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(54) **Title**: BONE PUTTY

(57) **Abstract**: The present invention relates to a macroporous material for filling bone voids. In particular, we describe an implant material comprising bioresorbabte polymer granules and a biocompatible water-miscib!e solvent, wherein the solvent at least partially dissolves and/or softens the polymer granules to form a mouldabie mass that can be used to fill a bone defect but hardens when water is added and/or the implant material is placed in an aqueous environment, and wherein the implant material has macroporosity suitable for bone in-growth.

# Bone Putty

The present invention relates to bone void fillers. In particular, the present invention relates to a macroporous material for filling bone voids.

The present invention concerns macroporous materials for bone repair and bone void filling. Ideally, the material should be mouldable/formable so that it can fill and conform to irregular shaped and sized bone defects. However, once implanted it ideally should set hard so that the implant material maintains its shape and, under some circumstances, be able to bear loads. The material should not break up and needs to be tough. Furthermore, the material should allow rapid bone in-growth and, ultimately, be degradable and fully replaced by bone. In order to facilitate bone repair the material may incorporate a drug or bioactive molecule which is released to stimulate bone healing and repair.

A number of bone void filler materials are known, but very few meet all the ideal requirements.

Poly(methyl methacrylate) bone cements are widely used to fixate joint replacements but these materials are non-porous and non-degradable so they are not replaced by bone. In addition, when the cement cures, heat is generated and the temperature of the material can rise to 90°C or above. This can damage any drug material or bioactive agent which have been added to the cement, particularly if the bioactive agent consist of proteins such as bone morphogeneic protein (BMP) etc.

Calcium phosphate ceramics, such as hydroxyapatite and tricalcium phosphate, are widely used for bone void filling. These fillers are available in a number of forms. For example, the use of dense and porous granules is known. These can be used to fill irregular shaped defects and allow bone growth into and between the granules. However, they cannot maintain a specific shape or form, and tend to migrate if not fully contained. Porous blocks in pre-formed shapes are also known. However, whilst these kinds of fillers maintain their shape, they cannot be used to fill irregular sized/shaped defects.

In addition, it is not easy to incorporate a drug or bioactive material into these ceramics as high temperatures are required in their manufacture. Drugs or bioactive agents can be adsorbed or coated onto the surface of these ceramics but they tend to be released very quickly.

Calcium phosphate cements have also been used as bone fillers. These kinds of fillers have the advantage of being mouldable, and even injectable, and once in place they set hard. However, whilst they may contain micropores, these tend not to allow significant levels of bone ingrowth. Some calcium phosphate cements have macropores but these generally compromise the mechanical strength of the material. In addition, calcium phosphate ceramics (blocks, cements etc) generally tend to form brittle materials.

There have been attempts to produce bone void fillers which harden in-situ; these combine ceramic granules with a polymer. US 2010/0041770 discloses a composite material formed by mixing a polymer phase with a solvent, adding a bioresorbable ceramic phase, and thereafter allowing the solvent to diffuse out of the polymer in the presence of water, to cause solidification of the polymer phase. The composite formed does not have initial porosity for rapid bone in-growth, though pores may form later by degradation of one of the phases.

US 2005/0251266 discloses a mouldable composite comprising ceramic granules coated with a biocompatible polymer and a plasticizer such that the polymer is initially deformable and then hardens upon removal of the plasticizer by placing in water. However, coating the granules is difficult and the specialist processes which need to be employed leads to an increase in cost. In addition, since all the granules are coated with polymer there is a delay in the osteoconductive effect of the bioceramic granules until at least some of the polymer degrades.

The present invention seeks to address at least some of these problems by providing a macroporous material for filling bone voids, which preferably includes one or more of the following characteristics: is mouldable/formable; sets to a hard and tough material; is able to bear loads; allows for rapid bone

in-growth; and is biodegradable and substantially replaced by bone without substantially compromising the structural integrity of the site of application.

In its broadest sense the present invention provides a bone void filler comprising a bioresorbable granulated polymer and a biocompatible water-miscible solvent.

According to the present invention there is provided an implant material for bone void filling comprising bioresorbable polymer granules and a biocompatible water-miscible solvent, wherein the solvent at least partially dissolves and/or softens the polymer granules to form a mouldable mass that can be used to fill a bone defect, but which hardens when the implant material is exposed to water, and wherein the implant material has macroporosity suitable for bone in-growth.

Suitably, the implant material contains pores of between about 50 and 3000 microns; preferably 100 and 2000 microns; more preferably 120 and 1500 microns, which pores provide a macroporosity level suitable for bone in-growth.

Suitably, the implant material has an open porosity greater than 15%. Preferably, the implant material has an open porosity of between about 15%-70%; more preferably about 20%-55%; most preferably about 25%-45%.

Upon addition of the biocompatible water-miscible solvent to the bioresorbable polymer granules the granules soften and/or partially or fully dissolve causing them to become "sticky" and form a mouldable or flowable mass that can be delivered to the bone defect and which conforms to the shape of the defect. In the presence of water or an aqueous environment, such as being placed in the body, the solvent is removed and the implant material hardens into a mass with interconnected macroporosity.

Suitably, the bioresorbable polymer granules include particles, flakes or powder.

Suitably, the implant material further includes a bioceramic material. Suitably, the bioceramic material is formed as a mixture with the bioresorbable polymer. Preferably, the bioceramic material comprises granules, flakes or powder. In embodiments comprising a bioceramic powder, the powder may be dispersed within the bioresorbable polymer or bioresorbable polymer granules.

Preferably, the bioceramic material is porous. Suitably, the bioceramic material contains pores of between about 10 and 1000 microns; preferably 15 and 500 microns; more preferably 20 and 300 microns.

Suitably, the bioresorbable polymer granules include a core formed of a different material. Suitably, the core is formed from a second bioresorbable polymer which is different to the polymer of the bioresorbable polymer granules. Alternatively, the core is formed from a bioceramic material. Preferably, the bioceramic material is a bioceramic granule or powder. Optionally, the core includes an inner core and an outer core, wherein the inner core is formed from a bioceramic material and the outer core is formed from a second bioresorbable polymer. The core may also be formed from a bioresorbable polymer having a bioceramic powder dispersed therein. In such embodiments, the powder may be uniformly or non-uniformly dispersed.

Optionally, the implant material includes a bioactive or therapeutic agent. Suitably, the core includes a bioactive or therapeutic agent. Preferably, the outer core includes a bioactive or therapeutic agent.

Preferably, the bioactive or therapeutic agent includes at least one of: a growth factor such as any bone morphogenic protein (BMP), platelet derived growth factor (PDGF), growth hormone, transforming growth factor-beta (TGF-beta), insulin-like growth factor; a bisphosphonate such as alendronate, zoledronate; an antibiotic such as gentamicin, vancomycin, tobramicin; an anti-cancer drug such as paclitaxel, mercatopurine; an anti-inflammatory agent such as salicylic acid, indomethacine; an analgesic such as salicylic acid.

The bioactive or therapeutic agent may also be incorporated into the implant material by: coating onto the bioceramic granules; incorporating within the bioceramic granules; coating onto the polymer granules; incorporating within the polymer granules; incorporating within the biocompatible solvent; adding at the time of mixing the components or any combination of these methods to give a desired dispersion and release profile.

Preferably, the second bioresorbable polymer is less soluble in the biocompatible solvent than the first bioresorbable polymer. In this way, when the solvent is added, the surface of the bioresorbable polymer granules becomes softened and/or partially dissolves but the outer core layer, preferably containing a bioactive or therapeutic agent, remains largely intact. The bioactive or therapeutic agent will be released from the outer core layer as the first bioresorbable polymer is absorbed.

Optionally, the same or a different bioactive or therapeutic agent can be incorporated into the first bioresorbable polymer. Suitably, where the bioactive or therapeutic agents are the same theyhave different release rates according to the different release characteristics and/or degradation rates of the first and second bioresorbable polymers.

Preferably, the bioceramic granules include at least one of: calcium phosphate, including hydroxyapatite, any substituted hydroxyapatite (e.g. silicon, carbonate, magnesium, strontium, fluoride), tricalcium phosphate, biphasic calcium phosphate, tetracalcium phosphate, octacalcium phosphate, dicalcium phosphate dihydrate (brushite), dicalcium phosphate (monetite), calcium pyrophosphate, calcium pyrophosphate dihydrate, heptacalcium phosphate, calcium phosphate monohydrate; calcium sulphate; any bioactive glass (e.g. Bioglass) or glass ceramic (e.g. apatite-wollastonite); or any combination of these. The granules may be dense or porous.

Preferably, the first bioresorbable polymer includes at least one of: any polymer from the poly-alpha-hydroxyacid group, including poly(lactic acid), poly(glycolic acid), poly-L-lactide, poly-DL-lactide, poly(lactide-co-glycolide), poly(lactide-co-

caprolactone), poly(L-lactide-co-DL-lactide), polycaprolactone; any bioresorbable polyanhydride, polyamide, polyorthoester, polydioxanone, polycarbonate, polyaminoacid, poly(amino-ester), poly(amido-carbonate), polyphosphazene, polyether, polyurethane, polycyanoacrylate, or any combination of these.

Preferably, the second bioresorbable polymer includes at least one of: a polymer from the poly-alpha-hydroxyacid group, including poly(lactic acid), poly(glycolic acid), poly-L-lactide, poly-DL-lactide, poly(lactide-co-glycolide), poly(lactide-co-caprolactone), poly(L-lactide-co-DL-lactide), polycaprolactone; any bioresorbable polyanhydride, polyamide, polyorthoester, polydioxanone, polycarbonate, polyaminoacid, poly(amino-ester), poly(amido-carbonate), polyphosphazene, polyether, polyurethane, polycyanoacrylate; a polysaccharide optionally including alginate, chitosan, carboxymethyl cellulose, hydroxypropylmethyl cellulose, dextran, hyaluronic acid, or any combination of these.

Preferably, the biocompatible, water miscible solvent includes at least one of: N-methyl-pyrollidone, dimethyl sulphoxide, acetone, poly(ethylene glycol), tetrahydrofuran, isopropanol, or caprolactone.

Optionally, the implant material includes a water soluble porogen that is not soluble in the biocompatible solvent. Preferably, the water soluble porogen includes at least one of: a soluble inorganic salt such as sodium chloride; any soluble organic compound such as sucrose; or a water soluble polymer such as poly(ethylene glycol), poly(vinyl alcohol), polysaccharide such as carboxymethylcellulose.

Compared with poly(methyl methacrylate) bone cements, aspects of the present invention are macroporous and fully bioresorbable.

Compared with bioceramic blocks, aspects of the present invention have the advantage of being injectable and/or mouldable and capable of conforming to irregular shaped bone defects.

Compared with bioceramic granules, aspects of the present invention have the advantage of hardening in-situ to form a cohesive mass, thus preventing the possibility of granules migrating. This could be particularly advantageous when the implant is being used to deliver a drug or therapeutic agent, particularly one which stimulates bone formation, such as BMP, as it reduces the possibility of bone forming in unwanted areas – particularly important if the implant is being used in areas such as the spine where there may be nerves etc near to the bone implant.

Compared with the implant material of US 2010/0041770, aspects of the invention described here have the advantage of having immediate connected macroporosity suitable for rapid bone in-growth.

Compared with the implant material of US 2005/0251266, aspects of the present invention keep at least some of the bioactive/therapeutic molecule within an intact coating layer which is not removed from the granules when the biocompatible solvent is added. This allows for better control and sustained release of the molecule. Also, in embodiments having more than one layer of polymer coating with different release and/or degradation profiles, the overall release of drug can be tailored or the system used to deliver different compounds with different release profiles. In addition, aspects of the invention do not require pre-coating of the ceramic granules, and furthermore, the fact that a portion of the granules comprise a bioresorbable polymer allows for the creation of greater porosity as the polymer granules degrade allowing more room for bone in-growth over time. In addition, we here disclose the use of water to modify the viscosity of the implant material prior to implantation in order to achieve the desired handling characteristics.

The viscosity of the implant material prior to hardening can be adjusted by the addition of water after the addition and mixing of the solvent. If an injectable/flowable material is desired then no water is added but by adding water prior to implantation a more putty-like/mouldable consistency can be achieved.

The above and other aspects of the invention will now be described with reference to the following drawings in which:

Figure 1 is a schematic illustration of a first embodiment, according to the present invention, of an implant material for bone void filling;

Figure 2 is a schematic illustration of a second embodiment, according to the present invention, of an implant material for bone void filling;

Figure 3 is a schematic illustration of a third embodiment, according to the present invention, of an implant material for bone void filling;

Figure 4 is a schematic illustration of a fourth embodiment, according to the present invention, of an implant material for bone void filling;

Figure 5 is a schematic illustration of a fifth embodiment, according to the present invention, of an implant material for bone void filling;

Figure 6 is a schematic illustration of a sixth embodiment, according to the present invention, of an implant material for bone void filling;

Figure 7 is a schematic illustration of a seventh embodiment, according to the present invention, of an implant material for bone void filling;

Figure 8 is a schematic illustration of an eighth embodiment, according to the present invention, of an implant material for bone void filling;

Figure 9 is a schematic illustration of a ninth embodiment, according to the present invention, of an implant material for bone void filling; and

Figure 10 is a close-up schematic view of the embodiment of Figure 9.

Referring to Figure 1, there is shown schematically an implant material precursor for bone void filling comprising polymer granules 10 and a biocompatible solvent 11. As the solvent 11 is mixed with the polymer granules the solvent softens and tackifies the outer surface of the polymer granules, giving them a 'sticky' character. In this state, the granules adhere together to form a cohesive, mouldable implant material. The implant material can then be used to fill bone voids and defects (not shown). The biocompatible solvent is preferably water-miscible. In the presence of water or an aqueous environment, such as being placed in the body, the solvent is removed and the implant material hardens into a mass with interconnected macroporosity. Consequently, the macroporous material allows for tissue ingrowth, particularly bone tissue ingrowth.

The polymer granules are formed from biosorbable materials such as poly(lactic acid), poly(glycolic acid), poly-L-lactide, poly-DL-lactide, poly(lactide-co-glycolide), poly(lactide-co-caprolactone), poly(L-lactide-co-DL-lactide), polycaprolactone; any bioresorbable polyanhydride, polyamide, polyorthoester, polydioxanone, polycarbonate, polyaminoacid, poly(amino-ester), poly(amido-carbonate), polyphosphazene, polyether, polyurethane, polycyanoacrylate, or any combination of these, and as the polymer degrades and is absorbed by the body new bone forms and advances to replace substantially all of the polymer material.

The biocompatible water miscible solvent may be selected from: N-methyl-pyrollidone, dimethyl sulphoxide, acetone, poly(ethylene glycol), tetrahydrofuran, isopropanol, or caprolactone.

As shown in Figures 2 and 4, a porogen 12 can be incorporated in the implant material leading to the formation of further macropores within the set composition. Typically, the porogen will be a soluble inorganic salt such as sodium chloride; a soluble organic compound such as sucrose; or a water soluble polymer such as poly(ethylene glycol), poly(vinyl alcohol), polysaccharide such as carboxymethylcellulose.

The implant material may also include a bioceramic material in the form of granules 13, as illustrated in Figure 3. The bioceramic material may be at least one of: calcium phosphate, including hydroxyapatite, a substituted hydroxyapatite (e.g. silicon, carbonate, magnesium, strontium, fluoride), tricalcium phosphate, biphasic calcium phosphate, tetracalcium phosphate, octacalcium phosphate, dicalcium phosphate dihydrate (brushite), dicalcium phosphate (monetite), calcium pyrophosphate, calcium pyrophosphate dihydrate, heptacalcium phosphate, calcium phosphate monohydrate; calcium sulphate; a bioactive glass or glass ceramic; or any combination of these.

According to this embodiment, the solvent softens and tackifies the outer surface of the polymer granules, making them sticky. The granules then adhere to each other and also the bioceramic granules, and as the solvent is removed, the polymer hardens and incorporates the bioceramic granules in the set macroporous structure. The bioceramic granules add strength and rigidity to the implant material, and are osteoconductive to encourage bone in-growth. Further, because only the outer surface of the polymer granules is softened, the polymer does not spread to coat the surface of the bioceramic granules, and therefore much of the outer surface of the biocermaic granules remains exposed. Accordingly, there is substantially no delay to initiation of the osteoconductive effect.

In further alternative embodiments shown in Figures 5 and 6, the biocompatible solvent fully dissolves the polymer granules in the presence of the bioceramic granules and forms a coating 14 over each surface. This can be achieved in the presence or absence of a porogen. Alternatively, a similar result can be achieved by pre-mixing the solvent and polymer and then adding the bioceramic granules, and optionally a porogen, to this mixture in order to form the implant material (Figures 7 and 8).

The implant material may also include a bioactive or therapeutic agent. Examples of such include, but are not limited to a growth factor such as a bone morphogenic protein (BMP), platelet derived growth factor (PDGF), growth hormone, transforming growth factor-beta (TGF-beta), insulin-like growth factor; a bisphosphonate such as alendronate, zoledronate; an antibiotic such as gentamicin, vancomycin, tobramicin; an anti-cancer drug such as paclitaxel, mercatopurine; an anti-inflammatory agent such as salicylic acid, indomethacine; or an analgesic such as salicylic acid.

