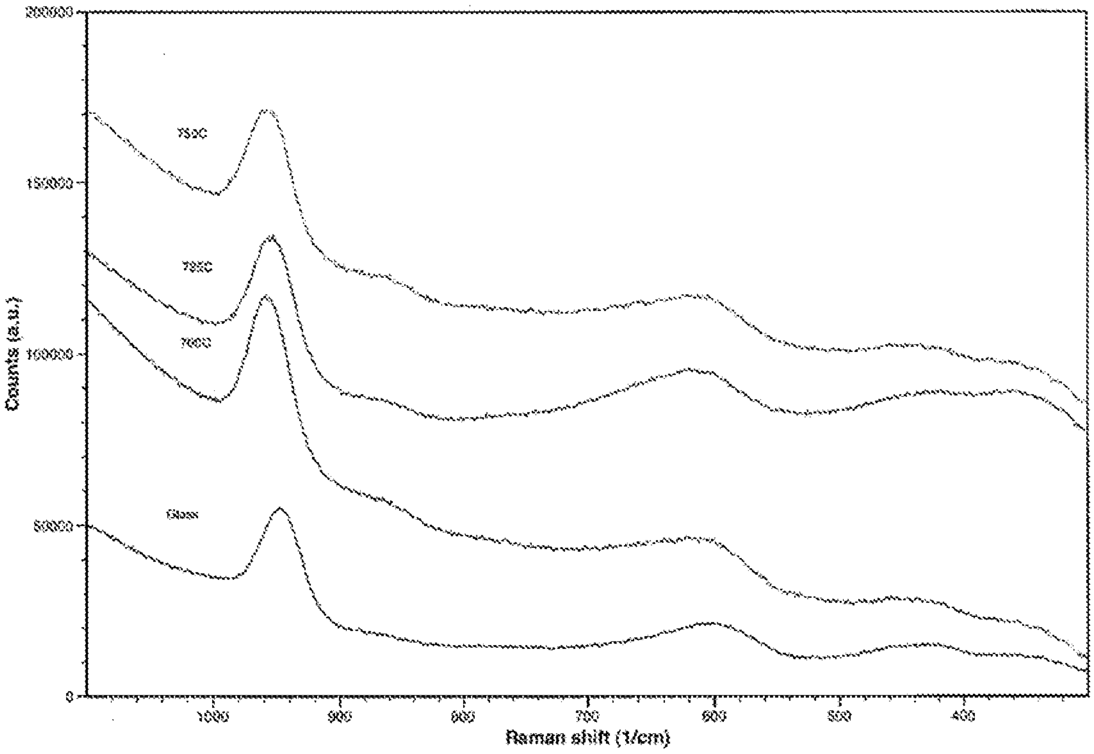
HP5
HP3
HP2
HP1
6P61
6P57
45S5

Figure 1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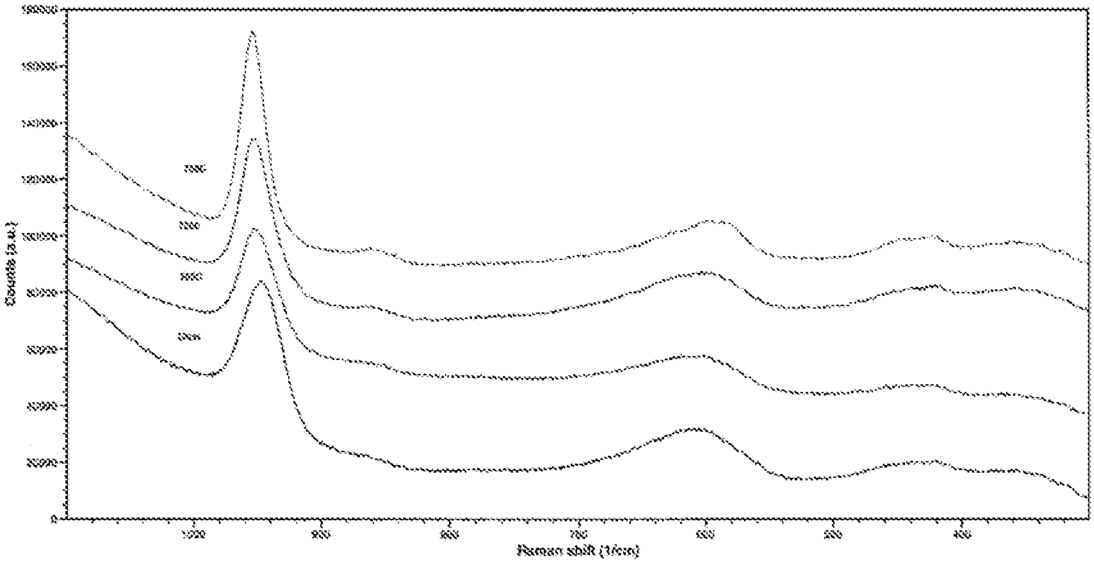
Raman shift (1/cm)

