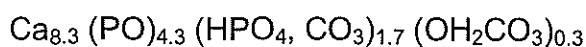


METHOD FOR PREPARING A BONE FILLER MATERIAL AND MATERIAL PREPARED BY SUCH A METHOD

The invention relates to a method for obtaining a material for osseous filling and a material obtained by such a method. The invention is particularly, but not exclusively, intended for the realization of endo-osseous implants, notably dental implants, or the realization of bone prostheses for medical or veterinary applications.

5 The invention aims to obtaining a synthetic osteomimetic material, suitable to carry out a graft against a bone tissue, the aforementioned material being adapted to be shaped in a piece, or implant, of preset form, with sufficient mechanical properties so as to mechanically substitute the aforementioned tissue, as of its implantation in said tissue and at least until the achievement of the consolidation of the graft, while also
10 aiming an quick osseointegration.

Calcium phosphate is the essential structural component of a bone. It lies in the aforementioned tissue in the form of a polysubstituted phosphocalcic apatite with, as composition:



15 This completely non-stoichiometric form, is characterized by a Ca/P ratio different from 1.67, said value of this ratio corresponding to stoichiometric apatites, in particular the calcium hydroxyapatite ($\text{Ca}_5(\text{PO}_4)_3\text{OH}$) or the calcium dihydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6\text{H}_2\text{O}$).

According to prior art, a graft principle in a bone tissue can be obtained by the
20 use of resorptive calcium phosphate compounds, i.e. slightly crystalline and non-stoichiometric compounds with a Ca/P ratio appreciably different from 1.67, which calcium compounds must, moreover, be nanostructured in terms of porosity. These characteristics favor the combined action of osteoclasts and osteoblasts, leading to the osseointegration of the implant in the tissue

25 US 7 517 539 discloses a cement, based on the use of hydrated calcium phosphate, which can be injected into a bone tissue in the form of a paste and which

hardens by an exothermic reaction to form a structure having the required characteristics of nanostructured porosity and of non-stoichiometry.

Nevertheless if this cement makes it possible to achieve part of the aims of the invention, it does not allow the realization of a piece suitable for mechanically substituting the bone tissue as of its implantation in said tissue.

FR 2 722 694 discloses a material and a method for obtaining a piece made of such a material by a method of injection molding. According to this prior art, said material consists of a composite made of a biocompatible thermoplastic polymer matrix filled, notably, with powders for achieving an intake of calcium phosphate in the form of stoichiometric dihydroxyapatite and of tricalcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$). This material exhibits high mechanical properties, particularly with regard to impact resistance, and an elastic modulus close to the bone's one. The presence of calcium phosphate compounds, promotes the integration of said material into the tissue. Nevertheless, since these compounds are not resorptive, and since the surface of the implant that is contacting the tissues is not nanostructured, nor even porous, because of the injection molding process, this osseointegration is slow.

DE 100 55 465 discloses a composite material consisting in a thermoplastic polymeric matrix filled with dihydroxyapatite in stoichiometric form, and a method for obtaining a piece made up of this material by selective laser sintering. This method makes it possible to obtain a piece with a nanostructured porosity but in its volume, so that this porosity has a negative impact on the mechanical properties of the piece. In addition, the hydroxyapatite not being in a resorptive form, the osseointegration of the piece in the tissue is also slow.

FR 2 848 856 discloses a material and a method for obtaining a piece made of such a material by injection molding. This document also discloses a surface pickling treatment of the molded piece, that enables to obtain a nanostructured porous surface on the surface of the piece. The molded material comprises a matrix made up of a thermoplastic polymer filled with compounds, for achieving a calcium intake in the form of tricalcium phosphate, monetite (CaHPO_4), dihydroxyapatite and hydroxyapatite, these apatites being in their stoichiometric form. After a surface

treatment, the calcium containing compounds, protruding from the surface of the piece are partially resorptive, and, combined with the nanostructured porosity of the aforesaid surface, will expedite the osseointegration of the piece when compared with the prior art mentioned hereabove.

5 The present invention constitutes a major improvement of this last prior art and aims at still accelerating the osseointegration of the implant made up with the material that is the subject of the invention.. To this end, the invention relates to a method for obtaining an osteomimetic material for the constitution of an endo-osseous implant of medical or veterinary use, which method comprises the steps
10 consisting in:

- I. obtaining a homogeneous mixture consisting in a biocompatible thermoplastic polymer and tricalcium phosphate in the beta form (β TCP),
- II. subjecting that mixture to an injection or extrusion molding operation
15 with a screw injection machine, at an injection temperature at least equal to the melting temperature of the aforesaid polymer and a pressure ranging between 70 MPa and 140 MPa so as to transform the aforementioned tricalcium phosphate into a non-stoichiometric calcium apatite $3(\text{Ca}_3(\text{PO}_4)_2)(\text{OH})_2\text{Ca}$ similar to the bone's one

Thus, the method subject of the invention makes it possible to combine the
20 mechanical characteristics of the molded part and to use advantageously the thermodynamic cycle associated with these injection molding conditions, to create a resorptive calcium apatite.

