



DESCRIPTION

MEDICAL SUPPLIES AND METHOD OF PRODUCING THE SAME

TECHNICAL FIELD

5 The present invention relates to medical supplies and, particularly, to an improvement in the antimicrobial activity of medical supplies such as artificial bones and osteosynthetic and fixation devices which are implanted in living bodies prior to use.

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BACKGROUND ART

 The recent development of medical technologies has led to the situation where many technologies are used clinically for grafting implants that repair and substitute bones and joints
15 which are defectives or have depleted functions in living bodies such as the human bodies. As to the characteristics required for each of the implants used in these technologies, the implants are desired to have the same strength as part of a living body before substituted and also, firstly compatibility with a living body,
20 that is, biocompatibility. Examples of biocompatible metallic materials having such characteristics include titanium, titanium alloys, stainless steel and Co-Cr alloys. However, these metallic materials have no living activity so that they are not chemically bonded to a bone, causing problems concerning the occurrences of
25 a gap and loosening during a long time of use.

 In light of such problems, there is described in, for example, Patent Document 1, a method of forming an oxide film in which a hydrogen peroxide-containing paste is brought into contact with the surface of a metal which is a base material to thereby convert



the surface of the base material into a metal oxide. It is described in the document that according to this technologies, an oxide film can be formed in a short time and good biocompatibility is obtained.

5 Further, separately from the above problems, these implants cause the problem that when these implants are grafted in living bodies, infections such as suppuration of diseased part are caused with high incidence.

To deal with such a problem, there is the idea of using, as implant materials, Cu and Ag that are widely known to exhibit excellent antimicrobial activity. For example, Non-Patent Document 1 reveals the results obtained by carrying out an experiment in which Ag known to exhibit high antimicrobial activity is transplanted as an implant (made of pure silver) to 15 an animal (hamster). According to these results, it is necessary to cautiously decide whether to use Ag as an implant material because a silver implant causes severer inflammation and swelling as compared with a titanium or stainless steel implant, showing that the silver implant is deteriorated in affinity to a living 20 body.

Further, Non-Patent Document 2 reports the result of an experiment concerning inhibition to pin-infections in the case of using an external fixation pin coated with Ag. According to these results, it is not observed that bacterial cells are 25 sufficiently reduced by the Ag coating and it is observed that a rise in Ag level in blood by the grafting of the Ag-coated external fixation pin in a living body.

PRIOR ART DOCUMENT

PATENT DOCUMENT

Patent Document 1: Japanese Patent Application Laid-Open
No. 2008-6164

5 NON-PATENT DOCUMENT

Non-Patent Document 1: C.N. Kraft, et al.: Journal of
Biomedical Materials Research Part A. Vol. 49 (1999) Issue 2, Pages
192-199

Non-Patent Document 2: A. Masse, et al.: Journal of
10 Biochemical Materials Research Part B: Applied Biomaterials, Vol.
53 (2000) Issue 5, Pages 600-604

DISCLOSURE OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

15 In light of the prior art problems like this, it is an object
of the present invention to provide medical supplies which can
inhibit infections with various bacteria for a long period of time,
have excellent antimicrobial activity, and are superior in the
durability of antimicrobial activity and also in superior in
20 biocompatibility, and to provide a method of producing the medical
supplies.

MEANS FOR SOLVING THE PROBLEMS

The inventors of the present invention focused their
25 attentions on iodine and iodine compounds as materials having
antimicrobial activity. Iodine has sterilizing activity and
antimicrobial activity, is also used as disinfectants and is said
to have small toxicity to living bodies. In light of this, the
inventors of the present invention have conceived of impregnating

the surface of an implant base material with iodine or iodine compounds to inhibit infections associated with an implant. The inventors of the present invention have conceived of an idea that if the surface of an implant base material is impregnated with iodine or iodine compounds and iodine is allowed to be discharged gradually, this enables the implant itself to be sterilized and is also very effective to maintain the antimicrobial activity afterward. The inventors of the present invention made further studies and as a result, found that when the base material was anodically oxidized in an electrolytic solution having a specific composition by using pulsed current having a frequency in a predetermined range, an oxide film having many micro pores was formed on the base material and also, these micro pores could be impregnated with iodine or iodine compounds, showing that these pores were very effective to improve the continuation of antimicrobial activity.

First, the fundamental experiment made by the inventors of the present invention will be described.

