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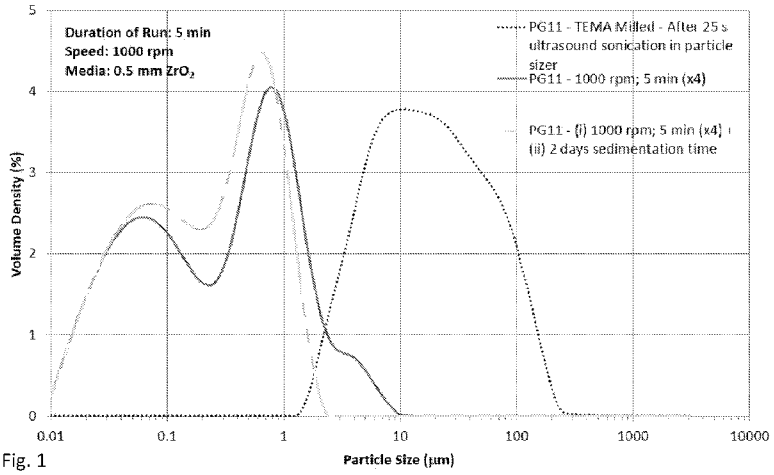

Fig. 1

(57) **Abstract**: Biocompatible composite materials are provided, comprising a polymeric matrix formed from at least one biocompatible polymer, and particles of a glassy material dispersed throughout the polymeric matrix. Owing to their improved toughness, stiffness and strength characteristics, as well as their tuneable dissolution properties, the biocompatible composite materials may be advantageously used in the manufacture of various implantable medical devices, such as stents, pins, rods and suture.

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COMPOSITE MATERIAL

INTRODUCTION

[0001] The present invention relates to biocompatible composite materials comprising particles of a glassy material dispersed within a polymeric matrix. More particularly, the present invention relates to biocompatible composite materials in which the glassy material is a phosphate-based glassy material. Methods of preparing the biocompatible composite materials, as well as implantable medical devices comprising them, are also disclosed.

BACKGROUND OF THE INVENTION

[0002] Biocompatible and bioresorbable polymers have received a great deal of interest in terms of their development for applications in medicine. In particular, one significant focus of research has been on polyesters derived from lactide moieties, which have been developed as materials for orthopaedic devices (e.g. plates, pins and screws), sutures, tissues and stents.

[0003] Poly(L-lactide) has several shortcomings in the context of mechanical performance and its degradation behaviour under physiological conditions. Most significantly, for practical purpose, it is a brittle material at ambient temperature for which the strain-at-break is typically 2 – 6 % deformation. In order to address this issue, numerous works have been undertaken in order to develop derivatives of poly(L-lactide) that exhibit ductile mechanical behaviour at ambient temperature.

[0004] Despite prior art attempts to optimize material properties by the incorporation of inorganic materials, there nonetheless remains a need for biocompatible materials having tunable characteristics, thereby rendering them useful in a variety of implantable articles.

[0005] The present invention was devised with the foregoing in mind.

SUMMARY OF THE INVENTION

[0006] According to a first aspect of the present invention there is provided a biocompatible composite material comprising

a) a polymeric matrix comprising at least one biocompatible polymer; and
b) greater than 0 but less than or equal to 70 wt% of particles of a biocompatible glassy material dispersed in the polymeric matrix, wherein the glassy material comprises 30–60 mol% of P_2O_5.

[0007] According to a second aspect of the present invention there is provided an implantable medical device comprising a biocompatible composite material as defined herein.

[0008] According to a third aspect of the present invention there is provided a process for the preparation of a biocompatible composite material as defined herein, the process comprising the steps of:

a) preparing particles of the biocompatible glassy material by:
   i. mixing together quantities of glassy material raw ingredients,
   ii. heating the glassy material raw ingredients to a molten state to provide a homogenous melt,
   iii. quenching the molten material, and
   iv. milling the resulting quenched glassy material; and
b) dispersing greater than 0 but less than or equal to 70 wt% of the particles within a polymeric matrix as defined herein.

[0009] According to a fourth aspect of the present invention there is provided a biocompatible composite material obtainable, obtained or directly obtained by a process defined herein.

DETAILED DESCRIPTION OF THE INVENTION

Biocompatible composite material

[0010] As described hereinbefore, the present invention provides a biocompatible composite material comprising

a) a polymeric matrix comprising at least one biocompatible polymer; and
b) greater than 0 but less than or equal to 70 wt% of particles of a biocompatible glassy material dispersed in the polymeric matrix, wherein the glassy material comprises 30–60 mol% of P_2O_5.

[0011] The biocompatible composite materials of the present invention provide numerous advantages when compared with existing biocompatible materials. Perhaps most notably, the composite materials of the invention exhibit improved stiffness and strength characteristics owing to the incorporation of rigid filler within the polymeric matrix. Moreover, the composite materials tolerate a variety of different polymeric materials, including combinations thereof, thereby allowing optimisation of the toughness and strain-at-break properties of the resulting material according to the particular application of interest. In addition, the specific nature of the particulate filler confers further advantages. In particular, the phosphate-based glassy materials forming part of the present invention are water soluble and their aqueous dissolution can be reliably tailored by varying the specific composition of the glassy material, thereby providing for

a range of composite materials, each exhibiting different dissolution properties under physiological conditions.

[0012] It will be understood that the term "biocompatible" refers herein to the ability of a material implanted in the body, either temporarily or permanently, to exist in harmony without causing deleterious changes. Accordingly, such biocompatible materials will be understood by the skilled person to be those that are substantially non-toxic and non-immunogenic to the organism for the period of time for which they are intended to be used.

[0013] It will also be understood that the term "glassy material" refers herein to materials comprising glass or glass-like properties. Suitably, the term "glassy material" refers to a non-crystalline material that shows a glass transition. A glass transition will be understood by a person skilled in the art as a reversible transition from a hard and relatively brittle state into a molten state. The "glassy material" may be a glass, more suitably a phosphate-based glass.

[0014] In any of the composites discussed herein, the term "comprising" may be substituted for "consisting essentially of" or "consisting of".

[0015] In an embodiment of the invention, the biocompatible composite material is biodegradable, bioresorbable and/or bioactive. Bioactive composites may be osteoproductive or osteoconductive. The terms "biodegradable" and "bioresorbable" synonymously refer herein to the ability of a material to be substantially or entirely absorbed by biological tissue over a given period of time *in vivo* to the extent that the material is substantially or entirely replaced by the surrounding tissue. The term "osteoproductive" refers herein to the ability of a material to bind with both soft biological tissue and bone and/or to induce or stimulate bone growth (e.g. Class A biomaterials). The term "osteoconductive" refers herein to the ability of a material to bind to bone (e.g. Class B biomaterials). In embodiments where the biocompatible composite material is biodegradable, bioresorbable, osteoproductive and/or osteoconductive, it will be understood that some or all of the components forming the composite material (e.g. biocompatible polymer(s) and biocompatible glassy material(s)) may also be biodegradable, bioresorbable, osteoproductive and/or osteoconductive.

[0016] In another embodiment, the biocompatible composite material comprises particles of a single glassy material dispersed within the polymeric matrix. Alternatively, the biocompatible composite material may comprise particles of two or more different types of glassy material dispersed within the polymeric matrix.

[0017] In addition to the presence of the glassy material, the biocompatible composite material may comprise other additives or fillers dispersed within the polymeric matrix. These additional additives (agents) may be incorporated into the biocompatible composite material in order to improve or modify the properties of the biocompatible composite material.

[0018] In another embodiment, the glassy material does not comprise SiO_2 as a glass-network former. It will be appreciated by those of skill in the art that, depending on the type of crucible used to form the glassy material, the resulting glassy material may contain small, unintentional quantities of SiO_2. Hence, the glassy material forming part of the invention does not include SiO_2 in glass-network forming quantities.

[0019] In another embodiment, the glassy material does not contain boron oxide (e.g. boron trioxide) in a glass-network forming quantity.

[0020] Suitably, the glassy material comprises 35–60 mol% of P_2O_5. More suitably, the glassy material comprises 35-50 mol% of P_2O_5. In a particularly suitable embodiment, the glassy material comprises 38-42 mol% of P_2O_5.

[0021] In another embodiment, the glassy material comprises 30–60 mol% of a suitable Group II metal oxide. Suitably, the glassy material comprises 35–55 mol% of a suitable Group II metal oxide. In a particularly suitable embodiment, the glassy material comprises 48-52 mol% of a suitable Group II metal oxide.

[0022] In another embodiment the glassy material comprises a suitable Group II metal oxide selected from CaO, MgO, SrO, BaO or combinations thereof. Suitably, the Group II metal oxide is selected from CaO, MgO or combinations thereof. More suitably, the Group II metal oxide is CaO. Most suitably, the glassy material comprises a single Group II metal oxide (e.g. CaO only).

[0023] In another embodiment, the glassy material comprises 0–15 mol% (e.g. 0.1–15 mol%) of a suitable Group I metal oxide. Suitably, the glassy material comprises 5–12 mol% of a suitable Group I metal oxide. In a particularly suitable embodiment, the glassy material comprises 8-12 mol% of a suitable Group I metal oxide

[0024] In another embodiment, the glassy material comprises a suitable Group I metal oxide selected from Na_2O, K_2O or combinations thereof. Suitably, the suitable Group I metal oxide is Na_2O. Most suitably, the glassy material comprises a single Group I metal oxide (e.g. Na_2O only).

[0025] In an embodiment, the glassy material comprises 35–60 mol% of P_2O_5, 30–60 mol% of a suitable Group II metal oxide and 0–15 mol% (e.g. 0.1–15 mol%) of a suitable Group I metal oxide.

[0026] In an embodiment, the glassy material comprises 35–50 mol% of P_2O_5, 35–55 mol% of a suitable Group II metal oxide and 5–12 mol% of a suitable Group I metal oxide.

[0027] Particular embodiments of the glassy material are recited in the following numbered paragraphs (1) to (5).

1) 30–60 mol% of P_2O_5;
   30–60 mol% of CaO; and
   0–15 mol% (e.g. 0.1–15 mol%) of Na_2O.
2) 30–60 mol% of P_2O_5;
   30–60 mol% of CaO; and
   5–12 mol% of Na_2O.
3) 30–50 mol% of P_2O_5;
   30–60 mol% of CaO; and
   0–15 mol% (e.g. 0.1–15 mol%) of Na_2O.
4) 35–50 mol% of P_2O_5;
   35–55 mol% of CaO; and
   0–15 mol% (e.g. 0.1–15 mol%) of Na_2O.
5) 35–50 mol% of P_2O_5;
   35–55 mol% of CaO; and
   5–12 mol% of Na_2O.

[0028] In a particular embodiment, the glassy material comprises, consists essentially of, or consists of 38–52 mol% P_2O_5, 38–52 mol% CaO and 8–12 mol% Na_2O.

[0029] In a particular embodiment, the glassy material comprises, consists essentially of, or consists of 37–52 mol% P_2O_5, 38–52 mol% CaO and 7–12 mol% Na_2O.

[0030] In a particular embodiment, the glassy material comprises, consists essentially of, or consists of 38–42 mol% P_2O_5, 48–52 mol% CaO and 8–12 mol% Na_2O.

[0031] In a particular embodiment, the glassy material comprises, consists essentially of, or consists of 38–42 mol% P_2O_5, 47–51 mol% CaO and 7–11 mol% Na_2O.

[0032] In a particular embodiment, the glassy material comprises, consists essentially of, or consists of 37–42 mol% P_2O_5, 46–52 mol% CaO and 7–12 mol% Na_2O.

[0033] The glassy material may further comprise one or more additional oxides (other than P_2O_5, Na_2O and CaO) in a quantity of 0-10 mol% (e.g. 0.1-10 mol%).

[0034] The glassy material may further comprise one or more additional oxides (other than P_2O_5, Na_2O and CaO) selected from Fe_2O_3, TiO_2, SiO_2, ZrO_2, Ag_2O, CuO and ZnO. Suitably the glassy material comprises 0-10 mol% (e.g. 0.1-10 mol%) of the additional oxide. More suitably, the glassy material comprises 0-5 mol% (e.g. 0.1-5 mol%) of the additional oxide.

[0035] In another embodiment, the biocompatible composite material comprises 5–70 wt% of particles (relative to the total weight of the composite material). Suitably, the biocompatible composite material comprises 5–50 wt% of particles. More suitably, the biocompatible

composite material comprises 5–40 wt% of particles. More suitably, the biocompatible composite material comprises 5–35 wt% of particles. Even more suitably, the biocompatible composite material comprises 5–30 wt% of particles. Most suitably, the biocompatible composite material comprises 10–30 wt% of particles.

[0036] Alternatively, the biocompatible composite material comprises 3–30 wt% (e.g. 4–30 wt% or 6–30 wt%) of particles. Suitably, the biocompatible composite material comprises 3–20 wt% of particles. More suitably, the biocompatible composite material comprises 3–18 wt% of particles. Even more suitably, the biocompatible composite material comprises 3–15 wt% of particles. Yet more suitably, the biocompatible composite material comprises 3–12 wt% of particles (for example 5–11 wt% or 8–12 wt%).

[0037] The particles of the biocompatible glassy material may have any suitable form. Suitably, the particles of glassy material are in granular (e.g. substantially spheroidal) form. In an embodiment, the particles have a BET surface area of 0.1–100 m^2/g. Suitably, the particles have a BET surface area of 0.5–50 m^2/g. More suitably, the particles have a BET surface area of 0.5–25 m^2/g. Most suitably, the particles have a BET surface area of 0.5–10 m^2/g. The BET surface area will be understood by a person skilled in the art to be the surface area determined by Brunauer–Emmett–Teller (BET) theory.

[0038] In another embodiment, the particles of the biocompatible glassy material are substantially non-porous. For example, the particles may have a BET surface area of <10 m^2/g by nitrogen adsorption.

[0039] In another embodiment, the surface of the particles may be modified in order to improve the interface between the particles and the polymeric matrix. The skilled person will appreciate that the particles may be modified in any suitable manner. Suitably, the surface of the particles is modified with one or more silane-type groups.

[0040] In an embodiment, the particles of the biocompatible glassy material have an average particle size of less than 20 µm. In a particular embodiment, the particles have an average particle size of less than 10 µm. In another embodiment, the particles have an average particle size of less than 1 µm (e.g. 0.1–0.99 µm). Particles having an average particle size of less than 1 µm are particularly suitable when the biocompatible composite material is used as part of a stent. The quoted particle sizes were determined through measurements made using a Malvern Instruments Mastersizer 3000 and are based on a “volume average”.

[0041] The polymeric matrix forming part of the biocompatible composite material may comprise one or more biocompatible polymers. The biocompatible polymer may be a homopolymer, a co-polymer or mixture or blend thereof. In an embodiment, the polymeric matrix comprises a single biocompatible homopolymer. In an alternative embodiment, the

polymeric matrix comprises one or more biocompatible co-polymers. The copolymer may be a random copolymer, an alternating copolymer or a block copolymer. Suitably, where the polymeric matrix comprises a copolymer, it is a block copolymer.

[0042] In an embodiment, the one or more biocompatible polymers is provided as a physical blend of two or more polymers (including copolymers). The blend may be phase-separated, having a number of distinct glass transition temperatures. For example the blend may have a number of glass transition temperatures corresponding to the number of polymers (or copolymers) constituting the blend (e.g. a blend containing two polymers and exhibiting separate glass transition temperatures in respect of each of the polymers). Alternatively, the blend may have fewer distinct glass transition temperatures than the number of polymers (or copolymers) constituting the blend (e.g. a blend containing three polymers and displaying only two distinct glass transition temperatures). Alternatively, the blend of two or more polymers (or copolymers) may have a single phase morphology, having only one glass transition temperature.

[0043] In an embodiment, the one or more biocompatible polymers is provided as a phase-separated physical blend of two polymers (or copolymers), wherein the blend has two distinct glass transition temperatures.

