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(54) Title: MEDICAL IMPLANT

(57) Abstract: The invention relates to a medical implant comprising a compound of a biostable polyester and an osteoconductive filler and to the treatment of a mammal by inserting the medical implant. The compound can comprise an impact modifier. The surface of the medical implant is preferably activated before the implant is placed into the body.



WO 2010/094798 A1

MEDICAL IMPLANT

The invention relates to a medical implant comprising a compound of a biostable polyester and an osteoconductive filler.

5 Osteoconductive compounds are used in medical applications. Commercial osteoconductive compounds, such as the Biocryl Rapide composite material of DePuy and the PLC material of Smith & Nephew, contain a calcium containing filler that stimulates tissue adhesion as well as bone cell activity.

10 In the above-mentioned osteoconductive compounds the calcium containing filler is combined with biodegradable materials. The use of biodegradable materials has the disadvantage that the physical properties of the biodegradable material will change over time. Degradation of the biodegradable materials in the body can also result in degradation products that can have harmful effects in the body.

15 An example of the combination of a calcium containing filler with non-biodegradable material is the combination of hydroxyapatite (HA) with polyetheretherketone (PEEK). This material was described by Kurz et al., Biomaterials 28 (2007), 4845-4869, as having the disadvantage that the material is too brittle. It was also shown that PEEK could not be integrated in the tissue.

20 For the use in a medical application in general and, more specific, in a medical implant it is not a prerequisite that the polymer in the implant is biodegradable. The physical properties of the implant material are of special importance when used in a medical implant. To be able to use the medical implant at positions where the implant has to bear a load, the medical implant has to be impact resistant and to resist deformation. These physical properties could not be obtained
25 so far with the implant materials that are now commercially available.

 The term "implant" generally has a broad meaning, referring to any foreign object that is placed in a living human or animal body. Implants can be temporary, such as implants in the form of pharmaceutical dosage forms for the controlled release of drugs, or implants that are biodegradable and are therefore used
30 for a temporary function. Implants can be permanent, such as a metal pin to support a broken leg. The term "permanent" will be readily understood as referring to anything that is intended to remain indefinitely in the body. This does not mean that the implant could not be removed, e.g. surgically, or could not accidentally disappear. The invention relates to such implants as are suitable for permanent implantation, hence to
35 biostable implants rather than to implants that are bioabsorbable or biodegradable. The

latter types of implant, while recognized as useful during bone growth processes, do have physical properties that change over time, caused by their biological instability. A biostable implant will remain as is, i.e. once a biologically acceptable implant is introduced into the body of a living human or animal, it is traceable which material is in fact implanted. In the case of an implant that degrades in the body, and/or is absorbed by the body, degradation, conversion or metabolic materials will eventually end up in the body. From a viewpoint of controlling the health of the subject receiving the implant, this is undesirable and represents additional clinical risk. Therefore the use of resorbable implants is typically restricted to applications where this added risk is balanced by a significant long-term clinical benefit. Moreover, a permanent implant will also be capable of indefinitely contributing to load-bearing.

The aim of the invention is to provide a medical implant, suitable for permanent implantation, that is capable of assuming an adequate load-bearing function and has osteoconductive properties, such that fast adhesion of the implant to adjacent tissue can be obtained. The fast adhesion of the implant will lead towards a better integration of the implant in the tissue.

An adequate load-bearing function is reflected by the strength and impact properties of the compound used to make (a part of) the implant.

This aim is achieved with a medical implant comprising a compound of a biostable thermoplastic polyester and an osteoconductive filler.

A permanent implant is not biodegradable. This means that the polyester in the compound that is used to make at least a part of the medical implant must also be not biodegradable.

The polyester in the compound can be a thermoplastic or a thermoset polyester.

A thermosetting polyester, also known as a thermoset, is a polyester material that irreversibly cures. The cure may be done through heat (generally above 200 °C), through a chemical reaction, or irradiation.

A thermoplastic polyester, also known as thermosoftening plastic is a polymer that turns to a liquid when heated and freezes to a very glassy state when cooled sufficiently. Most thermoplastics are high-molecular-weight polymers whose chains associate through weak Van der Waals forces. Thermoplastic polyesters differ from thermosetting polymers as they can, unlike thermosetting polymers, be remelted and remoulded.