A Ti alloy (mass% basis, 6% Al-4% V-rest Ti; JIS type-60 alloy) was used as the base material to produce disc-like test piece (plate thickness: 1.5 mm). These test pieces were subjected to degreasing treatment and then to anodic oxidation treatment. In the anodic oxidation treatment, the test piece was electrolyzed at a constant voltage (150 V) for 5 minutes in an acid electrolytic solution (solution temperature: room temperature) of a mixture bath containing sulfuric acid (35 g/l)-phosphoric acid (25 g/l)-aqueous hydrogen peroxide (10 g/l). In this case, though the current load was made to have an initial current density of 8 A/dm², the current value was dropped in order along with passage of time

because of the electrolysis at constant voltage. In this case, as the current, 50 to 10000 Hz pulsed current was used. The test was also made by using direct current (DC) as the current load.

Then, the anodically oxidized test piece was cleaned with water and then, subjected to iodine-impregnation treatment in which the test piece was dipped in an aqueous iodine compound solution prepared by dissolving 0.5 mass% of a polyvinyl pyrrolidone iodine (PVPI) which was an iodine compound in pure water, the test piece was arranged on the anode side and a pure Ti plate was arranged on the cathode side, and the test piece was electrolyzed at a constant voltage of 120 V for 5 minutes to cause electrophoresis, thereby impregnating an oxide film of the surface of the test piece with the iodine compound. In this impregnation with iodine compound, the initial current density was set to about 0.2 A/dm². A part of the test pieces were not subjected to the impregnation with iodine compound.

First, the anodically oxidized test pieces were subjected to a scanning electron microscope (magnification: 2500 times) to be used to observe the surface structure of the oxide film formed on the surface of the test piece. Each test piece was observed from five or more visual fields to measure the number of pores formed in the oxide film in each visual field. Then, an arithmetic average of the obtained values was calculated to determine the number of pores of the oxide film formed on the surface of each test piece. In this case, the section of each test piece was also observed by a scanning electron microscope (magnification: 2500 times) to measure the thickness of the formed oxide film.

Further, with regard to the test pieces subjected to anodic oxidation treatment and the test pieces subjected to anodic

oxidation treatment and iodine-impregnation treatment, an antimicrobial activity test was made by the film covering method according to the provisions of JIS Z 2801. *Escherichia coli* (JCM 1649 strains) was used as the pathogenic organ and the cells number left after a prescribed time (24 h) passed was measured to evaluate the antimicrobial activity of the test piece. The test was repeated two times each. As the cells number left after a prescribed time passed is smaller, the test piece is evaluated to be superior in antimicrobial activity. When the cells number which was, at first, 36000/ml (3.6×10^4 /ml) was decreased to less than 10/ml after a prescribed time (24 h) passed, this was rated as 4 (antimicrobial activity value), when the cells number was 10 or more and less than 100/ml, this was rated as 3 (antimicrobial activity value), when the cells number was 100 or more and less than 1000/ml, this was rated as 2 (antimicrobial activity value), when the cells number was 1000 or more and less than 10000/ml, this was rated as 1 (antimicrobial activity value), and when the cells number was 10000 or more, this was rated as 0 (antimicrobial activity value).

The obtained results are shown in Table 1.

[Table 1]

Test piece No.	Base material *	Anodic oxidation treatment		Iodine-impregnation treatment	Antimicrobial activity rating
		Current load			
		Type **	Frequency Hz		
1	A	b	—	Untreated	0
2	A	b	—	Treated	1
3	A	a	50	Untreated	0
4	A	a	50	Treated	2
5	A	a	500	Untreated	0
6	A	a	500	Treated	2

7	A	a	800	Untreated	0
8	A	a	800	Treated	3
9	A	a	1000	Untreated	0
10	A	a	1000	Treated	4
11	A	a	3000	Untreated	0
12	A	a	3000	Treated	4
13	A	a	5000	Untreated	0
14	A	a	5000	Treated	4
15	A	a	8000	Untreated	0
16	A	a	8000	Treated	3
17	A	a	10000	Untreated	0
18	A	a	10000	Treated	3

*) A: Ti alloy (JIS type-60 alloy)

**) a: pulsed current, b: direct current

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In the case where the iodine-impregnation treatment is not carried out but only anodic oxidation treatment is carried out, the antimicrobial activity value is 0 and no improvement in antimicrobial activity is observed. The antimicrobial activity is improved more significantly in the case of performing anodic oxidation treatment by adding pulsed current at a frequency of 50 Hz or more than in the case of performing anodic oxidation treatment by adding direct current. It is clarified that the antimicrobial activity is significantly improved when anodic oxidation treatment is performed by applying pulsed current at a frequency of, particularly, 800 Hz or more and more preferably 1000 to 5000 Hz. This is clarified from the relation between the density of the formed micro pores and the frequency of the pulsed current load in the anodic oxidation treatment as illustrated in Fig. 1. It is found from Fig. 1 that when the frequency of the pulsed current load is made to be 50 Hz or more, the density of micro pores to be formed is significantly increased to as high as $5 \times 10^4/\text{mm}^2$. When the frequency is 0, that is, when direct

