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(71) Applicant (for all designated States except US): **ORTHOGEM LIMITED** [GB/GB]; 3 Crowborough Ave, Wollaton, Nottingham NG8 2RN (GB).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **LO, Wei, Jen** [GB/GB]; 3 Crowborough Avenue, Wollaton, Nottingham NG8 2RN (GB).

(74) Agents: **ELSY, David** et al.; Withers & Rogers LLP, Golding House, 2 Hays Lane, London SE1 2HW (GB).

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(54) Title: BONE CEMENT

(57) Abstract: The invention relates to a bone substitute comprising a mixture of a bone cement and a ceramic material granules, the granules having a plurality of interconnecting micropores. Preferably two or more different sizes of granules are used. The bone substitute makes it suitable for use in the repair of bones and for use in, for example, orthopaedic surgery, including vertebrae repair, musculo skeletal reconstruction, fracture repair, hip and knee reconstruction, osseous augmentation procedures and oral/maxillofacial surgery.



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Bone Cement

The invention relates to a bone substitute comprising a mixture of a bone cement and a ceramic material granules, the granules having a plurality of interconnecting micropores. Preferably two or more different sizes of granules are used. The bone substitute makes it suitable for use in the repair of bones and for use in, for example, orthopaedic surgery, including vertebrae repair, musculo skeletal reconstruction, fracture repair, hip and knee reconstruction, osseous augmentation procedures and oral/maxillofacial surgery.

Bone cements for repairing bone and, for example, joining bones or attaching prosthetics to bone are well known in the art. Use of bone cement is a standard feature of the orthopaedic surgeon's repertoire.

Many different types of bone cement are known in the art. These include both organic polymers, such as polymethylmethacrylate (PMMA) and other such acrylates, including polyacrylic acid (PAA), and inorganic ceramic materials based on, for example, calcium phosphate and calcium sulphate.

Historically, PMMA has been established as the most common tool for fixation in joint replacement surgery. Polymerisation of methylmethacrylate is a reaction that results in a doughy substance that self-cures in a short time. PMMA is made of a methylmethacrylate monomer precursor that polymerises to form PMMA. There are a number of commercially manufactured PMMA cements available, each cement kit comprising an individually packaged granules and a liquid. The package granules typically contains PMMA as its major constituent, together with a liquid vial which contains the monomer sub-unit, methylmethacrylate. Additionally, there are a number of other chemicals included to start and regulate the polymerisation process (such as benzoyl peroxide). Additionally, opacifiers or oligomers of PMMA may also be contained. Polyacrylic acid has also been used as a cement, for example together with aluminosilicate to produce a glass ionomer cement (see US 6,479,565).

There are many different types of calcium phosphate- and calcium sulphate-based cements known in the art. Typically, these involve the mixing of, for example, a calcium source with a phosphate source in water, and allowing the mixture to harden to form a solid ceramic material. Calcium phosphate bone cements offer a route of obtaining orthocalcium phosphates in a monolithic form at physiological conditions, without sintering process, by means of a cementitious reaction. The calcium and phosphate precipitate within the mixture to form crystallites. Varying the calcium and phosphate ratio of the final precipitate allows the chemical characteristics and physical characteristics of the material to be varied. Different starting materials may be used, including phosphoric acid, monocalcium phosphate, dicalcium phosphate, dicalcium phosphate dihydrate, tricalcium phosphate (alpha and beta forms), tetracalcium phosphate, calcium oxide or calcium hydroxide. The precipitates formed in the setting cement will vary depending on the nature of the reactants and aggregate ratio of calcium and phosphorous in the mix. These include dicalcium phosphate dihydrate (DCPD), octacalcium phosphate (OCP), amorphous calcium phosphate (ACP) and hydroxyapatite (HA). This is summarised in, for example, the article by Komath M. (Bull. Meter. Sci. (2000), Vol. 23(2), pages 135-140).

Problems with conventional bone cements includes the ability to produce bone cements which have sufficient structural resilience and strength to be used for long periods of time within the body of a patient. Furthermore, there is a need to allow the patient's own bone tissue to inhabit and replace the bone cement. A number of attempts to prove the physicochemico properties of such materials have been made, including:

Santos L.A., *et al.* (Artificial Organs (2002), Vol. 27(5)) discloses a method of increasing the mechanical strength of α -tricalcium bone cement. The authors mixed the cement with acrylamide and ammonium polyacrylate to produce a polyacrylamide network within the cement. This was noted to reduce the porosity of the material.

US 6,479,565 discloses bone cements made from (a) microscopic pellets or anhydrous particles containing components of biological fluids, (b) bioactive glass or ceramic particles and (c) a resin such as bisphenol α -glycidyl methacrylate (BIS-GMA). The biological fluid components are dissolved in the body and act to corrode the surface of the

bioactive glass or ceramic. They also provide voids into which bone cells migrate. The bioactive glass comprises silicon, oxygen, hydrogen and phosphorous atoms in predetermined proportions.

US 6,027,742 discloses a bone cement made of a cement made of amorphous calcium phosphate and water, which hardens to form poorly crystalline apatitic (PCA) calcium phosphate. A wide range of biodegradable polymers, such as collagen, poly(L-lactide) and polyglycolide (PGA) are suggested as additives to enhance the strength of the PCA. Calcium deficient apatitic calcium phosphate materials prepared from amorphous calcium phosphate with a promoter and the biodegradable polymers are shown in US 6,331,312. WO 03/024316 discloses bone cements with pore-forming agents, including collagen, other polymers and bioactive glass compositions. Soft matrix material mixed with non-ceramic hydroxyapatite cement is disclosed in US 6,703,038.

