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(71) Applicant *(for all designated States except US)*: **SANDVIK INTELLECTUAL PROPERTY AB** [SE/SE]; S-811 81 Sandviken (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ÅSTRAND, Maria** [SE/SE]; Överbacka, ., S-SE 743 91 Storvreta (SE). **GENVAD, Axel** [SE/SE]; Trollesundsvägen 11, S-SE 124 32 Bandhagen (SE).

(74) Agent: **HÄGGLÖF, Henrik**; Sandvik Intellectual Property AB, S-811 81 Sandviken (SE).

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(54) **Title:** METHOD OF MAKING A COATED MEDICAL BONE IMPLANT AND A MEDICAL BONE IMPLANT MADE THEREBY

(57) **Abstract:** The present invention relates to a method of making a coated medical bone implant comprising the step of providing a substrate and then onto said substrate deposit a bioactive crystalline TiO_2coating using PVD (Physical Vapor Deposition) technique at a temperature of >50°C but<800°C. Coated implants obtained by the method according to the invention display an enhanced biomimetic response.

METHOD OF MAKING A COATED MEDICAL BONE IMPLANT AND A MEDICAL BONE IMPLANT MADE THEREBY

The present invention relates to a method of making a coated medical bone implant with a bioactive crystalline TiO_2 coating, where the TiO_2 coating has been deposited using PVD technique. Coated bone implants obtained by the method according to the invention display an enhanced biomimetic response.

Background

Applying coatings to medical bone implants such as hip joints etc. is well known in the art. Coatings are applied for different reasons, e.g., increased wear resistance, improved biocompatibility and/or bioactivity.

Titanium and titanium alloys are well recognized materials for dental and orthopedic implants due to their good biocompatibility. On bone implants made of titanium a thin surface layer of native titanium dioxide is immediately formed when exposed to air. Such layers have an amorphous crystal structure and are responsible for the good biocompatibility. By biocompatible is meant that the implant is inert and that it does not cause any toxicity or negative side effects to the tissue.

For some implant surfaces, i.e., those that are meant to bond with bone tissue, it is of high importance to have good bioactivity. By bioactive is meant that the material is capable of biochemically bonding to the natural tissue. This can only be achieved by having a more crystalline titanium oxide, i.e., an oxide with larger crystal grains. To obtain a more crystalline structure the oxidization can be forced by e.g., performing the oxidation of the Ti surface at an increased temperature. TiO_2 can also be deposited onto the surface of the implant as an additional coating/layer. This can for example be done by anodization, plasma spraying etc.

For implants such as dental and orthopedic implants it is in some cases very important that the implant is bonded to the natural bone tissue as fast as possible, i.e., that it is osseointegrated. This means that hydroxyapatite needs to be formed rapidly on the implant surface. This, in turn, requires that the surface of the implant is both biocompatible and bioactive.

Vapor deposition processes such as CVD (Chemical Vapor Deposition) and PVD (Physical Vapor Deposition) are common techniques for coating semiconductors,

optical surfaces, cutting tools etc. These techniques have also been used to coat implant surfaces where an increased wear resistance is wanted e.g., the contact zones in a hip joint, or as a corrosion barrier.

US 2003/0175444 A1 describes a method of coating artificial organs of organic and inorganic materials, such as vascular stents, artificial heart valves etc., with a plasma immersion ion implantation method (PIII). TiO_2 coatings, with a coating thickness of 0.05-5 μm, are deposited in a vacuum chamber by means of a metal arc plasma source which creates titanium plasma in the presence of oxygen gas or plasma. The artificial organs that are provided with the TiO_2 coating are suitable for implanting into human bodies and contacting blood. The artificial organs show improved blood compatibility i.e., improved anticoagulation properties. US 2003/0175444 A1 does not mention implants osseointegration i.e., implanting into bone.

WO 03/070288 describes a multilayered coating for implants comprising a first dense layer and a second bioactive layer. The first layer can be an oxide, nitride boride, carbide or mixtures thereof, preferably a nitride. The second layer is an apatite layer. The first layer will function as a corrosion barrier whereas the second layer is bioactive. The first layer can be deposited by PVD or CVD technique, oxides are preferably deposited using CVD.