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current is applied, only groovy unevenness is formed on the film and almost no micro pore is formed as shown in Fig. 3(a). When the frequency of the applied pulse current is 50 Hz on the contrary, the groovy unevenness disappears and many micro pores are clearly
5 formed on the film as shown in Fig. 3(b). Moreover, when the frequency of the applied pulse current is as high as 1000 Hz, many more micro pores are formed as shown in Fig. 3(c). It has been found from the comparison shown in Table 1 and Fig. 1 that the supplies which have a film having micro pores increased in pore
10 density to at least $5 \times 10^4/\text{mm}^2$ or more and which has been subjected to iodine-impregnation treatment are able to have excellent antimicrobial activity.

Further, as shown in Fig. 2, it has been found that if pulse current having a frequency of 50 Hz or more is applied to carry
15 out anodic oxidation treatment, many micro pores are formed and a film 3 μm or more in thickness can be formed.

It has been found from the above results that when pulse current having a frequency of 50 Hz or more is applied to carry out anodic oxidation treatment, a film which contains many micro
20 pores described above and has a thickness of, preferably 3 μm or more can be formed on the base material and that when the film is impregnated with iodine or iodine compounds, the antimicrobial activity of the base material is significantly improved.

The present invention has been completed based on the above
25 findings and further additional studies.

Specifically, the essential points of the present invention are as follows.

(1) Metallic medical supplies using a metal material as a base material, the medical supplies including a film having micro pores

and/or micro unevennesses on the surface of the base material, wherein the micro pores and/or micro unevennesses are impregnated with iodine or iodine compounds.

(2) The metallic medical supplies according to (1), wherein the
5 film includes the micro pores and/or micro unevennesses having a density of at least $5 \times 10^4/\text{mm}^2$ or more.

(3) The metallic medical supplies according to (1) or (2), wherein the film is formed by any one of electrochemical treatment, chemical treatment, thermal and/or mechanical treatment or a
10 combination of two or more of these treatments.

(4) The metallic medical supplies according to (3), wherein the electrochemical treatment is anodic oxidation treatment, the chemical treatment is medicine treatment, the thermal and/or mechanical treatment is any one of heating treatment, thermal
15 processing treatment and mechanical processing treatment.

(5) The metallic medical supplies according to any one of (1) to (4), wherein the iodine compound is polyvinyl pyrrolidone iodine, β -cyclodextrin iodine or silver iodide.

(6) The metallic medical supplies according to any one of (1) to
20 (5), wherein the metallic material is a pure metal selected from the group consisting of Ti and Co or an alloy selected from the group consisting of a Ti alloy, a Co alloy, stainless steel and a Co-Cr alloy.

(7) Metallic medical supplies using a metal material as a base
25 material, the medical supplies including a film subjected to anodic oxidation treatment having micro pores having a density of at least $5 \times 10^4/\text{mm}^2$ on the surface of the base material, wherein the micro pores are impregnated with iodine or iodine compounds.

(8) The metallic medical supplies according to (7), wherein the

iodine compound is polyvinyl pyrrolidone iodine, β -cyclodextrin iodine or silver iodide.

(9) The metallic medical supplies according to (7) or (8), wherein the film has a thickness of 3 μm or more.

5 (10) The metallic medical supplies according to any one of (7) to (9), wherein the base material is made of any one of Ti or Ti alloy, stainless steel, and a Co-Cr alloy.

(11) A method of producing metallic medical supplies, the method including using a metallic material as a base material, treating
10 the base material by carrying out any one of electrochemical treatment, chemical treatment, thermal and/or mechanical treatment or a combination of two or more of these treatments to form a film having micro pores and/or micro unevennesses having a density of $5 \times 10^4/\text{mm}^2$ on the surface of the base material, and
15 carrying out iodine-impregnation treatment to impregnate the film with iodine or iodine compounds, to make medical supplies.

(12) The method of producing metallic medical supplies according to (11), wherein the electrochemical treatment is anodic oxidation treatment, the chemical treatment is medicine treatment, the
20 thermal and/or mechanical treatment is any one of heating treatment, thermal processing treatment and mechanical processing treatment.