The polyester can be a homopolymer or a copolymer. Also blends of different types of polyesters can be used. Examples of polyesters are polyethyleneterephthalate (PET), polybutyleneterephthalate (PBT), polyethylenenaphthenate (PEN) and poly(cyclohexylene-dimethyleneterephthalate) (PCT). Here and in the rest of the description a polycarbonate is understood to be a polyester. Therefore a polycarbonate can also be mentioned as an example of a polyester that can be used in the compound. Preferably, the polyester is an ethylene terephthalate or butylene terephthalate containing polymer.

Preferably, the polyester is a thermoplastic polyester.

10 The compound in the implant according to the invention preferably comprises an impact modifier to improve the impact resistance of the compound.

An impact modifier is herewith defined as an additive, usually an elastomeric polymer, that is incorporated in the compound to improve the impact resistance of a medical implant.

15 Impact resistance is the ability of the finished article to withstand a sudden load without failure.

Impact modifiers can be chosen from polymers with elastomeric properties, for example polybutadiene, poly(phenylene oxide), low density polyethylene (LDPE) and thermoplastic elastomers (TPE) or thermoplastic polyurethanes(TPU).

20 The medical implant according to the invention comprises a compound that preferably comprises a thermoplastic elastomer (TPE) or thermoplastic polyurethanes(TPU) comprising a hard phase, and a soft phase as the impact modifier.

The hard phase in the TPE comprises a rigid polymer phase with a melting temperature (T_m) or a glass transition temperature (T_g) higher than 35 °C. The soft phase in the TPE comprises a flexible, amorphous polymer phase with a T_g lower than 35 °C, preferably lower than 0 °C.

The TPE comprises, for example, blends of the above-mentioned hard phase polymers with soft phase polymers and block copolymers. The hard and the soft phase can comprise one polymer type, but can also be composed of a mixture of two or more of the above-mentioned polymeric materials.

The TPE or TPU can be used as the polyester or in combination with the polyester that is used in the compound. When the TPE or TPU is used as the polyester at least the hard phase of the TPE or TPU has to be a polyester. In this case the soft phase in the TPE or TPU has the function of the impact modifier.

35 Preferably, the TPE or TPU is a blockcopolymer. When the TPE or

TPU is a block-copolymer, the TPE or TPU used in the compound comprises a polymer comprising hard blocks and soft blocks, wherein the hard blocks comprise a polymer chosen from the group consisting of polyester, polycarbonate, polyamide, polystyrene, polyacrylate and polyolefin and the soft blocks comprise a polymer chosen from the group consisting of polyether, polyester, polyacrylate, polyolefin and polysiloxane.

5 Examples of TPE block-copolymers are block-copolyesterester, block-copolyetherester, block-copolycarbonateester, block-copolysiloxaneester, block-copolyesteramide, block-copolymer containing polybutylene terephthalate (PBT) hard blocks and poly(oxytetramethylene) soft blocks, block-copolymer containing
10 polystyrene hard blocks and ethylene butadiene soft blocks (SEBS).

The term thermoplastic polyurethane (TPU) encompasses a family of polymers that usually includes three principal components. These are a macroglycol, a diisocyanate and a chain extender. They are generally classified as polyurethanes in as much as the backbone thereof includes urethane groups and often also urea
15 groups, which groups are recurring units within the polymer backbone.

With particular reference to the macroglycol component of polyurethanes in general, three primary families of macroglycols are available commercially at the present time. These are the polyester glycols, the polyether glycols and the polycarbonate glycols.

20 Also block polyurethane copolymers exist comprising hard and soft polymer blocks. The hard blocks of the block copolymer may preferably have a molecular weight of about 160 to 10,000, and more preferably about 200 to 2,000. The molecular weight of the soft segment is typically about 200 to 1,000,000 and preferably about 400 to 9000.

25 Generally known block polyurethane copolymers and methods to prepare these copolymers are described in, for instance, US 4739013, US 4810749, US 5133742 and US 5229431. These block polyurethane copolymers have a hard polycarbonate phase and are biostable.

The hard blocks in the TPE or TPU consist of a rigid polymer, as
30 described above, with a T_m or T_g higher than 35 °C. In principle the different polymers as described above can be used as the hard blocks.

Also copolymers of esters, amides, styrenes, acrylates and olefins can be used as the hard polymer block as long as the T_m or T_g of the hard polymer block is higher than 35 °C.

35 Preferably, the hard block of the TPE or TPU is a polyester block or a

polycarbonate block.