Attempts have been made to improve bone formation on bone cements by producing macropores made from bubbles in the cement (del Real R.P., *et al.*, J. Biomed. Mater. Res. (2003, Apr. 1), Vol. 65A(1), pages 30-36). This improved bone formation compared with non-porous material but is expected to reduce the mechanical strength of the material. Furthermore, this required the use of a complicated gas bubbling method to produce homogenous results. Alternative methods of producing macroporous cements are shown in WO 00/45867. This uses a calcium source, such as calcium sulphate hemihydrate or a calcium phosphate, water and a hydrophobic liquid such as an oil, to form a porous cement.

Another way of making porous bone cement is to mix a calcium source with a phosphate source, a carbonate and acid to form porous hydroxyapatite, as shown in US 6,547,866.

Flautre B., *et al.* (J. Biomed. Mater. Res. (2002), Vol. 63(4), pages 413-417) discloses injectable hydraulic cements in the presence of beta-tricalcium phosphate granules. This was stated to improve biomechanical function of the bone material.

US 6,458,375 discloses alternative malleable bone compositions comprising demineralised bone granules of 250 μm to 750 μm , bone chips of 0.1 to 10 mm diameter in a carrier

selected from an aqueous sodium-based phosphate buffered solution and a hydrogel consisting of a mucopolysaccharide.

Griffon D.J. (Academic Dissertation entitled "Evaluation of Osteopductive Biomaterials : allegraft, bone inducing agent, bioactive glass, and ceramics (Helsinki, 2002)) discusses osteopductive biomaterials in general but does not disclose any advantages or disadvantages of bone cements. Further, the experiments disclosed by Griffon do not use a bone cement or a bone cement precursor.

The Applicant developed an alternative method of producing artificial bone which allowed the controlled formation of macropores, including the diameter and orientation of the macropores. This was published as WO 02/11781. The method used in that application prepared a mixture of finely divided bio-compatible ceramic granules, an organic binder and a pore-forming agent in an inert liquid to form a body, causing at least some of the macropores to align along a common axis, prior to heating to fix the porous structure and further heating to eliminate residues of the organic binder and pore-forming agent, and to fuse it. This method was shown to produce a series of tube-like macroporous structures.

The Applicant has also identified methods for improving the distribution of micropores through bone material. This is disclosed in WO 2004/101013.

The Applicant has recognised that there is a requirement to produce a bone cement which has both improved structural properties and improved osteoconductivity to regenerate and heal the host bone tissue. The Applicant realised that distributing granulated microporous ceramic material within bone cement will provide improved structural properties for the hardened bone cement, whilst the microporous structure of the ceramic material granules allows host tissue to bind and regenerate around and within the bone cement-ceramic material mixture. Preferably at least two different preselected sizes, or ranges of sizes, of granulated material are used, e.g. in a similar manner to sand and gravel being used with cement to make concrete. The different size of the "sand and gravel" is thought to improve the strength of the material.

Accordingly, a first aspect of the invention provides: a bone substitute comprising a mixture of a bone cement or a bone cement precursor and ceramic material granules, the granules having a plurality of micropores of an average diameter of between 1 μm and 10 μm .

That is, the individual granules have micropores. Preferably, the micropores are interconnecting. They are preferably not confined to the surface of the granules but are found substantially throughout the cross-section of the granules. Preferably, the diameter of the granules particles is between 10 μm and 1 mm, preferably 400 μm and 1000 μm , especially 500-900 μm , 500-800 μm or 600-700 μm .

Preferably, at least two different sizes of granules, most preferably two, are used.

Preferably, small and/or large granules are used. The small granules may have a size range of 10 μm to 500 μm , especially 50 to 350 μm , most preferably 100 to 250 μm diameter. Preferably the large granules have a diameter of 250 μm to 1.5 mm, especially 500 μm to 1 mm, most preferably 600 μm to 800 μm .

The granules may each be substantially of the same size or two or more predetermined sizes. Alternatively, two or more distinct size ranges may be used with a variety of different sized particles within each range. Preferably two different sizes or ranges of sizes are used.

Preselected means that the sizes are predetermined and/or selected, prior to adding to the bone substitute.

Preferably, the granules each comprise a plurality of microparticles, substantially each microparticle being partially fused to one or more adjacent microparticles to define a lattice defining the micropores. Each microparticle preferably has an average diameter of 1 μm to 10 μm .

Preferably, the average diameter of the micropores is between 2-8 μm , most preferably 4-6 μm . The micropores may be irregular in shape. Accordingly, the diameter of the micropores, and indeed the midi-pores referred to below, are determined by adding the widest diameter of the pore to the narrowest diameter of the pore and dividing by 2.

Preferably, the ceramic material is evenly distributed throughout a cross-section of the hardened bone cement, that is substantially without clumps of ceramic material forming.

Preferably, the microparticles have an average diameter of at least 2 μm or 4 μm and/or less than 10 μm or less than 6 μm , most preferably 5-6 μm . This particle size range has been found to allow the controlled formation of the micropores.

The granules may also comprise a plurality of substantially spherical midi-pores having an average diameter of 5-150 μm , especially 50-100 μm or 60-100 μm in diameter. They substantially increase the total porosity of the ceramic material without compromising the mechanical strength of the materials. Furthermore, the midi-pores can be beneficially used to deliver drugs, cell growth factors or other biologically active agents.

The midi-pores are preferably interconnected via a plurality of micropores. That is, the midi-pores may be in fluid connection with each other via micropores.

The average porosity of the ceramic material itself is preferably at least 50%, more preferably greater than 60%, most preferably 70-75% average porosity.

The bone substitute comprises a mixture of a bone cement or a bone cement precursor with the ceramic material granules. That is, in the solidified bone substitute, the bone cement forms a matrix that binds together the ceramic material granules, in a similar manner to the lime or cement constituting the cementing material that binds together the sand and aggregate in a mortar or concrete.