(13) The method of producing metallic medical supplies according to (12), wherein the anodic oxidation treatment is a treatment
25 in which an acid electrolytic bath or an alkali electrolytic bath is used as an electrolytic solution, and pulsed current having a frequency of 50 to 10000 Hz is applied to the base material in the electrolytic solution to carry out electrolysis treatment.

(14) The method of producing metallic medical supplies according

to (12), wherein the medicine treatment is a treatment in which an alkali bath or acid bath having a liquid temperature of 30°C or more is used and the base material is dipped in the alkali bath or acid bath.

5 (15) The method of producing metallic medical supplies according to (12), wherein the mechanical processing treatment is a shot blasting.

(16) The method of producing metallic medical supplies according to any one of (11) to (15), wherein the iodine compound is polyvinyl
10 pyrrolidone iodine, β -cyclodextrin iodine or silver iodide.

(17) The method of producing metallic medical supplies according to any one of (11) to (16), wherein the base material is made of any one of Ti or Ti alloy, stainless steel, and a Co-Cr alloy.

15 EFFECTS OF THE INVENTION

According to the present invention, medical supplies which have excellent antimicrobial activity and are superior in the durability of antimicrobial activity and also in biocompatibility can be produced easily at low costs, producing an outstanding
20 industrial effect. Further, when the medical supplies according to the present invention are used as, for example, an implant to be grafted in a living body, such an effect is obtained that infections which are large problems when usual medical supplies are grafted in a living body can be inhibited for a long period
25 of time.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the relation between the pore density of a film formed in anodic oxidation treatment and the

frequency of pulse current load.

Fig. 2 is a graph showing the relation between the thickness of a film formed in anodic oxidation treatment and the frequency of pulse current load.

5 Fig. 3 is a scanning electron micrograph showing the surface state of a film formed by anodic oxidation treatment.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention relates to medical supplies using a
10 base material made of a metallic material, and is provided with a film having micro pores and/or micro unevennesses on the base material. The term "micro pores and/or micro unevennesses" used herein means the surface state of the base material changed from the initial state by artificially carrying out heat treatment,
15 mechanical treatment, electrochemical treatment or chemical treatment or combinations of these treatments. Then, the term "micro pore" means a circular or polygonal pore having an area-equivalent circle diameter of about 1 to 10 μm . Further, the term "micro unevennesses" means the surface state on which
20 unevennesses having a depth of several micrometers (μm) to several hundreds of micrometers (surface roughness R_a : about several micrometers (μm) to several hundreds of micrometers (μm)) exist as these pores are deformed or integrated.

The film to be formed on the surface of the base material
25 may be one only having micro pores and/or micro unevennesses such as those mentioned above and no particular limitation is imposed on a method of forming the film. However, the film is preferably one formed by any one of electrochemical treatment, chemical treatment, thermal and/or mechanical treatment or a combination

of two or more of these treatments. It is preferable to adopt anodic oxidation treatment as the electrochemical treatment, medicine treatment as the chemical treatment, heating treatment as the thermal treatment, thermal processing treatment as the thermal and mechanical treatment, and mechanical processing treatment as the mechanical treatment. These treatments enable easy formation of a film having micro pores and/or micro unevennesses having a desired density. The desired density of the micro pores and/or micro unevennesses is preferably at least $5 \times 10^4/\text{mm}^2$ or more. When such a film having micro pores and/or micro unevennesses having a desired density is formed on the surface of the base material, the surface of the base material can be impregnated stably and sufficiently with iodine or iodine compounds which improve the antimicrobial activity and sterilizing activity of the supplies.

Then, micro pores or micro unevennesses of the film are impregnated with iodine or iodine compounds. Since iodine has antimicrobial activity and sterilizing activity, the antimicrobial activity and sterilizing activity of the supplies are improved by the action of iodine which is gradually released from iodine or iodine compound with which the micro pores or micro unevennesses of the film are impregnated. When, particularly, micro pores or micro unevennesses of the film are impregnated with iodine or iodine compounds, this has such a merit that the area of the surface capable of holding iodine or iodine compounds is more increased than in the case of applying iodine or iodine compound to a plane, enabling the above iodine or iodine compound to be supported in a large amount and also, the release of iodine from iodine or iodine compounds is continued gradually for a long

time. This makes it possible to maintain the antimicrobial activity and sterilizing activity of the supplies for a long period of time.