The invention also relates to material obtained by the method subject of the invention, which comprises in weight contents:

- 25 a. 65 to 90% of a thermoplastic polymer;
- b. 10 to 35% of complementary compounds, at least in the form of non-stoichiometric calcium hydroxyapatite associated with resorptive calcic compounds.

Such a material can be shaped by machining and welding, in order to make out
30 all or part of pieces intended to be implanted in a bone tissue, and contains

resorptive calcic compounds, that expedite its osseointegration in said tissue, said compounds being revealed on its surface by machining or by a surface pickling operation.

The invention also relates to an endo-osseous implant made up of a material
5 according to the invention which implant comprises:

- x. a compact core;
- y. a nanostructured porous surface layer comprising resorptive calcic compounds.

Hence, compared to implants obtained by known methods of the prior art, the
10 implant, subject of the invention comprises, in particular on the surface, a more important concentration of resorptive calcic compounds, which expedites its osseointegration. The compact core of the implant confers to it a great mechanical resilience and in particular makes it possible to shape, whole or part of it, as deformable elastic zones in order to ease its primary mechanical anchoring into the
15 bone tissue.

The invention can be implemented according to the advantageous embodiments exposed hereafter that can be considered individually or according to any technically effective combination.

Advantageously, the thermoplastic polymer is made from polyetheretherketone
20 (PEEK). This thermoplastic polymer is indeed particularly biocompatible and exhibits an elastic modulus close to the bone's one, so that the elastic strain incompatibilities at the interface between the implant and implantation tissue are minimized.

Advantageously, the method subject of the invention comprises after step i) a step consisting in:

- 25 iii. incorporating into the mixture, a biocompatible and bioactive metal oxide.

Such compounds take part to the radio opacity of the implant as well as the cicatrization.

Advantageously, the incorporated metallic oxide is titanium dioxide (TiO₂) in the anatase form. Thus, the titanium dioxide in its anatase form takes part in the
30 cicatrization of the surgical operation site by its osteoclastic activation function.

Advantageously, the method subject of the invention comprises between steps i) and ii) a step consisting in:

iv. incorporating adenosine monophosphate (H_3PO_4) into the mixture

Thus, the presence of adenosine monophosphate (H_3PO_4) promotes the transmembrane exchanges as well as the regulation of the principles of phosphorylation in the cytosol.

According to a specific embodiment, the method of the invention comprises between steps i) and ii) a step consisting in:

v. incorporating into the mixture a weight percentage lower than 2% of non-stoichiometric hydroxyapatite.

Thus the content of non-stoichiometric hydroxyapatite can be slightly increased without increasing the proportion of filler in the material, i.e. without embrittlement of said material.

Advantageously, the non-stoichiometric hydroxyapatite content in the material subject of the invention is more than 2% by weight.

This high percentage of non-stoichiometric hydroxyapatite, makes it possible to expedite the osseointegration of the material.

Advantageously, the thickness of the porous surface layer of the implant according to the invention lies between 400 nm and 2000 nm. This surface layer thickness is sufficient to ensure the penetration of the graft and to ensure a strong anchoring of the implant in the tissue, without mechanically weakening the implant even in very thin areas, and without creating strain incompatibility stresses, between said layer and the core of the implant, once the graft is performed.

The invention is hereafter exposed according to its preferred embodiments, in no way limiting, and in reference to figures 1 to 3, in which:

- figure 1, is a sketch in section of an implant according to an exemplary embodiment of the invention, implanted in a bone tissue, with figure 1A showing a detail section view of the surface the implant and figure 1B a photomicrography of the surface in electronic microscopy showing the cellular colonization of the aforesaid surface;

- figure 2 represents a flowchart of the method of the invention ;
- and figure 3 shows an x-ray diffraction pattern performed on a pellet of the material obtained according to an exemplary embodiment of the method according to the invention.

5 Figure 1, according to a non-limiting exemplary embodiment, the invention relates to an endo-osseous implant (100), for example of dental type, suitable to be implanted in a maxillary (190). Said implant (100) is advantageously in the form a molded part, with more or less flexible reliefs (110) suitable for achieving the primary anchoring of the implant in the well of implantation, by side clamp. This capacity is
10 achieved by the flexibility and resilience of the polymer constituting the matrix of the implant (100).