When the hard block is a polycarbonate block the hard block consists of repeating units derived from at least one alkylene glycol and at least one aromatic dicarboxylic acid or an ester thereof. The alkylene group generally contains 2-6 carbon atoms, preferably 2-4 carbon atoms. Preferable for use as the alkylene glycol are ethylene glycol, propylene glycol and in particular butylene glycol. Terephthalic acid, 2,6-naphthalenedicarboxylic acid and 4,4'-diphenyldicarboxylic acid are very suitable for use as the aromatic dicarboxylic acid. Combinations of these dicarboxylic acids, and/or other dicarboxylic acids such as isophthalic acid may also be used. Their effect is to influence the crystallisation behaviour, e.g. melting point, of the hard polyester blocks.

The soft blocks in the TPE or TPU consist of a flexible polymer, as described above, with a T_g lower than 35 °C. In principle the polymers as described above can be used as the soft blocks. Also copolymers can be used as the soft polymer block as long as the T_g of the soft polymer block is lower than 35 °C.

Preferably, the soft block comprises a polyester or a polyether; more preferably an aliphatic polyester or polyether. A particular advantage of TPE's comprising polyester, or polyether soft blocks is that aliphatic polyesters, and polyethers feature a high chemical stability. Especially, alkylene carbonates and aliphatic polyesters are preferred as the soft block, which result in thermoplastic elastomers with particularly low moisture sensitivity and favourable adhesive properties.

The compound in the implant according to the invention preferably comprises an ethylene terephthalate or a butylene terephthalate containing polymer as the polyester. More preferably, the compound comprises an ethylene terephthalate or a butylene terephthalate blockcopolymer. Most preferably the blockcopolymer comprises a hard phase consisting of polyethylene terephthalate or polybutylene terephthalate and soft phase comprising a polymer chosen from the group consisting of polyether, polyester, polyacrylate, polyolefin and polysiloxane. In this blockcopolymer the hard phase is the polyester phase and the soft phase of the blockcopolymer functions as the impact modifier.

The compound in the implant according to the invention also comprises an osteoconductive filler. "Osteo" means "bone". Osteoconduction refers to the ability of certain fillers to serve as a scaffold on which bone cells can attach,

migrate (meaning move or "crawl"), and grow and divide. In this way, the bone healing response is "conducted".

Examples of osteoconductive fillers are, for example, calcium hydroxyapatite, monocalcium phosphate, dicalcium phosphate, α -tricalcium phosphate (5 α -TCP), β -tricalcium phosphate (β -TCP), octacalcium phosphate, tetracalcium phosphate, dicalcium phosphate, fluoroapatite, calcium sulphate, calcium fluoride and calcium oxide.

Calcium phosphate materials can be apatitic materials. These apatitic materials have been described, for example, in US-6117456, US-6953594, US-10 6013591 and US-6972130.

Examples of calcium phosphate apatites are $\text{Ca}_5(\text{PO}_4, \text{CO}_3\text{F})_3\text{R}$; $\text{Ca}_5(\text{PO}_4\text{CO}_3\text{OH})\text{OH}$; $\text{Ca}_5(\text{PO}_4)_3\text{Cl}$; $\text{Ca}_5(\text{PO}_4)_3\text{F}$; $\text{Ca}_5(\text{PO}_4)_3\text{OH}$; $\text{Ca}_{10}(\text{PO}_4)_6\text{CO}_3$; $\text{Ca}_{10}(\text{PO}_4)_6\text{O}$.

Nanocrystalline apatite material is commercially available, for 15 example, from Berkeley Advanced Biomaterials Inc.