Examples of the iodine compound with which the supplies are
5 impregnated may include;

inorganic compounds such as silver iodide, potassium iodide, nickel iodide, iron iodide and tin iodide;

organic compounds, for example, chain saturated hydrocarbons and their derivatives such as methyl iodide, ethyl
10 iodide, propyl iodide, butyl iodide, and isopropyl iodide;

also, chain unsaturated hydrocarbons and their derivatives such as vinyl iodide, anyl iodide, crotyl iodide, propargyl iodide, and phenylacetylene iodide;

also, aromatic hydrocarbons and their derivatives such as
15 iodobenzene, benzyl iodide, benzoyl iodide, phenacyl iodide, xylylene iodide, phthalein iodide, hydroquinone iodide, and cyclodextrin-iodine inclusion compounds;

also, hetero-compounds such as trimethylsulfonium iodide and triphenylsulfonium iodide; and

20 hetero-compound polymers such as polyvinyl pyrrolidone iodine and polyvinylphthalimide iodine.

Among the above iodine compounds, hetero-compound polymers such as polyvinyl pyrrolidone iodine, aromatic hydrocarbons and their derivatives such as β -cyclodextrin iodine or inorganic
25 compounds such as silver iodide are preferable as the iodine compound with which the supplies are impregnated, from the viewpoint of safety to the human body, environmental integrity and biocompatibility.

Though no particular limitation is imposed on the type of

metallic material to be used as the base material in the present invention insofar as the metallic material is suitable for use as medical supplies, Ti or Co is preferably used if it is a pure metal or a Ti alloy, Co alloy, stainless steel or Co-Cr alloy is
5 preferably used if it is an alloy. It is more preferable to use Ti and Ti alloy, stainless steel or Co-Cr alloy taking it into account to transplant the supplies to living bodies. Ti is preferably pure Ti prescribed as JIS type-1 or JIS type-2 or a Ti alloy prescribed as JIS type-60 (6% Al-4% V-Ti alloy), JIS
10 type-61 (3% Al-2% V-Ti alloy), 15-3-3 alloy, JIS type-11 or JIS type-12 are each applicable. Further, as the above stainless steel, austenite stainless steels such as SUS 302, SUS 304, SUS 316, SUS 316L, SUS 317J4L, SUS 329J1 and SUS 329J3L are preferable from the viewpoint of non-magnetism. Further, as the above Co-Cr
15 alloy, a stellite 20 alloy having a composition of 63.0% Cr-6.0% Mo-2.0% Ni-0.25% C-rest Cr is preferable from the viewpoint of strength and corrosion resistance.

Next, a method of producing medical supplies according to the present invention will be described.

20 A base material made of any one of the metallic materials is preferably formed into a predetermined shape, and is then subjected to degreasing treatment. Then, the base material is subjected to any one of electrochemical treatment, chemical treatment, thermal and/or mechanical treatment or a combination
25 of two or more of these treatments to form a film on the surface of the base material. It is preferable to adopt anodic oxidation treatment as the electrochemical treatment, medicine treatment as the chemical treatment, heating treatment as the thermal treatment, thermal processing treatment as the thermal and

mechanical treatment and mechanical processing treatment as the mechanical treatment. The method will be described concerning the case of performing anodic oxidation treatment to form a film on the surface of the base material as an example. It is needless
5 to say that the present invention is not limited to the anodic oxidation treatment.

In the anodic oxidation treatment, the base material formed into a predetermined shape is dipped in an electrolytic solution and used as the anode to apply current to electrolyze. As the
10 electrolytic solution to be used, an acid electrolytic bath or alkali electrolytic bath is used corresponding to the type of base material.

Examples of the acid electrolytic bath may include a sulfuric acid-water mixture bath (for example, content of sulfuric acid:
15 5 to 30 mass% and preferably 10 to 25 mass%), sulfuric acid-phosphoric acid-water mixture bath (for example, sulfuric acid 35 g/l and phosphoric acid 25 g/l), sulfuric acid-phosphoric acid-aqueous hydrogen peroxide-water mixture bath (for example, sulfuric acid 35 g/l, phosphoric acid 25 g/l, and aqueous hydrogen
20 peroxide 10 g/l), sulfuric acid-phosphoric acid-ascorbic acid-water mixture bath (for example, sulfuric acid 35 g/l, phosphoric acid 25 g/l and ascorbic acid 10 g/l) and hydrochloric acid-aqueous hydrogen peroxide-formalin-water mixture bath (for example, hydrochloric acid 40 mass%, aqueous hydrogen peroxide
25 2 mass% and formalin 10 mass%).