[0044] In an embodiment, the biocompatible polymer is selected from polyvinyl alcohols, aliphatic polyesters, polyolefins, polyaryletherketones (e.g. polyether ether ketone) or natural polymers (e.g. chitin). Suitably, the biocompatible polymer is selected from polyvinyl alcohols, aliphatic polyesters or natural polymers (e.g. chitin, chitosan, cellulose and starch).

[0045] In an embodiment, the at least one biocompatible polymer is selected from poly(lactide), poly(caprolactone), poly(glycolide), poly(trimethylene carbonate), poly(dioxanone), poly(ethylene glycol), poly(anhydrides), poly(ethylene adipate), poly(butylene succinate), or blends or copolymers thereof.

[0046] Suitably, the biocompatible polymer is selected from poly(lactide), poly(caprolactone), poly(glycolide), poly(trimethylene carbonate), poly(dioxanone) and poly(ethylene glycol), or blends thereof.

[0047] It will be understood to a person skilled in the art that the term “poly(lactide)” may comprise all forms of poly(lactide), including, for example, poly(L-lactide), poly(D-lactide) and poly(D,L-lactide).

[0048] It will be appreciated to a person skilled in the art that any suitable biocompatible polymer may be used in the biocompatible composite material of the present invention. In one

embodiment, the biocompatible polymer may be selected from one or more of the following biocompatible polymers:

poly(lactide) (PLA);

poly(D-L-lactide) (PDLA);

poly(L-lactide-co-D-lactide) (PDLA);

poly(L-lactide) (PLLA);

poly(glycolide) (PGA);

poly(ethylene glycol) (PEG) OR poly(ethylene oxide) (PEO);

poly(ε-caprolactone) (PCL);

poly(trimethylene carbonate) (PTMC);

poly(dioxanone) ;

poly(L-lactide-co-ε-caprolactone);

poly(L-lactide-co-glycolide);

poly(L-lactide-co-ethylene glycol);

poly(glycolide-co- ε-caprolactone);

poly(glycolide-co -ethylene glycol);

poly(glycolide-co-trimethylene carbonate);

poly(L-lactide)-block-poly(ethylene glycol);

poly(L-lactide)-block-poly(ε-caprolactone);

poly(L-lactide)-block-poly(glycolide);

poly(ε–caprolactone)-block-poly(ethylene glycol);

poly(L-lactide-co-D-lactide)-block-poly(L-lactide);

poly(L-lactide-co- ε-caprolactone)-block-poly(L-lactide);

poly(L-lactide-co- ε-caprolactone)-block-poly(ethylene glycol);

Poly(ethylene) (PE);

and/or

Poly(ether ether ketone) (PEEK).

[0049] Suitably, the at least one biocompatible polymer is selected from poly(lactide) homopolymer, poly(lactide-co-ε-caprolactone), poly(lactide-co-glycolide), poly(lactide-co-trimethylene carbonate), poly(caprolactone), poly(lactide)-*block*-poly(ethylene glycol), poly(ε–caprolactone)-*block*-poly(ethylene glycol) and poly(lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol). More suitably, the at least one biocompatible polymer is selected from poly(L-lactide) homopolymer, poly(L-lactide-co-ε-caprolactone) and poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol).

[0050] In another embodiment, the at least one biocompatible polymer is selected from poly(lactide) (e.g. poly(L-lactide), poly(lactide-co-ε-caprolactone), poly(lactide-co-glycolide), poly(lactide-co-trimethylene carbonate), poly(caprolactone), poly(lactide)-*block*-poly(ethylene glycol), poly(ε–caprolactone)-*block*-poly(ethylene glycol), poly(lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol) and a physical blend of two or more of these polymers.

[0051] In another embodiment, the at least one biocompatible polymer is a physical blend of poly(L-lactide) and at least one other polymer (including copolymers), wherein the at least one other polymer has a glass transition temperature that is lower than 37°C, and wherein the physical blend is phase-separated (i.e. exhibiting separate glass transition temperatures for poly(L-lactide) and the at least one other polymer). Suitably, the at least one biocompatible polymer is a physical blend of poly(L-lactide) and a copolymer comprising L-lactide monomeric units, wherein the copolymer has a glass transition temperature that is lower than 37°C, and wherein the physical blend is phase-separated.

[0052] In a particularly suitable embodiment, the at least one biocompatible polymer is selected from:

poly(L-lactide) (PLLA),

poly(L-lactide-co-ε-caprolactone), or

a physical blend of poly(L-lactide) and poly(L-lactide-co-ε-caprolactone),

wherein for those polymers containing poly(L-lactide-co-ε-caprolactone), the quantity of L-lactide monomeric units within the poly(L-lactide-co-ε-caprolactone) ranges from 60-90 mol% and the quantity of ε-caprolactone monomeric units ranges from 10-40 mol%.

[0053] Suitably, when the at least one biocompatible polymer is a physical blend of poly(L-lactide) and poly(L-lactide-co-ε-caprolactone), the quantity of L-lactide monomeric units within the poly(L-lactide-co-ε-caprolactone) copolymer ranges from 65-75 mol% and the quantity of ε-caprolactone monomeric units within the poly(L-lactide-co-ε-caprolactone) copolymer ranges from 25-35 mol%. The blend of poly(L-lactide) and poly(L-lactide-co-ε-caprolactone) yields particularly enhanced mechanical properties (i.e. Young's modulus, tensile strength and strain

at break) that are consistent with the properties of rubber toughened properties. The blend may have a single phase morphology (having a single glass transition temperature) or phase-separated (having two glass transition temperatures). Suitably, the blend is phase separated.

[0054] Suitably, when the at least one biocompatible polymer is a physical blend of poly(L-lactide) and poly(L-lactide-co-ε-caprolactone), the weight ratio of poly(L-lactide) to poly(L-lactide-co-ε-caprolactone) in the blend ranges from 5–85:15–95. More suitably, when the at least one biocompatible polymer is a physical blend of poly(L-lactide) and poly(L-lactide-co-ε-caprolactone), the weight ratio of poly(L-lactide) to poly(L-lactide-co-ε-caprolactone) in the blend ranges from 40–65:35–60.

[0055] Alternatively, when the at least one biocompatible polymer is a physical blend of poly(L-lactide) and poly(L-lactide-co-ε-caprolactone), the weight ratio of poly(L-lactide) to poly(L-lactide-co-ε-caprolactone) within the blend may be as follows:

i. 40–50:50–60 (poly(L-lactide):poly(L-lactide-co-ε-caprolactone)); or
ii. 55–65:35–45 (poly(L-lactide):poly(L-lactide-co-ε-caprolactone)); or
iii. 65–75:25–35 (poly(L-lactide):poly(L-lactide-co-ε-caprolactone)); or
iv. 75–85:15–25 (poly(L-lactide):poly(L-lactide-co-ε-caprolactone)).

[0056] The at least one biocompatible polymer may additionally comprise a quantity of poly(alkylene glycol) (e.g. poly(ethylene glycol), which may increase the degradation rate of the composite *in vivo*. For example, the at least one biocompatible polymer may additionally comprise a poly(alkylene glycol) *block* having a molecular weight (M_n) of 300–5000 Da. In a particular embodiment, poly(L-lactide-co-ε-caprolactone) (having any of the definitions recited hereinbefore) may additionally comprise a block of poly(ethylene glycol), thus yielding poly(lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol).

[0057] The biocompatible composite material may further comprise one or more additional agents. The additional agents may be selected from a radio-opaque agent and/or an antibacterial agent. Suitably, the biocompatible composite material comprises 0-10 wt% (e.g. 0.01-10 wt%) of the additional agent (e.g. a radio-opaque agent and/or antibacterial agent). More suitably, the biocompatible composite material comprises 0-5 wt% (e.g. 0.01-5 wt%) of the additional agent.

[0058] It will be understood that the terms “radio-opaque agent”, “radiocontrast agent” and “contrast agent” synonymously refer herein to species that improve the visibility of internal bodily structures in X-ray based imaging techniques. Exemplary radio-opaque agents may be barium-based, or iodine-based.

[0059] In an embodiment, the biocompatible composite material further comprises one or more radio-opaque agents selected from barium sulphate, bismuth subcarbonate, bismuth oxychloride, bismuth trioxide, tungsten and zirconium dioxide. Suitably, the radio-opaque agent is barium sulphate.

[0060] In another embodiment, the biocompatible composite material further comprises one or more antibacterial agents selected from Ag_2O, $AgNO_3$, AgCl, Ag_2CO_3,CuO, Cu_2O or ZnO. Suitably, the antibacterial agent is Ag_2O, $AgNO_3$ or CuO. More suitably, the antibacterial agent is Ag_2O.

Implantable medical devices

[0061] As described hereinbefore, the present invention also provides an implantable medical device comprising a biocompatible composite material as defined herein.

[0062] The implantable medical devices of the present invention provide numerous advantages when compared with prior art devices. Perhaps most notably, the implantable medical devices of the invention exhibit improved toughness, stiffness and strength characteristics owing to the incorporation of rigid filler within the polymeric matrix of the biocompatible composite material. In addition, the specific nature of the particulate filler within the biocompatible composite material confers further advantages. In particular, the phosphate-based glassy materials forming part of the present invention are water soluble and their aqueous dissolution can be reliably tailored by varying the specific composition of the glassy material, meaning that a variety of devices (e.g. pins, screws, plates, stents and suture) can be produced, each have dissolution properties tailored to suit the specific application in mind.

[0063] The implantable medical device may be biodegradable, bioresorbable and/or osteoconductive. By virtue of the biocompatible composite material, the specific properties of the device may be tailored to suit the physiological environment in which the device is intended to operate.

[0064] In an embodiment, the device is selected from stents, catheters, pins, rods, screws, plates, surgical staples, and suture. Certain devices, such as staples and suture, are intended to be absorbed by the bodily tissues at the end of a patient's recovery period. Other devices, such as pins, screws and plates, are intended to be markedly more long-lasting. The biocompatible composite materials of the invention allow a variety of different implantable medical devices to be realised.

[0065] In a particular embodiment, the implantable medical device is a stent.

[0066] In another particular embodiment, the implantable medical device is a fixation device (e.g. a screw, pin or plate).

Preparation of biocompatible composite materials

[0067] As described hereinbefore, the present invention also provides a process for the preparation of a biocompatible composite material as defined herein, the process comprising the steps of:

a) preparing particles of the biocompatible glassy material by:
   i. mixing together quantities of glassy material raw ingredients,
   ii. heating the glassy material raw ingredients to a molten state to provide a homogeneous melt,
   iii. quenching the molten material, and
   iv. milling the resulting quenched glassy material; and
b) dispersing greater than 0 but less than or equal to 70 wt% of the particles within a polymeric matrix as defined herein.

[0068] The biocompatible composite materials of the present invention are suitably prepared according to the above process. It will be appreciated that whilst the glassy material particles are advantageously prepared according to step a) above, the incorporation of these particles within the polymeric matrix forming part of composite material may be achieved by variety of different techniques that will be readily appreciated by the skilled person.

[0069] It will be appreciated that in step a)i), the "glassy material raw ingredients" refers to any suitable starting material for generating a glassy material as defined herein with the required content of P_2O_5 (and optionally a Group II metal oxide (e.g. CaO) and/or a Group I metal oxide (e.g. Na_2O) as defined herein). Hence, in step a)i), the quantity of raw ingredients used (e.g. monoammonium phosphate (and optionally a Group II carbonate (e.g. calcium carbonate) and/or a Group I metal carbonate (e.g. sodium carbonate)) is determined having regard to the envisaged oxide content of the resulting glassy material. The skilled person will appreciate that while the raw ingredients used may themselves not be oxides, under the high temperatures employed in step a)ii), the corresponding oxides are formed.

[0070] A skilled person will be able to select a suitable duration and temperature for step a)ii) based upon the composition of glassy material desired. In an embodiment, in step a)ii), the glassy material raw ingredients are heated to a temperature greater than 1150°C. Suitably, the glassy material raw ingredients are heated to a temperature of 1150–1400 °C.

[0071] Suitably, in step a)ii) the glassy material raw ingredients are heated in an environment comprising oxygen.

[0072] In another embodiment, the molten material is cast prior to being quenched.

[0073] The molten material may be quenched in any suitable way known in the art. For example, liquid nitrogen, dry ice or iced water may be used to quench the molten material in step a)iii), or the material may be quenched using a cooled metal plate or roller. Suitably, the molten material is quenched in water.

[0074] In another embodiment, in step a)iv), the quenched glassy material is milled by one or more dry or wet milling techniques. Suitably, the quenched glassy material is milled by one or more dry milling techniques. The duration of the dry-milling step is dependent on the desired particle size, which is in turn governed by the particular end application. In particular embodiments, the quenched glassy material may be dry-milled to an average particle size of 1–300 μm.

[0075] Optionally, when step a)iv) comprises a dry-milling step, said step may be followed by one or more wet-milling steps. Any suitable solvent may be used in the wet milling process. Suitably, the solvent is ethanol or iso-propyl alcohol. More suitably, the solvent is iso-propyl alcohol. The duration of the wet-milling step(s) is dependent on the desired particle size, which is in turn governed by the particular end application. In particular embodiments, the dry-milled powder may be wet-milled to yield a sub-10 μm particle size distribution.

[0076] In a particular embodiment, the quenched glassy material is milled by a dry-milling step, followed by a wet-milling step.

[0077] In another embodiment, following a wet-milling step, the resulting milled sample may be allowed to sediment for a period of time to separate out larger particles. Alternatively, particles of different sizes may be separated by a centrifugation step.

[0078] It will be appreciated that step b) may be achieved by a variety of different techniques. In an embodiment, step b) comprises the steps of:

i. providing a solution comprising at least one (e.g. one) biocompatible polymer dissolved in a solvent,
ii. mixing the solution with the particles to obtain a polymer-particles suspension, and
iii. drying the polymer-particles suspension.

[0079] Accordingly, the dried polymer-particles suspension resulting from step iii) may directly resemble a composite material of the invention, in which case step b)ii) comprises mixing the solution of biocompatible polymer dissolved in solvent with the amount of glassy material particles required to afford a composite material having the desired loading of glassy material particles.

[0080] When the composite material comprises a polymeric matrix that is a physical blend of two or more polymers, step b) ((i) to (iii)) may be performed separately in respect of each polymer within the blend. The resulting dried polymer-particles suspensions are then blended in appropriate quantities at a temperature higher the melting temperature of both polymers used in the blend in order to yield the finished composite material. Preparing blended composite materials in this manner, which includes a minimum number of processing steps, may result in a phase-separated composite material, having two distinct glass transition temperatures corresponding to each polymer used in the polymeric matrix blend.

[0081] Alternatively, step b) comprises the steps of:

i. providing a solution comprising a first biocompatible polymer dissolved in a solvent,
ii. mixing the solution with the particles to obtain a polymer-particles suspension,
iii. drying the polymer-particles suspension; and
iv. blending a quantity of the material resulting from step iii) with a second biocompatible polymer at a temperature higher than the melting temperature of the first and the second biocompatible polymer.

[0082] Accordingly, step b) may comprise preparing a batch of polymeric material containing dispersed glassy material particles, with portions of that batch then being incorporated into a separate neat quantity of an identical or different polymeric material. By determining the quantity of particles present within the dried polymer-particles suspension of step b)iii), an appropriate quantity of this material can be blended with the second neat biocompatible polymer in step b)iv) to provide a biocompatible composite material having a pre-determined quantity of glassy material particles.

[0083] When the composite material comprises a polymeric matrix that is a physical blend of two or more polymers, step b) ((i) to (iv)) may be performed separately in respect of each polymer within the blend. The materials resulting from each step b)iv) are then blended in appropriate quantities at a temperature higher the melting temperature of both polymers used in the blend in order to yield the finished composite material. Preparing blended composite materials in this manner, which includes a greater number of processing steps, may result in a composite material having a single glass transition temperature.