In further embodiments of the invention, shown in Figures 9 and 10, the bioresorbable polymer granules include a core formed of a different material. The core material may be a different bioresorbable polymer, having different properties to the first bioresorbable polymer granules, or may be a bioceramic material. In embodiments which incorporate a bioceramic core, the material will be a bioceramic granule or powder. In further embodiments, the core includes an inner core and an outer core, where the inner core is formed from a bioceramic material and the outer core is formed from a second bioresorbable polymer.

Referring to Figure 10, there is shown a polymer granule formed from a first bioresorbable polymer. The polymer granule includes a core having an inner core formed from a bioceramic material, and an outer core, formed from a second bioresorbable polymer. The first bioresorbable polymer will be at least partially soluble in the biocompatible solvent so that it provides adhesion between granules. If the first bioresorbable polymer includes a bioactive or

therapeutic agent, it may provide an initial release of that agent as the polymer starts to degrade and be absorbed.

The second bioresorbable polymer may be: a polymer comprising a poly-alpha-hydroxyacid group, including poly(lactic acid), poly(glycolic acid), poly-L-lactide, poly-DL-lactide, poly(lactide-co-glycolide), poly(lactide-co-caprolactone), poly(L-lactide-co-DL-lactide), polycaprolactone; any bioresorbable polyanhydride, polyamide, polyorthoester, polydioxanone, polycarbonate, polyaminoacid, poly(amino-ester), poly(amido-carbonate), polyphosphazene, polyether, polyurethane, polycyanoacrylate; a polysaccharide comprising alginate, chitosan, carboxymethyl cellulose, hydroxypropylmethyl cellulose, dextran, hyaluronic acid, or any combination of these. The second bioresorbable polymer is generally less soluble in the biocompatible solvent. Where bioactive or therapeutic agents are incorporated in the second bioresorbable polymer, this allows for a sustained release of said agent.

Examples

Example 1

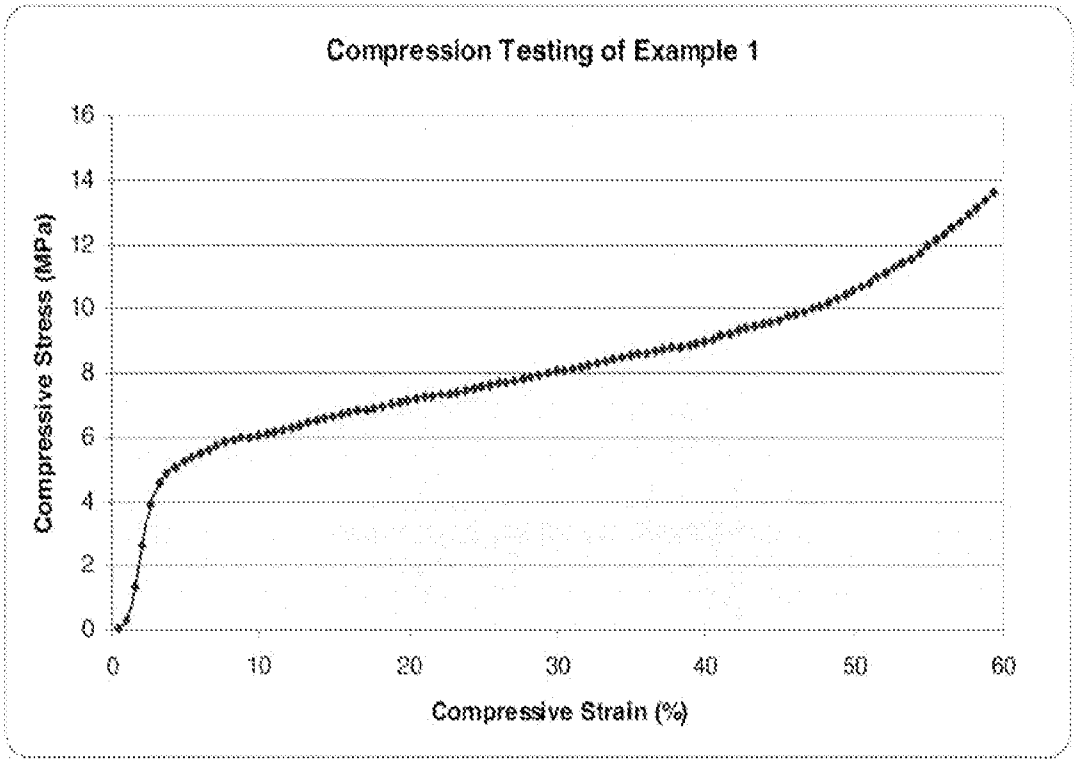
Materials: β-tricalcium phosphate granules (GenOs 1-2mm, supplied by Orthos Ltd); poly-DL-lactide-co-glycolide (PDLGA) 85:15 (Puresorb, supplied by Purac); N-methyl-pyrollidone (NMP) (supplied by Sigma-Aldrich).
Prior to use the PDLGA raw granules were reduced in particle size by cryo-milling for a total of about 6 minutes to a final particle size <1mm.

Method: 1ml TCP granules was mixed with 1ml PDLGA 85:15 granules. 0.5ml of NMP was added and the mixture was stirred and kneaded with a spatula until it formed a putty-like consistency. The mass could be moulded in the hands. It was placed in a cylindrical plastic mould (internal diameter = 11.8mm) and packed using finger pressure. The material was then pushed out of the mould and was seen to maintain its shape. It was placed in deionized water at room temperature. After approximately 5 minutes the sample was removed

and had hardened sufficiently that it was no longer mouldable. It was observed that the material had maintained porosity between the fused granules.

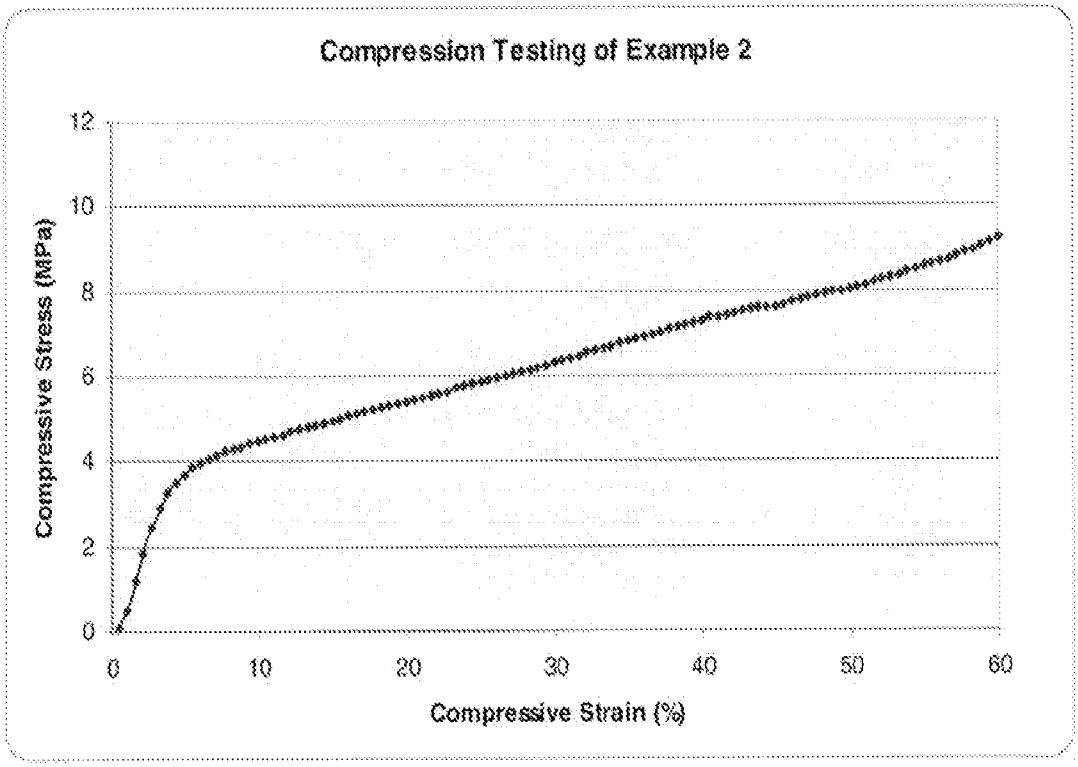
The sample was stored overnight in deionized water at 37°C. After 24 hours the cylindrical samples were all cut to a height of 1.5cm and tested in compression using an Instron 5569 Universal Testing Machine at a rate of 5mm/min.

Compression testing gave a yield stress of 5.5MPa. There was no peak in the stress-strain curve indicating a tough material.



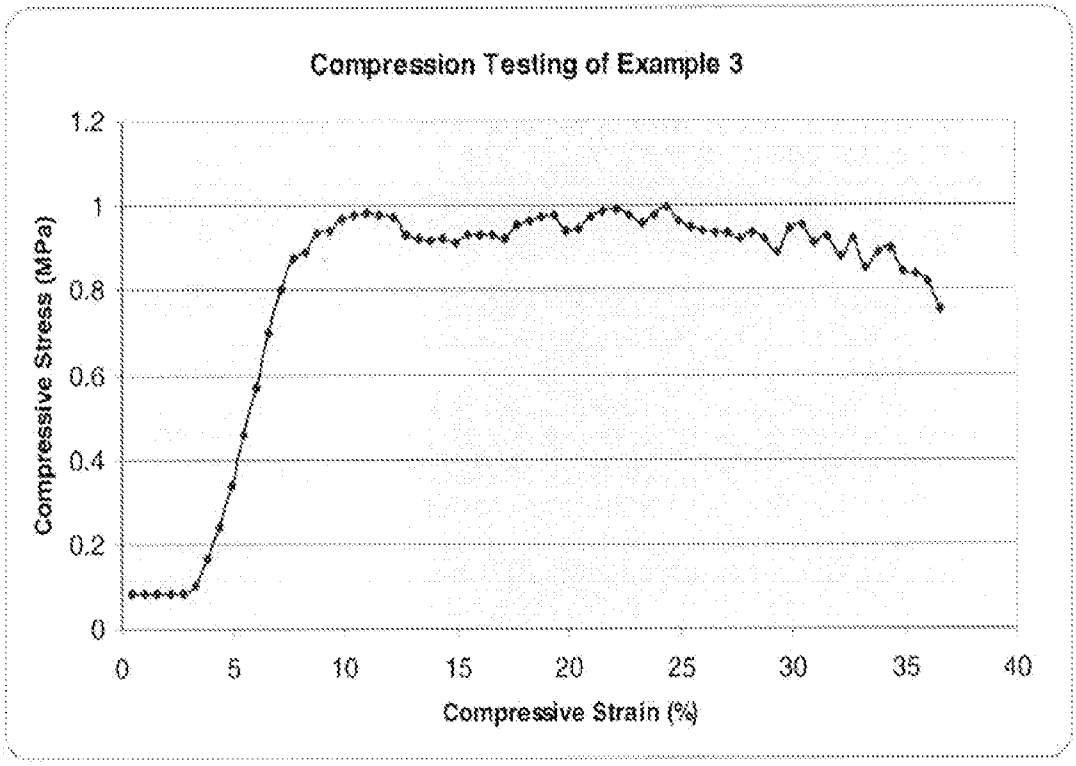

Example 2

Example 1 was repeated but this time 1ml of NMP was added. In this case the polymer granules fully dissolved and a solid plug was formed with less visible porosity. The sample was stored in deionized water at 37°C and tested in compression as described in Example 1. Compression testing gave a yield stress of 4MPa. There was no peak in the stress-strain curve indicating a tough material.



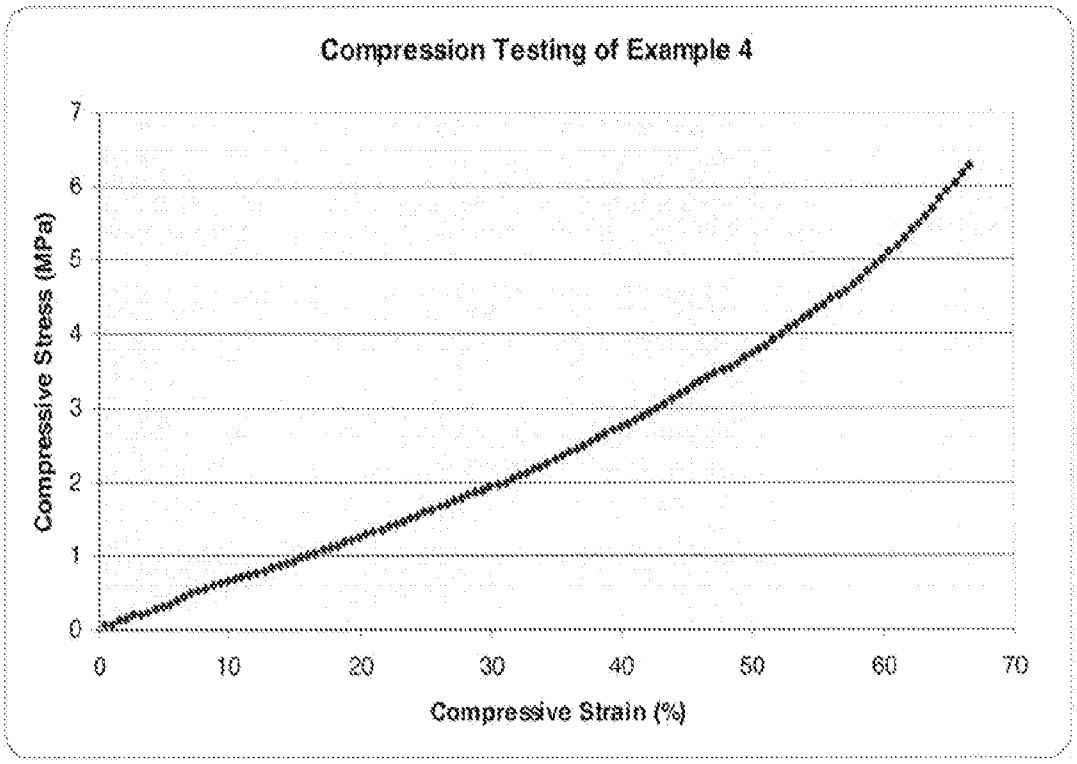

Example 3

1ml of TCP was mixed with 0.25ml of PDLGA 85:15. 1ml of NMP was then added and stirred to dissolve the polymer. The mixture in this case was flowable and less putty-like than the previous examples. However, when 1ml of water was added to the mass it immediately became more cohesive and putty-like. It was packed into the mould using finger pressure as before and then pushed out into deionized water. After about 5 minutes the sample was removed and the plug had hardened. It appeared more porous than examples 1 and 2. The sample was stored in deionized water at 37°C and tested in compression as described in Example 1. Compression testing gave a peak stress of 1MPa.



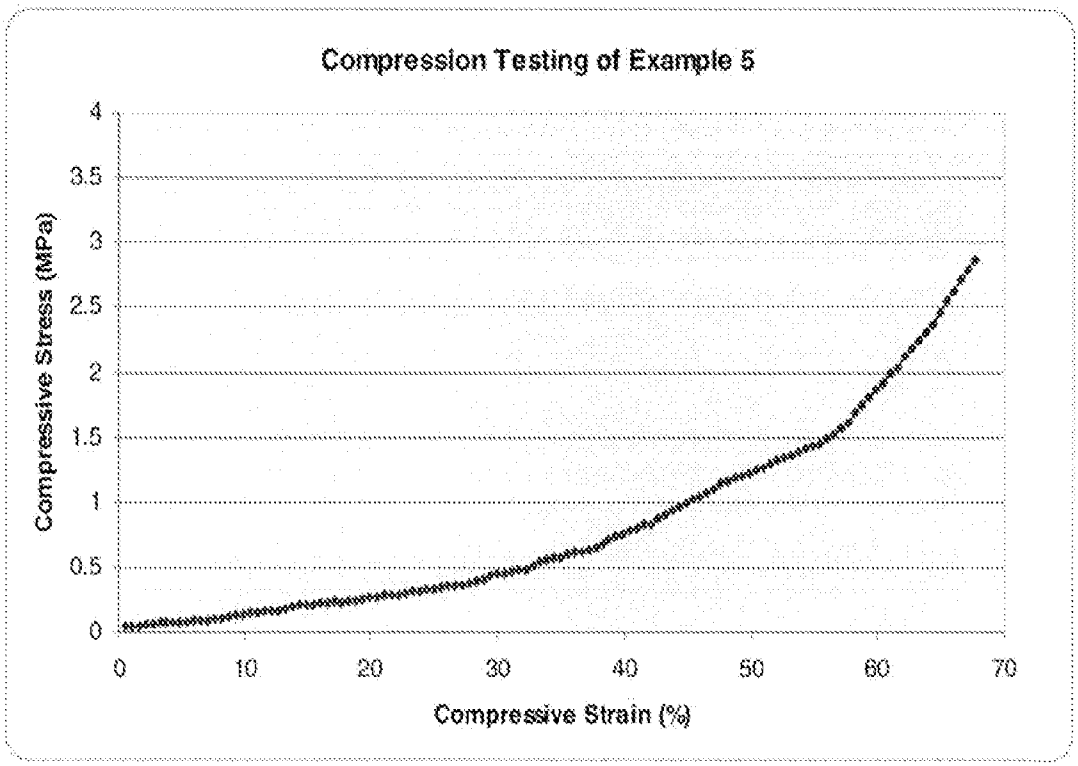

Example 4

0.5ml of TCP was mixed with 0.5ml sucrose (granulated – supplied by Sigma-Aldrich, Product Code 84097) and 0.5ml PDLGA 85:15. 0.5ml NMP was added to the mixture and stirred and kneaded with a spatula to form a putty. Again the mixture was packed into the mould then pushed out into water. After about 5 minutes the sample was removed and examined and seen to have hardened. Pores were visible between the granules and also from the dissolution of the sucrose. The sample was stored in deionized water at 37°C and tested in compression as described in Example 1. The sample gradually collapsed under compression and no yield point or peak stress was visible on the stress-strain curve.