Further, examples of the alkali electrolytic bath may include potassium hydroxide-potassium fluoride-sodium phosphate-aluminum hydroxide-water mixture bath (for example, potassium hydroxide 165 g/l, potassium fluoride 35 g/l, sodium

phosphate 35 g/l and aluminum hydroxide 35 g/l).

It is preferable to use the acid electrolytic bath when the base material is Ti or a Ti alloy or stainless steel, and the alkali electrolytic bath when the base material is a Co-Cr alloy.

5 In the electrolysis, pulsed current having a frequency of 50 Hz or more and preferably 10000 Hz or less is used as the current load. When pulsed current having a frequency of 50 Hz or more is used as the current load, a film including micro pores and/or micro unevennesses having a density of at least $5 \times 10^4/\text{mm}^2$ can be formed.

10 When the current load is direct current (DC), only a film containing neither micro pore nor micro-unevenness can be formed as shown in Fig. 3(a). Such a film can be insufficiently impregnated with iodine and an iodine compound with result that sufficient antimicrobial activity cannot be imparted to the supplies. In

15 this case, large-scaled equipment is required to generate pulsed current having a frequency exceeding 10000 Hz and therefore, the cost required for the equipment is increased, bringing about high production cost. From the above reason, the current applied in the anodic oxidation treatment in the invention is preferably 50

20 to 10000 Hz pulsed current. The frequency is more preferably 1000 to 5000 Hz from the viewpoint of the number of micro-pores to be formed.

Medicine treatment as the chemical treatment, heating treatment as the thermal treatment, heating processing treatment

25 as the thermal and mechanical treatment, or mechanical processing treatment as the mechanical treatment or a combination of two or more of these treatments may be adopted in place of the anodic oxidation treatment as the electrochemical treatment.

Examples of the medicine treatment may include a method in

which a high-temperature alkali-type bath or an acid bath is used and the base material is dipped in this bath to form chemically treated film having micro pores and/or micro unevennesses on the surface of the base material. A method in which as the
5 high-temperature alkali-type bath, for example, a 140°C sodium hydroxide-potassium nitrate-water mixture bath (for example, 60 parts by weight of sodium hydroxide, 40 parts by weight of potassium nitrate and 500 parts by weight of water) is used and the base material is dipped in this bath for 10 minutes and a method in
10 which as the acid bath, for example, a 30°C oxalic acid-hydrogen peroxide-water mixture bath (for example, 25 mass% of oxalic acid (100 g/l) and 3.5 mass% of hydrogen peroxide (30%)) is used and the base material is dipped in this bath for 30 minutes are exemplified. This treatment is preferably applied in the case of
15 using stainless steel such as SUS 304 as the base material.

Further, examples of the heating treatment may include a method in which the base material is heated (heating temperature: 600 to 800°C and preferably 700°C × 1 hr) in the atmosphere to form a film (oxide film) on the surface of the base material. Further,
20 examples of the thermal processing treatment may include methods in which the surface of the base material is irradiated with an electron beam or laser beam. Further, examples of the mechanical processing treatment may include methods using a shot blasting. In these treatments, it is essential to make an examination in
25 advance before determining the treatment conditions so that a film having micro unevennesses or micro pores having a desired surface structure. In this case, these treatments are preferably applied when stainless steel or a Co-Cr alloy is used as the base material.

In the present invention, treatment such as anodic oxidation

treatment is performed to form a film having micro pores or micro unevennesses on the surface of the base material and then, iodine-impregnation treatment is carried out to impregnate the film with iodine or iodine compounds.

5 The iodine-impregnation treatment can be carried out as follows: the base material which has been subjected to, for example, anodic oxidation treatment is cleaned with water, then dipped in an aqueous iodine or iodine compound solution and direct current is applied by using the base material as the anode to carry out
10 electrolysis at a constant voltage or constant current density. The aqueous solution used for the electrolysis is preferably an aqueous solution containing 0.1 to 1.0 mass% of iodine or iodine compounds. When the amount of iodine or iodine compounds is less than 0.1 mass%, the content of iodine with which the film is
15 impregnated is so small that desired antimicrobial activity cannot be developed. Even if iodine or iodine compound is added in an amount exceeding 1.0 mass% on the other hand, the effect is saturated and this is economically disadvantageous. The amount of iodine or iodine compound is more preferably 0.3 to 0.5 mass%.

20 Further, as the iodine compound to be added in the aqueous solution, the iodine compounds are all preferable. Among these compounds, polyvinyl pyrrolidone iodine (PVPI), β -cyclodextrin iodine (BCDI) and silver iodide are preferable from the viewpoint of biocompatibility.