Also other osteoconductive filler materials can be used such as, for example, non-calcium phosphate apatites, such as $\text{Ba}_5(\text{PO}_4)_3\text{Cl}$, $(\text{Sr}, \text{Ce})_5(\text{PO}_4)_3\text{OH}$, $(\text{Ce}, \text{Ca})_5(\text{PO}_4)_3(\text{OH}, \text{F})$, $(\text{Y}, \text{Ca})_5(\text{PO}_4)_3(\text{OH}, \text{F})$, $\text{Na}_3\text{Pb}_2(\text{SO}_4)_3\text{Cl}$, $\text{Na}_3\text{Ca}_2(\text{SO}_4)_3\text{OH}$, $\text{Ca}_5(\text{SiO}_4, \text{PO}_4, \text{SO}_4)_3(\text{Cl}, \text{F})$, $\text{Pb}_5(\text{AsO}_4)_3\text{Cl}$, $(\text{Ca}, \text{Sr})_5(\text{AsO}_4, \text{PO}_4)_3\text{OH}$, $\text{Pb}(\text{AsO}_4)_3\text{Cl}$, 20 $\text{Ca}_5(\text{SiO}_4, \text{PO}_4, \text{SO}_4)_3(\text{F}, \text{OH}, \text{Cl})$, $\text{Pb}_3\text{Ca}_2(\text{AsO}_4)_3\text{Cl}$, $\text{Ca}_5(\text{SiO}_4, \text{PO}_4, \text{SO}_4)_3(\text{OH}, \text{F}, \text{Cl})$, $\text{Ca}_5(\text{AsO}_4)_3\text{OH}$, $\text{Pb}_5(\text{AsO}_4)_3\text{Cl}$, $(\text{Ba}, \text{Ca}, \text{Pb})_5(\text{AsO}_4, \text{PO}_4)_3\text{Cl}$, $\text{Pb}_5(\text{PO}_4)_3\text{Cl}$, $\text{Sr}_5(\text{PO}_4)_3(\text{OH}, \text{F})$, $\text{Ca}_5(\text{AsO}_4)_3\text{F}$, $\text{Ca}_5(\text{AsO}_4, \text{PO}_4)_3\text{Cl}$, $\text{Pb}_5(\text{VO}_4)\text{Cl}$.

The average particle size of the osteoconductive filler has a range between 10 nm – 100 μm .

25 This is an average particle size ranging from nanoparticles or small crystals to agglomerates of small particles or crystals.

Preferably, the average particle size of the crystals and nanoparticles is between 1 and 50 μm which provides a compound which is good compatible with bone. More preferably the average particle size of the crystals and nanoparticles is 30 between 1 and 10 μm .

Agglomerates of small particles or crystals have an average particle size that is preferably smaller than 50 μm , more preferably smaller than 10 μm .

The compounds as described above can be prepared by using compounding processes known by the person skilled in the art, for example by mixing,

kneading, extrusion and pelletization. During compounding the average particle size of the osteoconductive filler can become smaller.

The amount of osteoconductive filler in the compound is lower than 40 wt.%, preferably lower than 20 wt.% and more preferably lower than 10 wt.%.

5 The amount of osteoconductive filler in the compound is higher than 1 wt.% and preferably higher than 5 wt.%.

The amount of impact modifier in the compound is lower than 95 wt.%, preferably lower than 75 wt.%, more preferably lower than 50 wt.%.

10 The amount of impact modifier in the compound is preferably higher than 1 wt.%, more preferably higher than 5 wt.%.

The compound can also contain other additives such as reinforcing agents, fillers, compatibilizers, flame retardants, pigments, tracing agents for e.g. radiology and other auxiliary additives like plasticizers, processing aids, such as mould release agents, stabilizers such as antioxidants and UV stabilizers, crystallization
15 accelerating agents or nucleating agents.

The compounds as described above can be used in medical applications, preferably in medical implants.

20 Examples of medical implants are screws, rods, plates, pins, shafts, anchors, rings, porous or open structures, scaffolds and spinal cages a spinal disk, a spinal body, a hip cup or a knee implant and/or components thereof.

The invention is also directed to a method for treating a mammal which comprises inserting a medical implant, as described here above, into an area of the mammal where bone is degenerated, damaged or missing.

25 The medical implants can be completely prepared out of the compound of a biostable polyester and an osteoconductive filler, but also only certain parts of the medical implant can be made out of the compound. The medical implant can also be, at least partially, coated with the compound.

30 Before the implant is brought into the body the surface of the medical implant is preferably activated. More preferably, the surface of the implant is activated after the implant has been given its final shape.

Activation is performed to roughen the surface of the implant to promote better access of the osteoconductive filler in the compound for (bone) cells to obtain better adhesion of the surrounding tissue to the medical implant.

35 By activation the top layer of the compound is, partially, removed. Activation can be performed by various mechanical and chemical treatments known to

the person skilled in the art; for example by milling, sanding, abrading, machining, scraping or chemical etching.