[0084] The first and second biocompatible polymers (in steps b)i) and b)iv) respectively) may be the same or different. Suitably, the first and second biocompatible polymers are the same. The first and second biocompatible polymers may be independently selected from any of the biocompatible polymers discussed herein.

[0085] In an embodiment, in step b)ii), the particles are provided as a suspension in a solvent, which, when mixed with the solution prepared in step b)i), provides the polymer-particles suspension. The particles may be suspended in any suitable solvent. Suitably, the particles are provided as a suspension in iso-propyl alcohol.

[0086] In another embodiment, in step b)ii), an additional agent (e.g. radio-opaque agent and/or antibacterial agent) may be mixed together with the particles and the solution prepared in step b)i) to provide the polymer-particles suspension. The additional agent e.g. radio-opaque agent and/or antibacterial agent) may be provided in any suitable form. In an embodiment, the additional agent (e.g. radio-opaque agent and/or antibacterial agent) agent is provided as a suspension in a suitable solvent. Suitably, the additional agent (e.g. radio-opaque agent and/or antibacterial agent) is provided as a suspension in iso-propyl alcohol.

[0087] In a particular embodiment, the process for the preparation of a biocompatible composite material as defined herein comprises the following key steps:

1) Production of a fused phosphate glass via a high-temperature fritting process
2) Preliminary dry-milling of the fused phosphate glass to produce a raw powder
3) Secondary wet-milling of the fused phosphate glass to produce a suspension of particulates of sub-10 µm size
4) Optionally, separately wet-milling barium sulphate salt to produce a second suspension of particulates sub-10 µm size
5) Sedimentation of the wet-milled suspensions to obtain a suspension of particulates of sub-2 µm size
6) Solvent-casting of polymer-inorganic composite films from a suspension of sub-2 µm particulates in a polymer solution
7) Melt-compounding of a polymer-inorganic composite by blending neat polymer with a quantity of dry solvent-cast polymer-inorganic composite film.

[0088] The following numbered paragraphs describe particular embodiments of the invention:

1) A biocompatible composite material comprising
    a. a polymeric matrix comprising at least one biocompatible polymer; and
    b. greater than 0 but less than or equal to 70 wt% of particles of a biocompatible glassy material dispersed in the polymeric matrix, wherein the glassy material comprises 30–60 mol% of P_2O_5.
2) The biocompatible composite material of paragraph 1, wherein the composite material is biodegradable, bioresorbable and/or bioactive.

3) The biocompatible composite material of paragraph 1 or 2, wherein the glassy material comprises 30–60 mol% of a suitable Group II metal oxide.
4) The biocompatible composite material of any of paragraphs 1, 2 or 3, wherein the glassy material comprises 35–55 mol% of a suitable Group II metal oxide.
5) The biocompatible composite material of paragraph 3 or 4, wherein the suitable Group II metal oxide is selected from CaO, MgO, SrO, BaO or combinations thereof.
6) The biocompatible composite material of paragraphs 3 to 5, wherein the suitable Group II metal oxide is CaO.
7) The biocompatible composite material of any preceding paragraph, wherein the glassy material comprises 0–15 mol% of a suitable Group I metal oxide.
8) The biocompatible composite material of any preceding paragraph, wherein the glassy material comprises 5–12 mol% of a suitable Group I metal oxide.
9) The biocompatible composite material of paragraph 7 or 8, wherein the suitable Group I metal oxide is selected from Na_2O, K_2O or combinations thereof.
10) The biocompatible composite material of any one of paragraphs 7 to 9, wherein the suitable Group I metal oxide is Na_2O.
11) The biocompatible composite material of any preceding paragraph, wherein the glassy material comprises 35–50 mol% of P_2O_5.
12) The biocompatible composite material of any preceding paragraph, wherein the polymeric matrix comprises 10–35 wt% of particles of the biocompatible glassy material.
13) The biocompatible composite material of any preceding paragraph, wherein the at least one biocompatible polymer is selected from polyvinyl alcohols, aliphatic polyesters, polyolefins, polyaryletherketones (e.g. polyether ether ketone) or natural polymers (e.g. chitin).
14) The biocompatible composite material of any preceding paragraph, wherein the at least one biocompatible polymer is selected from the list consisting of poly(lactide), poly(caprolactone), poly(glycolide), poly(trimethylene carbonate), poly(dioxanone) and poly(ethylene glycol).
15) The biocompatible composite material of any preceding paragraph, wherein the polymeric matrix comprises:
    i. a homopolymer of a biocompatible polymer;
    ii. a copolymer of two or more biocompatible polymers; or
    iii. a blend of two or more biocompatible polymers selected from a homopolymer or a copolymer.
16) The biocompatible composite material of paragraph 15, wherein the copolymer is a random copolymer or a block copolymer.

17) The biocompatible composite material of any preceding paragraph, wherein the polymeric matrix is formed from a polymer selected from poly(L-lactide) homopolymer, poly(L-lactide-co-ε-caprolactone), poly(caprolactone), poly(lactide)-*block*-poly(ethylene glycol) poly(ε-caprolactone)-*block*-poly(ethylene glycol) and poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol).

18) The biocompatible composite material of any preceding paragraph, wherein the composite material comprises one or more additional agents selected from a radio-opaque agent and/or an antibacterial agent.

19) The biocompatible composite material of paragraph 18, wherein the radio-opaque agent is barium sulphate, bismuth subcarbonate, bismuth oxychloride, bismuth trioxide, tungsten and zirconium dioxide.

20) The biocompatible composite material of paragraph 18, wherein the antibacterial agent is selected from Ag_2O, $AgNO_3$, AgCl, Ag_2CO_3, CuO, Cu_2O or ZnO.

21) The biocompatible composite material of any preceding paragraph, wherein the glassy material further comprises one or more additional oxides selected from Fe_2O_3, TiO_2, SiO_2, ZrO_2, Ag_2O, CuO, ZnO or combinations thereof.

22) The biocompatible composite material of any preceding paragraph, wherein the particles of the biocompatible glassy material are substantially non-porous.

23) The biocompatible composite material of any preceding paragraph, wherein the particles of the biocompatible glassy material have a BET surface area of 0.1–100 m^2/g.

24) The biocompatible composite material of any preceding paragraph, wherein the particles of the biocompatible glassy material have a BET surface area of 0.5–10 m^2/g.

25) The biocompatible composite material of any preceding paragraph, wherein the particles of the biocompatible glassy material have an average particle size of less than 1 μm.

26) The biocompatible composite material of any preceding paragraph, wherein the glass material comprises:

    i. 38–52 mol% of P_2O_5,
    ii. 38–52 mol% of CaO, and
    iii. 8–12 mol% of Na_2O.

27) An implantable medical device comprising the biocompatible composite material of any preceding paragraph.

28) The implantable medical device of paragraph 20, wherein the device is biodegradable, bioresorbable and/or osteoconductive.

29) The implantable medical device of paragraph 20 or 21, wherein the device is selected from stents, catheters, pins, rods, screws, plates, surgical staples, and suture.

30) The implantable medical device of any of paragraphs 20, 21 or 22, wherein the device is a stent.

31) A process for the preparation of a biocompatible composite material as defined in any preceding paragraph, the process comprising the steps of:

a. preparing particles of the biocompatible glassy material by:
    i. mixing together quantities of glassy material raw ingredients,
    ii. heating the glassy material raw ingredients to a molten state to provide a homogeneous melt,
    iii. quenching the molten material, and
    iv. milling the resulting quenched glassy material; and
b. dispersing greater than 0 but less than or equal to 70 wt% of the particles within a polymeric matrix as defined in any preceding paragraph.

32) The process of paragraph 31, wherein the glassy material raw ingredients are heated to a temperature greater than 1150 °C.

33) The process of paragraph 31 or 32, wherein the glassy material raw ingredients are heated to a temperature of 1150–1400 °C.

34) The process of any of paragraphs 31 to 33, wherein the molten material is quenched in water.

35) The process of any of paragraphs 31 to 34, wherein the quenched glassy material is dry milled, and optionally thereafter wet milled.

36) The process of any of paragraphs 31 to 35, wherein step b) comprises the steps of:
    i. providing a solution comprising a first biocompatible polymer dissolved in a solvent,
    ii. mixing the solution with the particles to obtain a polymer-particles suspension,
    iii. drying the polymer-particles suspension; and
    iv. blending a quantity of the material resulting from step iii) with a second biocompatible polymer at a temperature higher than the melting temperature of the first and second biocompatible polymer.

37) The process of paragraph 36, wherein the first and second biocompatible polymers are the same.

38) The process of paragraph 36 or 37, wherein step b)ii comprises mixing the solution with a suspension of the particles in a solvent to obtain the polymer-particles suspension

39) The process of paragraph 38, wherein the solvent is selected from ethanol or iso-propyl alcohol.

40) The process of any of paragraphs 31 to 39, wherein step b) further comprises dispersing a radio-opaque agent within the polymeric matrix.

41) The process of any of paragraphs 37 to 40, wherein step b)ii further comprises mixing a radio-opaque agent together with the solution and the particles to obtain the polymer-particles suspension.

42) The process of paragraph 41, wherein the radio-opaque agent is provided as a suspension within a solvent prior to being mixed together with the solution and the particles.

43) The process of paragraph 42, wherein the solvent is selected from water, ethanol or iso-propyl alcohol.

EXAMPLES

[0089] Exemplary embodiments of the invention will now be described, by way of example only, with reference to the accompanying figures, in which:

Fig. 1 shows a comparison of the particle size distributions of fused phosphate glass (P_2O_5:CaO:Na_2O = 40:50:10) particulates in suspension after dry milling in a TEMA mill, followed by wet-milling using a Pulverisette 7 and, subsequently, after a period of sedimentation.

Fig. 2 shows the change in the particle size distribution of barium sulphate particles following successive milling trials.

Fig. 3 shows the aqueous dissolution of various phosphate glass compositions showing release of (a) calcium, (b) phosphorous and (c) sodium ions.

Fig. 4 shows the SEM images of the fracture surfaces of: (a) PLLA, (b) PURASORB PLC7015 and (c) PLLA/PURASORB PLC7015 blend composites containing 10 wt% of fused phosphate glass (PG11).

Fig. 5 shows (a) an SEM image of the fracture surface of the PLA-CL(80:20)-PEG550 copolymer (VORNIA Ltd.) with 10 wt% of PG11 and 2 wt% of BaSO4. (b) a SEM back-scattering image of the same fracture surface providing contrast between PG11 (grey) and BaSO4 particles (white). (c) the X-ray spectrum of Particle A, a phosphate glass particulate. (d) the X-ray spectrum of Particle B, a barium sulphate particulate.

Methods and materials

Dry-milling

[0090] A TEMA Laboratory Disk Mill TS 750/1000 was used to prepare dry-milled powders of the phosphate glasses. A 100 cm^3 grinding barrel was filled with the glassy material, as quenched. The mill was operated at a motor speed of 100 rpm in cycles of 2 min duration.

Wet-milling

[0091] Wet-milling of the dry-milled phosphate glass and inorganic powders was performed using a Fritsch Pulverisette 7 double-planetary mill. Each 80 ml zirconia-lined milling vessel was loaded with 100.0 g of 0.5 mm diameter zirconia ball media. An appropriate quantity of inorganic material was weighed and added to each vessel in equal proportion along with a suitable volume of isopropyl alcohol. Milling cycles of 5 min duration were run at 1000 rpm where a suitable period was allowed for the vessels to cool between successive cycles.

[0092] Alternatively, wet-milling of the dry-milled phosphate glass and inorganic powders was performed using a Fritsch Pulverisette 6 single-planetary mill. The 250 ml zirconia-lined milling vessel was loaded with 100.0 g of 0.5 mm diameter zirconia ball media. An appropriate quantity of inorganic material was weighed and added to the vessel with a suitable volume of isopropyl alcohol. Milling cycles of 5 min duration were run at 550 rpm where a suitable period was allowed for the vessels to cool between successive cycles.

Particle Size Analysis

[0093] Evaluation of the particle size distributions produced by milling of the inorganic powders was undertaken using a Malvern Instruments Mastersizer 3000. For each experiment 500 ml of ethanol was added as dispersant to the instrument vessel. A small quantity, 0.5 – 1 ml, of wet-milled inorganic suspension was then added to the ethanol to provide an appropriate measurement signal. Five repeated measurements were performed during the experiments.

[0094] The experimental data was analysed using the instrument software package provided by Malvern Instruments which utilises Mie Scattering Theory to calculate the particle size distribution. The methodology is volume-based, in that, the calculation derives the total volume of the particles corresponding to each increment in particle volume. One of the assumptions of Mie Theory is that the particles are spherical. Therefore, values obtained for the particle sizes are, in fact, based on “equivalent spheres”. This means that any particle of a given volume, including those irregular in shape, will be represented by a sphere of equivalent volume with a diameter corresponding to the particle size.

Dissolution Tests

[0095] The dissolution behaviour of the phosphate glasses was measured using the inductively coupled plasma optical emission spectroscopy (ICP-OES) technique. A Thermo Jarrell Ash IRIS Advantage ICP-OES equipped with Burgener nebuliser with a glass cyclonic spray chamber was used for these tests. Aqueous phosphate glass suspensions were sampled and analysed after 30 min, 1 hr and 2 hr to evaluate the quantity of dissolved phosphorous, calcium and sodium ions.

Melt-compounding Composites

[0096] Melt-compounding of the composites was performed using HAAKE PolyLab & Mixer OS600 equipment. The Mixer OS 600 was fitted with Banbury Rotors. A rotational-speed of 200 rpm was employed to blend the polymer and inorganic fillers at a temperature appropriate to each polymer or copolymer.

Scanning Electron Microscopy

[0097] Fracture surfaces were prepared by submerging each composite in liquid nitrogen for 4-5 min before removing and immediately striking the specimen with a mallet.

[0098] Images of sample fracture surfaces were obtained using a JEOL JSM6490-LV scanning electron microscope (SEM) working under high-vacuum conditions with an applied accelerating voltage of 5kV.

Differential Scanning Calorimetry

[0099] Differential scanning calorimetry (DSC) was performed using a TA Instruments DSC TAQ2000. The samples were first cooled and left to equilibrate at -80°C. The temperature was then ramped at 20°C/min to 250°C. Samples were then cooled to -80°C at the same rate. Finally, the temperature of samples was increased again, ramping at 20°C/min to 250°C before allowing samples to equilibrate at 25°C.

Thermo-gravimetric Analysis

[00100] Thermo-gravimetric analysis (TGA) was performed using a TA instruments Q500 TGA equipped with platinum crucible. The machine was programmed to heat samples from room temperature to 800°C at a constant heating rate of 20°C/min. The weight of the sample was monitored as a function of increasing temperature and recorded at regular intervals.

Injection Moulding

[00101] Dumbbell specimens for tensile tests, with a 20 mm gauge-length, were prepared using a DSM Xplore IM 5.5 injection-moulding machine. Operating parameters, such as,

temperature and pressure for injection, filling and holding cycles of the injection-moulding process were optimised for each of the materials accordingly.

Tensile Testing

[00102] Tensile testing of the injection-moulded dumbbell specimens was performed under ambient conditions using Hounsfield Tensile Testing Machine at extension rate of 5 mm/min. The nominal stress and strain were evaluated from the recorded force and displacement, respectively.

Example 1 - Preparation of glass samples

[00103] A glass comprising phosphorous oxide (P_2O_5), calcium oxide (CaO) and sodium oxide (Na_2O) with the molar composition, P_2O_5:CaO:Na_2O = 40:50:10, was prepared by, first, sieving altogether 60.5 wt% of monoammonium phosphate, 32.9 wt% of calcium carbonate and 6.5 wt% of sodium carbonate dry powder. The powder mixture was added to a quartz crucible located within a gas-fired kiln which had been heated to a peak-temperature of 1300 °C. Over a period of several hours the homogeneity of the molten material was evaluated by appearance. After, the molten material was quenched in water to form the glass.