The term "bone cement precursor" is intended to mean one or more compounds which, upon curing or solidifying, form a substantially solid bone cement matrix. For example,

with PMMA, methylmethacrylate monomer is polymerised to form the PMMA bone cement. The monomer is a bone cement precursor. Similarly, to form inorganic materials, such as calcium phosphate, bone cement may be formed, for example, by mixing dicalcium phosphate dihydrate with tetracalcium phosphate. These two compounds act as precursors to the final bone cement. Upon wetting, the two materials react and solidify to form a solidified bone cement.

Accordingly, the bone substitute may be a liquid, paste, gel or dough, and preferably hardens to a substantially solid solidified material.

Preferably, the bone cement, which may be made from the bone cement precursor, is a polymeric material or an inorganic ceramic material. Preferably, the organic material is a poly (meth) acrylate material, such as PMMA or PAA (polyacrylic acid).

PMMA cements are well known in the art. See for example, Planell J.A., *et al.* (Encyclopaedic Handbook of Biomaterials and Bioengineering, Part B: Applications, Vol. 2, chapter 32 (1995), pages 879-921, edited by D.L. Wise, Marcel Dekker Inc., New York). PAA has been used, for example in combination with aluminosilicate glass to form silicate cement, for a number of years (discussed in Wilson and Kent (Journal of Applied Chemistry and Biotechnology (1971), Vol. 21, page 318) to form so-called "glass ionomer cement" (GIC).

PMMA has also been replaced by bisphenol-alpha-glycidyl methacrylate resin (BIS-GMA) to form alternative organic bone cements. This is discussed in, for example, US 6,479,565.

Inorganic ceramic material, based on, for example, calcium phosphate or calcium sulphate is well known in the art, as indeed discussed in the article by Komath, *et al.* (Supra). Preferably, the bone cement precursor is selected from one or more of: anhydrous phosphoric acid, anhydrous monocalcium phosphate, anhydrous dicalcium phosphate, dicalcium phosphate dihydrate, alpha or beta tricalcium phosphate, tetracalcium phosphate, calcium oxide and calcium hydroxide. The final bone cement may be dicalcium phosphate

dihydrate (DCPD), octacalcium phosphate, amorphous calcium phosphate or hydroxyapatite. These are all made using techniques well known in the art.

Preferably, the bone cement is a poorly crystalline apatitic calcium phosphate, for example of the type shown in US 6,027,742, with or without the supplementary material disclosed in that document. Amorphous calcium phosphate materials are disclosed in, for example, US 6,027,742 and US 6,331,312. Calcium phosphate cements are disclosed in, for example, US 6,537,589. The cement may also be a calcium phosphate and calcium sulphate. For example, Bohner, M. and Schmid, H. disclose hydraulic cements based on alpha-tricalcium phosphate-calcium sulphate dihydrate mixtures (European Cells and Materials (2003), Vol. 5, pages 3-4). Calcium phosphate-calcium sulphate bone cements are also disclosed in the article by Gisepp A. and Rahn B. (European Cells and Materials (2004), Vol. 7, pages 34-35).

The bone cement precursor may additionally comprise one or more additional materials such as accelerators or regulators in order to control the curing of the bone cement. Catalysts of organic polymerisation reactions include peroxides, such as benzyl peroxide. Accelerators of inorganic cements are known, for example disodium hydrogen phosphate is known to be used as an accelerator. Opacifiers or colorants may also be included.

Additionally, polystyrene may be included as this improved the handling of the properties of the cement. The weight ratio of precursor : ceramic material granules may be between 100:1 to 1:100, especially 10:1 to 1:10, more preferably 1:1.

The micropores within the ceramic material are predefined, prior to mixing with the bone cement precursor or bone cement. That is, they are prior formed prior to, for example, being used on a patient.

The bone substitute may additionally comprise one or more pharmaceutically and/or biologically active compounds. These may be incorporated into the micropores and/or midpores and in use may be used to stimulate cell growth around and into the biomaterial. For example, growth factors, such as transforming growth factor (TGF- β 1), bone morphogenetic protein (BMP-2) or osteogenic protein (OP-1) may be incorporated into the

biomaterial. Further materials such as enzymes, vitamins (including Vitamin D) and trace material such as zinc (for example in the form of salt) may also be incorporated.

The ceramic material used to produce the granules may be any non-toxic ceramic known in the art, such as calcium phosphate and glass ceramics. Preferably the ceramic is not a silicate. Most preferably the ceramic material is a calcium phosphate, especially α - or β -tricalcium phosphate or hydroxyapatite, or mixtures thereof. Most preferably, the mixture is hydroxyapatite and β -tricalcium phosphate, especially more than 50% w/w hydroxyapatite, most preferably 70% hydroxyapatite and 30% β -tricalcium phosphate.

A second aspect of the invention provides a process for preparing a biomaterial, such as the biomaterial according to the first aspect of the invention, which comprises:

- (i) preparing a mixture of finely divided bio-compatible ceramic micro-particles with a coating agent;
- (ii) causing the coating agent to coat the ceramic micro-particles to form coated particles;
- (iii) causing the coated particles to form a body;
- (iv) heating the body to eliminate residues of the coating agent and to partially fuse the ceramic micro-particles, thereby to produce a fused biomaterial;
- (v) grinding the fused biomaterial to produce ceramic material granules; and
- (vi) mixing the ceramic material granules with a bone cement precursor.

The inventors have found that coating the particles improves the distribution of the particles through the finely fused product and produces a substantially uniform product with substantially evenly distributed micropores.

Suitable coating agents include those comprising starch, agar, polyethylene glycol (PEG), hydroquinone, ethyl cellulose or tetrapropylammonium. The starch is preferably provided as corn flour, potato starch or rice granules, most preferably tapioca granules.

Where the coating agent is liquid, for example PEG, simply mixing the ceramic particles in the coating agent may coat the particles. Alternatively, some coating agents, such as the

starch and agar coating agents may be mixed with an inert liquid, such as water, in a granules form, and heated to allow the starch or agar to form a polymer coating around the particles. Heating liquids containing starch causes the starch to polymerise and causes it to thicken the liquid in a similar manner to adding corn flour to thicken gravy when cooking.