25 In the iodine-impregnation treatment, the constant voltage anodizing is preferably carried out at a constant voltage ranging from 100 to 200 V for 1 to 10 minutes. The constant current density anodizing is preferably carried out at a constant current density ranging from 0.05 to 10 A/dm² for 1 to 10 minutes.

The present invention will be described in more detail by way of Examples.

EXAMPLES

5 (Example 1)

A Ti alloy (mass% basis, 6% Al-4% V-rest Ti; JIS type-60 alloy) and stainless steel (SUS 304) were used as base materials to manufacture discs (plate thickness: 2.0 mm) as test pieces for in-vitro test and external fixation pins for a rabbit as test pieces
10 for in-vivo test.

Among these test pieces, the Ti alloy test pieces were subjected to degreasing treatment and then to anodic oxidation treatment. In the anodic oxidation treatment, the test piece was electrolyzed at a constant voltage (150 V) for 5 minutes in an
15 acid electrolytic solution (solution temperature: ambient temperature) of a mixture bath containing sulfuric acid (35 g/l)-phosphoric acid (25 g/l)-aqueous hydrogen peroxide (10 g/l). In this case, though the current load was made to have an initial current density of 8 A/dm², the current value was dropped in order
20 along with passage of time because of the electrolysis at constant voltage. In this case, as the current, pulsed current having a frequency of 10000 Hz was used. The test pieces which the anodic oxidation treatment was not performed was regarded as comparative examples.

25 First, the anodically oxidized test pieces (Ti alloy test pieces) were subjected to a scanning electron microscope (magnification: 2500 times) to observe the surface structure of the oxide film formed on one surface of each test piece in five or more visual fields, thereby measuring the number of pores formed

in the oxide film in each visual field. Then, an arithmetic average of the values obtained in the visual fields was calculated to determine the number of pores of the oxide film formed on the surface of each test piece. Further, the section of each test
5 piece was observed by a scanning electron microscope (magnification: 2500 times) in five visual fields to measure an average thickness of the oxide film formed on the surface.

Then, the anodically oxidized test pieces (Ti alloy test pieces) were cleaned with water for one minute. After cleaning
10 with water, the test piece was dipped in an aqueous iodine compound solution prepared by dissolving 0.5 mass% of polyvinyl pyrrolidone iodine (PVPI) which was an iodine compound in pure water and the test piece was settled on the anode side and a pure Ti plate was settled on the cathode side to perform electrolysis at a constant
15 voltage of 120 V, thereby carrying out iodine-impregnation treatment. In the iodine-impregnation treatment, the initial current density was set to about 0.2 A/dm^2 to cause electrophoresis to impregnate the oxide film formed on the surface of the test piece with the iodine compound.

20 In this case, the test pieces which were not anodically oxidized were degreased and cleaned with water for one minute prior to the test.

Then, using a part of these treated obtained test pieces (discs), an antimicrobial activity test was made for in-vivo test
25 according to the provisions of JIS Z 2801. As the pathogenic organ, *Staphylococcus aureus* (ATCC 25923) and *Escherichia coli* (MG 1455) were used. The test was repeated 15 times for each test piece. As the cells number left after a predetermined time passed is smaller, the test piece is evaluated to be superior in

antimicrobial activity.

Further, using the obtained test piece (semicircular plate), the cytotoxicity of the test piece was evaluated for in-vitro test by the colony forming method using rat fibroblast cell line V79.

5 The test piece was dipped in a culture fluid contained in a Petri dish and the above V79 was inoculated on the test piece to confirm the formation of colonies for the evaluation.

Further, using the obtained rabbit external fixation pin, 6 Japan white house rabbits were used and the pin was made to pierce

10 through each of the thighbones for in vivo test. After 14 days, the rabbit was made to die a gentle and easy death to make histological analysis and the degrees of the inflammation and infection of the tissue around the pin-pierced part were observed to give percentile scores to these degrees to evaluate. The

15 evaluation items are as follows: inflammation of the pin-pierced part, abscess around the pin, marrow, and inflammation around the tip of the pin. The point was 2 when the inflammation or formation of abscess caused by the pin was serious illness, 1 when the inflammation or formation of abscess was minor, 2 when marrow

20 formed abscess and 1 when the marrow was minor and 0 in other cases, to evaluate by the total points of the evaluation items. As the total point of the evaluation items is smaller, inflammation and infection are regarded as small. Further, at the same time, osteoid formation on the surface of the pin was confirmed to

25 evaluate osteoconductivity.