[00104] Another glass comprising phosphorous oxide (P_2O_5), calcium oxide (CaO) and sodium oxide (Na_2O) with the molar composition, P_2O_5:CaO:Na_2O = 45:45:10, was prepared by, first, sieving altogether 64.5 wt% of monoammonium phosphate, 28.8 wt% of calcium carbonate and 6.7 wt% of sodium carbonate. The powder mixture was then added to a quartz crucible located within a gas-fired kiln which had been heated to a peak-temperature of 1220 °C. Over a period of several hours the homogeneity of the molten material was evaluated by appearance. After, the molten material was quenched in water to form the glass.

[00105] A further glass comprising phosphorous oxide (P_2O_5), calcium oxide (CaO) and sodium oxide (Na_2O) with the molar composition, P_2O_5:CaO:Na_2O = 50:40:10, was prepared by, first, sieving altogether 69.6 wt% of monoammonium phosphate, 24.1 wt% of calcium carbonate and 6.3 wt% of sodium carbonate-. The powder mixture was then added to a quartz crucible located within a gas-fired kiln which had been heated to a peak-temperature of 1220 °C. Over a period of several hours the homogeneity of the molten material was evaluated by appearance. After, the molten material was cast and quenched in water to form the glass.

[00106] In total twelve glasses comprising phosphorous oxide (P_2O_5), calcium oxide (CaO) and sodium oxide (Na_2O) in the following ranges: 40 – 50 mol % of P_2O_5, 35 – 60 mol % CaO and 0 – 15 % of Na_2O were prepared. The full compositions of the 12 samples are outlined in Table 1a below.

Table 1a *- Composition of phosphate-based glasses*

Number	Weight % of Raw Materials			Molar % of Oxides in Glass		
	Monoammonium Phosphate (MAP)	Calcium Carbonate (WHITING)	Sodium Carbonate	Phosphorus Oxide (P_2O_5)	Calcium Oxide (CaO)	Sodium Oxide (Na_2O)
PG1	69.5	30.5	0.0	50	50	0
PG2	69.6	27.2	3.2	50	45	5
PG3	69.6	24.1	6.3	50	40	10
PG4	69.5	21.0	9.5	50	35	15
PG5	65.6	34.6	0.0	45	55	0
PG6	64.6	32.0	3.4	45	50	5
PG7	64.5	28.8	6.7	45	45	10
PG8	64.5	25.5	10.0	45	40	15
PG9	60.9	39.1	0.0	40	60	0
PG10	60.7	35.9	3.4	40	55	5
PG11	60.6	32.9	6.5	40	50	10
PG12	60.5	29.8	9.7	40	45	15

[00107] Table 1b below provides further compositional data for PG11.

Table 1b *– Inorganic composition of six different PG11 batches evaluated by XRF and compared with the nominal glass composition (calculated). Crystalline component (X_c) in the form of alpha calcium pyrophosphate (α-$Ca_2P_2O_7$) determined by XRD.*

Material	**Inorganic Mass Percentages (%)**				**Inorganic Molar Percentages (%)**				**X_c**
	P_2O_5	**CaO**	**Na_2O**	**SiO_2**	**P_2O_5**	**CaO**	**Na_2O**	**SiO_2**	**(%)**
PG11 - 1	61.69	30.20	5.43	2.32	39.53	48.99	7.97	3.51	0.0
PG11 - 2	61.63	30.22	5.46	2.35	39.46	48.98	8.01	3.55	n/a
PG11 - 3	60.97	30.69	5.64	1.95	39.04	49.74	8.27	2.95	4.9
PG11 - 4	61.11	30.80	5.66	2.16	38.89	49.61	8.25	3.25	5.9
PG11 - 5	60.70	30.79	5.69	2.31	38.63	49.60	8.29	3.47	0.0
PG11 - 6	60.58	30.72	5.75	2.71	38.36	49.24	8.34	4.05	2.3
NOMINAL	*62.35*	*30.46*	*6.41*	*0.37*	*40.22*	*49.74*	*9.47*	*0.56*	*0.0*

Example 2 - Particle formation

[00108] The quenched phosphate-based glasses were dry-milled using a TEMA mill to produce a raw powder. The particle size distribution of the powder was evaluated using a Malvern Instruments Mastersizer 3000 yielding particle sizes in the range 1 – 300 μm.

Method 1

[00109] A raw powder of phosphate-based glass with composition (P_2O_5:CaO:Na_2O = 40:50:10), prepared according to the methods given in Example 1, was wet-milled using a Fritsch Pulverisette 7. 100 g of zirconia 0.5 mm diameter ball media was placed in to the 80 ml milling vessel. 20 g of glass raw powder was placed on top of the zirconia media. 20 g of iso-propyl alcohol was poured in to the vessel which was then sealed. After mounting the milling vessel in the instrument, the mill was run for a period of 5 min at 1000 rpm rotational speed. This procedure was repeated three times after which the particle size distribution of a sample drawn from the milled suspension was measured using a Malvern Instruments Mastersizer 3000 revealing a sub-10 micron particle size distribution. The suspension of particles was then left to sediment in order to separate-out particles of size greater than 1 μm. The particle size distribution of sample drawn from the milled suspension after sedimentation was measured using a Malvern Instruments Mastersizer 3000 to demonstrate the sub-micron particle size-distribution of the particulates remaining in suspension.

Method 2

[00110] A raw powder of phosphate-based glass with composition (P_2O_5:CaO:Na_2O = 40:50:10), prepared according to the methods given in Example 1, was wet-milled using a Fritsch Pulverisette 6. 400 g of zirconia 0.5 mm diameter ball media was placed in to the 250 ml milling vessel. 60 g of glass raw powder was placed on top of the zirconia media. 60 g of iso-propyl alcohol was poured in to the vessel which was then sealed. After mounting the milling vessel in the instrument, the mill was run for a period of 5 min at 550 rpm rotational speed. This procedure was repeated ten times after which the particle size distribution of a sample drawn from the milled suspension was measured using a Malvern Instruments Mastersizer 3000 revealing a sub-10 micron particle size distribution. The suspension of particles was then left to sediment in order to separate-out particles of size greater than 1 μm. The particle size distribution of sample drawn from the milled suspension after sedimentation was measured using a Malvern Instruments Mastersizer 3000 to demonstrate the sub-micron particle size-distribution of the particulates remaining in suspension.

Example 3 - Incorporation of radio-opaque agents

[00111] A raw powder of barium sulphate salt (Sigma-Aldrich) was wet-milled using a Fritsch Pulverisette 7. 100 g of zirconia 0.5 mm diameter ball media was placed in to the 80 ml milling vessel. 5 g of barium sulphate powder was placed on top of the zirconia media. 15 g of iso-

propyl alcohol was poured in to the vessel which was then sealed. After mounting the milling vessel in the instrument, the mill was run for a period of 5 min at 1000 rpm rotational speed. This procedure was repeated three times after which the particle size distribution of a sample drawn from the milled suspension was measured using a Malvern Instruments Mastersizer 3000 revealing a sub-10 micron particle size distribution.. The suspension of particles was then left to sediment in order to separate-out particles of size greater than 1 μm. The particle size distribution of sample drawn from the milled suspension after sedimentation was measured using a Malvern Instruments Mastersizer 3000 to demonstrate the sub-micron particle size-distribution of the particulates remaining in suspension.

Example 4 – Preparation of neat melt-compounded blends

Using physical blend of poly(L-lactide) and poly(L-lactide-co-ε-caprolactone) copolymer

[00112] A series of four melt-compounded physical blends were prepared using poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP) and poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) copolymer (LA:CL=70:30) in the following weight ratios: 46:54, 60:40, 70:30, 80:20 (PLLA:PLC7015). No inorganic filler was added.

[00113] Each blend was prepared using a HAAKE PolyLab RheoDrive7 and Mixer OS600 system equipped with Banbury Rotors. In each case a total of 45 g of poly(L-lactide) and poly(L-lactide- co-ε-caprolactone) neat polymer pellets, weighed-out in the respective quantities needed for each of the four formulations, were blended above the melt-temperature of PLLA. The duration of the mixing process was defined to be sufficient to obtain a stable melt-temperature and torque.

[00114] Tensile test results obtained on dumbbell specimens prepared from the materials are reported in Table 6.

[00115] Thermal analysis of each blend glass-transition temperature, crystallisation temperature, melting temperature and degradation temperature are recorded in Table 10.

Example 5 - Preparation of melt-compounded composites

Using poly(L-lactide)

[00116] A series of five melt-compounded composites was prepared using poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP) as the polymer matrix and a phosphate-glass with the composition (P_2O_5:CaO:Na_2O = 40:50:10) as the inorganic filler. The nominal loadings of phosphate-glass particles with the matrix were 5, 10, 20, 40 wt%.

[00117] 5 g of poly(L-lactide) homopolymer was dissolved completely in 40 ml of chloroform in a 250 ml beaker under magnetic stirring at ambient temperature. 30 ml of milled suspension after sedimentation, prepared according to the method in Example 2, was then added to the polymer solution under magnetic stirring. The suspension, after extraction from the milling vessel and dilution in iso-propyl alcohol, contained 5-10 wt% of particles. An additional 5 ml of chloroform was added to aid in the dissolution of small amounts of precipitated polymer. The blend of milled suspension and polymer solution was mixed until homogeneous in appearance and then cast into a Petri-dish and allowed to dry at ambient temperature to form a composite film. The film was then further dried in an oven overnight above the polymer glass-transition temperature to drive-off residual solvent. The mass fraction of phosphate-based glass particles within the dry composite film was determined through measurement of the total film mass. This process was repeated as required to obtain sufficient loading of filler.

[00118] Melt-compounded composites of the desired filler loading were prepared using a HAAKE PolyLab RheoDrive7 and Mixer OS600 system equipped with Banbury Rotors. In each case neat PLLA homopolymer pellets were blended above the melting temperature of PLLA with an appropriate quantity of composite film to obtain melt-compounded composites with net loadings of either 5,10, 20 or 40 wt% of inorganic glass. The duration of the mixing process was defined to be sufficient to obtain a stable melt-temperature and torque.

[00119] Tensile test results obtained on dumbbell specimens prepared from the materials are reported in Table 2.

Using poly(L-lactide-co-ε-caprolactone)

[00120] A series of five melt-compounded composites was prepared using poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30))(PURAC® PURASORB™ PLC 7015) copolymer (mole ratio of L-lactide (L) monomeric units to caprolactone (CL) monomeric units (e.g. L:CL) = 70:30) as the polymer matrix and a phosphate-glass with the composition (P_2O_5:CaO:Na_2O = 40:50:10) as the inorganic filler. The nominal loadings of phosphate-glass particles with the matrix were 5, 10, 20, 40 wt%.

[00121] 5 g of poly(L-lactide-co-ε-caprolactone) copolymer was dissolved completely in 30 ml of chloroform in a 250 ml beaker under magnetic stirring at ambient temperature. 30 ml of milled suspension after sedimentation, prepared according to the method in Example 2, was then added to the polymer solution under magnetic stirring. The milled suspension after extraction from the milling vessel and dilution in iso-propyl alcohol contained 5-10 wt% of particles. An additional 5 ml of chloroform was added to aid in the dissolution of small amounts

of precipitated polymer. The blend of milled suspension and polymer solution was mixed until homogeneous in appearance and then cast into a Petri-dish and allowed to dry at ambient temperature to form a composite film. The film was then further dried in an oven overnight above the polymer glass-transition temperature to drive-off residual solvent. The mass fraction of phosphate-based glass particles within the dry composite film was determined through measurement of the total film mass. This process was repeated as required to obtain sufficient loading of filler.

[00122] Melt-compounded composites of the desired filler loading were prepared using a HAAKE PolyLab RheoDrive7 and Mixer OS600 system equipped with Banbury Rotors. In each case, neat poly(L-lactide-co-ε-caprolactone) copolymer flakes were blended above the polymer melting temperature with an appropriate quantity of composite film to obtain melt-compounded composites with net loadings of 5, 10. 20 and 40 wt% of inorganic glass. The duration of the mixing process was defined to be sufficient to obtain a stable melt-temperature and torque.

[00123] Tensile test results obtained on dumbbell specimens prepared from the materials are reported in Table 3.

Using poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol) copolymer

[00124] The following composite was prepared using poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol) copolymer (PL-CL(80:20)-PEG550) (L:CL = 80:20; M_n(PEG) = 550 Da) (VORNIA Ltd.) as the polymer matrix and a phosphate-glass with the composition (P_2O_5:CaO:Na_2O = 40:50:10) as the inorganic filler. In this example, barium sulphate ($BaSO_4$) (Sigma Aldrich) salt was also incorporated into the polymer matrix as a radio-opaque marker. Nominal loadings of filler were 10 wt% of phosphate-glass filler and 2 wt% of barium sulphate.

[00125] 5 g of poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol) copolymer (L:CL = 80:20; M_n(PEG) = 550 Da) was dissolved completely in 40 ml of chloroform in a 250 ml beaker under magnetic stirring at ambient temperature. 30 ml of milled suspension after sedimentation, prepared according to the method in Example 2, was then added to the polymer solution under magnetic stirring. The milled suspension after extraction from the milling vessel and dilution in iso-propyl alcohol contained 5-10 wt% of particles. 1 ml of barium sulphate suspension, prepared according to the method in Example 3, comprising 5 wt% of particulates was then added to the mixture. An additional 5 ml of chloroform was added to aid in the dissolution of small amounts of precipitated polymer. The blend of milled suspension and polymer solution was mixed until homogeneous in appearance and then cast into a Petri-dish and allowed to dry at ambient temperature to form a composite film. The film was then further

dried in an oven overnight above the polymer glass-transition temperature to drive-off residual solvent. The total mass fraction of phosphate-based glass and barium sulphate particles within the dry composite film was determined through measurement of the total film mass. This process was repeated as required to obtain sufficient loading of filler.

[00126] A melt-compounded composite of the desired filler loading was prepared using a HAAKE PolyLab RheoDrive7 and Mixer OS600 system equipped with Banbury Rotors. Neat poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol) copolymer (L:CL = 80:20) copolymer flakes were blended above the polymer melting temperature with an appropriate quantity of composite film to obtain a melt-compounded composite of 10 wt% of inorganic glass and 2 wt% barium sulphate. The duration of the mixing process was defined to be sufficient to obtain a stable melt-temperature and torque.

[00127] Tensile test results obtained on dumbbell specimens prepared from the materials are reported in Table 4.

Using physical blend of poly(L-lactide) and poly(L-lactide-co-ε-caprolactone) copolymer

Method 3

[00128] The following composite was prepared using a physical blend of poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP) and poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) copolymer (L:CL = 70:30) as the polymer matrix and a phosphate-glass with the composition (P_2O_5:CaO:Na_2O = 40:50:10) as the inorganic filler The weight ratio of the two polymers was 46:54 respectively.

[00129] Poly(L-lactide)/phosphate-based glass and poly(L-lactide-co-ε-caprolactone)/phosphate-based glass composite films were prepared as described in Example 5.

[00130] A melt-compounded composite blend of the desired filler loading was prepared using a HAAKE PolyLab RheoDrive7 and Mixer OS600 system equipped with Banbury Rotors. Neat poly(L-lactide) pellets and poly(L-lactide-co-ε-caprolactone) copolymer flakes were blended above the melting temperature of PLLA with an appropriate quantity of each composite film to obtain a melt-compounded composite blend of 10 wt% of inorganic glass. The duration of the mixing process was defined to be sufficient to obtain a stable melt-temperature and torque.

[00131] Tensile test results obtained on dumbbell specimens prepared from the materials are reported in Table 5.