The Applicant has found that where the mixture of ceramic particles and coating agent needs to be heated, then it is convenient to mix the components, including where necessary the inert liquid, and then heat the mixture in a steam generator, such as a rice cooker. Heating the mixture in steam allows the mixture to be heated in a controlled manner, whilst allowing the mixture to remain moist. The time will, of course, vary depending on the quantities used. Heating such mixtures of material, typically produces a body having a dough-like consistency. Preferably the mixture is heated to about 100°C for typically 20-30 minutes.

The body is finally heated to eliminate residues of the coating agent and to partially fuse the ceramic particles to produce a fused biomaterial. This final heating step is also known as an annealing or sintering step and typically uses temperatures of about 1200°C to about 1450°C, preferably 1200-1350°C. Temperature and duration of heating will depend upon the size of the sample and the initial ceramic concentration and the type of ceramic material used. Furthermore, the temperature is controlled to prevent fusion of the micropores. Typically, the body is annealed for 1 to 2 hours.

Typically the weight ratio between the ceramic granules and the total amount of carbohydrate and gluten granules is between about 1.087 to about 1.163. The weight ratio of ceramic granules to inert liquid is typically about 1.042 to 1.316.

This process, as well as producing the biomaterial of the first aspect of the invention, has been found to reduce the appearance of large voids within the material, thus reducing wastage of biomaterial which would otherwise be disposed of due to the voids.

The ceramic micro-particles may also be mixed, prior to coating, with a dispersing agent. The dispersing agent allows the ceramic particles to be homogeneously mixed with, for example, the inert liquid such as water. Without the dispersing agent, the ceramic particles will separate from the water within minutes. The function of the dispersing agent is to prevent the precipitation of the granules and to allow it to be homogeneously dispersed within the water.

Preferred dispersing agents include acid-based solutions, polymers such as phosphates and acrylate polymers, ammonia, phosphoric acids such as orthophosphoric acid, or an ammonium salt of an acrylate or methacrylate polymer such as ammonium polyacrylate and ammonium polymethacrylate. Relatively small amounts of the dispersing agent need be used, for example for 100 ml. of inert liquid only 0.5 ml. to 1 ml. of dispersing agent may be required.

The body formed from the coated particles may be mixed with an organic binder prior to the final heating step. The organic binder is preferably a carbohydrate granules, such as corn flour or wheat flour. However, the inventor has identified that adding high-gluten flours (also known as strong flours), or indeed extracted gluten, improves formation of the final product. Gluten is the reserve protein of seeds, such as wheat grain. Typically, it contains at least 85% protein and is a mixture of gliadin and glutenin, along with globulin and albumin.

If desired, midipores may be formed, then it is necessary to use a pore-forming agent. This agent is allowed to form a pore-forming structure in the body and then is heated to fix the porous structure. This heating step may be at a lower temperature than the final sintering step, typically 100, 130 or 150-230°C. This is preferably in a humidity-controlled oven, for example in steam. Generally, this stabilisation of the pore-forming structure can be achieved in less than 1 hour, generally 5-50 minutes, for example 15-45 minutes. This will vary depending on the size of the body.

The pore-forming agent may be mixed with the organic binder and the body may be a chemical pore-forming agent such as hydrogen peroxide, disodium diphosphate or sodium bicarbonate. However, most preferably the pore-forming agent is a micro-organism such as a yeast or bacterium. Such micro-organisms preferably form carbon dioxide by metabolising a carbohydrate, such as a sugar which may be added to the organic binder. The advantage of using a micro-organism is that the size of the macropores may be carefully controlled. Furthermore, the pore-forming action of the micro-organism can be easily stopped simply by heating the body to kill the micro-organism.

If yeast is used, then preferably a yeast enhancer is also incorporated into the organic binder.

Preferably, there is a step of additionally causing at least some of the pore-forming agent to align along a common axis. This may be achieved, for example, by placing the body containing the pore-forming agent into an elongated mould with space to expand at the

ends of the mould. The pore-forming agent, such as yeast, is allowed to produce the pores within the confines of the sides of mould, thus forcing the body to elongate along the length of the mould. Alternatively, the pore-forming agent may be aligned simply by extruding the body. This is also described in WO 02/11781. This forms elongated macropores.

The ceramic particles are preferably as defined for the first aspect of the invention.

The process preferably comprises a step of additionally incorporating a biologically or pharmaceutically active compound into or onto the fused biomaterial. These compounds are preferably as defined for the first aspect of the invention. They may simply be incorporated by soaking the fused body into a suitable solution containing the biologically or pharmaceutically active compound, prior to drying the product. This allows, for example, the active compound to diffuse within the micropores, midi-pores and macropores of the product.

The ceramic material granules may be formed from the fused biomaterial by milling or grinding using, for example, a ball mill. The size of the granules may be adjusted using, e.g. one or more sieves.

Two or more different sized particles, or ranges of sizes of particles, may be used. These particles may be as defined above.

The bone precursors are preferably as defined above.

Method of the invention preferably additionally comprises a step of allowing the bone cement precursor to solidify to form bone cement. This solidification may be formed, for example, by the addition of a suitable catalyst, or alternatively by the chemical reaction of the precursors, for example together with water or another solvent.

The invention also provides biomaterials obtainable by such processes. Bone implants, dental implants or ear, nose or throat (ENT) implants comprising both substitute materials according to the invention are also provided. Additionally, the invention provides the use of the bone substitute as a bone replacement, in dental implants or maxillofacial repair materials for the repair of bone breaks or fractures, osteoporotic bone, intervertebral space, or as a bone glue or putty or a load bearing surface on a bone. Furthermore, the bone

substitute may be used, for example, to create attachment points for devices such as screws or plates.