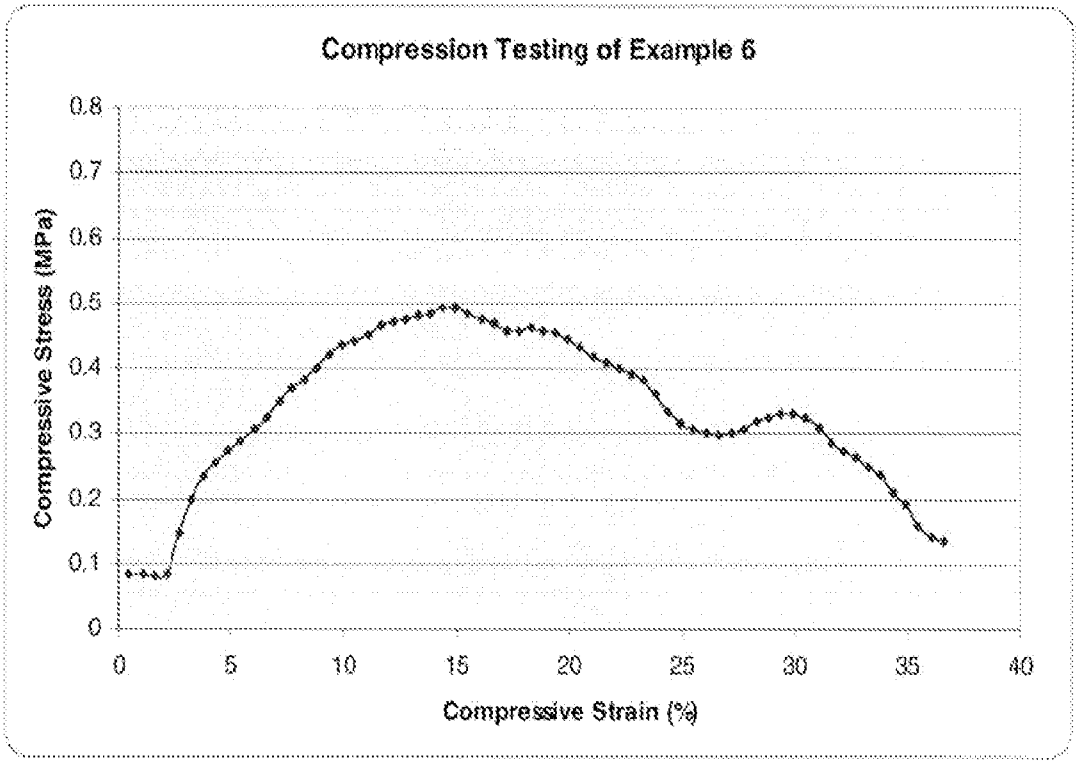

Example 5

0.5ml TCP was mixed with 0.5 ml sucrose and 0.25 ml PDLGA 85:15. 1 ml of NMP was added. As for Example 3, a flowable system was formed. 0.5 ml water was added and this caused the mixture to form a putty-like consistency. Again it was packed into the mould and pushed out into water. After about 5 minutes the sample was examined and seen to have hardened. Pores were visible between the granules and also from the dissolution of the sucrose. The sample was stored in deionized water at 37°C and tested in compression as described in Example 1. The sample gradually collapsed under compression and no yield point or peak stress was visible on the stress-strain curve.




Example 6

1ml TCP was mixed with 0.5ml powdered PDLGA 50:50 (supplied by Aldrich (The PLGA was not cryo-milled as it was already in powdered form). 0.2ml NMP was added dropwise to the dry constituents and thoroughly mixed by hand with a spatula to form a loosely cohesive mass. Five drops of deionised water were then added with further mixing to produce a mouldable putty. This was packed and compressed into the mould and then pushed out into deionised water. The sample quickly hardened to form a porous cylindrical plug. The sample was stored in deionized water at 37°C and tested in compression as described in Example 1. Compression testing gave a peak stress of 0.5MPa.




Example 7

1ml TCP was mixed with 0.2ml powdered PDLGA (50:50). 0.15ml NMP was added dropwise to the dry constituents and thoroughly mixed by hand with a spatula to form a loosely cohesive mass. Five drops of deionised water were then added with further mixing to produce a mouldable putty. This was packed and compressed into the mould and then pushed out into deionised water. The sample quickly hardened to form a porous cylindrical plug. The sample was stored in deionized water at 37°C and tested in compression as described in Example 1. Compression testing gave a peak stress of 1.25MPa.

Example 8

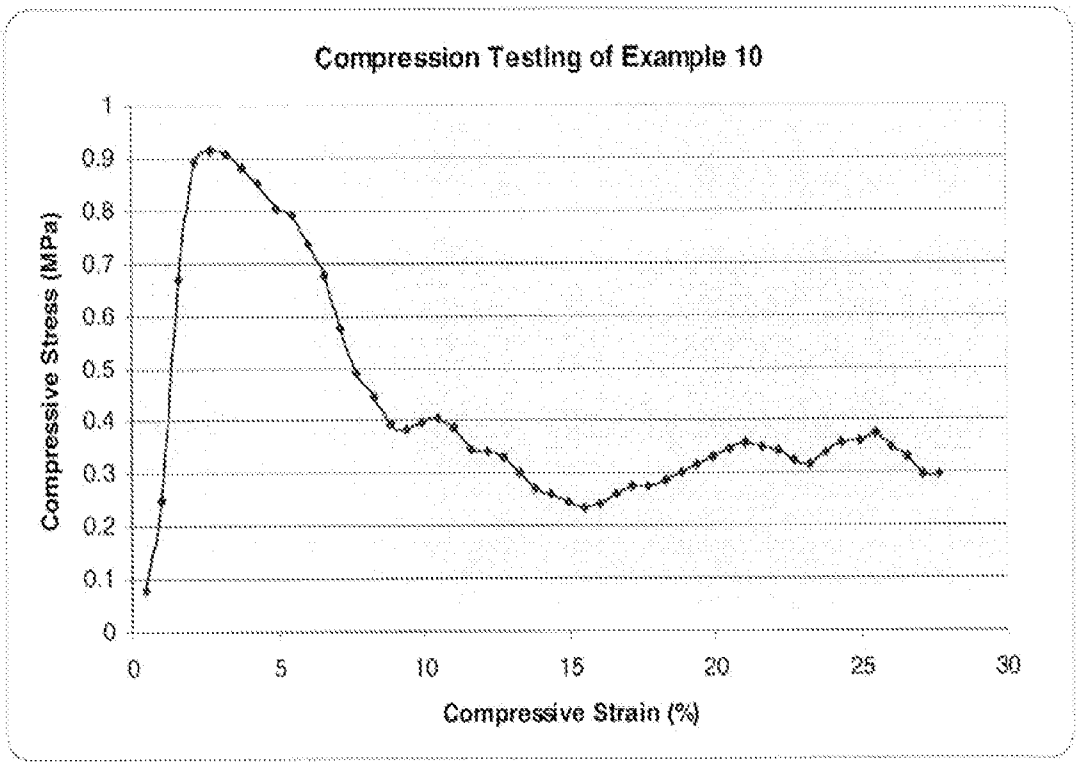
1ml TCP was mixed with 0.1ml powdered PDLGA (50:50). 0.15ml NMP was added dropwise to the dry constituents and thoroughly mixed by hand with a spatula to form a loosely cohesive mass. Five drops of deionised water were then added with further mixing to produce a mouldable putty. This was packed and compressed into the mould and then pushed out into deionised water. The sample quickly hardened to form a porous cylindrical plug. The sample was too friable to undergo compression testing.

Example 9

0.5ml TCP granules were combined with 0.5ml hydroxyapatite granules (2-3 mm – supplied by Plasma Biotal Ltd)) and 0.2ml powdered PDLGA (50:50). 0.25 ml NMP was added dropwise to the dry mixture and thoroughly mixed with a spatula. The further addition of 5 drops of deionised water produced a cohesive putty that was packed into the mould and then released out into deionised water. The sample quickly hardened to form a porous cylindrical plug. The sample was too friable to undergo compression testing.

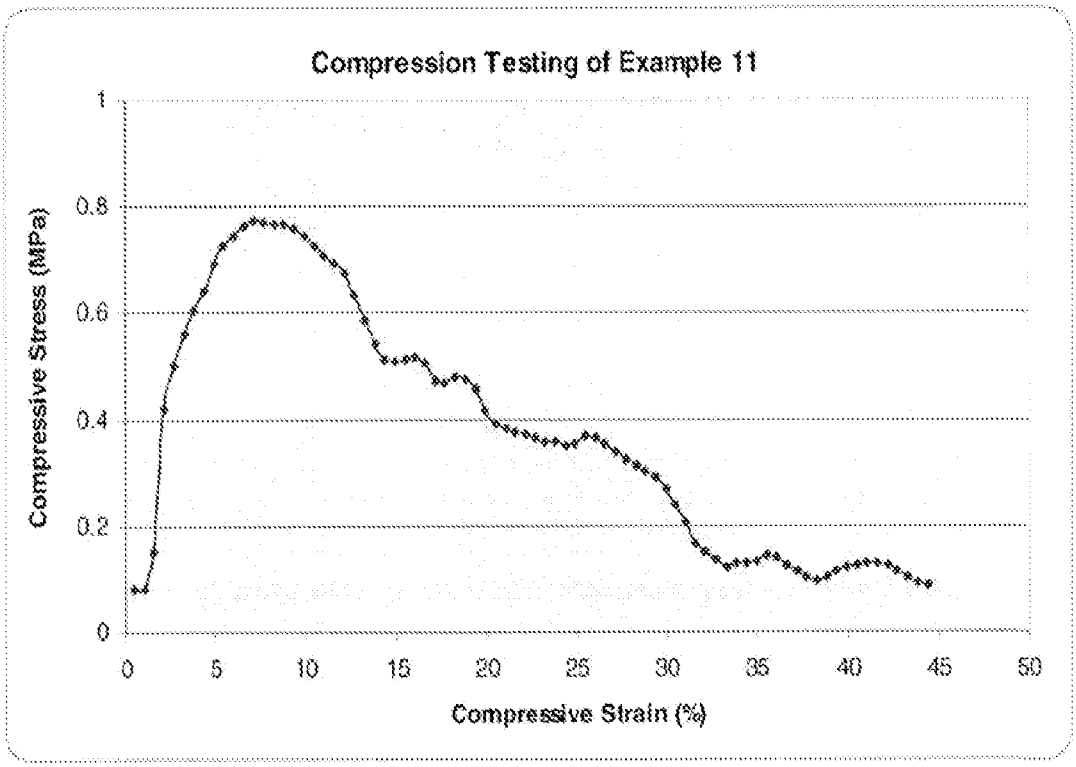
Example 10

0.4ml TCP granules were combined with 1.2ml hydroxyapatite granules (2-3 mm) and 0.8ml powdered PDLGA (50:50). 0.25 ml NMP was added dropwise to the dry mixture and thoroughly mixed with a spatula. The further addition of 5 drops of deionised water produced a cohesive putty that was packed into the mould and then released out into deionised water. The sample quickly hardened to form a porous cylindrical plug. The sample was stored in deionized water at 37°C and tested in compression as described in Example 1. Compression testing gave a peak stress of 0.9MPa.



Example 11

1ml of TCP was mixed with 0.25ml of PDLGA (85:15). 1ml of ε-caprolactone (supplied by Acros Organics) was then added and stirred to form a flowable mass. The material was packed into the mould and 1ml of water was added. The plug could then be pushed out of the mould into deionized water. After about 5 minutes the sample was removed and examined. It was a cohesive porous cylinder but still quite soft; it had fully hardened after 16 hours. The sample was stored in deionized water at 37°C and tested in compression as described in Example 1. Compression testing gave a peak stress of 0.8MPa.




Example 12

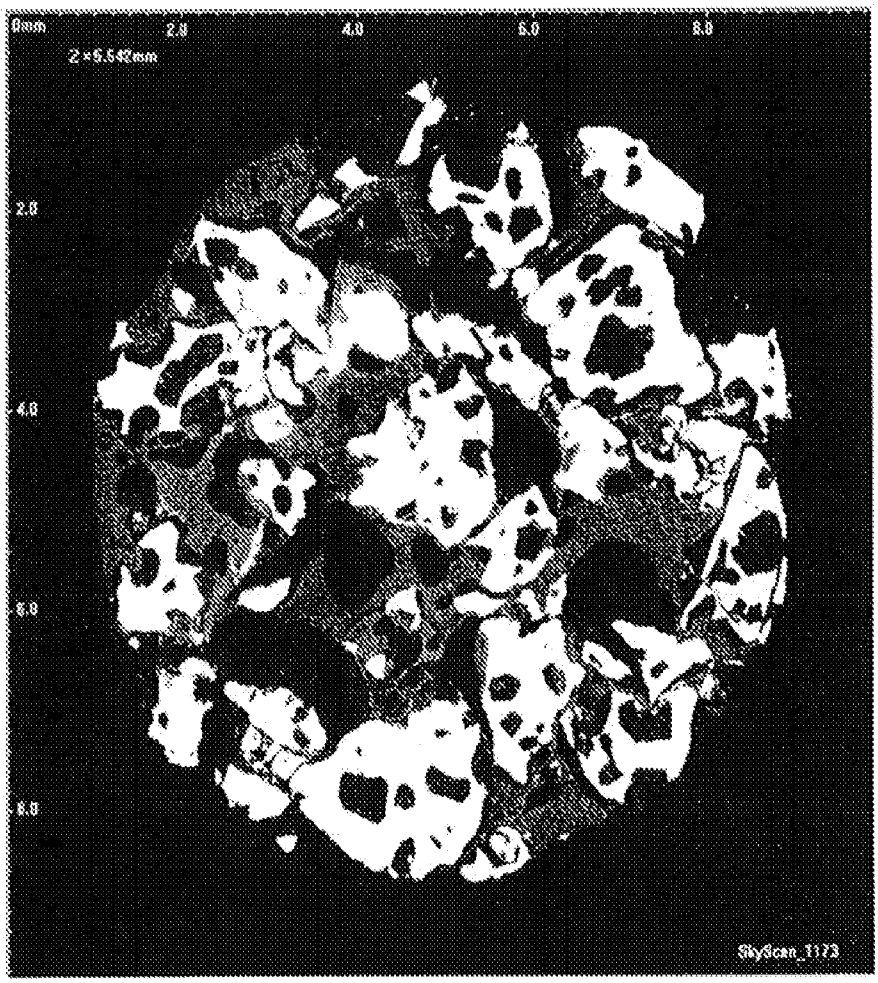
1ml TCP was mixed with 0.25ml PDLGA 85:15 and then 0.98g NMP was added. The mixture was stirred to form a mouldable mass and was then packed into a cylindrical mould (internal diameter = 8.5mm) and compressed using finger pressure. The plug of material was pushed out into deionized water and was seen to harden instantly on contact with the water.

The sample was stored in deionized water for 24hours and then removed and air dried.

The sample was prepared for Micro-CT analysis by mounting the bone void filler specimen directly onto a brass pin sample holder using an adhesive tab on the base of the bone void filler. Micro-CT images were acquired on a Skyscan 1173 Micro-CT using a micro focused X-ray source with a voltage of 85kV and a current of 68µA. X-ray shadow images were acquired with a 0.4 deg step size over a 180 deg acquisition angle, with 4 averages and 6µm resolution. The X-ray shadow images were reconstructed into a stack of 2D cross-sections using a reconstruction program (N-Recon) supplied by Skyscan. The Micro-CT images were reconstructed using a smoothing factor of 2, a ring artefact correction of 12 and a beam hardness correction factor between 50%-65%.

The results from the micro-CT scanning were as follows:

| | |
|---|---|
| % Open Pore Space | 41.0 |
| % Closed Pore Space | 0.9 |
| Total % Pore Space | 41.9 |
| % Material | 58.1 |




The sample was then tested in compression using an Instron 5569 Universal testing Machine at a rate of 2.5mm/min. The sample had a compressive modulus of 2.33MPa and a failure stress of 0.13MPa.