Method 4

[00132] Two series of composites were prepared using physical blends of poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP) and poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) copolymer (L:CL = 70:30) as the polymer matrices and a phosphate-glass with the composition (P_2O_5:CaO:Na_2O = 40:50:10) as the inorganic filler. The respective weight ratios of polymers in each series were 46:54 and 60:40. The nominal loadings of phosphate-glass particles within the matrices were 10, 20, 40 wt%.

[00133] Three pre-loaded feedstock materials of both poly(L-lactide)/phosphate-based glass and poly(L-lactide-co-ε-caprolactone)/phosphate-based glass melt-compounded composites were separately prepared to the specified net loadings of 10, 20 or 40 wt% phosphate-glass respectively following the methods described earlier in Example 5.

[00134] Melt-compounded composite blends of the desired filler loading were prepared using a HAAKE PolyLab RheoDrive7 and Mixer OS600 system equipped with Banbury Rotors. Within each series (46:54 and 60:40 polymer blends) each composite blend of either 10, 20 or 40 wt% inorganic filler was prepared using feedstock of PLLA/phosphate glass and PL-CL(70:30)/phosphate composites pre-loaded with 10, 20 , 40 wt% of the filler respectively. The combined mass of composite feedstock for 10 wt%, 20 wt% and 40 wt% loadings were 50 g, 56.3 g and 75 g where in each case 45 g of the total mass would correspond to polymer. The proportions of the two feedstock composites were adjusted according to the specified weight ratio of PLLA to PL-CL(70:30). Materials were blended above the melting temperature of PLLA. The duration of the mixing process was defined to be sufficient to obtain a stable melt-temperature and torque.

[00135] Tensile test results obtained on dumbbell specimens prepared from the 46:54 composite blend materials are reported in Table 7.

[00136] Tensile test results obtained on dumbbell specimens prepared from the 60:40 composite blend materials are reported in Table 8.

<u>Using physical blend of poly(L-lactide) and poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol) copolymer</u>

Method 5

[00137] The following composite was prepared using a physical blend of poly(L-lactide) (PLLA) (PURAC® PURASORB™ PL 38) and poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol) (PL-CL(70:30)) (L:CL = 70:30; M_n(PEG) = 550 Da) (VORNIA Ltd.) copolymer as the

polymer matrix and a phosphate-glass with the composition (P_2O_5:CaO:Na_2O = 40:50:10) as the inorganic filler. The weight ratio of the two polymers was 60:40. Nominal loadings of filler were 40 wt% of phosphate-glass filler and 0.5 wt% of barium sulphate.

[00138] 18 g of poly(L-lactide) homopolymer was dissolved completely in 350 ml of chloroform in a 1000 ml beaker under magnetic stirring at ambient temperature. 121 g of milled suspension containing 10.4 wt% particles after sedimentation, prepared according to Method 2 in Example 2, was then added to the polymer solution under magnetic stirring. 3 g of barium sulphate suspension containing 3 wt% of particles after sedimentation was added to the polymer/phosphate glass suspension. An additional 350 ml of chloroform was added to aid in the dissolution of precipitated polymer. The blend of milled suspension and polymer solution was mixed until homogeneous in appearance and then cast into a HDPE tray and allowed to dry at ambient temperature to form a composite film. The film was then further dried in an oven overnight above the polymer glass-transition temperature to drive-off residual solvent.

[00139] 55 g of poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol) was dissolved completely in 450 ml of chloroform in a 1000 ml beaker under magnetic stirring at ambient temperature. 376.1 g of milled phosphate-glass suspension containing 9.8 wt% particles after sedimentation, prepared according to Method 2 in Example 2, was then added to the polymer solution under magnetic stirring. 6 g of barium sulphate suspension containing 4.6 wt% of particles after sedimentation was added to the blend of polymer and phosphate glass suspension. The blend of milled suspensions and polymer solution was mixed until homogeneous in appearance and then cast into a HDPE tray and allowed to dry at ambient temperature to form a composite film. The film was then further dried in an oven overnight above the polymer glass-transition temperature to drive-off residual solvent.

[00140] A melt-compounded composite blend of the desired filler loading was prepared using a HAAKE PolyLab RheoDrive7 and Mixer OS600 system equipped with Banbury Rotors. 30 g of the poly(L-lactide)/phosphate glass/barium sulphate composite film and 20 g of the poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol)/phosphate/barium sulphate composite film, each pre-loaded 40.5 wt% of the filler, were blended above the melting temperature of PLLA. The duration of the mixing process was defined to be sufficient to obtain a stable melt-temperature and torque.

[00141] Tensile test results obtained on dumbbell specimens prepared from the 60:40 composite blend materials are reported in Table 9.

Example 6 - Glass particle size analysis

[00142] Fig. 1 shows A comparison of the particle size distributions of fused phosphate glass (P_2O_5:CaO:Na_2O = 40:50:10) particulates in suspension after dry milling in a TEMA mill, followed by wet-milling using a Pulverisette 7 and, subsequently, after a period of sedimentation.

[00143] Fig. 2 shows the change in the particle size distribution of barium sulphate particles following successive milling trials.

Example 7 - Glass dissolution properties

[00144] Fig.3 shows the aqueous dissolution of various phosphate glass compositions showing release of (a) calcium, (b) phosphorous and (c) sodium ions.

Example 8 - SEM analysis of polymer-glass composites

[00145] Fig. 4 shows SEM images of the fracture surfaces of: (a) poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP), (b) poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) and (c) PLLA:PL-CL(70:30) blend composites containing 10 wt% of fused phosphate glass (PG11).

[00146] Fig. 5 (a) shows an SEM image of the fracture surface of the PL-CL(80:20)-PEG550 copolymer (VORNIA Ltd.) with 10 wt% of PG11 and 2 wt% of $BaSO_4$; (b) shows a SEM back-scattering image of the same fracture surface providing contrast between PG11 (grey) and $BaSO_4$ particles (white); (c) shows the X-ray spectrum of Particle A, a phosphate glass particulate; and (d) shows the X-ray spectrum of Particle B, a barium sulphate particulate.

Example 9 - Mechanical properties of polymer-glass composites

[00147] The mechanical properties of composite materials of the invention were recorded against those of the corresponding pure polymer (i.e without glass particles).

[00148] Table 2 below provides a summary of the mechanical properties of poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP) and poly(L-lactide) composites containing 5,10, 20 and 40 wt% fused phosphate glass (PG11).

Table 2 *- Mechanical properties of poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP) and poly(L-lactide) composites containing* 5,10, 20 and 40 wt% *fused phosphate glass (PG11)*

Material	Young's Modulus (MPa)	Tensile Strength (MPa)	Strain-at-break (%)
PLLA	1440 ± 60	54 ± 8	10 ± 2
PLLA + 5 wt% PG11	1460 ± 10	53 ± 5	5 ± 1
PLLA + 10 wt% PG11	1470 ± 50	48 ± 6	4 ± 1
PLLA + 20 wt% PG11	1440 ± 90	38 ± 4	2.8 ± 0.5
PLLA + 40 wt% PG11	1800 ± 100	33 ± 4	1.9 ± 0.1

[00149] The results in Table 2 show that there is a significant increase in the Young's Modulus of the poly(L-lactide) composite at 40 wt% loading of phosphate glass.

[00150] Table 3 below provides a summary of the mechanical properties of poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) and poly(L-lactide-co-ε-caprolactone) composites containing 5,10, 20 and 40 wt% fused phosphate glass (PG11).

Table 3 *- Mechanical properties of poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) and poly(L-lactide-co-ε-caprolactone) composites containing 5,10, 20 and 40 wt% fused phosphate glass (PG11).*

Material	Young's Modulus (MPa)	Max. Nominal Stress (MPa)	Strain-at-break (%)
PL-CL(70:30)	1.3 ± 0.2	5 ± 1[(a)]	> 350[(a)]
PL-CL(70:30)+ 5 wt% PG11	1.8 ± 0.1	8.2 ± 0.6[(a)]	
PL-CL(70:30) + 10 wt% PG11	2.0 ± 0.3	8 ± 2[(a)]	
PL-CL(70:30) + 20 wt% PG11	2.4 ± 0.2	17 ± 2[(a)]	
PL-CL(70:30)+ 40 wt% PG11	2.1 ± 0.1	17 ± 2[(a)]	

(a) Specimens slipped from the tensile grips before failure.

[00151] The results in Table 3 show that there is a significant increase in the Young's modulus and maximum nominal stress of the *poly(L-lactide-co-ε-caprolactone)* composite at 5 wt% loading of phosphate glass.

[00152] Table 4 below provides a summary of the mechanical properties of poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol) (PL-CL(80:20)-PEG550) (VORNIA Ltd.) and a poly(L-

lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol)composite containing 10 wt% fused phosphate glass (PG11) and 2 wt% barium sulphate.

Table 4 *- Mechanical properties of* poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol) (PL-CL(80:20)-PEG550) (VORNIA Ltd.) *and a poly(L-lactide-co-ε-caprolactone)-block-poly(ethylene glycol) composite containing 10 wt% fused phosphate glass (PG11) and 2 wt% barium sulphate.*

Material	Young's Modulus (MPa)	Tensile Strength (MPa)	Strain-at-break (%)
PL-CL(80:20)-PEG550	540 ± 20	14.4 ± 0.3	480 ± 30
PL-CL(80:20)-PEG550 + 10 wt% PG11 + 2wt % $BaSO_4$	541 ± 6	23.0 ± 0.8	570 ± 60

[00153] The results in Table 4 show that there is a significant increase in the tensile strength of the poly(L-lactide-co-ε-caprolactone)-block-poly(ethylene glycol) (PL-CL(80:20)-PEG550) (VORNIA Ltd.) composite at 10 wt% loading of phosphate glass and 2 wt% of barium sulphate. There is no significant reduction in strain-at-break. The polymer matrix is toughened by the addition of the phosphate glass particles.

[00154] Table 5 below provides a summary of the mechanical properties of poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP): poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) blend and a poly(L-lactide):poly(L-lactide-co-ε-caprolactone) composite blend containing 10 wt% fused phosphate glass (PG11).

Table 5 *- Mechanical properties of a poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP): poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) blend and a poly(L-lactide):poly(L-lactide-co-ε-caprolactone) composite blend containing 10 wt% fused phosphate glass (PG11).*

Material	Young's Modulus (MPa)	Tensile Strength (MPa)	Strain-at-break (%)
PLLA:PL-CL(70:30) blend	870 ± 50	37 ± 3	450 ± 80
PLLA:PL-CL(70:30) blend + 10wt% PG11	1000 ± 100	37 ± 1	510 ± 40

[00155] The results in Table 5 show that there is no significant reduction or increase in the Young's modulus, tensile strength or strain-at-break of the poly(L-lactide): *poly(L-lactide-co-ε-caprolactone)* composite at 10 wt% loading of phosphate glass.

[00156] Table 6 provides a summary of the mechanical properties of a series of poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP): poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) neat polymer blends.

Table 6 *- Mechanical properties of poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP): poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) neat polymer blends.*

Material (weight ratio)	**Young's Modulus (MPa)**	**Tensile Strength (MPa)**	**Strain-at-break (%)**	**% Reduction in Dynamic Storage Modulus at 37 °C**
PLLA:PL-CL(70:30) (46:54)	870 ± 50	37 ± 3	450 ± 80	41 ± 2
PLLA:PL-CL(70:30) (60:40)	1000 ± 50	50 ± 3	350 ± 30	21 ± 1
PLLA:PL-CL(70:30) (70:30)	1110 ± 20	60.8 ± 0.3	8 ± 1	13 ± 1
PLLA:PL-CL(70:30) (80:20)	1120 ± 20	62 ± 2	7 ± 1	4 ± 1

[00157] The results in Table 6 show that 46:54 and 60:40 blends are significantly toughened at ambient temperature with high modulus, strength and strain-at-break. Reduction in dynamic modulus at 37 C decreases as the weight percentage of the elastomeric poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) decreases. The optimal blend is 60:40 weight ratio of the two polymers. Importantly, as shown below in Table 10 the blends comprise two distinct phases within their morphology: (i) a low glass-transition temperature phase associated with poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) and (ii) a high glass-transition temperature phase associated with poly(L-lactide). Due to this difference in glass-transition temperature, as noted in Tables 2 and 3, these two polymers have intrinsically different mechanical behaviours from ambient temperatures (approx. 20 °C) through to 37 °C. Toughening of the blend is consistent with the established means of "rubber-toughened polymers".

[00158] Table 7 provides a summary of the mechanical properties of composites formed from poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP): poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) (46:54) composite blends and containing 10, 20 and 40 wt% fused phosphate glass (PG11).

Table 7 *- Mechanical properties of poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP): poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) (46:54) composite blends containing fused phosphate glass (PG11)*

Material	Young's Modulus (MPa)	Tensile Strength (MPa)	Strain-at-break (%)	% Reduction in Dynamic Storage Modulus at 37 °C
PLLA:PL-CL(70:30) (46:54)[(b)] + 10 wt% PG11	1100 ± 100	40 ± 2	4.9 ± 0.3	92 ± 5
PLLA:PL-CL(70:30) (46:54)[(b)] + 20 wt% PG11	920 ± 30	36 ± 2	4.4 ± 0.6	90 ± 9
PLLA:PL-CL(70:30) (46:54)[(b)] + 40 wt% PG11	1300 ± 110	30 ± 1	2.5 ± 0.1	85 ± 2

(b) Only one glass-transition temperature was observed in DSC analysis between 34 ± 2 °C corresponding to a single amorphous phase.

[00159] The results in Table 7 show that the Young's modulus of the 46:64 composite blend is significantly reinforced at 40 wt% loading of phosphate glass. Reduction in dynamic modulus at 37 C is greater than the neat blend shown in Table 6. A single-glass transition temperature was measured by differential scanning calorimetry indicating a single phase morphology and that the two polymers had been blended intimately via the two stage process described earlier in Method 4. The lower strain-at-break values at ambient temperature are likely due to a combination of defects caused by the concentration of filler particles and the testing of specimens below the single glass-transition temperature resulting in embrittlement. Table 8 provides a summary of the mechanical properties of composites formed from poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP): poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) composite blends (60:40) and containing 10, 20 and 40 wt% fused phosphate glass (PG11).

Table 8 *- Mechanical properties of poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP): poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) (60:40) composite blends containing fused phosphate glass (PG11)*

Material	Young's Modulus (MPa)	Tensile Strength (MPa)	Strain-at-break (%)	% Reduction in Dynamic Storage Modulus at 37 °C
PLLA:PL-CL(70:30) (60:40)[(c)] + 10 wt% PG11	1100 ± 100	34 ± 2	3.3 ± 0.4	64 ± 4
PLLA:PL-CL(70:30) (60:40)[(c)] + 20 wt% PG11	1100 ± 200	31 ± 2	2.6 ± 0.4	60 ± 20
PLLA:PL-CL(70:30) (60:40)[(c)] + 40 wt% PG11	1500 ± 50	30 ± 6	2.0 ± 0.5	57 ± 4

(c) Only one glass-transition temperature was observed in DSC analysis between 44 ± 2 °C corresponding to a single amorphous phase.

[00160] The results in Table 8 show that the Young's modulus of the 60:40 composite blend is significantly reinforced at 40 wt% loading of phosphate glass. Reduction in dynamic modulus at 37 C is, however, significantly reduced compared to the neat blend shown in Table 6. Again, a single-glass transition temperature was measured by differential scanning calorimetry indicating a single phase morphology and that the two polymers had been blended intimately via the two stage process described earlier in Method 4. The low strain-at-break values at ambient temperature are likely due to a combination of defects caused by the concentration of filler particles and the testing of specimens below the single glass-transition temperature resulting in embrittlement.