Preferably, the bone substitute material is injectable. That is, the size of the granules allows it to be injected through the bore of a needle from, for example, a syringe, into position on the surface of a bone under repair. Hence, preferably the maximum size of the particles is 1.5 mm.

Preferably, the bone substitute material is made by mixing a bone cement precursor, as defined above, together with the ceramic material, as defined above, to form a paste and the bone precursor is caused to convert to a substantially solid bone substitute material comprising a bone cement and a ceramic material by, for example, the use of a catalyst or the reaction of the bone precursor materials.

Preferably, the paste is applied to a bone or tooth socket to be repaired in a patient prior to the bone substitute material solidifying.

Kits comprising: (i) a bone cement precursor; and (ii) ceramic material granules having a plurality of micropores of an average diameter of between 1 μm and 10 μm for use to produce a bone substitute material according to the invention, are also provided. The kit may additionally comprise one or more instructions, syringes, needles, bone cement formation accelerators or inhibitors, catalysts, and for example sterile water. Two or more different sizes or ranges of sizes of particles are used, as defined above.

Bone cement precursors and ceramic material granules are defined above.

The invention will now be described by way of example only, with reference to the following examples:

Figures 1A to 1C show samples of biomaterial prepared without the step of coating the ceramic particles prior to fusing, prior to pulverising into granules.

Figure 1D shows a sample prepared using the additional coating step of the invention.

The figures show that the coating step of the invention produces thinner connecting walls, better defined macropores and substantially evenly distributed micropores.

Figure 2a is a schematic diagram which shows the theoretical porous structure of the Applicant's synthetic bone graft material. The midpores make up the porous connected walls between the elongated macropores.

Figure 2b is scanning electron microscope (SEM) picture at magnification 60X which shows the 2-D cross section of the actual materials. The midpores can be easily identified.

Figure 2c is a back light optical microscope picture at magnification 60X shows the 3-D porous structure of the materials. The picture shows the macropores are interconnected and midpores appeared among the macropores.

Figure 2d is a SEM image at magnification 2000X which shows the microporous structures which are substantially throughout the whole materials.

Example

Hydroxyapatite granules is mixed with water (38 ml.), and a dispersing agent (1 ml.).

Tapioca (9 g.) or other coating agent is then blended into the mixture within a heatproof vessel. This produces a liquid suspension or slurry. The mixture is then placed within a steamer, such as a rice cooker, and heated to approximately 100°C. A steamer, such as a rice cooker, is particularly advantageous because it prevents the material drying out. This produces a moist "dough".

A mixture of wheat gluten (13 g.) and white strong flour with a high gluten content (15 g.) optionally, together with a yeast enhancer (vital wheat gluten, diastatic malt and ascorbic acid) and yeast (7 g.), such as *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Saccharomyces carlsbergiensis* or another carbon dioxide producing micro-organism, is prepared. An additional source of carbohydrate, such as a sugar, may also be incorporated. This is mixed with the cooled dough of coated ceramic particles, together with a little water. The mixing may be carried out by hand or may also be mixed using, for example, a food processor. The mixture may then be compressed in order to exclude any large voids which have appeared within the mixture by mixing.

The final mixture again has a dough-like consistency. This may be placed within, for example, an elongated mould made of any suitable material, such as aluminium. By placing the dough within the mould with a space at each end of the elongated mould, the yeast produces carbon dioxide and causes the dough to expand along the length of the mould. The dough is prevented from expanding widthways in the mould by the walls of the mould. Depending on the micro-organism used, the generation of carbon dioxide is achieved by "proving" in a similar manner to bread. That is, the dough is maintained at a temperature of 40-45°C to allow the yeast to produce carbon dioxide. If another pore-forming agent, such as sodium bicarbonate is used, it may be advantageous to add an acid, such as citric acid, which reacts with the sodium bicarbonate to produce carbon dioxide.

The porous structure is set by heating, for example, to 100°C in a steam cooker for approximately 20-25 minutes. This kills the yeast and also sets the organic binder, such as gluten. It also expands the dough to fit the mould, in a similar manner to bread dough which is expanded to fit a bread mould. Adjusting the size of the mould and ensuring that the mould is closed, rather than open-ended, allows the density of the product to be adjusted. The body with the fixed porous structure is then allowed to cool. At this stage it is possible to shape the material as it typically has a moist bread-like consistency and texture. It is therefore easily cut to a desired shape. Freezing or refrigerating the product at this stage improves the ability to shape the product. The shaped product is then sintered to a sufficiently high temperature to partially fuse the ceramic particles. This temperature will vary depending on the ceramic particles used. Typically, hydroxyapatite uses a temperature of 1350°C, tricalcium phosphate uses approximately 1200°C.

Using a mixture of hydroxyapatite and tricalcium phosphate has been found by the inventors to improve the rate at which cells distribute themselves through the product.

The ceramic material is then pulverised, for example using a ball mill or other milling machinery. The size of the granules may be adjusted, for example, by sieving through a mesh of the desired size to regulate the size of the granules.

The granules are then mixed with bone cement precursor, in a similar manner to adding aggregate to cement to form concrete. The cement precursor may be PMMA. PMMA is preferably purchased from the manufacturer. Cement kits usually consist of an individually packed granules and a liquid which is typically sterilised by gamma irradiation and

ultra-filtration. The packaged granules contains PMMA as its major constituent. The liquid contains the monomer sub-unit, methylmethacrylate. Additionally, one or more other ingredients include chemicals that are responsible for the polymerisation reaction rate, as well as the handling properties of the cement and the resistance to degradation. An initiator polymerisation, such as benzoyl peroxide, is provided to start the polymerisation reaction.

Additionally, polystyrene may be included as this improved the handling of the properties of the cement. The weight ratio of precursor : ceramic material granules may be between 100:1 to 1:100, especially 10:1 to 1:10, more preferably 1:1.

An inorganic bone cement material may be used instead of PMMA. The bone cement precursors may be obtained from manufacturers and used according to the manufacturers' instructions, with the addition of the ceramic material granules which is mixed and dispersed within the bone cement prior to its setting.