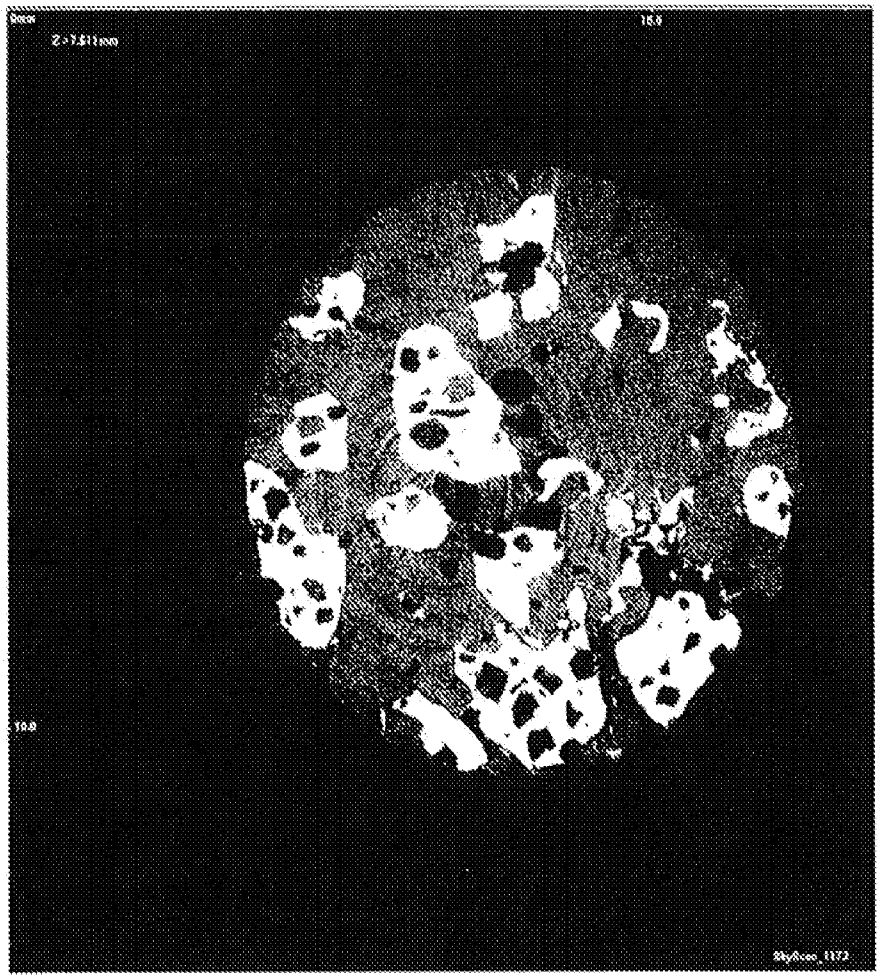
Example 13

1ml TCP was mixed with 1ml PDLGA 85:15 and then 0.5g NMP was added. The mixture was stirred to form a mouldable mass and was then packed into a cylindrical mould (internal diameter = 8.5mm) and compressed using finger pressure. The plug of material was pushed out into deionized water and was seen to harden instantly on contact with the water.

The sample was stored in deionized water for 24hours and then removed and air dried.

The sample was analysed by micro-CT as described in Example 12. The results from the micro-CT scanning were as follows:

| | |
|---|---|
| % Open Pore Space | 19.8 |
| % Closed Pore Space | 1.6 |
| Total % Pore Space | 21.4 |
| % Material | 78.6 |



The sample was then tested in compression as described in Example 12. The sample had a compressive modulus of 77.0MPa and a failure stress of 3.78MPa.

Example 14

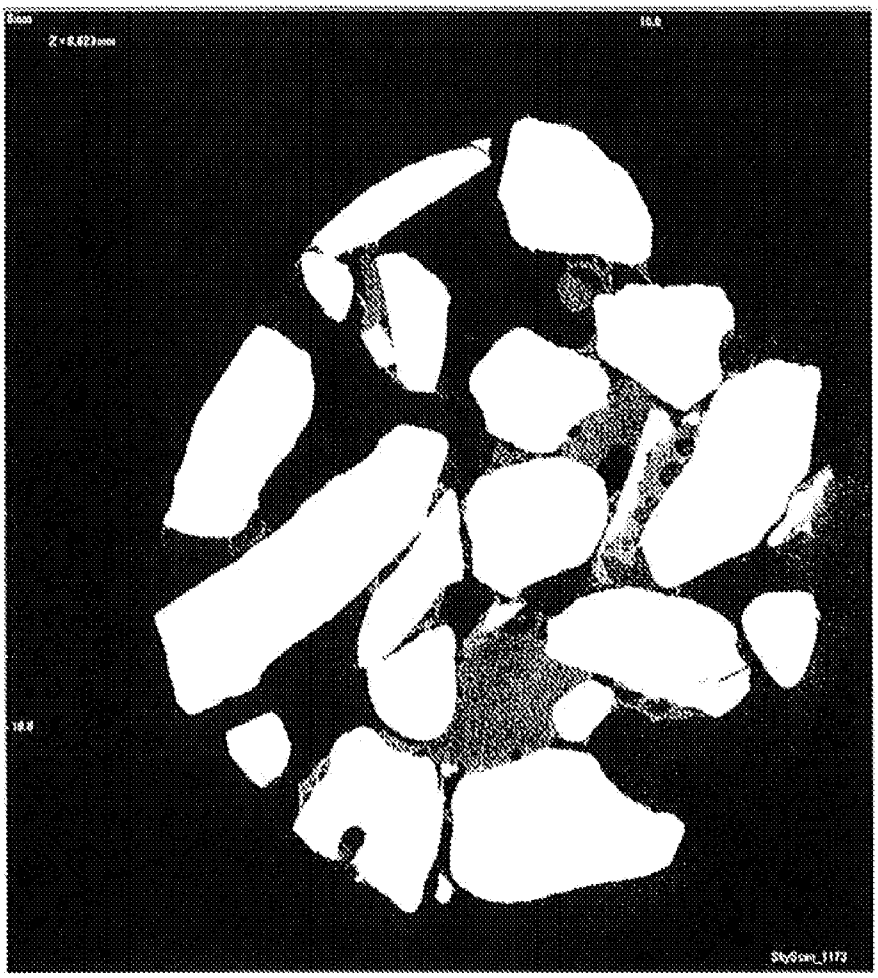
2ml (=2.13g) HA granules (2-3mm, Plasma Biotal) was mixed with 0.24g PDLGA 85:15 and then 0.49g NMP was added. The mixture was stirred to dissolve the polymer and coat the ceramic particles. This formed a mouldable mass which was then packed into a cylindrical mould (internal diameter = 11.8mm) and compressed using finger pressure. The plug of material was

pushed out into deionized water and was seen to harden instantly on contact with the water.

The sample was stored in deionized water for 24hours and then removed and air dried.

The sample was analysed by micro-CT as described in Example 12. The results from the micro-CT scanning were as follows:

| | |
|---|---|
| % Open Pore Space | 41.8 |
| % Closed Pore Space | 0.1 |
| Total % Pore Space | 41.9 |
| % Material | 58.1 |



The sample was then tested in compression as described in Example 12. The sample had a compressive modulus of 1.92MPa and a failure stress of 0.14MPa.

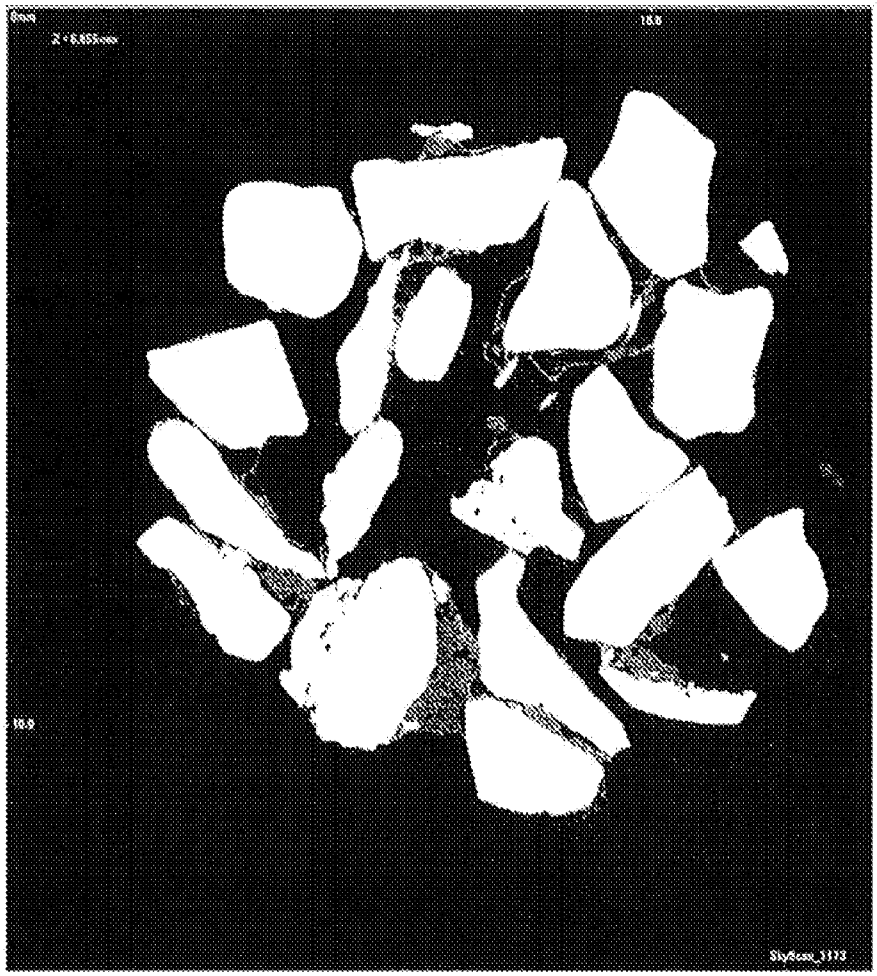
Example 15

0.19g PDLGA 85:15 was mixed with 0.37g NMP to dissolve the polymer. 2ml (=2.12g) HA granules (2-3mm, Plasma Biotal) was then mixed into the polymer solution. The mixture was stirred coat the ceramic particles. This formed a mouldable mass which was then packed into a cylindrical mould (internal diameter = 11.8mm) and compressed using finger pressure. The plug of material was pushed out into deionized water and was seen to harden instantly on contact with the water.

The sample was stored in deionized water for 24hours and then removed and air dried.

The sample was analysed by micro-CT as described in Example 12. The results from the micro-CT scanning were as follows:

| | |
|---|---|
| % Open Pore Space | 39.7 |
| % Closed Pore Space | 0.1 |
| Total % Pore Space | 39.8 |
| % Material | 60.2 |



The sample was then tested in compression as described in Example 12. The sample had a compressive modulus 3.21 and a failure stress of 0.18MPa.

Example 16

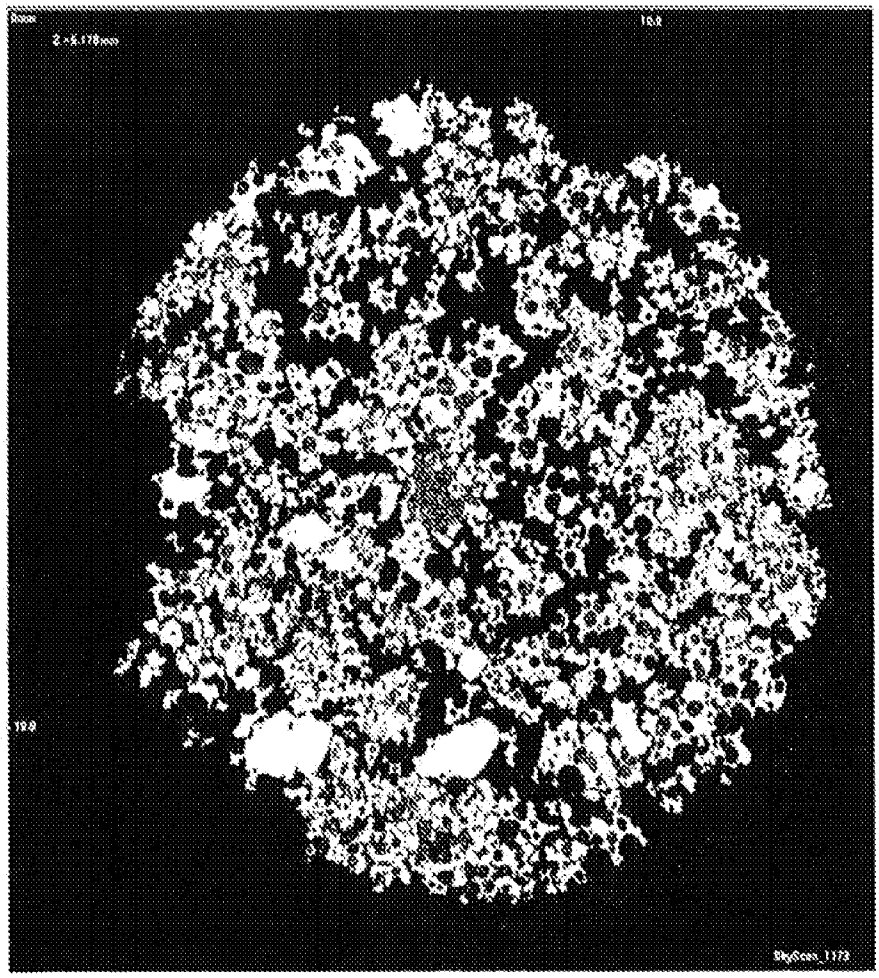
A 33.3% w/w solution of PLGA 85:15 in NMP was prepared by mixing 3g PDLGA with 6g NMP and allowing to stand overnight at room temperature until the polymer was fully dissolved.

4ml (=1.46g) HA/TCP granules (0.8-1.5mm, supplied by Ceramisys Ltd) was mixed with 0.52g of the 33.3% PDLGA solution and stirred thoroughly to coat the granules. The resulting mass was packed into a cylindrical mould (internal diameter = 11.8mm) and compressed using finger pressure. The plug of material was pushed out into deionized water and was seen to harden instantly on contact with the water.

The sample was stored in deionized water for 3 days and then removed and air dried.

The sample was analysed by micro-CT as described in Example 12. The results from the micro-CT scanning were as follows:

| | |
|---|---|
| % Open Pore Space | 44.5 |
| % Closed Pore Space | 0.4 |
| Total % Pore Space | 44.9 |
| % Material | 55.1 |



The sample was then tested in compression as described in Example 12. The sample had a compressive modulus of 3.96MPa and a failure stress of 0.24MPa.

Example 17

2ml (=2.18g) HA granules (2-3mm, plasma Biotal) was mixed with 0.53g of the 33.3% PDLGA solution used in Example 16 and stirred thoroughly to coat the granules. The resulting mass was packed into a cylindrical mould (internal diameter = 11.8mm) and compressed using finger pressure. The plug of material was pushed out into deionized water and was seen to harden instantly on contact with the water.

The sample was stored in deionized water for 3 days and then removed and air dried.

The sample was analysed by micro-CT as described in Example 12. The results from the micro-CT scanning were as follows:

| | |
|---|---|
| % Open Pore Space | 42.9 |
| % Closed Pore Space | 0.0 |
| Total % Pore Space | 42.9 |
| % Material | 57.1 |

The sample was then tested in compression as described in Example 12. The sample had a compressive modulus of 13.3MPa and a failure stress of 0.37MPa.