[00161] Table 9 provides a summary of the mechanical properties of a composite formed from poly(L-lactide) (PLLA) (PURAC® PURASORB™ PL38): poly(L-lactide-co-ε-caprolactone)-block-poly(ethylene glycol) (PL-CL(70:30)-PEG550) (VORNIA Ltd.) (60:40) composite blends containing 40 wt% fused phosphate glass (PG11) and barium sulphate.

Table 9 *- Mechanical properties of poly(L-lactide) (PLLA) (PURAC® PURASORB™ PL38): poly(L-lactide-co-ε-caprolactone)-block-poly(ethylene glycol) (PL-CL(70:30)-PEG550) (VORNIA Ltd.) (60:40) composite blends containing fused phosphate glass (PG11) and barium sulphate*

Material	Young's Modulus (MPa)	Tensile Strength (MPa)	Strain-at-break (%)	% Reduction in Dynamic Storage Modulus at 37 °C
PLLA:PL-CL(70:30)-PEG550 (60:40)[d] + 40 wt% PG11 + 0.5 wt% $BaSO_4$	1270 ± 50	25 ± 2	2.1 ± 0.1	33 ± 3

(d) Two glass-transition temperatures were observed in DSC analysis at 21 ± 7 °C and 51 ± 1 °C corresponding to two distinct amorphous phases.

[00162] The results in Table 9 show that the Young's modulus of the 60:40 composite blend is significantly reinforced at 40 wt% loading of phosphate glass. Reduction in dynamic modulus at 37 C was 33% and comparable to the similar (but not identical) blend reported in Table 6. A two-phase morphology was found by differential scanning calorimetry characterised by two distinct glass-transition temperatures. The low strain-at-break at ambient temperature is likely due to defects caused by the high-concentration of filler particles at 40 wt% loading.

Example 10 - Thermo-gravimetric analysis studies

[00163] Differential scanning calorimetry and thermo-gravimetric analysis were performed on various of poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP): poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) neat polymer blends. The results are presented in Table 10 below:

Table 10 *- Thermal properties of poly(L-lactide) (PLLA) (NatureWorks® Ingeo™ 2500HP): poly(L-lactide-co-ε-caprolactone) (PL-CL(70:30)) (PURAC® PURASORB™ PLC 7015) neat polymer blends.*

Material (weight ratio)	Thermal Transition Temperatures				
	T_{g1} (°C)	T_{g2} (°C)	T_c (°C)	T_m (°C)	T_{deg} (°C)
PLLA:PL-CL(70:30) (46:54)	25 ± 1	55.1 ± 0.4	111 ± 1	175 ± 1	364 ± 4
PLLA:PL-CL(70:30) (60:40)	24 ± 2	55 ± 2	107 ± 2	174 ± 1	365 ± 4
PLLA:PL-CL(70:30) (70:30)	24 ± 1	56 ± 1	105 ± 1	174 ± 1	363 ± 2
PLLA:PL-CL(70 :30) (80:20)	27 ± 5	54 ± 2	100 ± 1	174 ± 2	366 ± 2

[00164] The total weight loadings of inorganic filler within composite materials of the invention were measured by thermo-gravimetric analysis.

[00165] Tables 11a and 11b below provide a summary of the residual mass of material measured by TGA on heating composite specimens to 800 °C.

Table 11a *- Residual mass of material measured by TGA on heating composite specimens to 800 °C.*

Material	Residual Mass %
PLLA (NatureWorks® Ingeo™ 2500HP) + 10 wt% PG11	9 ± 2
PL-CL(70:30) (PURAC® PURASORB™ PLC 7015) + 10 wt% PG11	9.0 ± 0.9
PLLA:PL-CL(70:30) + 10 wt% PG11	6 ± 4
PL-CL(80:20)-PEG550 + 10 wt% PG11 + 2wt % $BaSO_4$	12.1 ± 0.3

Table 11b *- Residual mass of material measured by TGA on heating composite specimens to 800 °C.*

Polymer	Nominal PG11 Content (wt%)	Nominal $BaSO_4$ Content (wt%)	Residual Mass (%)
PLLA (NatureWorks® Ingeo™ 2500HP)	10	0	10 ± 2
	20	0	20.30 ± 0.02
	40	0	39.3 ± 0.3
PL-CL(70:30) (PURAC® PURASORB™ PLC 7015)	10	0	9.1 ± 0.7
	20	0	19.3 ± 0.2
	40	0	36.5 ± 0.5
PLLA:PL-CL(70 :30) (46:54)	10	0	6 ± 4
	10	0.5	9.5 ± 0.2
	20	0.5	19.4 ± 0.3
	40	0.5	
	70	0	68.0 ± 0.1
PLLA:PL-CL(70:30) (60:40)	10	0.5	10.1 ± 0.4
	20	0.5	19.50 ± 0.01
	40	0.5	38.7 ± 0.2
PLLA (PURAC® PURASORB™ PL 38): PL-CL(70:30)-PEG550 (60:40)	40	0.5	39.0 ± 0.5
PCL-PEG550	40	0.5	36.7 ± 0.1
PL-CL(80:20)-PEG550	10	2	12.1 ± 0.3

[00166] The results presented in Tables 11a and 11 b demonstrate that the methods of composite preparation described in Example 5 provide a good correlation between nominal and measured wt% loadings of inorganic filler.

Example 11 - Toxicity studies

[00167] The toxicity properties of various composites and neat polymers were assessed based on DIN EN ISO 10993-5. Cell line L929 was used as recommended by the ISO standard. A direct assay format was used where cells were placed in direct contact with the material. Cells were seeded onto material discs (in quadruplicate) and incubated for 24h. After the incubation the supernatant (containing dead and non-adhered cells) was used to measure the amount of dead cells as a measure of material toxicity. The adherent cells were then subjected to a cell viability assay to measure the amount of adherent healthy cells. Last the cells were used to measure an indicator of apoptosis.

[00168] Cell viability was measured using the CellTiter-Blue® Cell Viability Assay (Promega). This assay measures metabolic activity via intracellular conversion of resazurin to the fluorescent resorufin. In this way cells with an intact metabolism are seen as healthy (viable). Ideal cell growth on tissue culture-treated polystyrene was used a positive control..

[00169] Toxicity was measured via the CytoTox-ONE™ Homogeneous Membrane Integrity Assay (Promega). This assay measures the number of cells with a damaged cell membrane by measuring the amount of leaked enzyme (Lactate dehydrogenase). Complete lysis of cells directly prior to the assay was used as a positive control.

[00170] Apoptosis, a process of programmed cell death, is measured using the Apo-ONE® Homogeneous Caspase-3/7 Assay (Promega). The assay detects caspase-3 and caspase-7 activity which are key effectors of apoptosis. Apoptosis induction using 100 mM Staurosporine was used as positive control.

[00171] The results are presented in Table 12 below:

Table 12 *– Results of multiplex cell assays using line L929 results for cell viability, cytotoxicity and apoptosis*

Material	Viability (% of TCPS control)	Cytotoxicity (% of lysis control)	Apoptosis (% of apoptosis control)
PLLA (PURAC® PURASORB™ PL 38)	84 ± 5	1.7 ± 0.1	1.1 ± 0.3
PLLA-PEG550	72 ± 5	1.8 ± 0.2	1.2 ± 0.8
PCL-PEG550	85 ± 7	2.1 ± 0.1	10 ± 4
PL-CL(80:20)-PEG550	99 ± 3	1.5 ± 0.5	1.9 ± 0.8
PL-CL(70:30)-PEG550	92 ± 8	2 ± 1	1.4 ± 0.2
PCL-PEG550 + 40 wt% + 0.5 wt% PG11	80 ± 10	1.0 ± 0.4	10 ± 4
PL-CL(80:20)-PEG550 + 10 wt% PG11 + 0.5 wt%	85 ± 8	2 ± 1	4 ± 2
PLLA (PL38):PL-CL(70:30)-PEG550 + 40 wt% PG11 + 0.5 wt%	71 ± 4	0.2 ± 0.1	10 ± 4

[00172] The results show that cell viability is good with values > 70 % measured relative to the control for all formulations. Low values of cytotoxicity are also observed < 2% of the control. Apoptosis varies with material formulation. Those with lowest apoptotic induction (<2%) were poly(L-lactide), poly(L-lactide)-*block*-poly(ethylene glycol) and poly(L-lactide-co-ε-caprolactone). PCL-PEG550 had a value at 10%. The addition of phosphate glass filler may also increases the extent of apoptosis as seen for the composite examples above.

[00173] In addition, haemolysis was evaluated according to DIN EN ISO 10993-4. Fresh human blood (heparinated to prevent coagulation) was diluted in 0.9% NaCl and incubated on top of the materials for 1 hr at 37°C with mechanical agitation. Then the cells were removed by centrifugation and the absorbance of haemoglobin measured. If red blood cells were to rupture during incubation haemoglobin would be released. Polystyrene (empty well of the well plate) was used as negative control. For the positive control cells were lysed using pure water as diluent instead of the physiologic salt solution.

[00174] The results are presented in Table 13 below:

Table 13 *– Results of haemolysis assays using heparinated human blood.*

Material	Haemolysis (% of lysis control)
PLLA-PEG550	0.0 ± 0.2
PCL-PEG550	0.3 ± 0.2
PL-CL(80:20)-PEG550	0.6 ± 0.2
PL-CL(70:30)-PEG550	0.0 ± 0.3
PCL-PEG550 + 40 wt% + 0.5 wt% PG11	0.2 ± 0.2
PL-CL(80:20)-PEG550 + 10 wt% PG11 + 0.5 wt%	1.6 ± 0.2
PLLA (PL38): PL-CL(70:30)-PEG550 + 40 wt% PG11 + 0.5 wt%	1.9 ± 0.1

[00175] All materials can be considered not to induce haemolysis with values < 2% relative to the control.

[00176] While specific embodiments of the invention have been described herein for the purpose of reference and illustration, various modifications will be apparent to a person skilled in the art without departing from the scope of the invention as defined by the appended claims.

[00177] The work leading to this invention has received funding from the European Union Seventh Framework Programme (*FP7/2007-2013*) under *grant agreement* n°604251.

CLAIMS

1. A biocompatible composite material comprising
   a) a polymeric matrix comprising at least one biocompatible polymer; and
   b) greater than 0 but less than or equal to 70 wt% of particles of a biocompatible glassy material dispersed in the polymeric matrix, wherein the glassy material comprises 30–60 mol% of P_2O_5.

2. The biocompatible composite material of claim 1, wherein the composite material is biodegradable, bioresorbable and/or bioactive.

3. The biocompatible composite material of claim 1 or 2, wherein the glassy material comprises at least one Group II metal oxide.

4. The biocompatible composite material of claim 3, wherein the at least one Group II metal oxide is selected from CaO, MgO, SrO, BaO or combinations thereof.

5. The biocompatible composite material of claim 3 or 4, wherein the at least one Group II metal oxide is a single Group II metal oxide.

6. The biocompatible composite material of any of claims 3, 4 or 5, wherein the at least one Group II metal oxide is a single Group II metal oxide being CaO.

7. The biocompatible composite material of any of claims 3 to 6, wherein the glassy material comprises 30–60 mol% of at least one Group II metal oxide.

8. The biocompatible composite material of any of claims 3 to 7, wherein the glassy material comprises 35–55 mol% of at least one Group II metal oxide.

9. The biocompatible composite material of any preceding claim, wherein the glassy material comprises at least one Group I metal oxide.

10. The biocompatible composite material of claim 9, wherein the at least one Group I metal oxide is selected from Na_2O, K_2O or combinations thereof.

11. The biocompatible composite material of claim 9 or 10, wherein the at least one Group I metal oxide is a single Group I metal oxide.

12. The biocompatible composite material of any of claims 9, 10 or 11, wherein the at least one Group I metal oxide is a single Group I metal oxide being Na_2O.

13. The biocompatible composite material of any of claims 9 to 12, wherein the glassy material comprises 0.1–15 mol% of at least one Group I metal oxide.

14. The biocompatible composite material of any of claims 9 to 13, wherein the glassy material comprises 5–12 mol% of at least one Group I metal oxide.

15. The biocompatible composite material of any preceding claim, wherein the glassy material comprises 35–50 mol% of P_2O_5.

16. The biocompatible composite material of any preceding claim, wherein the polymeric matrix comprises 3–40 wt% of particles of the biocompatible glassy material.

17. The biocompatible composite material of any preceding claim, wherein the polymeric matrix comprises 3–18 wt% of particles of the biocompatible glassy material

18. The biocompatible composite material of any preceding claim, wherein the at least one biocompatible polymer is selected from the list consisting of poly(lactide), poly(caprolactone), poly(glycolide), poly(trimethylene carbonate), poly(dioxanone) and poly(ethylene glycol), or a mixture of two or more thereof.

19. The biocompatible composite material of any preceding claim, wherein the polymeric matrix comprises:
    i. a homopolymer of a biocompatible polymer;
    ii. a copolymer of two or more biocompatible polymers; or
    iii. a blend of two or more biocompatible polymers selected from a homopolymer or a copolymer.

20. The biocompatible composite material of any preceding claim, wherein the polymeric matrix is formed from one or more polymers selected from poly(L-lactide) homopolymer, poly(L-lactide-co-ε-caprolactone), poly(caprolactone), poly(lactide)-*block*-poly(ethylene glycol) poly(ε-caprolactone)-*block*-poly(ethylene glycol) and poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol).

21. The biocompatible composite material of any preceding claim, wherein the at least one biocompatible polymer is selected from poly(L-lactide) (PLLA), poly(L-lactide-co-ε-

caprolactone), poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol), or a physical blend of two or more of these polymers.

22. The biocompatible composite material of any preceding claim, wherein the at least one biocompatible polymer is a physical blend of poly(L-lactide) and at least one other polymer, wherein the at least one other polymer has a glass transition temperature that is lower than 37°C, and wherein the physical blend is phase-separated.

23. The biocompatible composite material of any preceding claim, wherein the at least one biocompatible polymer is a physical blend of

a) poly(L-lactide) and poly(L-lactide-co-ε-caprolactone, or

b) poly(L-lactide) and poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol), wherein the quantity of L-lactide monomeric units within the poly(L-lactide-co-ε-caprolactone) copolymer (or the poly(L-lactide-co-ε-caprolactone) copolymeric block) ranges from 60-90 mol% and the quantity of ε -caprolactone monomeric units within the poly(L-lactide-co-ε-caprolactone) copolymer (or the poly(L-lactide-co-ε-caprolactone) copolymeric block) ranges from 10-40 mol%.

24. The biocompatible composite material of any preceding claim, wherein the at least one biocompatible polymer is a physical blend of

a) poly(L-lactide) and poly(L-lactide-co-ε-caprolactone),

b) poly(L-lactide) and poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol) wherein the weight ratio of poly(L-lactide) to poly(L-lactide-co-ε-caprolactone) or poly(L-lactide-co-ε-caprolactone)-*block*-poly(ethylene glycol) in the blend ranges from 40–65:35–60.

25. The biocompatible composite material of any preceding claim, wherein the composite material comprises one or more additional agents selected from a radio-opaque agent and/or an antibacterial agent.

26. The biocompatible composite material of any preceding claim, wherein the particles of the biocompatible glassy material are substantially non-porous.

27. The biocompatible composite material of any preceding claim, wherein the particles of the biocompatible glassy material have a BET surface area of 0.5–10 m^2/g.

28. The biocompatible composite material of any preceding claim, wherein the particles of the biocompatible glassy material have an average particle size of less than 1 μm.

29. The biocompatible composite material of any preceding claim, wherein the glass material comprises:
    i. 37–42 mol% of P_2O_5,
    ii. 46–52 mol% of CaO, and
    iii. 7–12 mol% of Na_2O.

30. An implantable medical device comprising the biocompatible composite material of any preceding claim.

31. The implantable medical device of claim 30, wherein the device is biodegradable, bioresorbable and/or osteoconductive.