Initial results indicate that the addition of the ceramic material granules increases the strength and improves bone tissue growth into the material.

Claims

1. A bone substitute comprising a mixture of a bone cement or a bone cement precursor and ceramic material granules, the granules each having a plurality of micropores of an average diameter of between 1 μm and 10 μm .
2. A bone substitute according to claim 1, comprising at least two different preselected sizes, or range of sizes, of granules.
3. A bone substitute according to claim 1 or claim 2, wherein the granules of ceramic material have a diameter of 10 μm to 1.5 mm, preferably 400 μm to 1000 μm , most preferably 500 μm to 800 μm .
4. A bone substitute according to any preceding claim comprising small granules of the ceramic material, the small granules having a diameter of from 10 μm to 500 μm .
5. A bone substitute according to any preceding claim comprising large granules of the ceramic material, the large granules having a diameter of from 250 μm to 1.5 mm.
6. A bone substitute according to any preceding claim, wherein the granules each comprise a plurality of microparticles, substantially each microparticle being partially fused to one or more adjacent microparticles to define a lattice defining micropores.
7. A bone substitute according to claim 6, wherein each microparticle has an average diameter of 1 μm to 10 μm .
8. A bone substitute according to any preceding claim wherein the granules comprise a plurality of substantially spherical midi-pores having an average diameter of 5 μm to 150 μm .
9. A bone substitute according to any preceding claim wherein the bone cement is a polymeric material or an inorganic ceramic material.

10. A bone substitute according to claim 9, wherein the bone cement, or the bone cement that the precursor on conversion to bone cement makes, comprises PMMA, PAA, a calcium phosphate, or calcium sulphate.
11. A bone substitute according to any preceding claim additionally comprising one or more biologically or pharmaceutically active compounds.
12. A bone substitute according to claim 11, wherein the pharmaceutically active compound is a cell growth factor or bone morphogenic protein.
13. A bone substitute according to any preceding claim wherein the ceramic material is at least one type of calcium phosphate.
14. A bone substitute according to claim 13, wherein the calcium phosphate is α or β tricalcium phosphate or hydroxyapatite or mixtures thereof.
15. A process of preparing a bone substitute according to any preceding claim, comprising:
 - (i) preparing a mixture of finely divided bio compatible ceramic micro-particles with a coating agent;
 - (ii) causing the coating agent to coat the ceramic micro-particles to form coated particles;
 - (iii) causing the coated particles to form a body;
 - (iv) heating the body to eliminate residues of the coating agent and to partially fuse the ceramic micro-particles, thereby to produce a fused biomaterial;
 - (v) grinding the fused biomaterial to produce ceramic material granules; and
 - (vi) mixing the ceramic material granules with a bone cement precursor.

16. A process according to claim 15, wherein the coating agent comprises starch, agar, polyethylene glycol, hydroquinone, ethyl cellulose or tetrapropylammonium.
17. A process according to claim 16, wherein the starch is provided as tapioca granules, corn-flour, potato starch or rice granules.
18. A process according to any one of claims 15 to 17, wherein the mixture of ceramic particles and coating agent is heated to cause the coating agent around the particles to form coated particles.
19. A process according to any one of claims 15 to 18 comprising mixing a dispersing agent with the finely divided biocompatible ceramic particles.
20. A process according to any one of claims 15 to 19 additionally comprising the step of mixing the body with an organic binder.
21. A process according to claim 20, wherein the organic binder comprises gluten.
22. A process according to any one of claims 15 to 21, additionally comprising the steps of mixing the body with a pore-forming agent, allowing the pore-forming agent to form a pore-forming structure, and heating the body to fix the porous structure, prior to heating to partially fuse the ceramic particles.
23. A process according to claim 22, wherein the pore-forming agent is a micro-organism.
24. A process according to any one of claims 22 or 23, additionally comprising the step of causing at least some of the pore-forming agent to align along a common axis.
25. A process according to any one of claims 15 to 24, additionally comprising the step (vii) of allowing the bone cement precursor to solidify to form bone cement.
26. A biomaterial obtainable by a process according to any one of claims 15 to 25.
27. A bone implant, dental implant or an ear, nose or throat (ENT) implant comprising a bone substitute according to any one of claims 1 to 14 or 26.

28. The use of a bone substitute according to any one of claims 1 to 14 or 26 as a bone replacement in a dental implant or maxillo facial repair material, for the repair of bone breaks or fractures, osteoporotic bone, intervertebral space, as a bone glue or putty for a load-bearing surface on a bone.