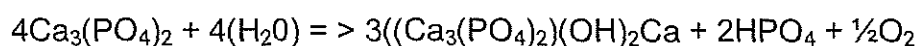
Figure 1A, in a detail section view, the implant material comprises a polymer (120) matrix, filled with ceramics particles (130), notably for achieving a calcium intake. The surface layer (115) of the implant is porous nanostructured.

15 Figure 1B, the implant, subject of the invention, performs a graft by the colonization, in less than 30 days, of the surface layer (115) of the implant by the cells (195) of the bone tissue. This implant (100) with a compact core and comprising a porous nanostructured surface layer (115), which contains resorptive calcium compounds (130), is said osteomimetic, because, on the one hand, its elastic
20 modulus, mainly influenced by the selection of the polymer making up the matrix (120), is close to the bone's elastic modulus, and on the other hand, the porous surface layer (115) promotes the activity of osteoclasts and osteoblasts of the recipient tissue so as to obtain a fast osseointegration (figure 1B) of the implant (100) in the said recipient tissue (190). Compared with the prior art, osseointegration is
25 accelerated by the presence in the implant, and more particularly in its surface layer (115), of an increased proportion, greater than 2% by weight, of non-stoichiometric and resorptive apatites, approaching the hydroxyapatite that makes up the structural substrate of the bone tissue. The thickness of said surface layer (115) is comprised between 400 nm (10^{-9} m) and 2000 nm depending on the nature of the fillers and of
30 the way the surface is pickled.

Figure 2, these outstanding characteristics are obtained by the implementation of the method subject of the invention. According to an exemplary embodiment of this method, said method comprises a first preparation step (210), consisting in evenly mixing a biocompatible thermoplastic polymer making up a matrix structure with tricalcium phosphate of the beta type: β TCP $\text{Ca}_3(\text{PO}_4)_2$. This tricalcium phosphate is chosen in a grade so-called 'pure extra' in the powder form with a grain size close to $200 \mu\text{m}$ (10^{-6} m). This grade of β TCP is, for example, marketed by the company VWR international Haasrode Reasearchpark Zone 3 GELDENAACKSEBAAN 464 B - 3001 LEUVEN Belgium.

During an injection step (220), the aforementioned mixture undergoes a molding operation on a screw injection molding machine. This injection step is carried out at a temperature at least equal to the melting temperature of the polymer constituting the matrix and preferentially between 300°C and 400°C depending on the nature of the implemented polymer. The thermodynamic cycle of pressure and temperature undergone by the mixture produces the transformation of calcium phosphate into resorptive crystals and non-stoichiometric calcium apatite molecules, therefore resorptive.

The transformation at the time of the molding operation is carried out according to the reaction:



$3((\text{Ca}_3(\text{PO}_4)_2)(\text{OH})_2\text{Ca})$ corresponds appreciably to the hydroxyapatite of the bone. This apatite is fully non-stoichiometric, therefore resorptive, which makes it possible to confer to the material, integration properties of the graft type.

Pressures typically reached during the injection/extrusion operation are ranging between 70 MPa and 140 MPa .

The physicochemical characteristics of the biological filler of the non-stoichiometric apatitic ceramics type, are essential to their biological activity. As resorptive, they condition their solubility and thus their interactions with the biological environment, as the basis of their main biological characteristics.

This non-stoichiometric resorptive apatite, similar to the bone's one, promotes

the transmembrane exchanges of the calcium ions as well as the transforming reactions of adenosines phosphates in the cytosol.

The above mentioned reaction occurs partially and the final molded material also contains residual tricalcium phosphate of the beta type. This residual tricalcium
5 phosphate is also resorptive and advantageously provides a healing function.

The thermoplastic polymer that makes up the matrix is advantageously selected among the polyether etherketone, polyether ketone, polyetherketone etherketone, polysulfone, polytetrafluoro-ethylene, the polyaramide, polyether block amides or polyimide, this list being not exhaustive. Preferably the thermoplastic polymer is a
10 polyetheretherketone (PEEK).

The method of the invention optionally comprises a step (215) consisting in adding metal ceramic compounds to the mixture obtained at the preceding step. Thus, several biocompatible and bioactive metallic oxides are chosen among ceramics like titanium dioxide (TiO_2) in the anatase form, zirconium dioxide (ZrO_2) or
15 aluminium oxide (Al_2O_3) as well as barium sulfate. These metal oxides play a catalyst role for the chemical reaction, moreover, their high molecular weight allow to improve the radio-opacity of the thermoplastic polymer constituting the matrix. The aforementioned metallic oxides also make it possible to control the ionic concentrations of the biological environments met.