32. The implantable medical device of claim 30 or 31, wherein the device is selected from stents, catheters, pins, rods, screws, plates, surgical staples, and suture.

33. The implantable medical device of any of claims 30, 31 or 32, wherein the device is a stent.

34. A process for the preparation of a biocompatible composite material as claimed in any preceding claim, the process comprising the steps of:
    a) preparing particles of the biocompatible glassy material by:
        i. mixing together quantities of glassy material raw ingredients,
        ii. heating the glassy material raw ingredients to a molten state to provide a homogeneous melt,
        iii. quenching the molten material, and
        iv. milling the resulting quenched glassy material; and
    b) dispersing greater than 0 but less than or equal to 70 wt% of the particles within a polymeric matrix as defined in any preceding claim.

35. The process of claim 34, wherein the glassy material raw ingredients are heated to a temperature greater than 1150 °C.

36. The process of claim 34 or 35, wherein the glassy material raw ingredients are heated to a temperature of 1150–1400 °C.

37. The process of any of claims 34 to 36, wherein the molten material is quenched in water.

38. The process of any of claims 34 to 37, wherein the quenched glassy material is dry milled, and optionally thereafter wet milled.

39. The process of any of claims 34 to 38, wherein step b) comprises the steps of:
    i. providing a solution comprising a first biocompatible polymer dissolved in a solvent,
    ii. mixing the solution with the particles to obtain a polymer-particles suspension,
    iii. drying the polymer-particles suspension; and optionally
    iv. blending a quantity of the material resulting from step iii) with a second biocompatible polymer at a temperature higher than the melting temperature of the first and second biocompatible polymer.

40. The process of claim 39, wherein the first and second biocompatible polymers are the same.

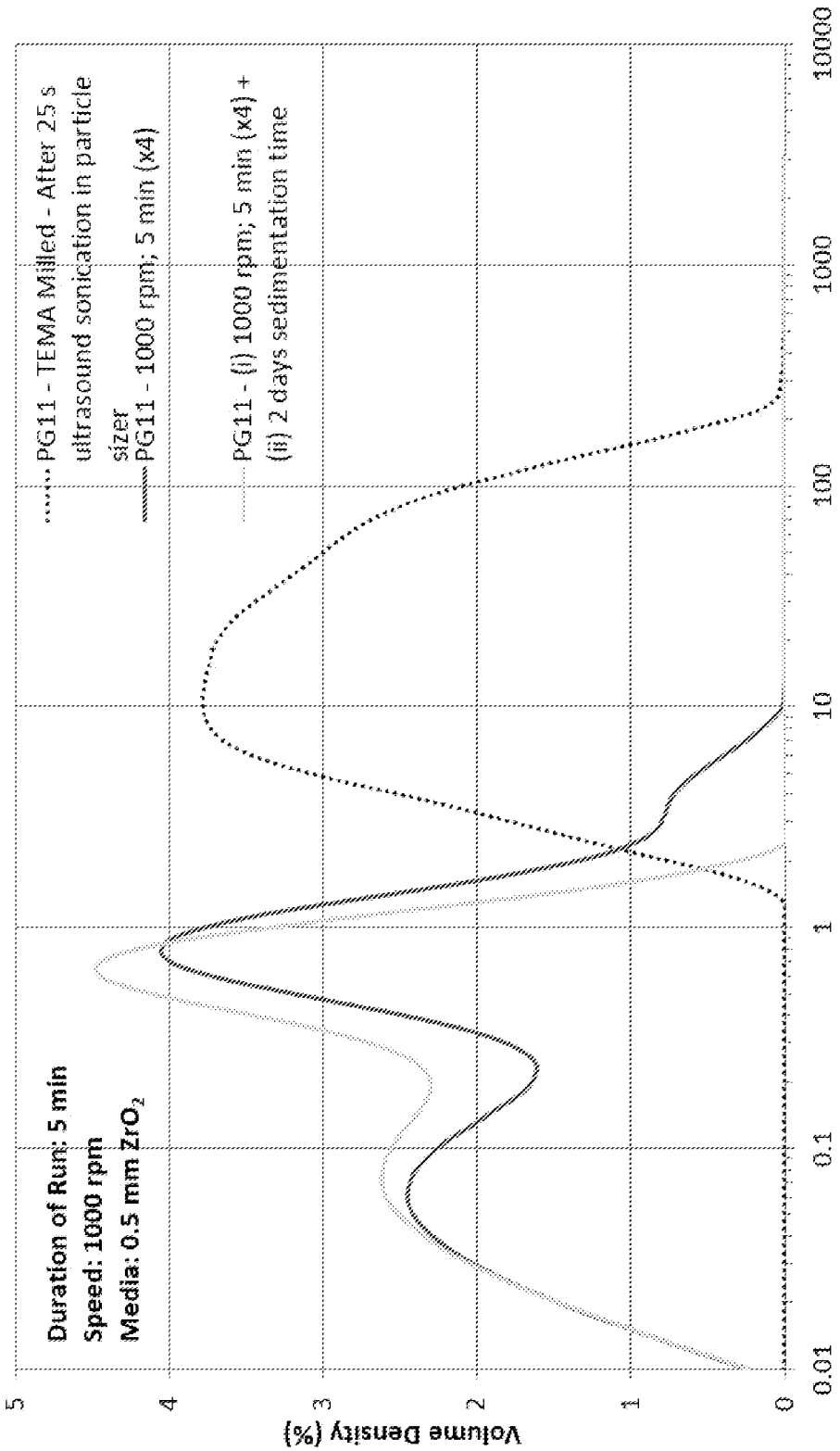
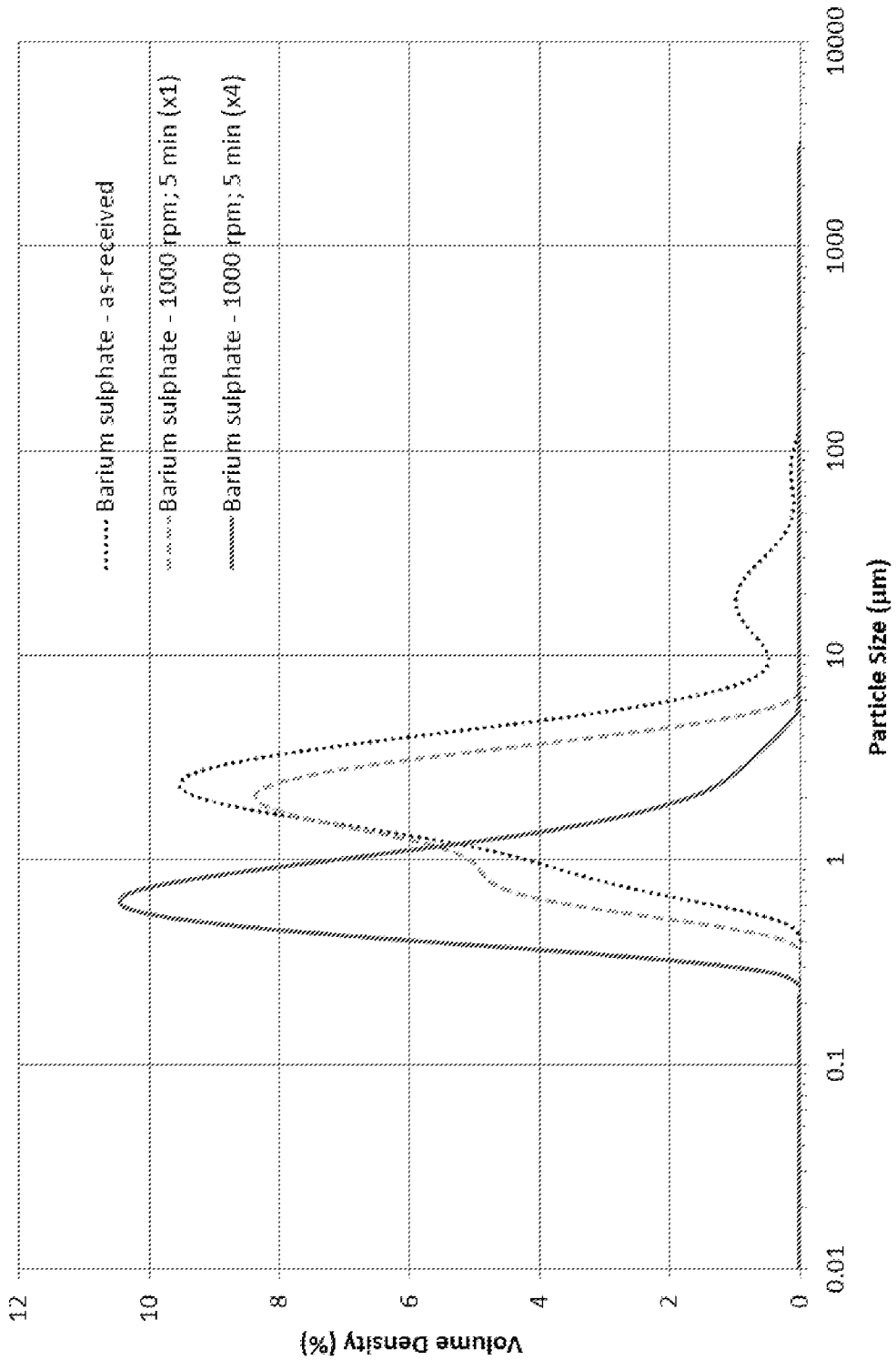

PG11 - TEMA Milled - After 25 s ultrasound sonication in particle sizer
PG11 - 1000 rpm; 5 min (x4)
PG11 - (i) 1000 rpm; 5 min (x4) + (ii) 2 days sedimentation time
Duration of Run: 5 min
Speed: 1000 rpm
Media: 0.5 mm ZrO2
Volume Density (%)
Particle Size (µm)
0
1
2
3
4
5
0.01
0.1
1
10
100
1000
10000

Fig. 1


Barium sulphate - as-received
Barium sulphate - 1000 rpm; 5 min (x1)
Barium sulphate - 1000 rpm; 5 min (x4)
Volume Density (%)
Particle Size (µm)
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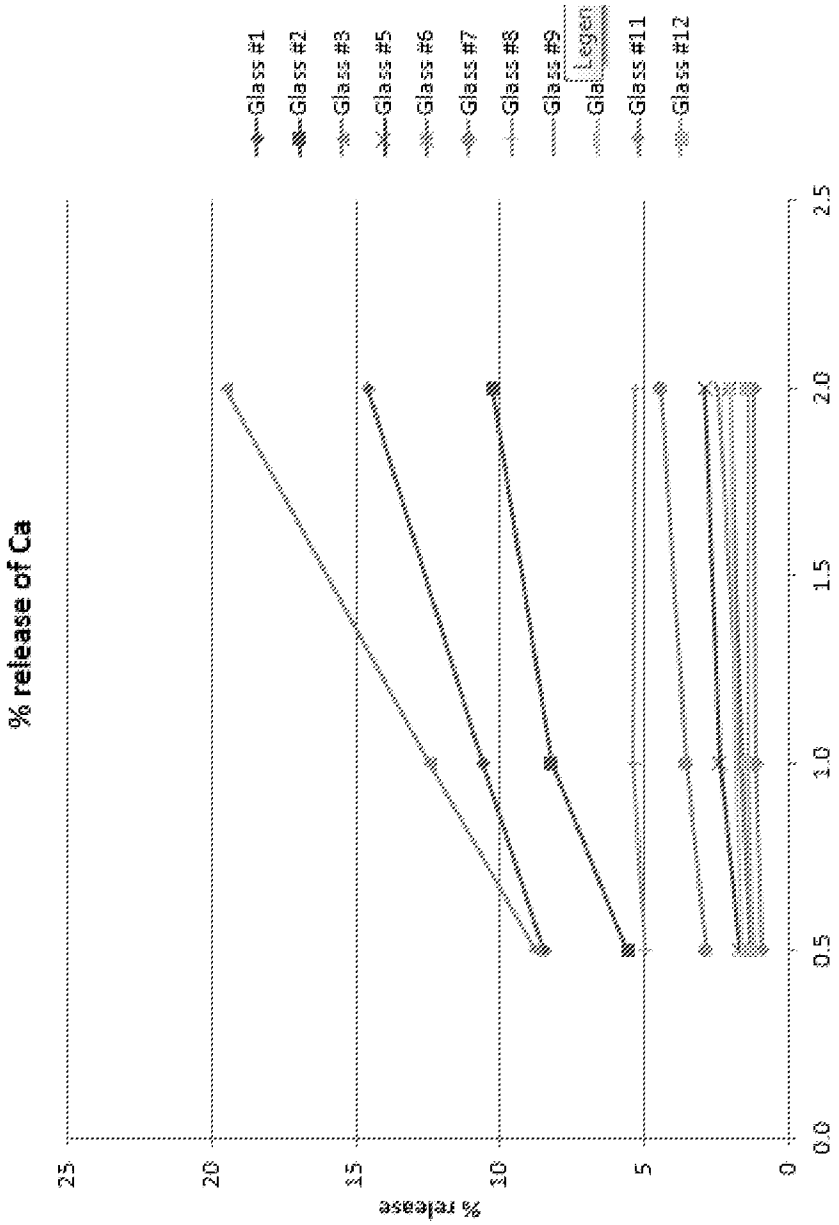
2
4
6
8
10
12
0.01
0.1
1
10
100
1000
10000

Fig. 2


% release of Ca
% release
Time (h)
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5
10
15
20
25
0.0
0.5
1.0
1.5
2.0
2.5
Glass #1
Glass #2
Glass #3
Glass #5
Glass #6
Glass #7
Glass #8
Glass #9
Glass #11
Glass #12
Legen

Fig. 3(a)

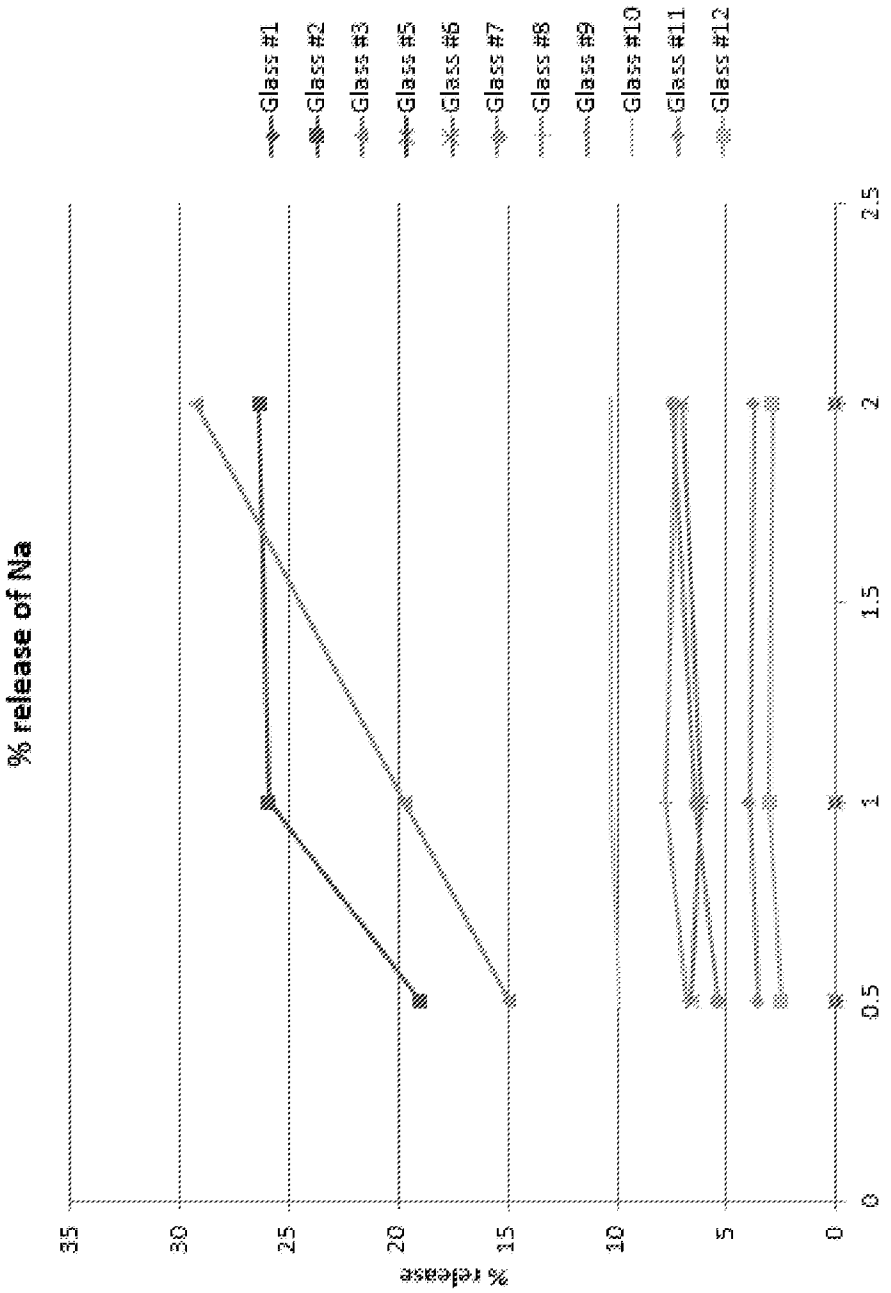

% release of Na
% release
Time (h)
Glass #1
Glass #2
Glass #3
Glass #5
Glass #6
Glass #7
Glass #8
Glass #9
Glass #10
Glass #11
Glass #12
0
5
10
15
20
25
30
35
0
0.5
1
1.5
2
2.5