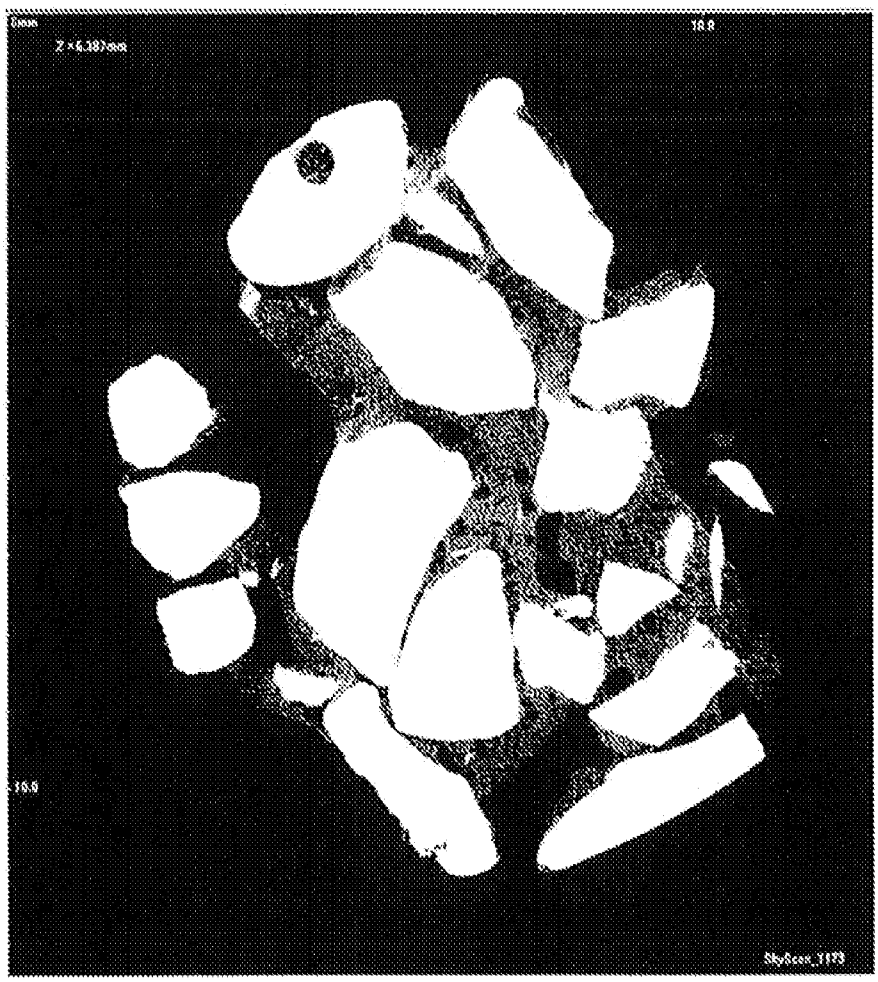
Example 18

2ml (=2.12g) HA granules (2-3mm, plasma Biotal) was mixed with 0.70g of the 33.3% PDLGA solution used in Example 16 and stirred thoroughly to coat the granules. The resulting mass was packed into a cylindrical mould (internal diameter = 11.8mm) and compressed using finger pressure. The plug of material was pushed out into deionized water and was seen to harden instantly on contact with the water.

The sample was stored in deionized water for 24 hours and then removed and air dried.

The sample was analysed by micro-CT as described in Example 12. The results from the micro-CT scanning were as follows:

| | |
|---|---|
| % Open Pore Space | 36.0 |
| % Closed Pore Space | 0.1 |
| Total % Pore Space | 36.1 |
| % Material | 63.9 |



The sample was then tested in compression as described in Example 12. The sample had a compressive modulus of 31.5MPa and a failure stress of 1.52MPa.

Example 19

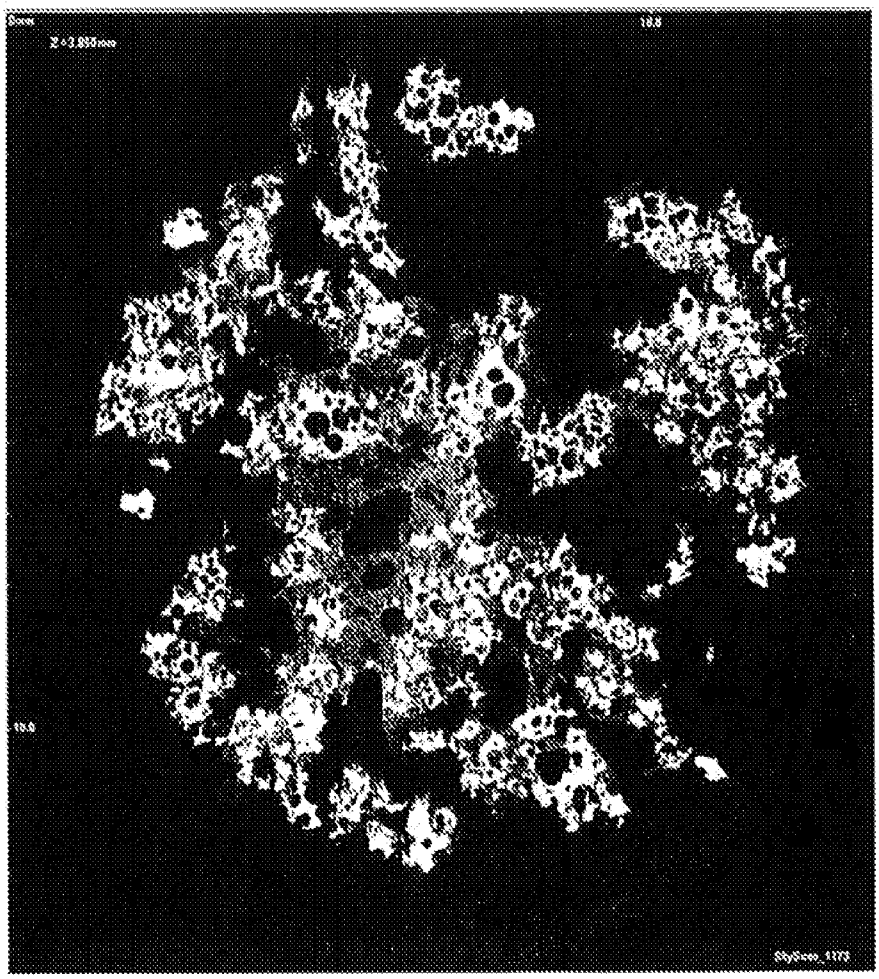
2ml (=0.72g) HA/TCP granules (0.8-1.5mm, Ceramisys) was mixed with 2ml (=1.72g) sucrose, then further mixed with 0.70g of the 33.3% PDLGA solution used in Example 16 and stirred thoroughly to coat the granules. The resulting

mass was packed into a cylindrical mould (internal diameter = 11.8mm) and compressed using finger pressure. The plug of material was pushed out into deionized water and was seen to harden instantly on contact with the water but with some shedding of ceramic particles. The sucrose was also seen to dissolve, creating pores.

The sample was stored in deionized water for 24 hours and then removed and air dried.

The sample was analysed by micro-CT as described in Example 12. The results from the micro-CT scanning were as follows:

| | |
|---|---|
| % Open Pore Space | 55.3 |
| % Closed Pore Space | 0.5 |
| Total % Pore Space | 55.8 |
| % Material | 44.2 |



The sample was then tested in compression as described in Example 12. The sample had a compressive modulus of 6.07MPa and a failure stress of 2.13MPa.

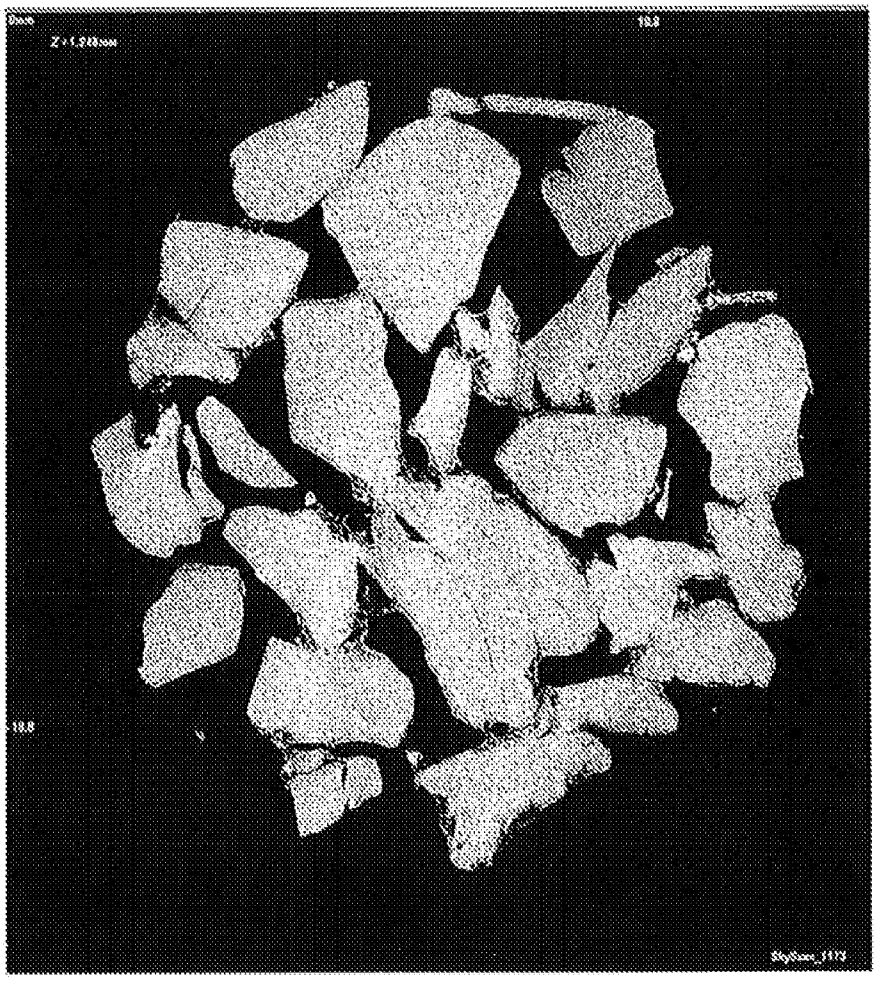
Example 20

2.5ml PDLGA 85:15 granules (as received – not cryo-milled) was mixed with 0.32g NMP. The NMP made the polymer granules tacky so that a mouldable cohesive mass was formed. This was packed into a cylindrical mould (internal diameter = 11.8mm) and compressed using finger pressure. The plug of material was pushed out into deionized water and was seen to harden instantly on contact with the water.

The sample was stored in deionized water for 24 hours and then removed and air dried.

The sample was analysed by micro-CT as described in Example 12. The results from the micro-CT scanning were as follows:

| | |
|---|---|
| % Open Pore Space | 37.7 |
| % Closed Pore Space | 0.2 |
| Total % Pore Space | 37.9 |
| % Material | 62.1 |



The sample was then tested in compression as described in Example 12. The sample had a compressive modulus of 26.5MPa and a failure stress of 3.65MPa.

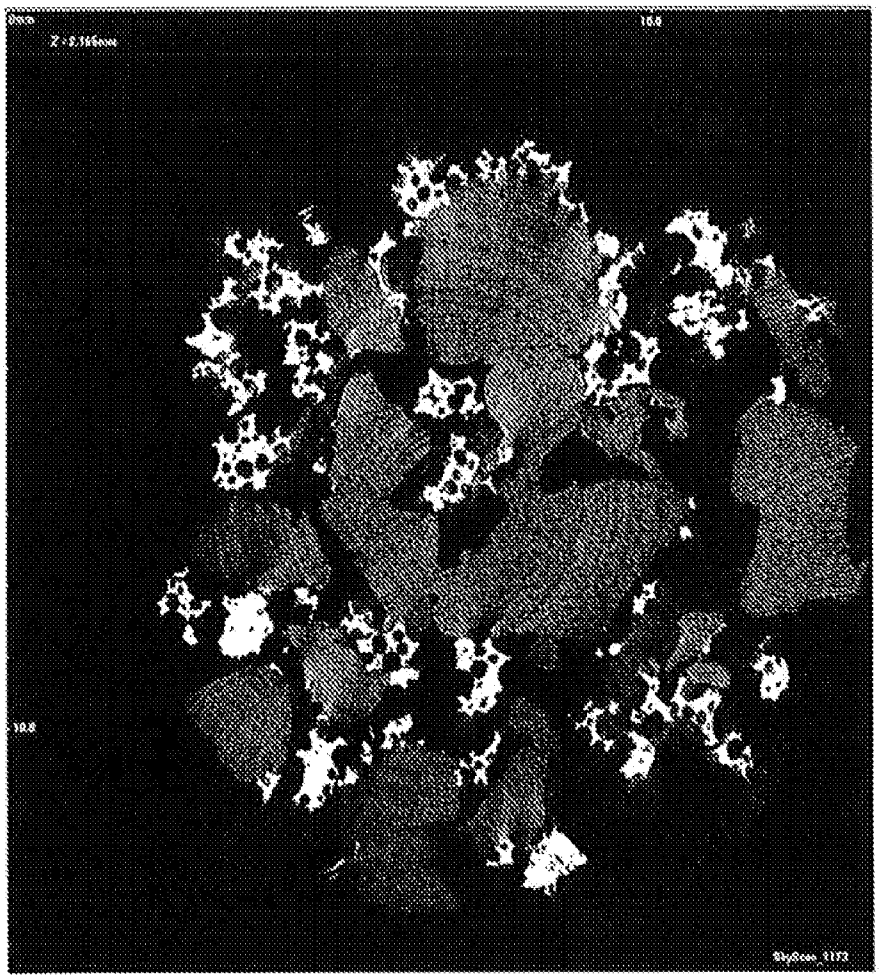
Example 21

1.25ml PDLGA 85:15 granules (as received – not cryo-milled) was mixed with 1.25ml HA/TCP (0.8-1.5mm, Ceramisys) and further mixed with 0.33g NMP. The NMP made the polymer granules tacky so that a mouldable cohesive mass was formed. This was packed into a cylindrical mould (internal diameter = 11.8mm) and compressed using finger pressure. The plug of material was pushed out into deionized water and was seen to harden instantly on contact with the water. There was some shedding of ceramic particles from the surface when the plug was dispensed into water.

The sample was stored in deionized water for 24 hours and then removed and air dried.

The sample was analysed by micro-CT as described in Example 12. The results from the micro-CT scanning were as follows:

| | |
|---|---|
| % Open Pore Space | 42.6 |
| % Closed Pore Space | 1.2 |
| Total % Pore Space | 43.8 |
| % Material | 56.2 |



The sample was then tested in compression as described in Example 12. The sample had a compressive modulus of 0.97MPa and a failure stress of 0.16MPa.

Table 1 below summarises the compositions and results from Examples 1-11

| | | | | | | | | | | | Compression Test | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Example No. | Ceramic Type | PDLGA Type | Porogen Type | Solvent | Ceramic Vol. (ml) | PDLGA Vol. (ml) | Solvent Vol. (ml) | Porogen Vol. (ml) | Water | | Load at Yield (MPa) | Peak Load (MPa) |
| 1 | TCP Porous Granules (1-2mm) | 85:15 | None | NMP | 1 | 1 | 0.5 | 0 | None | | 5.5 | NA |
| 2 | TCP Porous Granules (1-2mm) | 85:15 | None | NMP | 1 | 1 | 1 | 0 | None | | 8 | NA |
| 3 | TCP Porous Granules (1-2mm) | 85:15 | None | NMP | 1 | 0.25 | 1 | 0 | None | | N/A | 1 |
| 4 | TCP Porous Granules (1-2mm) | 85:15 | Sucrose | NMP | 0.5 | 0.5 | 0.5 | 0.5 | None | | N/A | N/A |
| 5 | TCP Porous Granules (1-2mm) | 85:15 | Sucrose | NMP | 0.5 | 0.25 | 1 | 0.5 | 0.5ml | | N/A | N/A |
| 6 | TCP Porous Granules (1-2mm) | 85:50 | None | NMP | 1 | 0.5 | 0.2 | 0 | 5 drops | | N/A | 0.5 |
| 7 | TCP Porous Granules (1-2mm) | 50:50 | None | NMP | 1 | 0.2 | 0.15 | 0 | 5 drops | | N/A | 1.25 |
| 8 | TCP Porous Granules (1-2mm) | 50:50 | None | NMP | 1 | 0.1 | 0.15 | 0 | 5 drops | | Not tested | |
| 9 | TCP Porous Granules: HA Dense granules 50:50 | 50:50 | None | NMP | 1 | 0.2 | 0.25 | 0 | 5 drops | | Not tested | |
| 10 | TCP Porous Granules: HA Dense granules 25:75 | 50:50 | None | NMP | 1.6 | 0.8 | 0.25 | 0 | 5 drops | | N/A | 0.9 |
| 11 | TCP Porous Granules (1-2mm) | 85:15 | None | Caprolactone | 1 | 0.25 | 1 | 0 | None | | N/A | 0.8 |

Table 2 below summarises the compositions from Examples 12-21.

| Example No | Ceramic Type | PDLGA Type | Ceramic Vol (ml) | Ceramic Mass (g) | PDLGA Vol (ml) | PDLGA mass (g) | NMP mass (g) | Porogen (Sucrose) mass (g) |
|---|---|---|---|---|---|---|---|---|
| 12 | TCP Porous Granules (1-2mm) | Cryo-milled | 1 | | 0.25 | | 0.88 | 0 |
| 13 | TCP Porous Granules (1-2mm) | Cryo-milled | 1 | | 1 | | 0.50 | 0 |
| 14 | HA Dense Granules (2-3mm) | Cryo-milled | 2 | 2.13 | | 0.24 | 0.49 | 0 |
| 15 | HA Dense Granules (2-3mm) | Cryo-milled | 2 | 2.12 | | 0.19 | 0.37 | 0 |
| 16 | HA/TCP Porous Granules (0.8-1.5mm) | Solution | 4 | 3.46 | | 0.17 | 0.35 | 0 |
| 17 | HA Dense Granules (2-3mm) | Solution | 2 | 2.18 | | 0.18 | 0.35 | 0 |
| 18 | HA Dense Granules (2-3mm) | Solution | 2 | 2.12 | | 0.23 | 0.47 | 0 |
| 19 | HA/TCP Porous Granules (0.8-1.5mm) | Solution | 2 | 0.72 | | 0.23 | 0.47 | 1.72 |
| 20 | None | As received granules | 0 | | 2.5 | | 0.32 | 0 |
| 21 | HA/TCP Porous Granules (0.8-1.5mm) | As received granules | 1.25 | | 1.25 | | 0.33 | 0 |

Table 3 below summarises the testing results from Examples 12-21.

| Example No | % Open Pore Space | % Closed Pore Space | Total % Pore Space | % Material | Modulus (MPa) | Stress at Failure (MPa) |
|---|---|---|---|---|---|---|
| 12 | 41.0 | 0.9 | 41.9 | 58.1 | 2.33 | 0.13 |
| 13 | 19.8 | 1.6 | 21.4 | 78.6 | 77.00 | 3.78 |
| 14 | 41.8 | 0.1 | 41.9 | 58.1 | 1.92 | 0.14 |
| 15 | 39.7 | 0.1 | 39.8 | 60.2 | 3.21 | 0.18 |
| 16 | 44.5 | 0.4 | 44.9 | 55.1 | 3.96 | 0.24 |
| 17 | 42.9 | 0.0 | 42.9 | 57.1 | 13.30 | 0.37 |
| 18 | 36.0 | 0.1 | 36.1 | 63.9 | 31.50 | 1.52 |
| 19 | 55.3 | 0.5 | 55.8 | 44.2 | 6.07 | 2.13 |
| 20 | 37.7 | 0.2 | 37.9 | 62.1 | 26.50 | 3.65 |
| 21 | 42.6 | 1.2 | 43.8 | 56.2 | 0.97 | 0.16 |

The results in tables 1 and 3 show that materials able to withstand stresses up to 5MPa or higher are achievable, while still maintaining a high level of porosity. The compressive strength of cancellous bone is typically in the range 2-12MPa so it can be seen that it is possible to make bone void filling materials with strengths in this range (Examples 1, 2, 13, 19 and 20). The Young's modulus of cancellous bone is typically in the range 4-350MPa and it can also be seen that it is possible to make materials with compressive moduli in this range (Examples 13, 16, 17, 18, 19, 20). All the samples had a high degree of porosity (20-60%) as seen in Table 3 and importantly most of this is interconnected porosity with only very low levels of closed pore space, thus allowing bone in-growth throughout the material. Inclusion of a porogen (such as in Example 19) can be seen to increase the porosity.