EXAMPLES

5

Materials

- Arnitel[®] CM551 (block copolymer; hard block: polybutylene terephthalate (PBT), soft block: polycarbonate) from DSM N.V.
- Arnitel[®] EL250 (block copolymer; hard block polybutylene terephthalate (PBT), soft block: polytetramethyleneoxide (PTMO)) from DSM N.V.
- Arnitel[®] EM400 (block copolymer; hard block: polybutylene terephthalate (PBT), soft block: polytetramethyleneoxide (PTMO)) from DSM N.V.
- Arnitel[®] EM460 (block copolymer; hard block polybutylene terephthalate (PBT), soft block: polytetramethyleneoxide (PTMO)) from DSM N.V.
- Arnitel[®] EM550 (block copolymer; hard block polybutylene terephthalate (PBT), soft block: polytetramethyleneoxide (PTMO)) from DSM N.V.
- Arnitel[®] EM630 and 630-H (block copolymer; hard block polybutylene terephthalate (PBT), soft block: polytetramethyleneoxide (PTMO)) from DSM N.V. (H means heat stabilized)
- Arnitel[®] EM740 (block copolymer; hard block polybutylene terephthalate (PBT), soft block: polytetramethyleneoxide (PTMO)) from DSM N.V.
- PBT: Arnite[®] T04201 from DSM N.V.
- PEEK: Ketron[®] PEEK-1000 from Eriks

25

Example I: Biocompatibility

- Samples of Arnitel[®] EL250, EM400, EM740 and CM551 were tested under GLP conditions according to ISO 10993 parts 3, 5, 6, 7, 10, and 11:
- ISO10993-3 Tests for genotoxicity, carcinogenicity, and reproductive toxicity.
 - ISO 10993-5 Tests for in vitro cytotoxicity.
 - ISO 10993-6 Test for local effects after implantation.
 - ISO 10993-7 Ethylene oxide residuals.
 - ISO 10993-10 Test for irritation and delayed-type hypersensitivity.
 - ISO 10993-11 Test for systemic toxicity

Each of these material grades passed all of the above biocompatibility tests, demonstrating the safety of Arnitel® TPE as an implant material.

Example II: Sterilization testing

5 Samples of Arnitel® types CM551, EL250, EM550, EM630, EM630-H, EM400, EM460, EL630, and EL740 were tested for the effects of gamma sterilization up to 100 KGray (roughly 4 times a typical sterilization dose). These samples were subsequently mechanically tested to determine the effects on E-modulus, Stress at Break, and Strain at Break. In all instances little or no changes in the material
10 properties were observed.

Example III: Shock absorption

 In order to compare the shock-absorbing capacity of a thermoplastic polyester material with a traditional PEEK material, the displacement and energy
15 dissipated under a 2000N load (maximum ISO axial load) was estimated. Energy was estimated as the area under the force/displacement curve and was calculated via numerical integration as show in Table 1 below for Arnitel® EL740. The implant height was 10mm, the area was 50 mm².

20 Table 1

Strain	dx (mm)	Stress (MPa)	F*dx (J)
0%	0	0	
5%	0.5	18	0.225
10%	0.5	28	0.575
150%	0.5	40	0.85
			Total 1.65J

 With PEEK of 4000 MPa modulus, at 1% final deformation, the energy dissipated was 0.1 J. The thermoplastic polyester used in accordance with the invention was capable of deforming to a much higher extent, and thus absorbed the
25 impact energy rather than merely transmitting it to the surrounding tissue as PEEK does.

Example IV: Growth of osteoblasts on various materialsMaterials

The β -TCP used, was a β -TCP with a particle size of 1-10 μm ; the agglomerates had an average particle size of 70 μm .

- 5 A. Arnitel[®] CM622 (block copolymer; hard block: polybutylene terephthalate (PBT), soft block: polyhexamethylene carbonate ester) from DSM N.V.
- B. A compound containing 80 wt% Arnitel[®] CM622 as defined above and 20 wt% β -TCP.
- C. Arnitel[®] CM551 (block copolymer; hard block: polybutylene terephthalate (PBT),
10 soft block: polycarbonate, modulus 140 MPa) from DSM N.V.
- D. A compound containing 80 wt% Arnitel[®] CM551 as defined above and 20 wt% β -TCP.
- E. A compound containing 65 wt% Arnitel[®] CM551 as defined above and 35 wt% PBT homopolymer (Arnite[®] T04201 from DSM N.V.).
- 15 F. A compound containing 80 wt% of a compound as defined under E and 20 wt% β -TCP.
- G. Ketron[®] PEEK-1000 from Eriks (reference)
- H. The tissue culture plate (reference)

20 Compound manufacturing

All of the above mentioned materials A-F were compounded on a HAAKE PolyLab OS RheoDrive 16 and a Rheomix OS at 240 °C and compression molded in a plaque with a thickness of 1 mm on a Fontijne press. The materials were melted at 260 Celsius before pressing at 150kN for 5-10min (cool down phase).