However, very few attempts have been done to use vapor deposition techniques to deposit bioactive coatings, i.e., coatings that will create biochemical bonds to bone tissue.

The bioactivity of PVD deposited TiO_2 has been evaluated in "Plasma-controlled nanocrystallinity and phase composition of TiO_2: a smart way to enhance biomimetic response", J. Biomed. Mater. Res. Part. ADOI 10.1002 (2007) 453-464. The TiO_2 coatings have been deposited at room temperature, without preheating, by reactive DC magnetron technique. The bioactivity was evaluated by measuring the hydroxyapatite growth after immersion in simulated body fluid (SBF). The effect on bioactivity of the two different TiO_2 phases, rutile and anatase, were investigated.

However, there are some disadvantages with coatings deposited at room temperature of which one is related to the presence of water vapor. It is very

important that all water is evaporated from the substrate surface prior to deposition. If water is still present on the surface, the adhesion of the coating will be compromised which would be a big disadvantage, especially on a medical implant that is aimed to stay in the body for a long time.

It is an object of the present invention to provide a method of making a medical bone implant having a bioactive crystalline TiO_2 coating resulting in improved biomimetic response.

It is another object of the present invention to provide a method which gives coatings with good adhesion to the substrate.

Detailed description of the invention

The present invention relates to a method of making a coated medical bone implant comprising the step of:

-providing a substrate, and

-onto said substrate deposit a bioactive crystalline TiO_2 coating by using PVD (Physical Vapor Deposition) technique at a temperature of >50°C but <800°C.

By bone implant is meant any medical implant comprising at least one surface that is aimed for osseointegration, i.e., that the implant bonds to natural bone tissue being either human or animal. Examples of such implants are orthopedic prostheses for the hip, knee, ankle, shoulder, elbow and spine as well as dental implants. With bone implants are also meant devices for attachment of implants such as screws, nails etc..

PVD techniques suitable for the present invention are any PVD technique known in the art. Preferably any one of cathodic arc evaporation, magnetron sputtering or e-beam evaporation, most preferably cathodic arc evaporation, is used.

Prior to placing the substrates in the PVD chamber, the substrates are mounted on a rotating substrate holder. For complex geometries, a 3-fold rotation is preferably used.

The PVD process comprises several steps. First, the pressure is reduced in the chamber by removing the air by pumping, then the substrates are preheated to a suitable temperature after which the substrates are ion-etched, preferably using Ar

ions, to remove any surface contaminants. Thereafter, the substrates are coated with titanium oxide using one or more pure Ti sources and by introducing oxygen into the deposition chamber. Evaporation of Ti atoms and/or ions can be performed using different techniques. For example, in cathodic arc evaporation, the source material is vaporized by melting a spot on the source using an arc, whereas in magnetron sputtering the Ti ions are vaporized by ion bombardment of the source surface. In e-beam evaporation the Ti is melted and vaporized using an electron beam. The degree of ionization of the Ti atoms depends on the chosen technique, however the Ti ions in the plasma will react with the oxygen, resulting in a film of TiO_2.

The deposition time varies depending on the chosen PVD technique and the wanted coating thickness.

The coating thickness for the deposited TiO_2 coating according to the present invention can be >3 nm, preferably >5 nm and most preferably >10nm, but <5000 nm, preferably <1000 nm, and most preferably <500 nm.

The coating process according to the present invention is performed at a temperature of >50°C, preferably >70°C, and most preferably >100°C, but <800°C, preferably <700°C, and most preferably <550°C.

In one embodiment, the PVD technique used is cathodic arc evaporation. Then, the substrate bias is suitably 0 to -500 V, preferably -5 to -300 V, and most preferably -10 to -200 V. The arc current suitably is 50 to 250 A, preferably 65 to 240 A, and most preferably 80 to 220 A. The reactive gas flow preferably is 50 to 2000 sccm, and most preferably 200 to 1500 sccm.

The bioactive crystalline TiO_2 coating according to the present invention can have any crystalline phase but are preferably rutile or anatase or a mixture thereof.