Figure 2(a)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600
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Figure 2(b)

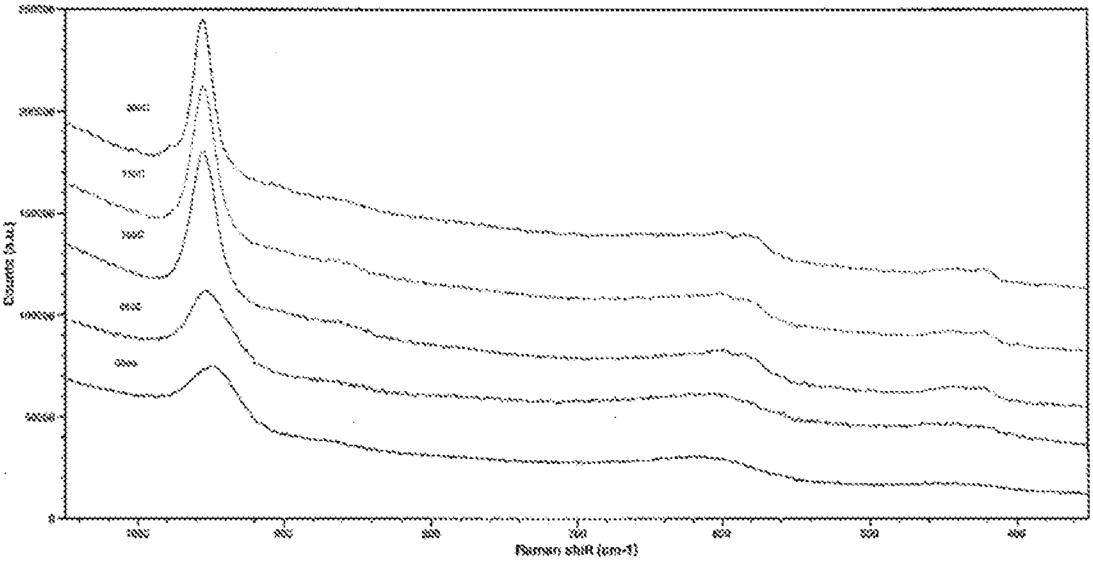
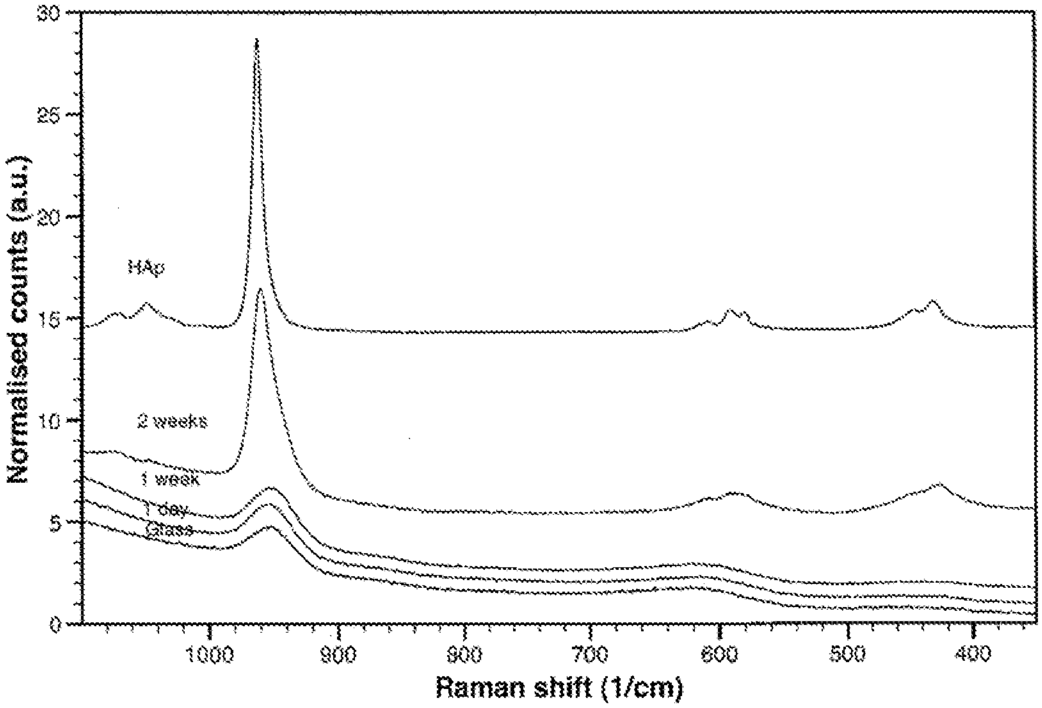