- 25 From these plaques discs were punched with a diameter of 5 mm and a thickness of 1 mm. A total of 48 discs was prepared for testing.

 One side of the discs was mechanically activated by treatment with sandpaper on a Schaublin 125 machine. The sandpaper that was used was No 220. The roughening was done under reproducible conditions by using a spring to control
30 the pressure and the distance: the total force on a disc was 78.5 N, duration 1 sec., min. erosion 10 μm / max. erosion 30-40 μm .

 The discs of materials A-F were chemically treated by submerging the discs for 12 hours in a 1.0 molar NaOH solution. The discs were washed thoroughly to remove remaining NaOH solution.

The PEEK samples were cut from a rod with a diameter of 5 mm. This cutting of the discs caused a roughening of the surface of the discs. 12 PEEK discs were tested.

It proved not to be possible to compound PEEK with 20 wt% β -TCP and maintain the mechanical integrity of the PEEK. PEEK is a chemically inert material that can not be etched by using a 1.0 molar NaOH solution.

Growth of osteoblasts

Primary human osteoblasts (hOBs) were suspended in a hOB growth medium. The growth medium contained Alpha Modified Eagle Medium (α -MEM) containing 10% fetal bovine serum (FBS) (Invitrogen) and 1% Penicillin/Streptomycin (Invitrogen).

About 4950 hOB's suspended in 40 μ l growth media were seeded onto each 1cm x 1cm scaffold in 24 well plates. The pre-seeded scaffolds were then incubated overnight at 37°C before top up with 1mL of the growth medium.

Induction of osteogenic differentiation

The osteogenic medium consisted of 100 nM dexamethasone, 50 μ M ascorbic acid-2-phosphate and 5 mM β -Glycerophosphate in the hOB growth medium as described above.

The growth media of pre-seeded scaffolds were replaced by osteogenic media after one week and followed by subsequent weekly osteogenic media change.

Scanning electron microscopy (SEM)

The same pre-seeded scaffolds were fixed with 3% glutaraldehyde and stored at 4°C until SEM processing.

0.1 M cacodylate buffer was used for washing the scaffolds to remove any glutaraldehyde residue for three times at 10 minutes each. The scaffolds were treated with 1% osmium tetroxide before dehydrated sequentially with ethanol. The dehydration process started with 2 changes of 10 minutes each with 50% ethanol, followed by 70% ethanol for 10 mins, followed by 90% for 10 minutes and subsequently 100% for 15 minutes.

Lastly, the scaffolds were air dried after incubation in hexamethyldisilazane (HMDS). They were then mounted on sputter stubs, followed by

gold coating using Biorad SC500. Viewing and analysis were performed using Quanta 200 Scanning Electron Microscope (FEI).

Alizarin Red test

- 5 Alizarin Red is used in a biochemical assay to determine, quantitatively by colorimetry, the presence of calcific deposition by cells of an osteogenic lineage. As such it is an early stage marker (days 10–16 of in vitro culture) of matrix mineralisation, a crucial step towards the formation of calcified extracellular matrix associated with true bone. The test is described in the following three articles:
- 10 1. H. Putschler, S. Meloan, M.S. Terry, On the history and mechanism of alizarin and alizarin red S stains for calcium, *J. Histochem, Cytochem.* 17 (1969) 110–124;
2. M. Lievremont, J. Potus, B. Guillou, Use of alizarin red S for histochemical staining of Ca²⁺ in the mouse; some parameters of the chemical reaction in vitro, *Acta Anat.* 114 (1982) 268–280;
- 15 3. C.M. Stanford, P.A. Jacobson, E.D. Eanes, L.A. Lembke, R.J. Midura, Rapidly forming apatitic mineral in an osteoblastic cell line (UMR 106-01 BSP), *J. Biol. Chem.* 270 (1995) 9420–9428

Table 2

Material	SEM (3 days)	Alizarin Red (28 days) Fluorescence intensity
A	±	0.160
B	+	0.212
C	±	0.126
D	+	0.184
E	±	0.045
F	+	0.102
G	–	n.d.
H	n.d.	0.004

n.d.: not determined

+: a smooth surface is observed when enlarged 1000 times.