CLAIMS:

1. An implant material for bone void filling comprising bioresorbable polymer granules and a biocompatible water-miscible solvent, wherein the solvent at least partially dissolves and/or softens the polymer granules to form a mouldable mass that can be used to fill a bone defect but which hardens when the implant material is exposed to water, and wherein the implant material has macroporosity suitable for bone in-growth.

2. An implant material according to claim 1 comprising pores of between about 50 and 3000 microns; preferably 100 and 2000 microns; more preferably 120 and 1500 microns, which pores provide a macroporosity level suitable for bone in-growth.

3. An implant material according to claim 1 or claim 2, wherein the bioresorbable polymer granules comprise particles, flakes or powder.

4. An implant material according to any one of claims 1 to 3, wherein the implant material further comprises a bioceramic material.

5. An implant material according to claim 4, wherein the bioceramic material is formed as a mixture or dispersion with the bioresorbable polymer.

6. An implant material according to claim 4 or claim 5, wherein the bioceramic material is porous and comprises granules, flakes or powder.

7. An implant material according to any one of claims 4 to 6, wherein the bioceramic material comprises pores of between about 10 and 1000 microns; preferably 15 and 500 microns; more preferably 20 and 300 microns.

8. An implant material according to any one of the preceding claims, wherein the bioresorbable polymer granules include a core formed of a different material.

9. An implant material according to claim 8, wherein the core is formed from a bioceramic material.

10. An implant material according to claim 8, wherein the core includes an inner core and an outer core, and wherein the inner core is formed from a bioceramic material and the outer core comprises a second bioresorbable polymer.

11. An implant material according to claim 10, wherein the outer core further comprises a bioactive or therapeutic agent.

12. An implant material according to any one of claims 1 to 10, wherein the implant material comprises a bioactive or therapeutic agent.

13. An implant material according to claim 12, wherein the first bioresorbable polymer further comprises the bioactive or therapeutic agent.

14. An implant material according to any one of claims 11 to 13, wherein the bioactive or therapeutic agent comprises at least one of: a growth factor such as any bone morphogenic protein (BMP), platelet derived growth factor (PDGF), growth hormone, transforming growth factor-beta (TGF-beta), insulin-like growth factor; a bone anabolic agent such as parathyroid hormone or teriparatide; an anti-resorptive agent such as a bisphosphonate (including etidronate, clodronate, tiludronate, pamidronate, neridronate, olpadronate, alendronate, ibandronate, risedronate, zoledronate),or strontium ranelate; an antibiotic such as gentamicin, vancomycin, tobramycin, erythromycin, clindamicin; an anti-cancer drug such as paclitaxel, mercatopurine; an anti-inflammatory and/or analgesic agent such as acetylsalicylic acid, ibuprofen, naproxen,indomethacine, ketoprofen or diclofenac.

15. An implant material according to claim 10 or claim 11, wherein the second bioresorbable polymer is less soluble in the biocompatible solvent than the first bioresorbable polymer.

16. An implant material according to any one of the preceding claims, wherein the bioceramic material comprises at least one of: calcium phosphate, including hydroxyapatite, a substituted hydroxyapatite (e.g. silicon, carbonate, magnesium, strontium, fluoride), tricalcium phosphate, biphasic calcium phosphate, tetracalcium phosphate, octacalcium phosphate, dicalcium phosphate dihydrate (brushite), dicalcium phosphate (monetite), calcium pyrophosphate, calcium pyrophosphate dihydrate, heptacalcium phosphate, calcium phosphate monohydrate; calcium sulphate; a bioactive glass or glass ceramic.

17. An implant material according to any one of the preceding claims, wherein the first bioresorbable polymer comprises at least one of: a polymer comprising a poly-alpha-hydroxyacid group, including poly(lactic acid), poly(glycolic acid), poly-L-lactide, poly-DL-lactide, poly(lactide-co-glycolide), poly(lactide-co-caprolactone), poly(L-lactide-co-DL-lactide), polycaprolactone; a bioresorbable polyanhydride, polyamide, polyorthoester, polydioxanone, polycarbonate, polyaminoacid, poly(amino-ester), poly(amido-carbonate), polyphosphazene, polyether, polyurethane, or polycyanoacrylate.

18. An implant material according to any one of the preceding claims, wherein the second bioresorbable polymer comprises at least one of: a polymer comprising a poly-alpha-hydroxyacid group, including poly(lactic acid), poly(glycolic acid), poly-L-lactide, poly-DL-lactide, poly(lactide-co-glycolide), poly(lactide-co-caprolactone), poly(L-lactide-co-DL-lactide), polycaprolactone; a bioresorbable polyanhydride, polyamide, polyorthoester, polydioxanone, polycarbonate, polyaminoacid, poly(amino-ester), poly(amido-carbonate), polyphosphazene, polyether, polyurethane, polycyanoacrylate; a polysaccharide comprising alginate, chitosan, carboxymethyl cellulose, hydroxypropylmethyl cellulose, dextran, or hyaluronic acid.

19. An implant material according to any one of the preceding claims, wherein the biocompatible, water miscible solvent comprises at least one

of: N-methyl-pyrollidone, dimethyl sulphoxide, acetone, poly(ethylene glycol), tetrahydrofuran, isopropanol, or caprolactone.

20. An implant material according to any one of the preceding claims, wherein the implant material includes a water soluble porogen that is not soluble in the biocompatible solvent.

21. An implant material according to claim 20, wherein the water soluble porogen comprises at least one of: a soluble inorganic salt such as sodium chloride, calcium chloride, strontium chloride, magnesium chloride, a soluble organic compound such as sucrose, glucose, lactose, calcium gluconate, calcium lactate; or a water soluble polymer such as poly(ethylene glycol), poly(ethylene oxide), poly(ethylene oxide-b-propylene oxide), poly(vinyl alcohol), poly vinyl acetate, polyacrylic acid, poly vinyl pyrrolidone, poly(vinyl phosphonic acid), polysaccharide such as carboxymethylcellulose, sodium alginate, chitosan, or dextran.

22. An implant material according to any one of the preceding claims, wherein the implant material has an open porosity of greater than 15%.

23. An implant material according to claim 22, wherein the implant material has an open porosity of between about 15%-70%; more preferably about 20%-55%; most preferably about 25%-45%.

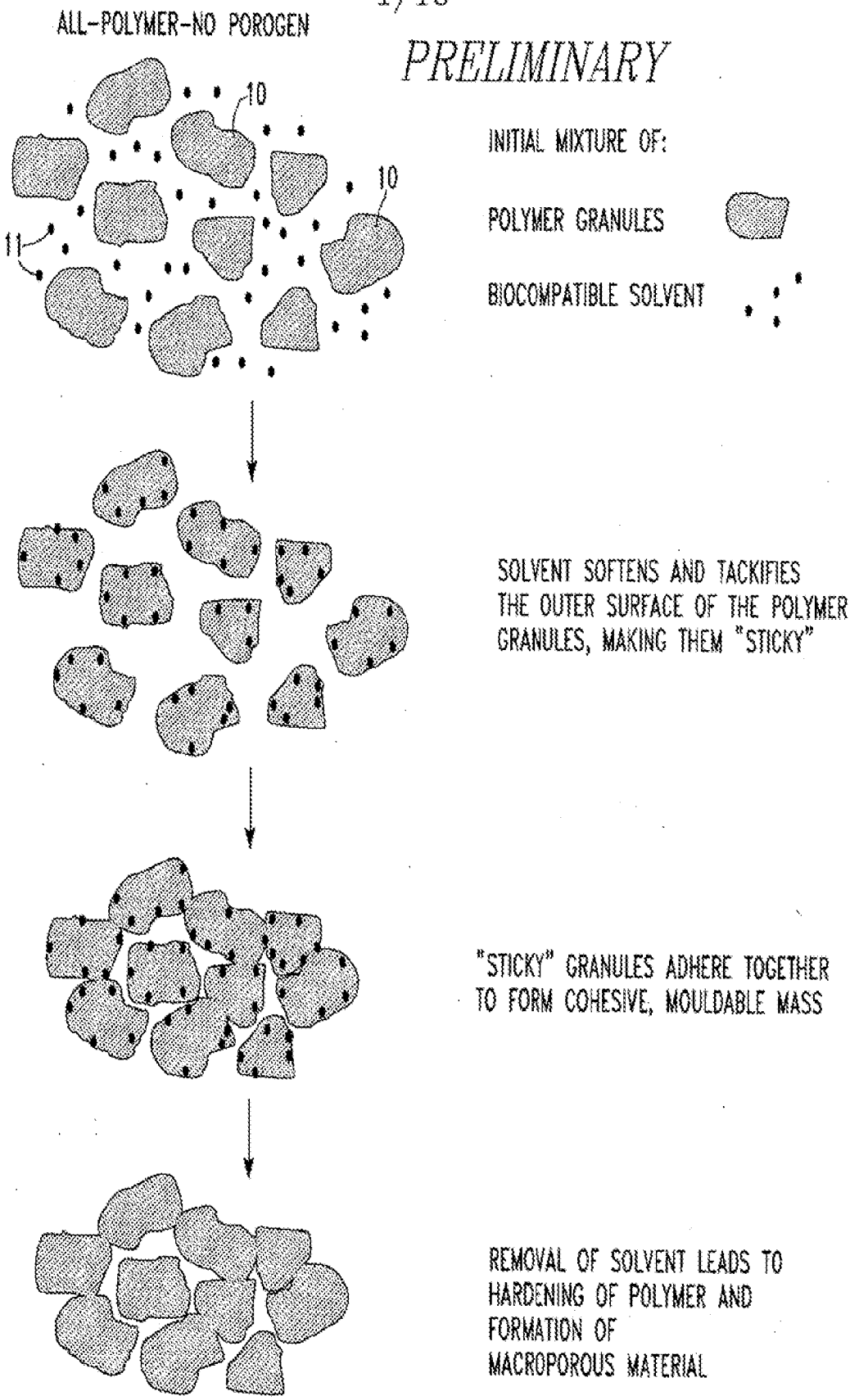

ALL-POLYMER-NO POROGEN
PRELIMINARY
10
10
11
INITIAL MIXTURE OF:
POLYMER GRANULES
BIOCOMPATIBLE SOLVENT
SOLVENT SOFTENS AND TACKIFIES THE OUTER SURFACE OF THE POLYMER GRANULES, MAKING THEM "STICKY"
"STICKY" GRANULES ADHERE TOGETHER TO FORM COHESIVE, MOULDABLE MASS
REMOVAL OF SOLVENT LEADS TO HARDENING OF POLYMER AND FORMATION OF MACROPOROUS MATERIAL

FIG.1

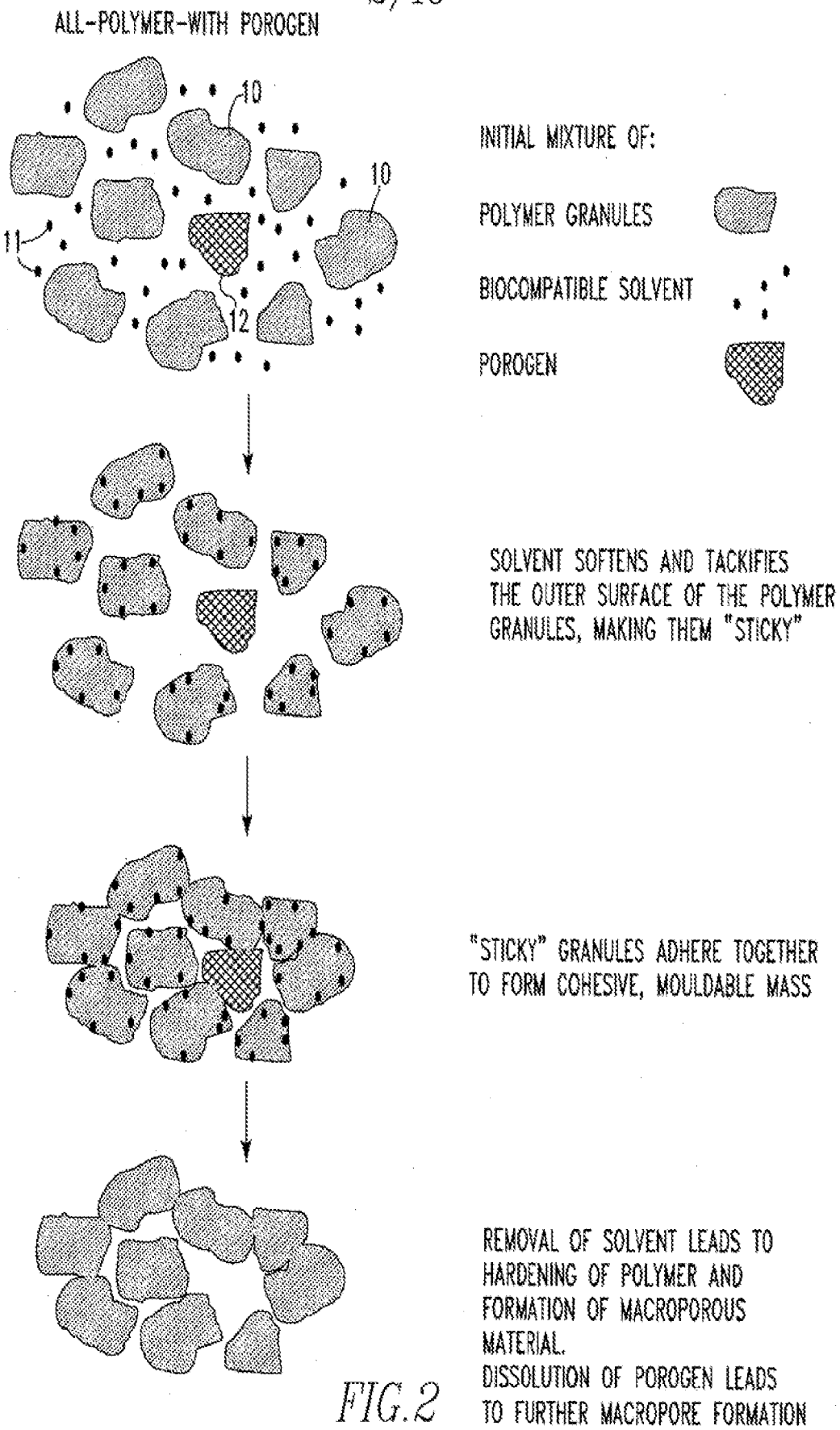

ALL-POLYMER-WITH POROGEN
10
10
11
12
INITIAL MIXTURE OF:
POLYMER GRANULES
BIOCOMPATIBLE SOLVENT
POROGEN
SOLVENT SOFTENS AND TACKIFIES THE OUTER SURFACE OF THE POLYMER GRANULES, MAKING THEM "STICKY"
"STICKY" GRANULES ADHERE TOGETHER TO FORM COHESIVE, MOULDABLE MASS
REMOVAL OF SOLVENT LEADS TO HARDENING OF POLYMER AND FORMATION OF MACROPOROUS MATERIAL.
DISSOLUTION OF POROGEN LEADS TO FURTHER MACROPORE FORMATION