More particularly, the titanium dioxide (TiO_2) in the anatase form allows a
20 cleaning of the intervention site of the surgery, thus promoting a faster cicatrization, by its osteoclastic activation function.

Another optional step (216) of the method of the invention, consists in adding adenosine monophosphate (H_3PO_4) which promotes transmembrane exchanges and
25 the regulation of phosphorylation principles in the cytosol. As a component of the subunits of nucleic acids by forming nucléotides, it thus integrates the nucleic acids and is also used to transport the chemical energy in their easily hydrolized acid-anhydride bonds, but can also bind to other groups to form enzymes which are specific messengers in the cells.

30 Associated with labile calcium ions, contained in the non-stoichiometric apatitic

formula obtained by the injection/extrusion process, it potentiates the healing process and therefore the biological acceptance of the pieces.

Finally, according to another optional step, the method of the invention comprises an addition (217) of a small proportion, less than 2%, of a non-stoichiometric calcium apatite in the mixture previously obtained.

To keep a moldable material exhibiting the required resistance, the thermoplastic polymer makes at least 65% by weight of the final material. Moreover, in order to bring sufficient chemical intended to promote the biological integration, complementary components such as phosphoric acid, beta type tricalcium phosphate, non-stoichiometric calcium apatite and metal oxide (TiO_2), associated with resorptive calcium compounds, account advantageously for between 10 and 35% in weight of the final material.

At the end of the molding operation (220), the resulting piece may undergo optional finishing operations (230) like machining by material removal so as to give it the desired macroscopic shape.

Finally, in a last step (240), the part undergoes a pickling operation aiming at creating a porous surface layer. The sterilization of the part is conveniently carried out during this pickling operation. An example of a pickling treatment leading to the formation of a nanostructured porous surface layer, promoting osseointegration, is described in the document FR 2 848 856 which is hereby incorporated by reference.

Examples:

Basic mixtures are carried out starting with polyether etherketone (PEEK), tricalcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$) of beta type, titanium dioxide (TiO_2) in the anatase form and non-stoichiometric hydroxyapatite.

Another basic mixture is prepared starting from polyether etherketone (PEEK), tricalcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$) in the beta form and titanium dioxide (TiO_2) of the anatase type.

PEEK comes in the form of a powder or granules of approximately 100 μm , distributed for example by the Company EVONIK: Evonik Degussa GMBH Paul-

Baumann-Str. 145772 Marl Germany

The used reference of PEEK is called VESTAKEEP® in fine powder, or PEEK 450P, particularly for its presentation in terms of granulometry and its purity, in order to optimize the biocompatibility of the mixture with the other components.

- 5 If calcium dihydroxyapatite is included in the mixture, it is always in the non-stoichiometric form. Said hydroxyapatite is in the form of a white powder.

Titanium dioxide in the anatase form, is in the form of a powder with a grain size larger than 200 µm. It is, for example, distributed by VWRinternational Haasrode Reasearchpark Zone3 GELDENAANKSEBAAN 464 B - 3001 LEUVEN Belgium.

10 a) Proportions

The above mentioned compounds are present in the following proportions:

1st Mix (10% of fillers)

- PEEK: 90% in weight
- 15 • βTCP: 5% in weight
- TiO₂ anatase: 90% in weight
- Non-stoichiometric Hydroxyapatite: 1% in weight

2nd Mix (20% of fillers)

- 20 • PEEK: 80% in weight
- βTCP: 9% in weight
- TiO₂ anatase : 9% in weight
- non-stoichiometric Hydroxyapatite: 2% in weight

3rd Mix (30% of fillers)

- 25 • PEEK: 70% in weight
- βTCP 14% in weight
- TiO₂ anatase : 14% in weight
- Hydroxyapatite 2% in weight

4th Mix (40% of fillers)

- PEEK: 65% in weight
- β TCP 16.5% in weight
- TiO₂ anatase : 16.5% in weight
- Non-stoichiometric Hydroxyapatite: 2% in weight

5th Mix

- PEEK: 80% in weight
- β TCP 10% in weight
- TiO₂ anatase: 10% in weight

b) Malaxation

The components of each mixture are placed in a turbine mixer until obtaining a perfect homogenisation.

c) Drying

Each homogeneous mixture obtained is dried in a drying oven with circulation of air during 3 hours at 150 °C.

d) Extrusion granulation

This operation makes it possible to obtain in a die, a filament or a tube which can be cut in segments of different length in order to obtain pellets, simple or multiple tubes, of all dimensions.

e) Molding

The molding operation is carried out on an injection molding FANUC electric 30 tons machine.