Fig. 3(b)

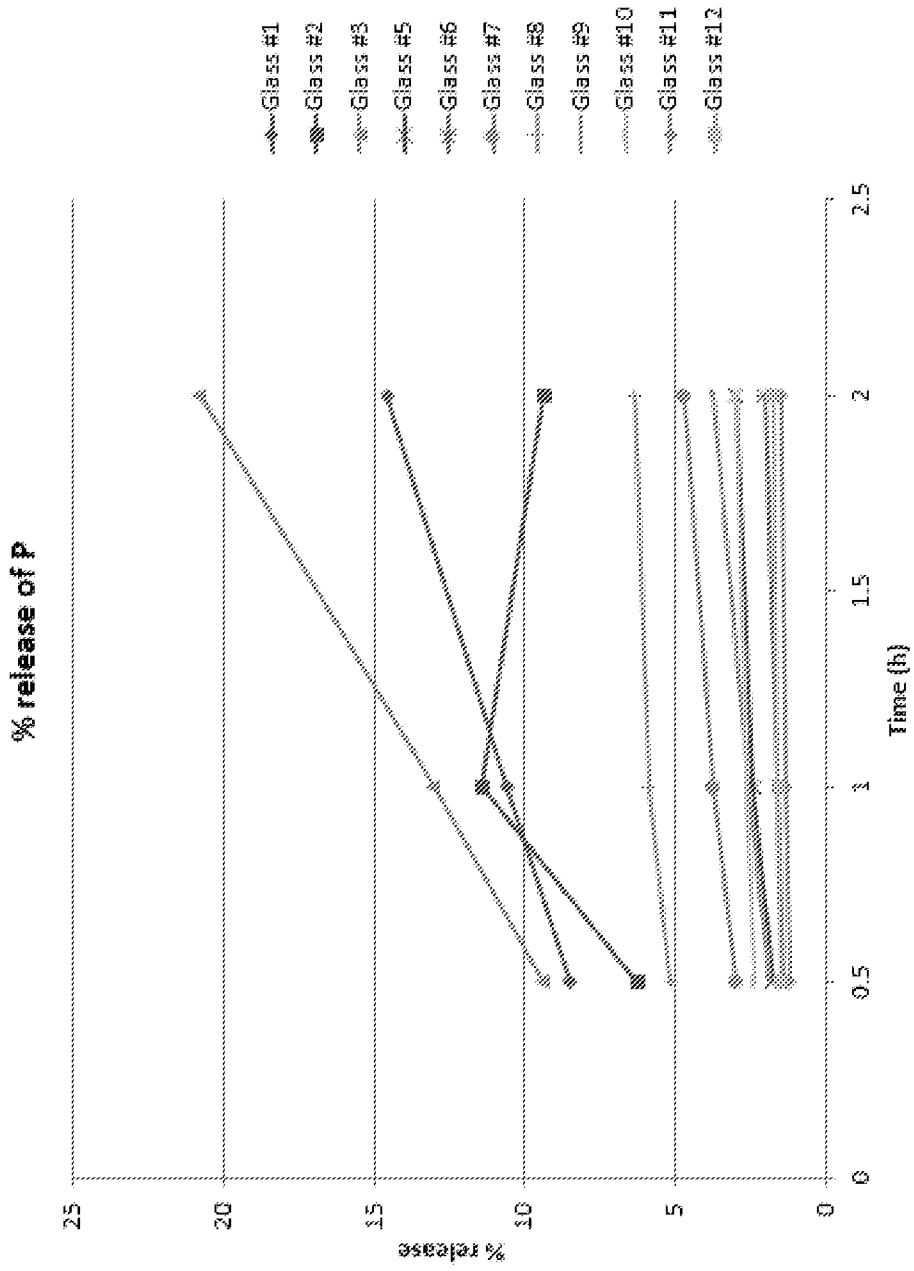
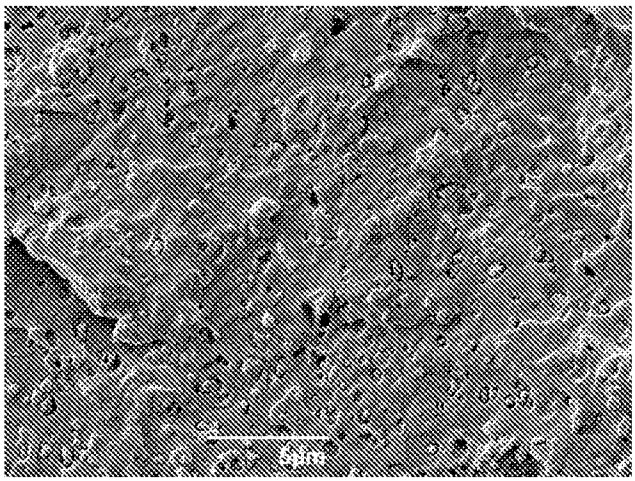
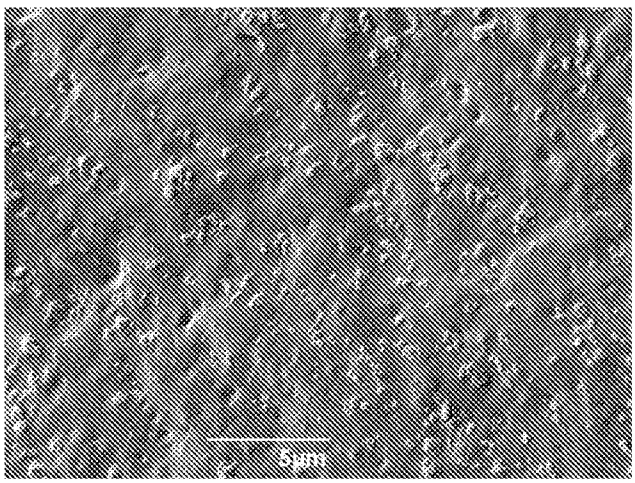

% release of P
% release
Time (h)
Glass #1
Glass #2
Glass #3
Glass #5
Glass #6
Glass #7
Glass #8
Glass #9
Glass #10
Glass #11
Glass #12
0
5
10
15
20
25
0
0.5
1
1.5
2
2.5

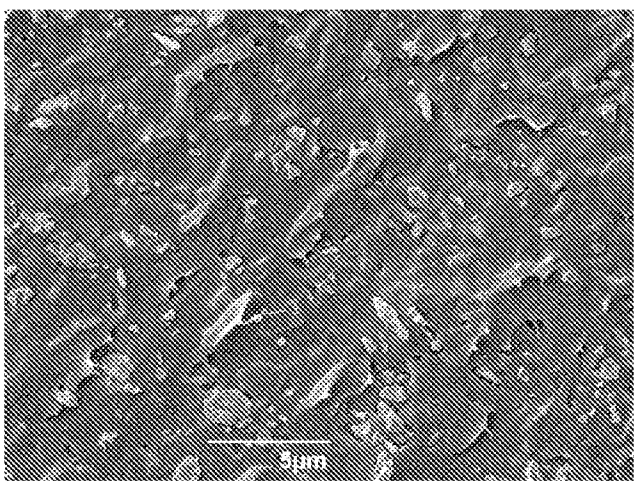
Fig. 3(c)



(a)

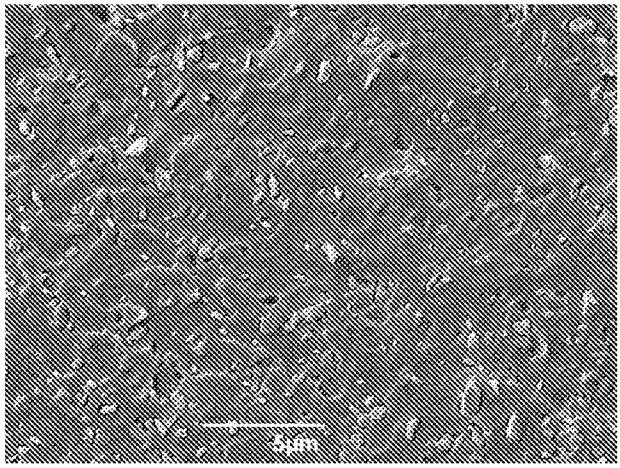


(b)

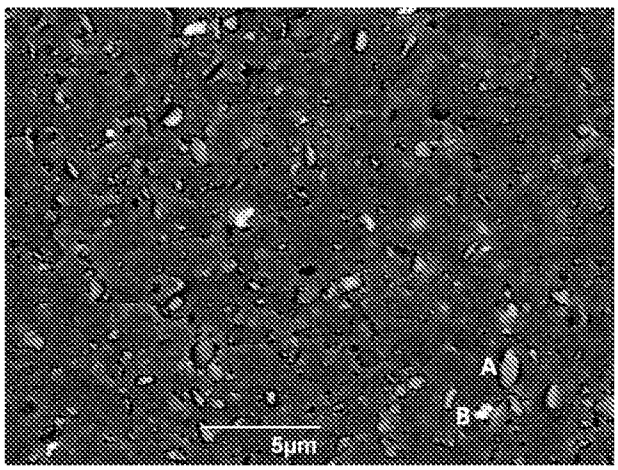


(c)

Figure 4

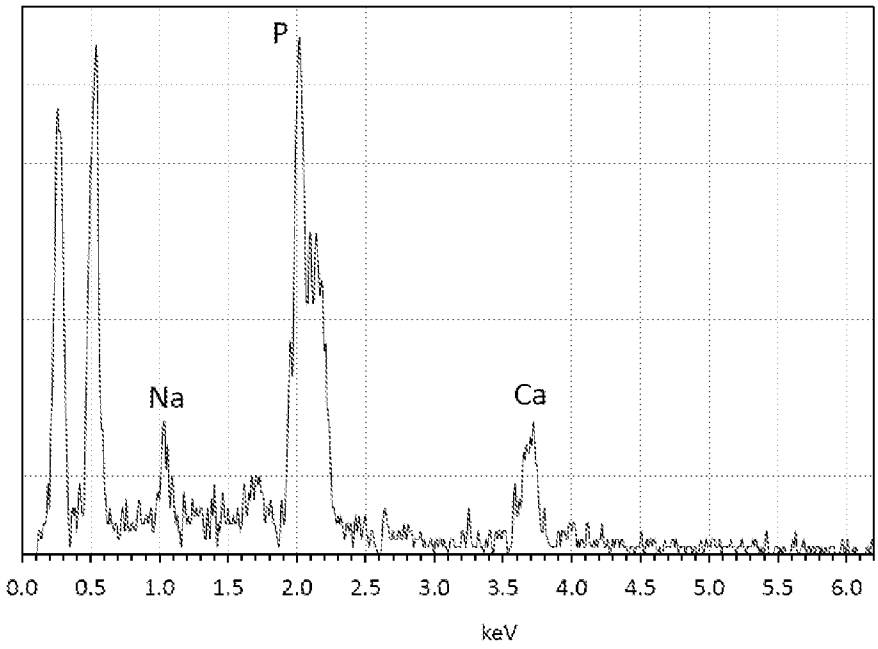


(a)

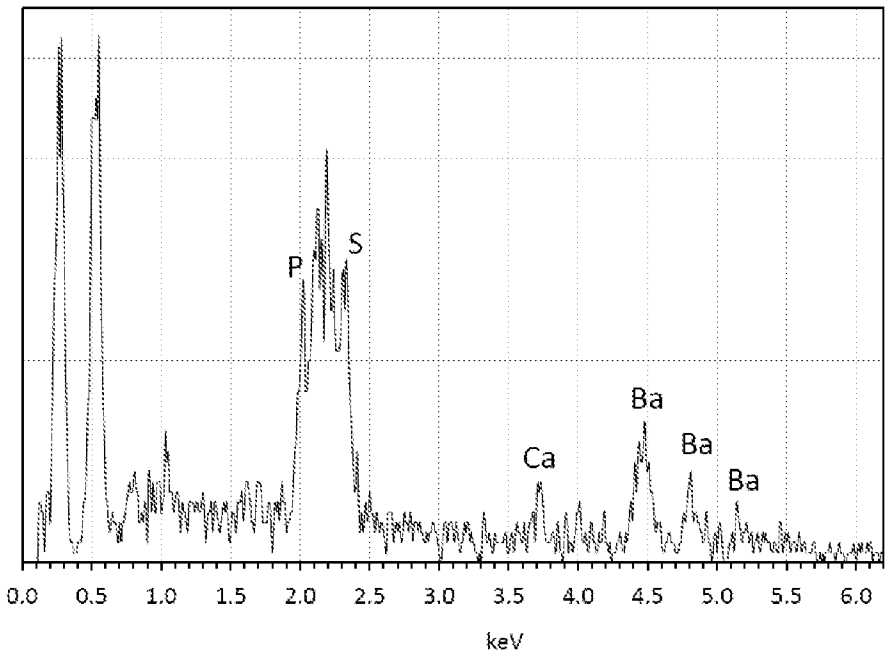


(b)

Fig. 5


P
Na
Ca
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
keV

(c)


P
S
Ca
Ba
Ba
Ba
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
keV

(d)

Fig. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2016/052248

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L27/46 A61L31/12
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015/018878 A1 (RIZK SAID [US] ET AL) 15 January 2015 (2015-01-15) paragraphs [0002], [0037], [0039], [0063] -----	1-40
A	DATABASE WPI Thomson Scientific, London, GB; AN 2012-F46850 XP055305933, & CN 102 430 149 A (UNIV EAST CHINA SCI&TECHNOLOGY) 2 May 2012 (2012-05-02) abstract -----	1-40
A	US 8 425 591 B1 (WANG YUNBING [US] ET AL) 23 April 2013 (2013-04-23) column 2, lines 40-41 column 6, lines 12-24 -----	33

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 2016	04/10/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Siebum, Bastiaan

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2016/052248

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2015018878 A1	15-01-2015	CA 2917427 A1	15-01-2015
		EP 3019209 A1	18-05-2016
		US 2015018878 A1	15-01-2015
		WO 2015006596 A1	15-01-2015
CN 102430149 A	02-05-2012	NONE	
US 8425591 B1	23-04-2013	US 8425591 B1	23-04-2013
		US 2013253637 A1	26-09-2013