FIG.2

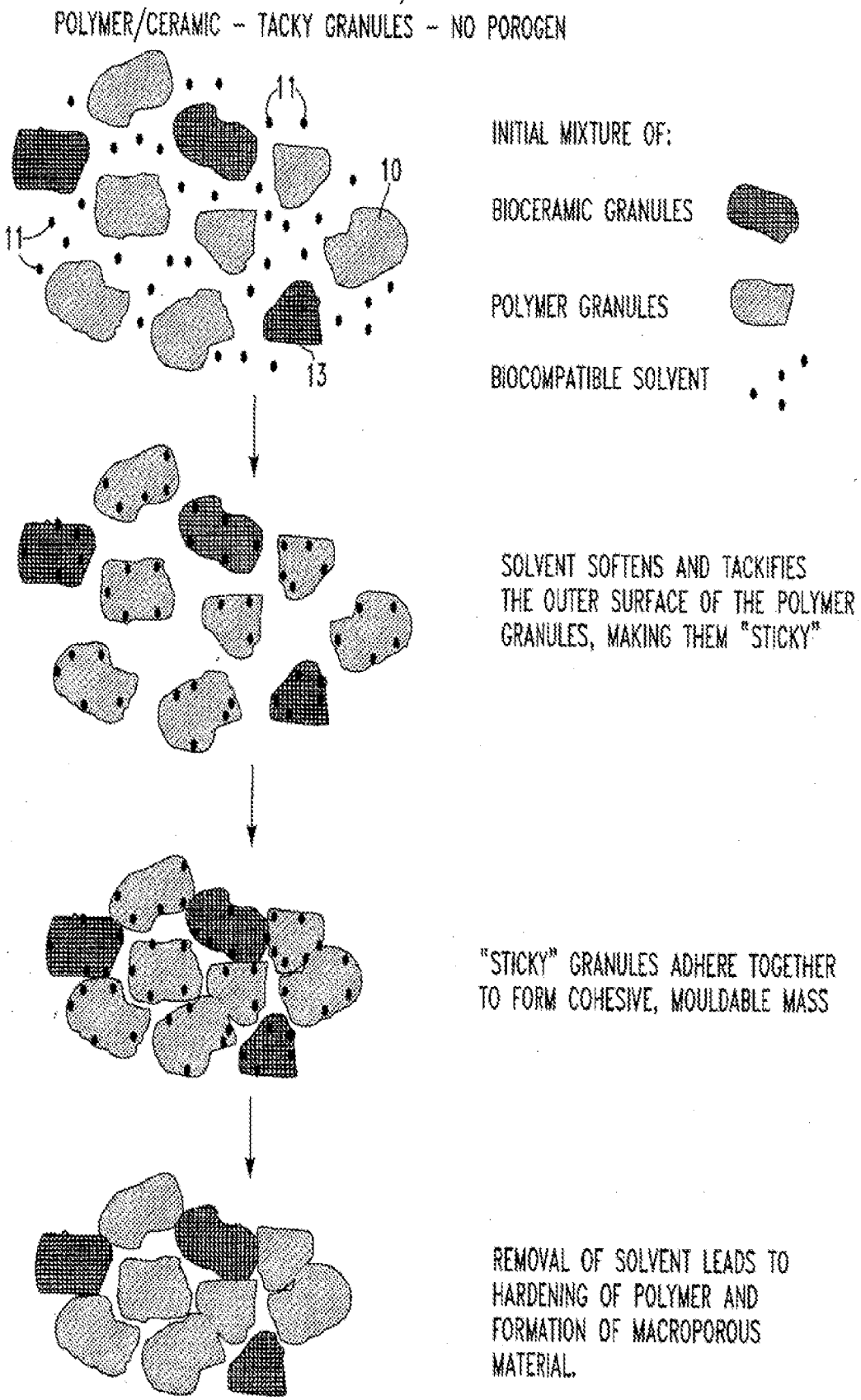

POLYMER/CERAMIC - TACKY GRANULES - NO POROGEN
11
10
11
13
INITIAL MIXTURE OF:
BIOCERAMIC GRANULES
POLYMER GRANULES
BIOCOMPATIBLE SOLVENT
SOLVENT SOFTENS AND TACKIFIES THE OUTER SURFACE OF THE POLYMER GRANULES, MAKING THEM "STICKY"
"STICKY" GRANULES ADHERE TOGETHER TO FORM COHESIVE, MOULDABLE MASS
REMOVAL OF SOLVENT LEADS TO HARDENING OF POLYMER AND FORMATION OF MACROPOROUS MATERIAL.

*FIG. 3*

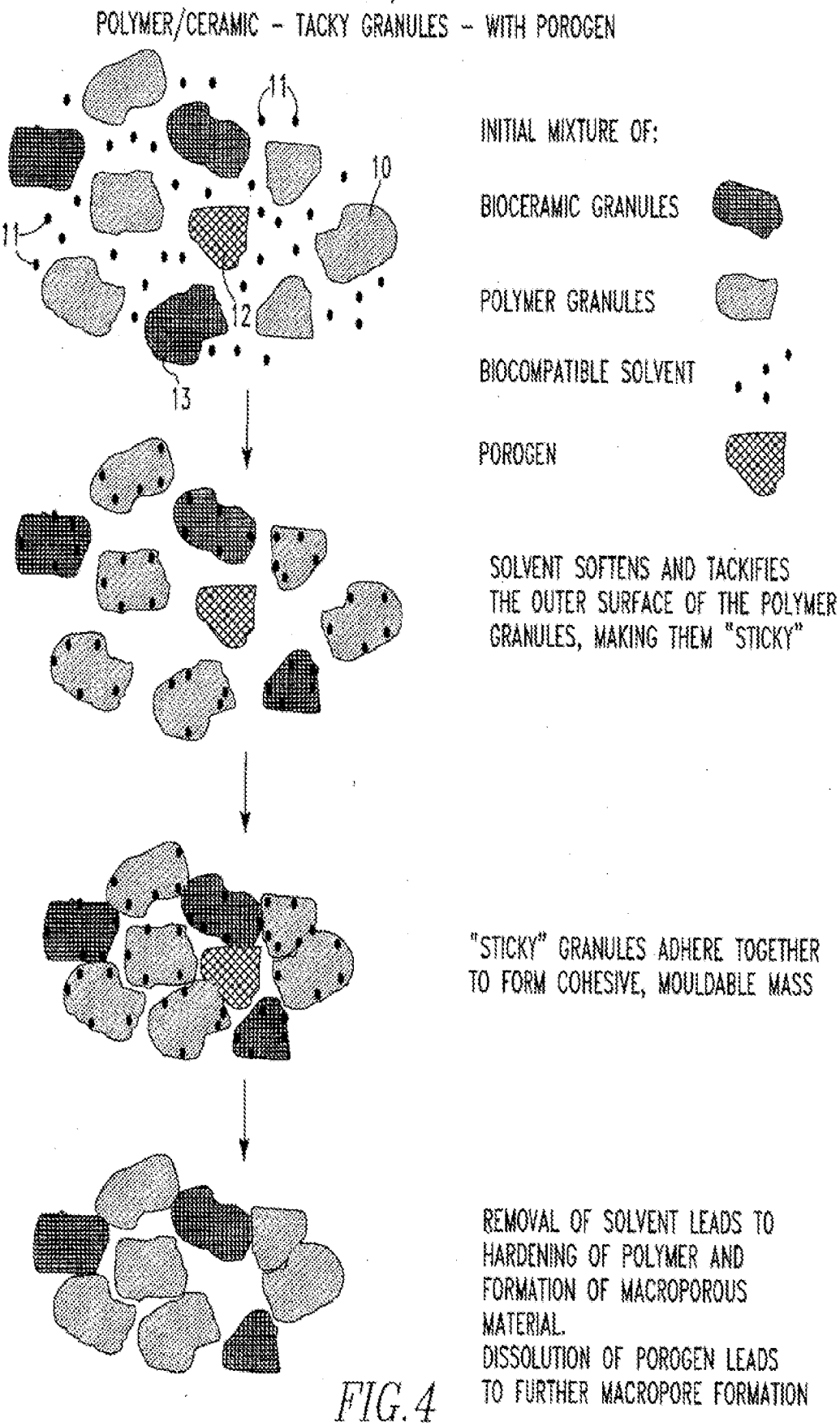

POLYMER/CERAMIC - TACKY GRANULES - WITH POROGEN
11
10
11
12
13
INITIAL MIXTURE OF:
BIOCERAMIC GRANULES
POLYMER GRANULES
BIOCOMPATIBLE SOLVENT
POROGEN
SOLVENT SOFTENS AND TACKIFIES THE OUTER SURFACE OF THE POLYMER GRANULES, MAKING THEM "STICKY"
"STICKY" GRANULES ADHERE TOGETHER TO FORM COHESIVE, MOULDABLE MASS
REMOVAL OF SOLVENT LEADS TO HARDENING OF POLYMER AND FORMATION OF MACROPOROUS MATERIAL.
DISSOLUTION OF POROGEN LEADS TO FURTHER MACROPORE FORMATION