Figure 2(c)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20
15
10
5
0
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1 week
1 day
Glass
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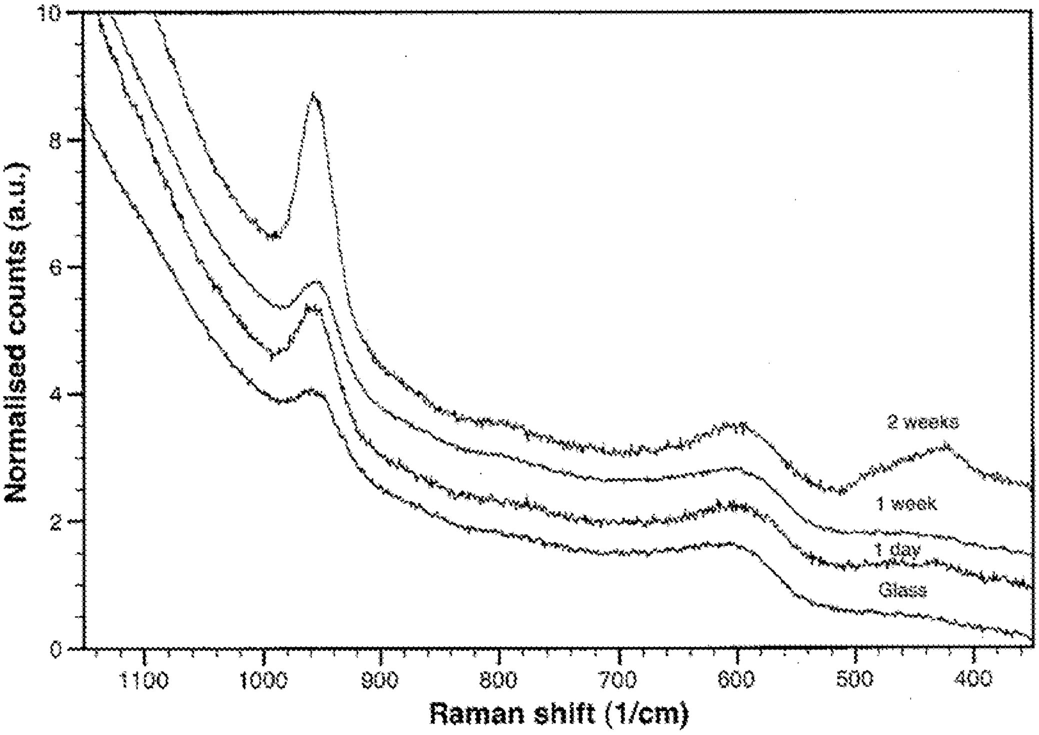
900
800
700
600
500
400
Raman shift (1/cm)

Figure 3(a)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4
6
8
10
1100
1000
900
800
700
600
500
400
Raman shift (1/cm)
2 weeks
1 week
1 day
Glass

Figure 3(b)

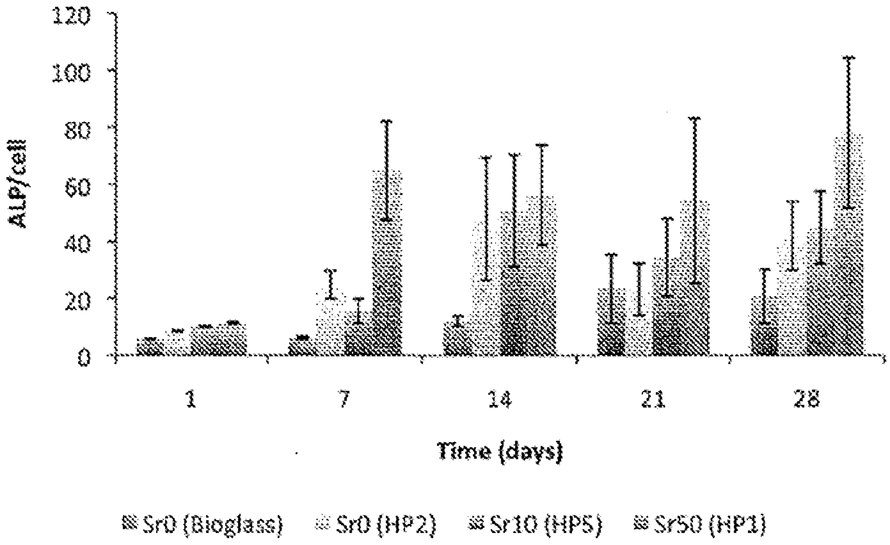
ALP/cell
120
100
80
60
40
20
0
1
7
14
21
28
Time (days)
Sr0 (Bioglass)
Sr0 (HP2)
Sr10 (HP5)
Sr50 (HP1)

Figure 4