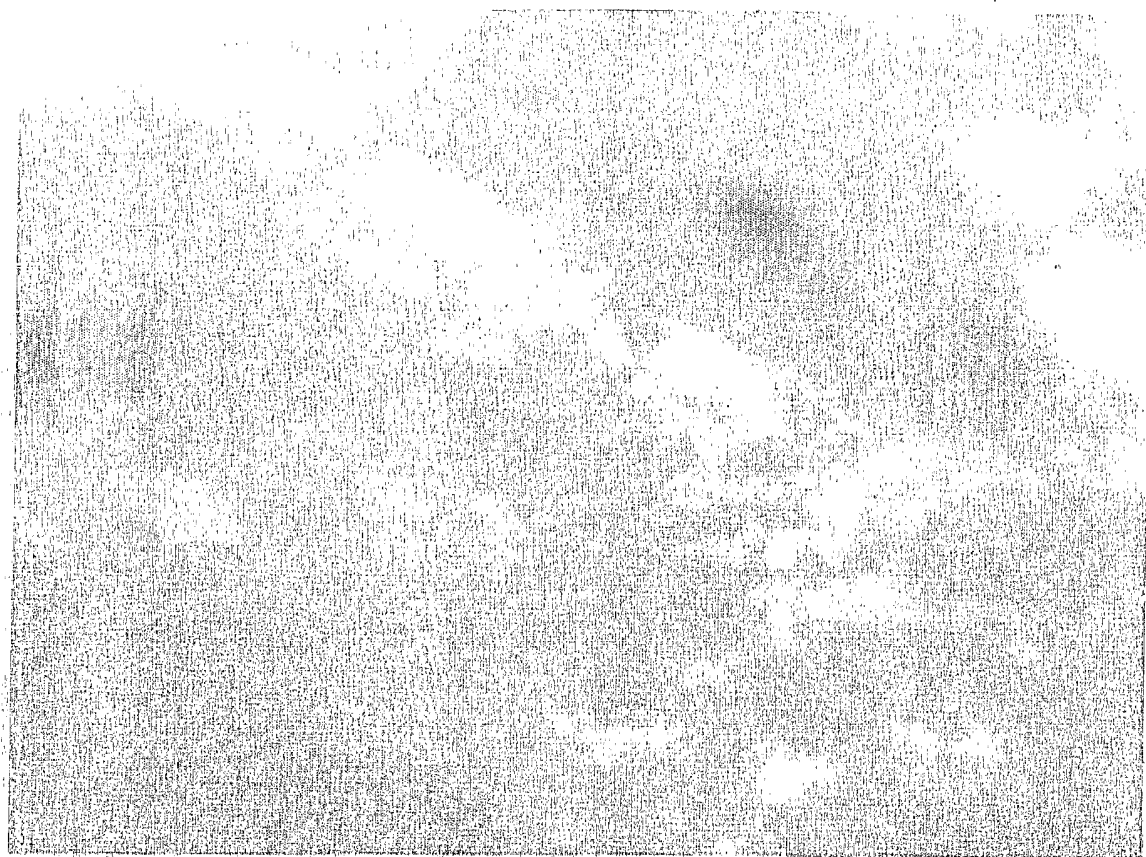
29. A method of making a bone-substitute material according to any one of claims 1 to 14, comprising mixing a bone cement precursor with the ceramic material granules to form a paste and causing the bone precursor to convert into a substantially solid bone substitute material comprising the bone cement and the ceramic material.

30. A method according to claim 29, wherein the paste is applied to a bone or tooth socket to be repaired in a patient prior to the bone-substitute material solidifying.

31. A kit comprising (i) a bone cement precursor and (ii) a ceramic material granules having a plurality of micropores of an average diameter of between 1 μm and 10 μm , for use to produce a bone substitute according to any one of claims 1 to 14 or 26.