*FIG.4*

POLYMER/CERAMIC - COATED GRANULES - NO POROGEN

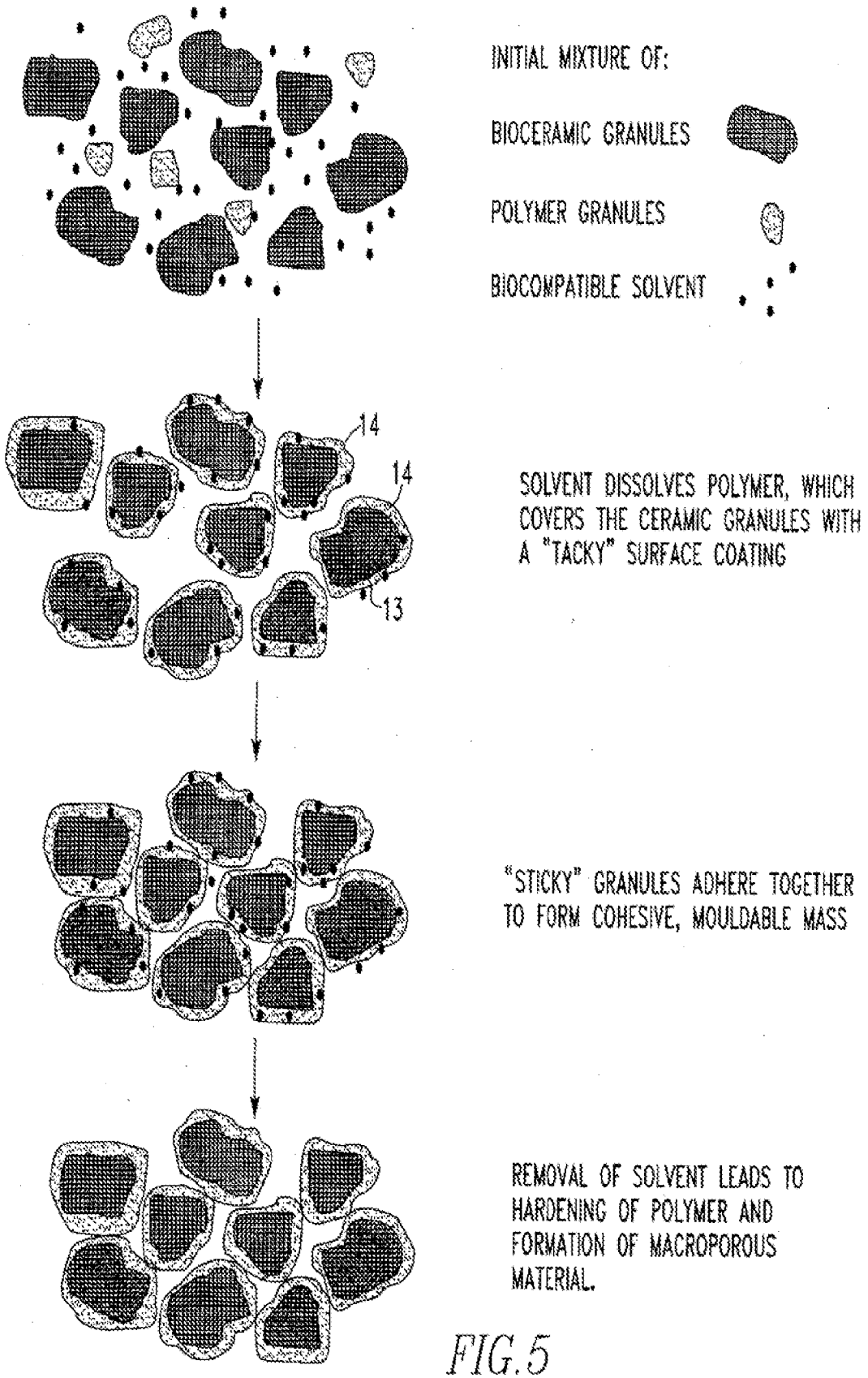



FIG.5

POLYMER/CERAMIC - COATED GRANULES - WITH POROGEN

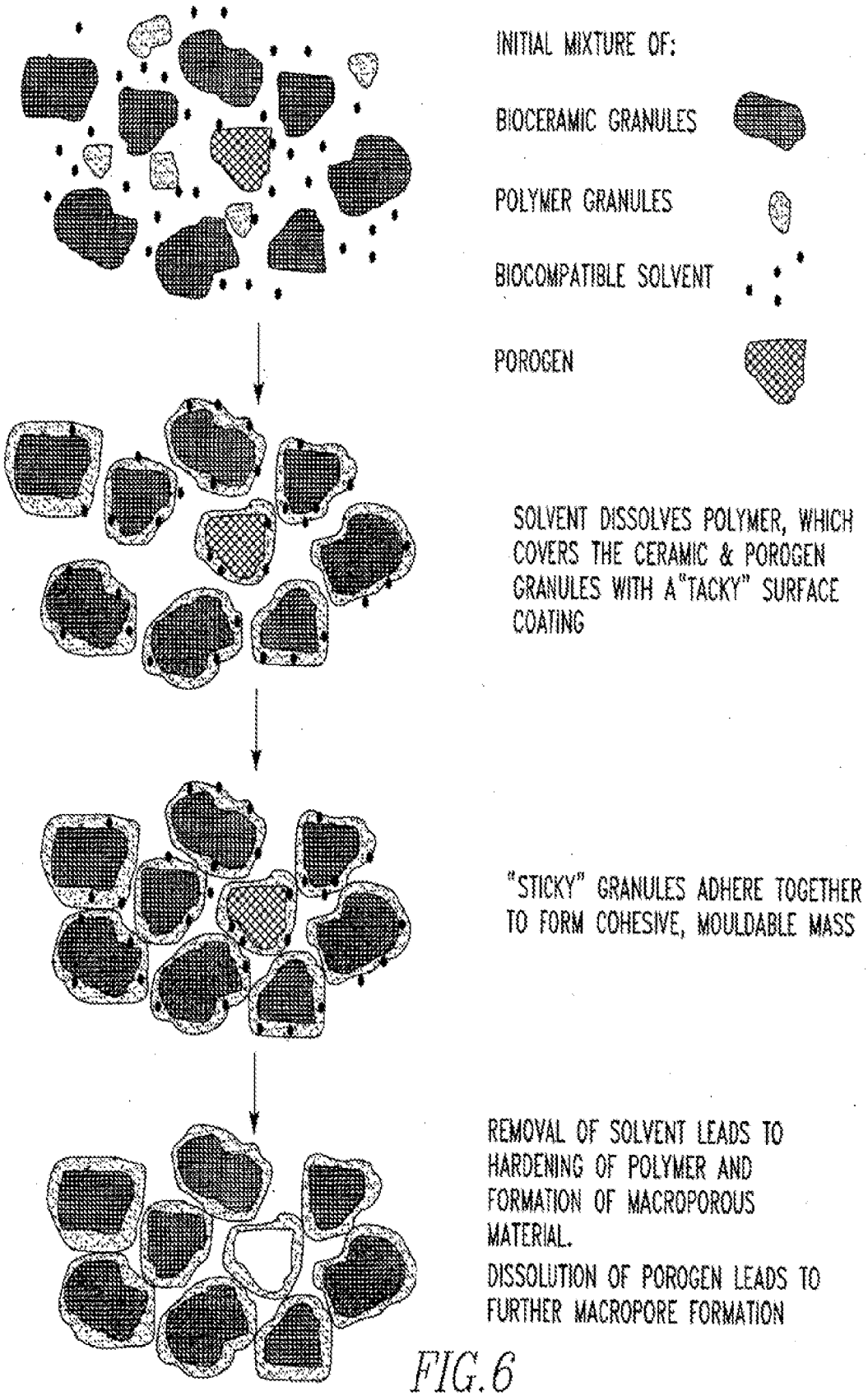



FIG.6

POLYMER/CERAMIC - POLYMER IN SOLUTION - NO POROGEN

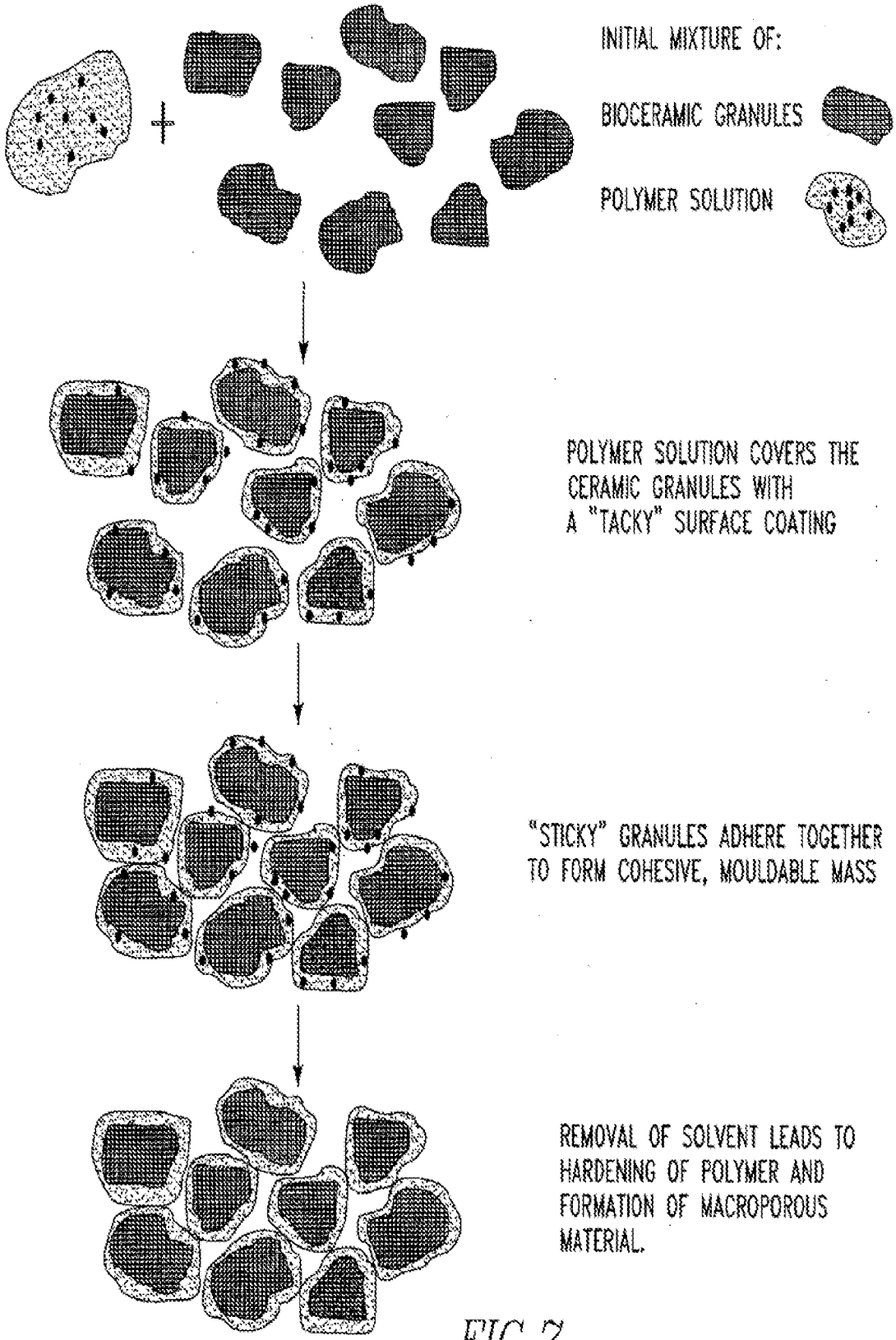



FIG. 7

POLYMER/CERAMIC - POLYMER IN SOLUTION - WITH POROGEN

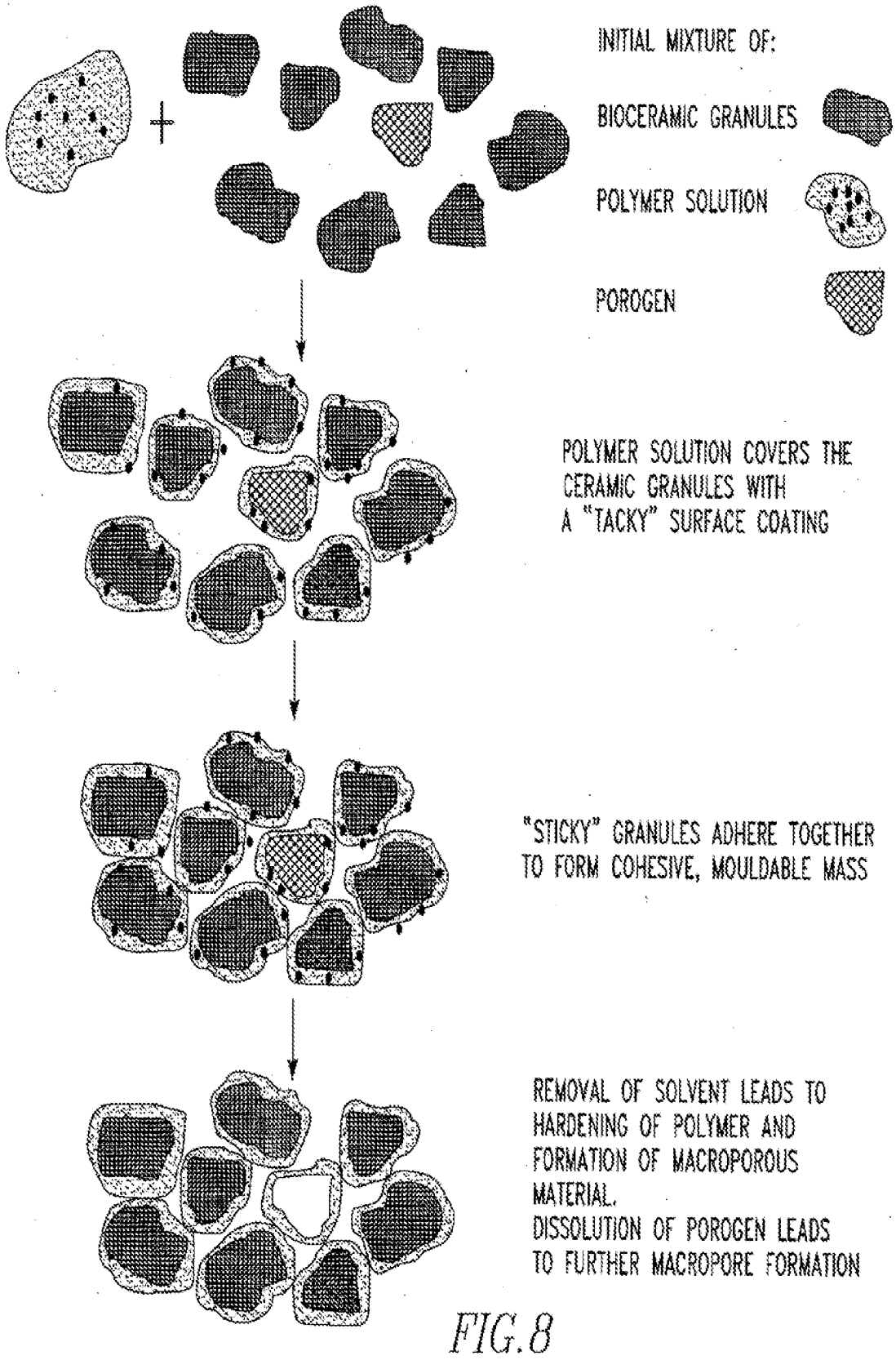



FIG.8

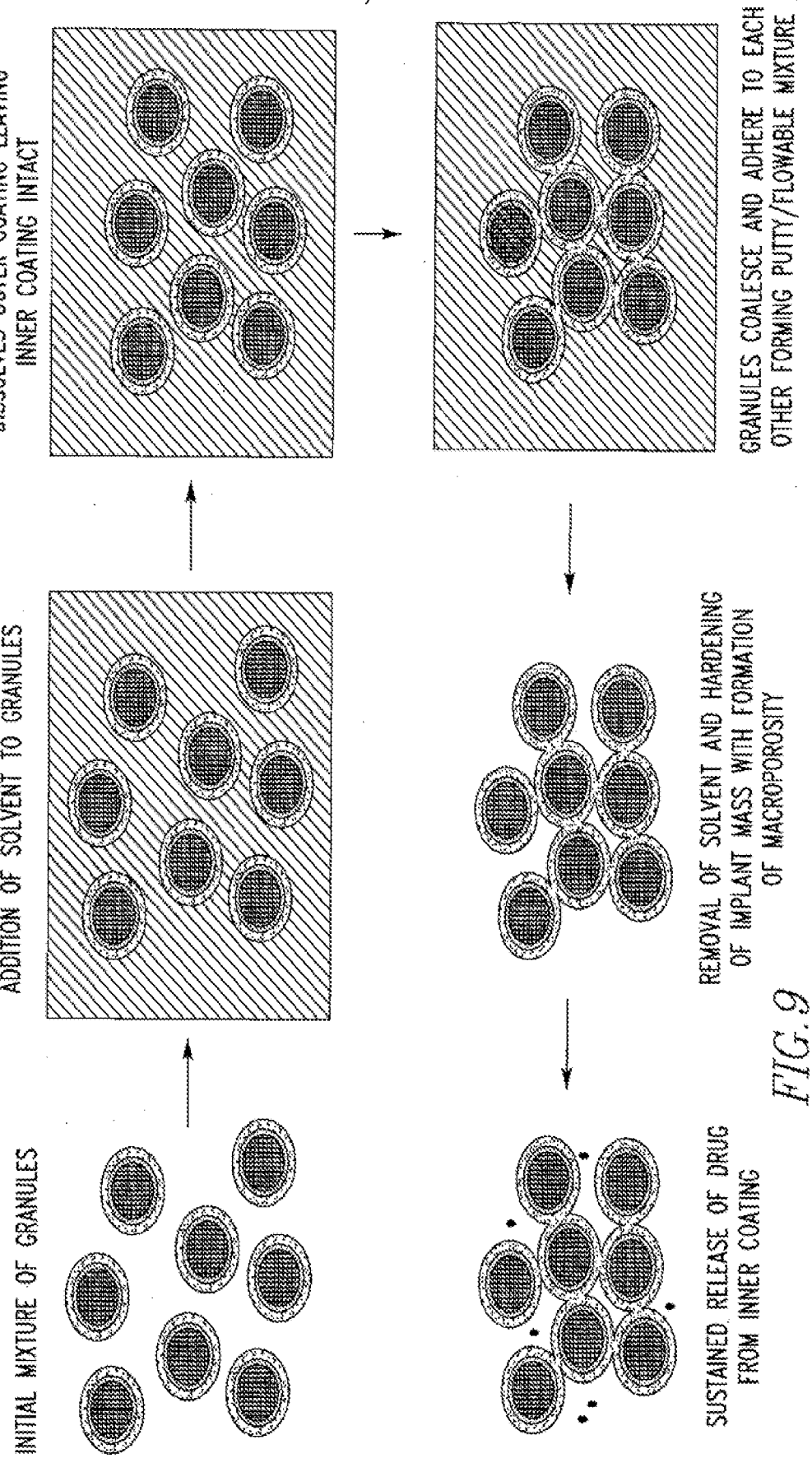

INITIAL MIXTURE OF GRANULES
ADDITION OF SOLVENT TO GRANULES
SOLVENT SOFTENS AND/OR PARTIALLY DISSOLVES OUTER COATING LEAVING INNER COATING INTACT
GRANULES COALESCE AND ADHERE TO EACH OTHER FORMING PUTTY/FLOWABLE MIXTURE
REMOVAL OF SOLVENT AND HARDENING OF IMPLANT MASS WITH FORMATION OF MACROPOROSITY
SUSTAINED RELEASE OF DRUG FROM INNER COATING

FIG. 9

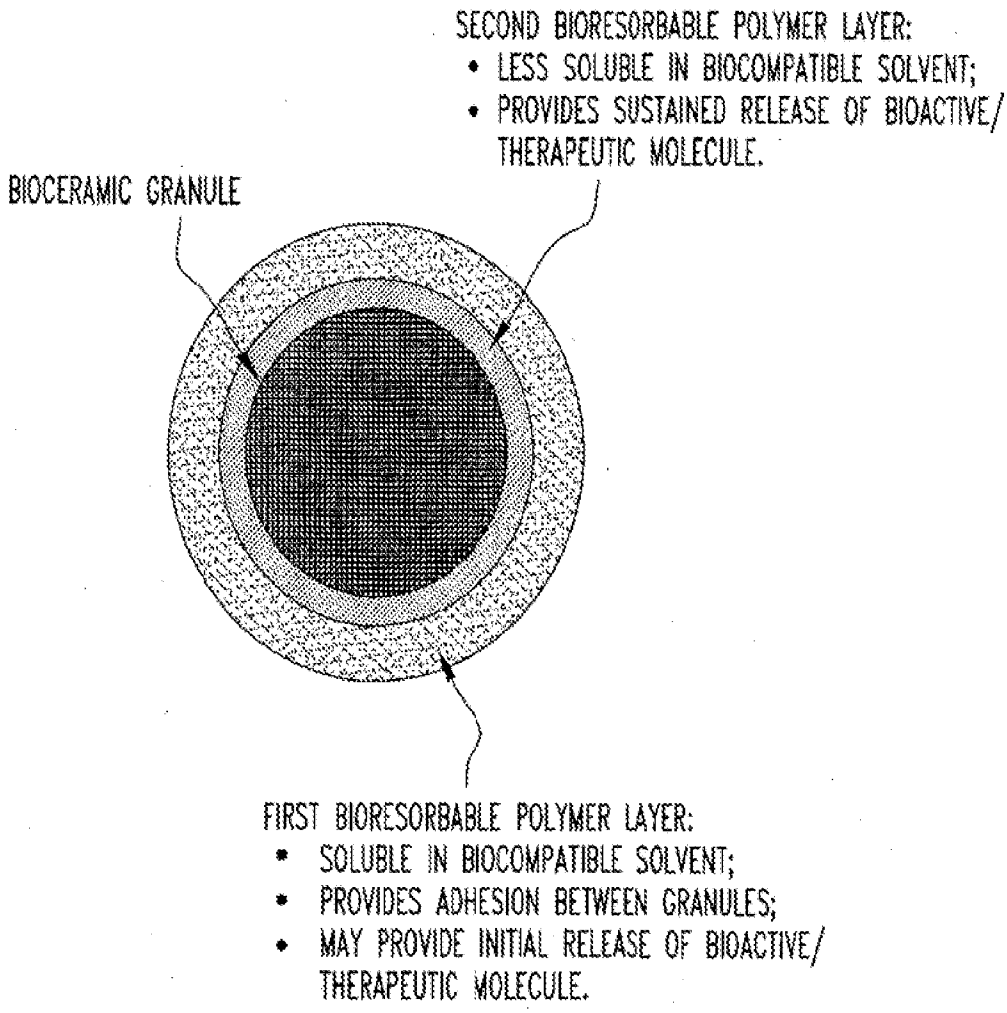

SECOND BIORESORBABLE POLYMER LAYER:
• LESS SOLUBLE IN BIOCOMPATIBLE SOLVENT;
• PROVIDES SUSTAINED RELEASE OF BIOACTIVE/ THERAPEUTIC MOLECULE.
BIOCERAMIC GRANULE
FIRST BIORESORBABLE POLYMER LAYER:
• SOLUBLE IN BIOCOMPATIBLE SOLVENT;
• PROVIDES ADHESION BETWEEN GRANULES;
• MAY PROVIDE INITIAL RELEASE OF BIOACTIVE/ THERAPEUTIC MOLECULE.

*FIG.10*

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/032066

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L24/00
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 | WO 2005/107826 A2 (DEGRADABLE SOLUTIONS AG [CH]; MASPERO FABRIZIO ALEXANDRO [CH]; RUFFIEU) 17 November 2005 (2005-11-17) cited in the application page 16; claims 1-11 ----- | 1-23 |

☐ 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 application or patent 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

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 4 October 2013 | 11/10/2013 |

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

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/032066

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2005107826 A2 | 17-11-2005 | AU 2005239825 A1 | 17-11-2005 |
| | | CA 2564164 A1 | 17-11-2005 |
| | | EP 1753474 A2 | 21-02-2007 |
| | | JP 5049119 B2 | 17-10-2012 |
| | | JP 2007536038 A | 13-12-2007 |
| | | US 2005249773 A1 | 10-11-2005 |
| | | US 2005251266 A1 | 10-11-2005 |
| | | WO 2005107826 A2 | 17-11-2005 |