By crystalline TiO_2 is herein meant that the coating results in diffraction spots or rings when analyzed using Selected Area Electron Diffraction Transmission Electron Microscopy (SAED-TEM). A crystalline TiO_2 coating according to the present invention can, if the measurements are performed by using X-ray Diffraction (XRD), appear to be amorphous. This can either be due to the low thickness and/or the small crystallites in the coating. Hence TEM analysis is, or can be, necessary to detect the crystallinity of the coating.

In one embodiment of the present invention, the bioactive crystalline TiO_2 coating has a crystalline phase which is a mixture of rutile and anatase. The different phases are identified by measurements either by X-ray Diffraction (XRD) or Selected Area Electron Diffraction Transmission Electron Microscopy (SAED-TEM).

Although, the present invention relates to a TiO_2 coating some deviation from the exact stoichiometry can be present.

The stoichiometry of the crystallites is close to TiO_2, as analysed using TEM. However, the coating in its whole might consist of small crystallites of stoichiometric TiO_2 in an amorphous non-stoichiometric matrix and hence the overall composition of the coating might deviate from TiO_2 stoichometry. Hence, high-resolution microscopy such as TEM is necessary to evalute the stoichiometry of the crystallites in the coating.

The bioactive crystalline TiO_2 coating can also contain other elements but then at a level of a technical impurity.

In one embodiment of the present invention the bioactive crystalline TiO_2 layer is the outermost layer i.e., there can be other coatings present at the substrate surface, under the bioactive crystalline TiO_2 layer.

The substrate material can be any material suitable for implants. Examples of such materials are titanium, titanium-alloys, cobalt, cobalt alloys, tool steel, stainless steel, cobalt, Co-Cr-Mo-alloys.

Example 1

Substrates in the form of metal plates, 20x20x1 mm, were coated with TiO_2 using a cathodic arc evaporation PVD process. Three different substrate materials were used: commercially pure Ti grade 2, TiAl6V4 and Stainless steel, medical grade AISI type 316L.

Prior to deposition, the substrates were ultrasonically cleaned in acetone for 10 minutes followed by 10 minutes in ethanol before they were dried in hot air.

The substrates were mounted on a 3-fold rotating table which then was placed inside the PVD chamber, in which 4 sources of pure Ti had been mounted. The substrates were then heated for a period of 50 minutes to the aimed deposition temperature, see Table 1 below, followed by 36.5 min of Ar etching to remove any

surface contaminants. During deposition the flow rate of oxygen was 800 sccm. The substrate bias was -60 V, the arc source power was 5-6 kV and the arc current 150 A. The deposition time, the deposition temperature and the thickness of the TiO_2 layer is given in Table 1. The thickness of the coatings was measured with a scanning electron microscope (SEM). Also, the crystal structure of the coatings was analyzed by X-ray diffraction (XRD). All coatings showed a mixture of rutile and anatase crystal structure.

Table 1

Sample	Substrate	Deposition temp. (°C)	Deposition time (min)	Coating thickness (nm)
Invention 1	Ti, grade 2	320	40	1450
Invention 2	Ti, grade 2	500	10	290
Invention 3	Ti, grade 2	200	10	370
Invention 4	TiAl6V4	320	10	350
Invention 5	Stainless steel	320	10	350
Invention 6	Ti, grade 2	320	1	50

Example 2

A substrate of commercially pure Ti grade 2, in the form of metal plates, 20x20x1 mm, was coated with TiO_2 using a magnetron sputtering PVD process.

The substrates were first ultrasonically cleaned, first 6 minutes in a basic solution, then the substrates were rinsed before ultrasonically cleaned in ethanol for 6 minutes. Finally the samples were rinsed and dried in pure nitrogen gas.

The substrates were mounted on a holder that moves in a circular orbit and at the same time rotates around its own axis which then was placed inside the PVD chamber, in which one solid Ti source had been mounted. The substrates were then heated for a period of 60 minutes to the aimed deposition temperature, followed by 6 min of Ar etching to remove any surface contaminants. The substrate bias was +150 V, the total pressure during deposition was 4.2 μbar and the ratio of $Ar:O_2$ was 30:70. The deposition temperature was 200°C.

Table 2

	Substrate	Deposition time (min)	Coating thickness (nm)
Invention 7	Ti, grade 2	40	170

The thickness of the coating was measured by a scanning electron microscope (SEM). Also, the crystal structure of the coating was analyzed by X-ray diffraction (XRD). The coating showed a mixture of rutile and anatase crystal structure as measured by XRD.