32. A kit according to claim 31 comprising at least two different preselected sizes or ranges of sizes of granules.

FIGURE 1



A

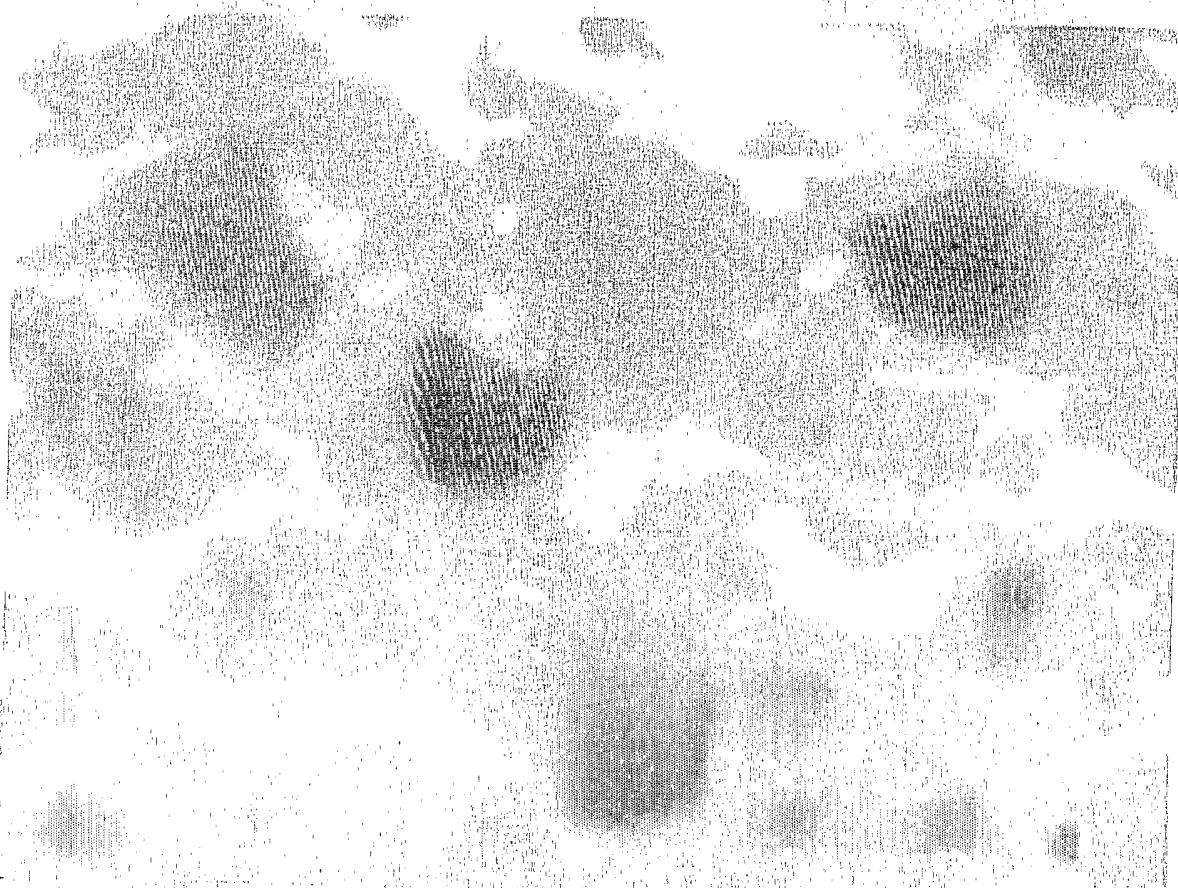


B

FIGURE 1 CONTINUED



C



D

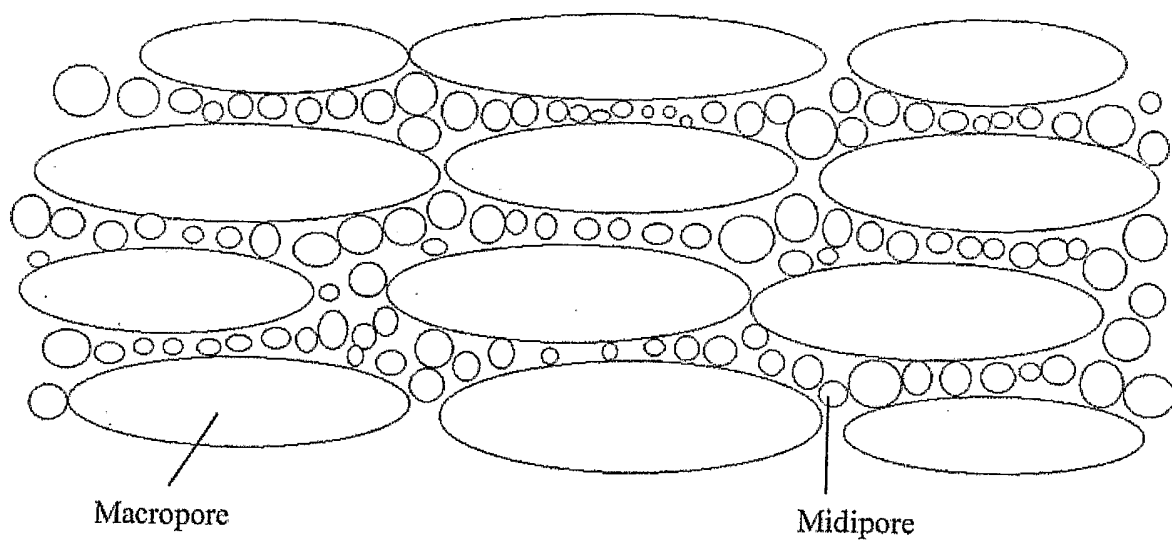


Figure 2a

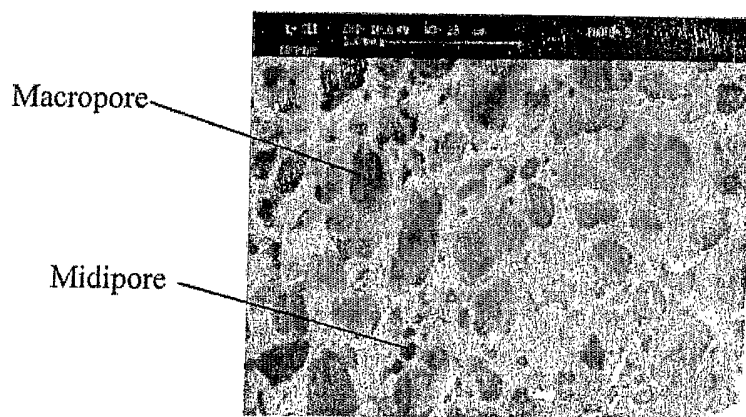


Figure 2b

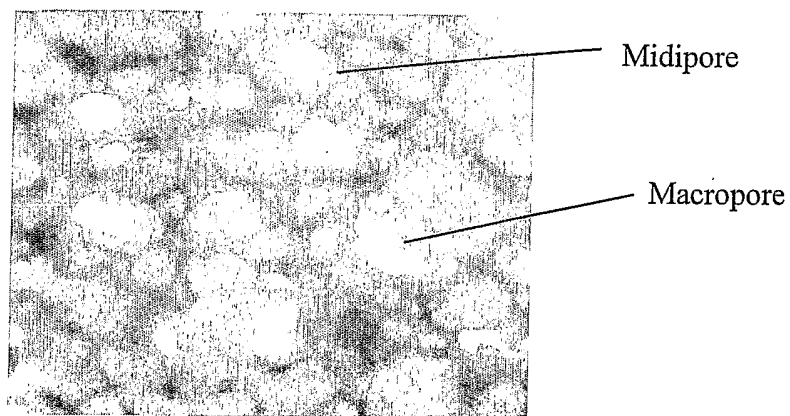


Figure 2c

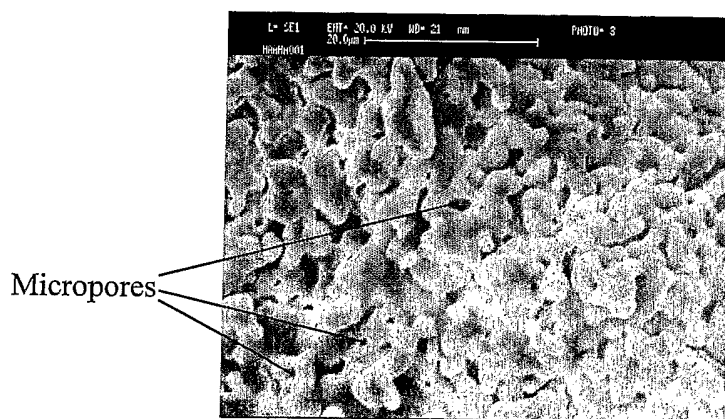


Figure 2d

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2006/000416

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61L24/00 A61L24/06 A61L27/46 A61L27/56 A61F2/28

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 practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	page 2, paragraph 5 - page 9, paragraph 2	2-14, 27, 29
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 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *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
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

24 April 2006

Date of mailing of the international search report

02/05/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Buchmann, G

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/000416

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2006/000416

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 28, 30
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2006/000416

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