The device preparation and the molding conditions of the mixture correspond to those used for pure PEEK.

The PEEK being a semicrystalline thermoplastic, it is necessary to heat the

mold, in order to avoid the formation of a surface veil in amorphous state. Thermoregulation of the mold is provided by a heating system able to maintain it at a temperature of about 160°C.

The molding is carried out at a temperature ranging between 340°C and 400°C
5 and with an injection pressure ranging between 70 and 140 MPa.

The mold may be conformed according to the kind of part to obtain, for example, for a bone prosthesis, notably for dental and orthopedic applications.

A block of material can also be molded which is then cut or machined according to the desired shape, for example for an osseous filling or an implant, like a spinal
10 intersomatic cage.

According to specific embodiments, filaments can be extruded which, after knitting or weaving, are used as sleeving membranes for protection or support purposes, or sheets with variable thickness, possibly perforated with holes or of microholes, in order to produce membranes.

15

Results

Chemical analysis trial

Figure 3, the X-rays diffraction pattern of the 5th mixture, i.e. containing PEEK
20 (80%), tricalcium phosphate (10%) of beta type and titanium dioxide (10%) in anatase form, is performed on a pellet after the molding operation and reveals, by the appearance of the peaks (301,302, 303, 304, 305), the presence of the non-stoichiometric calcium hydroxyapatite in the molded material, of the same type as the principal mineral component of the human bone.

25 A biopsy is performed on an implant, consisting of a material corresponding to the 1st mixture after a 30 days implantation.

The histological analysis reveals the absence of any inflammatory zone, and especially cytoplasmic prolongations as well as cells inserted in the surface layer of the material.

30 The XPS analysis reveals the presence of nitrogen in the material up to more

than 900 nanometers. This nitrogen is linked to the material by covalent bonds. It should be reminded that the material does absolutely not contain any nitrogen before implantation. Thus this nitrogen comes from the cells in contact with the material.

Moreover, the nitrogen is linked to radicals containing hydrogen making amino
5 sequences related to the implanted material. This analysis makes it possible to show a graft principle, induced between the osseous cells and the material.

The foregoing description and the exemplary embodiments, show that the invention achieves the targeted aims, in particular, it makes it possible to obtain an osteomimetic material, exhibiting a fast osseointegration.

CLAIMS

1. A method for obtaining a material for the constitution of an osteomimetic endo-osseous implant of medical or veterinary use, characterized in that it comprises the steps consisting in:
 - i. obtaining a homogeneous mixture consisting in a biocompatible thermoplastic polymer and tricalcium phosphate in the beta form (β TCP),
 - ii. subjecting that mixture to an injection or extrusion molding operation by a screw injection machine, at an injection temperature at least equal to the melting temperature of the aforesaid polymer and a pressure ranging between 70 MPa and 140 MPa so as to transform the aforementioned tricalcium phosphate into a non-stoichiometric calcium apatite $3(\text{Ca}_3(\text{PO}_4)_2)(\text{OH})_2\text{Ca}$ similar to the bone's one.
- 2.. Material obtained by the method according to claim 1, which material is characterized in that it comprises, in weight contents:
 - a. 65 to 90% of a thermoplastic polymer;
 - b. 10 to 35% of complementary compounds, at least in the form of non-stoichiometric calcium hydroxyapatite associated with resorptive calcic compounds.
3. Endo-osseous implant (100) made up of the material according to claim 2, characterized in that it comprises:
 - x. a compact core (120) ;
 - y. a nanostructured porous surface layer (115) comprising resorptive calcic compounds (130).
4. The method according to claim 1, characterized in that the thermoplastic polymer consists of polyether éthercétone (PEEK).

5. The method according to claim 2, characterized in that it further comprises the steps of:
 - iii. incorporating (215) into the mixture a biocompatible and bioactive metal oxide .
- 5 6. The method according to claim 5, characterized in that the incorporated metallic oxide is titanium dioxide (TiO_2) in the anatase form
7. The method according to claim 1, characterized in that it comprises between steps i) and ii) a step consisting in:
 - iv. incorporating adenosine monophosphate (H_3PO_4) into the mixture
- 10 8. The method according to claim 1, characterized in that it comprises between steps i) and ii) a step consisting in:
 - v. incorporating (217) into the mixture a weight percentage lower than 2% of non-stoichiometric hydroxyapatite.
- 15 9. A material according to claim 2, characterized in that its non-stoichiometric hydroxyapatite content is higher than 2% in weight.
10. An implant according to claim 3, characterized in that the thickness of the porous surface layer (115) lies between 400 nm and 2000 nm.