Example 3

To evaluate the bioactivity i.e., the hydroxyapatite (HA) forming ability of the TiO_2 coatings biomimetics was used where the surface is tested in a simulated body fluid (SBF).

The samples from Example 1 and 2 were tested as well as reference samples as shown in Table 3:

Table 3

	Substrate	Method
Ref. 1	Ti, grade 2	Exposure to air (Native TiO_2)
Ref. 2	Ti, grade 2	Thermal oxidation
Ref. 3	TiAl6V4	Thermal oxidation

All samples were soaked in SBF. SBF is a fluid which has an ion composition and concentration similar to those of blood plasma. The SBF used in these tests were Dulbecco's phosphate buffered saline (PBS).

The samples were soaked in the SBF for a period of one week in 37˚C and then rinsed and dried. The growth of HA onto the TiO_2 coating surface was visually determined by a scanning electron microscope (SEM) and graded as good or poor. By "good" is herein meant that the HA layer is smooth and is covering the whole TiO_2 surface. By "poor" is meant that the HA growth does not cover the TiO_2 surface completely. The results are shown in Table 4.

Table 4

Sample	Substrate	Coating method	TiO_2 (nm)	HA growth
Invention 1	Ti, grade 2	Arc	1450	Good
Invention 2	Ti, grade 2	Arc	290	Good
Invention 3	Ti, grade 2	Arc	370	Good
Invention 4	TiAl6V4	Arc	350	Good
Invention 5	Stainless steel	Arc	350	Good
Invention 6	Ti, grade 2	Arc	50	Good
Invention 7	Ti, grade 2	Sputtring	170	Good
Ref. 1	Ti, grade 2	None, Native oxide	n.a.	None
Ref. 2	Ti, grade 2	Thermal oxidation	n.a.	Poor
Ref. 3	TiAl6V4	Thermal oxidation	n.a.	None

Claims

1. A method of making a coated medical bone implant, comprising the steps of:

-providing a substrate,

-onto said substrate deposit a bioactive crystalline TiO_2 coating,

c h a r a c t e r i z e d in that the deposition is performed using PVD technique at a deposition temperature of >50°C but <800°C.

2. A method according to claim 1 c h a r a c t e r i z e d in that the PVD technique is a cathodic arc evaporation.

3. A method according to any of the preceding claims c h a r a c t e r i z e d in that the substrates, during deposition, is subjected to a 3-fold rotating motion.

4. The method according to any of the preceding claims c h a r a c t e r i z e d in that the deposited TiO_2 coating has a thickness of >3 nm but <5000 nm.

5. The method according to any of the preceding claims c h a r a c t e r i z e d in that the bioactive crystalline TiO_2 coating is the outermost coating.

6. The method according to any of the preceding claims c h a r a c t e r i z e d in preheating the substrate before deposition.

7. A coated medical bone implant comprising a substrate and a coating c h a r a c t e r i z e d in that the coating comprises a bioactive crystalline TiO_2 PVD coating.

8. A coated medical bone implant according to claim 7 c h a r a c t e r i z e d in that the PVD coating is a cathodic arc evaporation coating.

9. A coated medical bone implant according to claims 7 or 8 c h a r a c t e r i z e d in that the TiO_2 coating has a thickness of >3 nm but <5000 nm.

10. A coated medical bone implant according to claims 7-9 c h a r a c t e r i z e d in that the bioactive crystalline TiO_2 coating is the outermost coating.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2009/050035

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
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)

IPC: A61F, A61L, C23C

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

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20030175444 A1 (HUANG, NAN ET AL), 18 Sept 2003 (18.09.2003), figure 1, paragraphs [0001]-[0003], [0058], [0060]-[0062], [0069]	1-10
	--	
X,P	WO 2008056323 A1 (STRÖMME, MARIA), 15 May 2008 (15.05.2008), paragraphs [0002], [0032]-[0036], [0040]	1,4-5,7,9-10
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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US	20030175444	A1	18/09/2003	NONE
WO	2008056323	A1	15/05/2008	NONE