±: a surface with uneven structure is observed when enlarged 1000 times.

5 -: a surface with a very uneven structure is observed when enlarged 1000 times.

PEEK (material G) does not promote cell adhesion and does not trigger tissue integration. It was now shown that on a mechanically activated surface of PEEK some cell growth could be observed at the site of the mechanically activated surface. No chemical etching of PEEK was possible. It also proved not to be possible to make a compound of PEEK and 20 wt% of β -TCP, as PEEK lost its mechanical integrity during compounding.

10

The above results in Table 2 clearly show that when β -TCP was incorporated in the compound the bone matrix and mineral deposition increased over the values found for a compound wherein no β -TCP was incorporated.

15

CLAIMS

1. Medical implant comprising a compound of a biostable polyester and an
5 osteoconductive filler.
2. Medical implant according to claim 1, wherein the biostable polyester is a
thermoplastic polyester.
3. Medical implant according to claim 1 or 2, wherein the biostable polyester
comprises an impact modifier.
- 10 4. Medical implant according to anyone of claims 1-3, wherein the polyester is an
ethylene terephthalate or butylene terephthalate containing polymer.
5. Medical implant according to anyone of claims 1-4, wherein the polyester is a
block copolymer.
6. Medical implant according to anyone of claims 1-5, wherein the
15 blockcopolymer comprises a hard phase consisting of polyethylene
terephthalate or polybutylene terephthalate and soft phase comprising a
polymer chosen from the group consisting of polyether, polyester,
polyacrylate, polyolefin and polysiloxane.
7. Medical implant according to anyone of claims 1-6, wherein the
20 osteoconductive filler is a calcium phosphate.
8. Medical implant according to anyone of claims 1-7, wherein the calcium
phosphate is β -tricalcium phosphate.
9. Medical implant according to anyone of claims 1-8, wherein the
osteoconductive filler has an average particle size of 10 nm - 100 μ m.
- 25 10. Medical implant according to anyone of claims 1-9, which comprises the
compound of the biostable polyester and the osteoconductive filler, at least
partially, as a coating on the outside of the medical implant.
11. Medical implant according to anyone of claims 1-10, wherein the surface of
the medical implant is activated before the implant is brought into the body.
- 30 12. Medical implant according to anyone of claims 1-11, wherein the surface of
the implant is activated after the implant has been given its final shape.
13. Medical implant according to anyone of claims 1-12, wherein the activation is
carried out by a mechanical and/or chemical treatment.
14. Medical implant according to anyone of claims 1-13, wherein the medical
35 implant is a screw, a rod, a plate, a pin, a shaft, an anchor, a ring, a porous or

open structure, a scaffold and a spinal cage, a spinal disk, a spinal body, a hip cup or a knee implant and/or components thereof.

15. Method for treating a mammal which comprises inserting a medical implant according to any one of claims 1-14 into an area of the mammal where bone is
5 degenerated, damaged or missing.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/052209

A. CLASSIFICATION OF SUBJECT MATTER
 INV: C08K3/00 A61L27/44 A61L27/46
 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 C08K A61F A61C C08L

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, WPI Data, CHEM ABS 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 00/48552 A (TNO [NL]; ISOTIS B V [NL]; CARTON ERIC PETER [NL]; BLITTERSWIJK CLEMEN) 24 August 2000 (2000-08-24) page 2, line 29 - line 31 page 4, line 7 - line 11 page 4, line 17 - line 18 page 8, line 29 - line 31 example 4	1-15
X	US 4 202 055 A (HEIDE HELMUT [DE] ET AL) 13 May 1980 (1980-05-13) column 1, line 8 - line 12 column 2, line 12 - line 16 column 2, line 39 - line 45 column 4, line 50 - line 55 column 5, line 1 - line 28 claims 3,4	1-15
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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	"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
"E" earlier document but published on or after the international filing date	"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
"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)	"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.
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 1 June 2010	Date of mailing of the international search report 28/06/2010
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Behm, Sonja
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/052209

C(Continuation). 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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A	KURTZ, DEVINE: "PEEK biomaterials in trauma, orthopedic, and spinal implants" BIOMATERIALS, vol. 28, 7 August 2007 (2007-08-07), pages 4845-4869, XP002585205 the whole document -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/052209

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