The results obtained are shown in Table 2.

Test piece No.	Base material	Anodic oxidation treatment	Current load		Structure of an oxide film		Antimicrobial activity			Cytotoxicity		Histological evaluation		Remarks
			Type	Frequency Hz	Number of micro pores (number/mm ²)	Film thickness μ m	Cells number after holding for 24 hr***	Staphylococcus aureus	Escherichia coli	V79 CELL	Colony formability	Total score of inflammation and infection	Osteo-conductivity	
A1	A	Treated	a	1000	1.5×10^6	5.2	0.07	0		Good		2.92	O	Example of the present invention
A2	A	Untreated	-	-	-	-	181		1281	Good		4.42	O	Comparative Example
A3	R	Untreated	-	-	-	-	347		1600	Good		4.92	A	Comparative Example

[Table 2]

*) A: Ti alloy (JIS type-60), R: stainless steel (SUS304)

**) a: pulsed

***) Initial number of bacteria: about 2000

It is found that an oxide film having micro pores as many as $5 \times 10^4/\text{mm}^2$ or more in number is formed in Example of the present invention (test piece No. A1).

Further, in Example of the present invention (test piece
5 No. A1), the formation of colonies is significantly suppressed,
so that the number of Staphylococcus aureus which is about 2000
before the start of the antimicrobial test is reduced to an average
of 0.07 after 24 hr and also, the number of Escherichia coli which
is about 2000 before the start of the antimicrobial test is reduced
10 to an average of 0 after 24 hr, showing that Example of the present
invention is superior in antimicrobial activity. In Comparative
Examples, on the other hand, the cells number observed after 24
hr is 181 (test piece No. A2) and 347 (test piece No. A3) in the
case of Staphylococcus aureus and 1281 (test piece No. A2) and
15 1600 (test piece No. A3) in the case of Escherichia coli. These
differences may be said to have statistical significance.

Further, in Example of the present invention, the total point
of the evaluation of inflammation and infection is significantly
lower than in Comparative Examples and therefore, it may be said
20 that Example of the present invention is reduced in inflammation
and infection. Further, this difference from Comparative
Examples also has statistical significance and this shows that
Example of the present invention reduces infection induced by a
pin and is superior in antimicrobial activity and biocompatibility.
25 Further, Example of the present invention is similar to titanium
in good osteoid and bone formation and it may be said that Example
of the present invention has sufficient osteoconductivity.

Moreover, it has been confirmed that Example of the present
invention is similar to Comparative Examples in that the colonies

of rat fibroblast cell line V79 are well formed, so that it has no cytotoxicity.

(Example 2)

Stainless steel (SUS 304) was used as a base material to manufacture disc-like test pieces (plate thickness: 2 mm) for antimicrobial test. These test pieces were each washed with an acid and then subjected to anodic oxidation treatment or to medicine treatment. In the acid washing treatment, the test pieces were dipped in an aqueous mixture solution of nitric acid (5%)-hydrofluoric acid (3%) at a liquid temperature of 40°C for 3 minutes. In the anodic oxidation treatment, the test pieces were electrolyzed at a constant voltage (100 V) for 15 minutes by using the test piece as the anode and pure Ti plate as the cathode in an acid electrolytic solution (solution temperature: ambient temperature) of a mixture bath containing hydrochloric acid (47 mass%)-aqueous hydrogen peroxide (2 mass%)-formalin (10 mass%)-water. As the current load, pulsed current having a frequency of 3000 Hz was used. The initial current value was 3.5 A/dm². In the medicine treatment, the test pieces were dipped in a 30°C mixture bath of oxalic acid (25 mass%)-hydrogen peroxide (3.5 mass%)-distilled water which was a high-temperature acid bath for 30 minutes.

The test pieces which were anodically oxidized or treated using a medicine were subjected to a scanning electron microscope (magnification: 2500 times) to observe the surface structure of the film (oxide film) formed on the surface of each test piece in five or more visual fields, thereby measuring the number of pores formed in the film in each visual field. Then, an arithmetic average of the values obtained in the visual fields was calculated

to determine the number of pores of the film formed on the surface of each test piece. Further, the section of each test piece was observed by a scanning electron microscope (magnification: 2500 times) in five visual fields to measure an average thickness of the film formed on the surface.

Then, a part of the test pieces were cleaned with water. After cleaning with water, the test piece was dipped in an aqueous iodine compound solution prepared by dissolving 0.5 mass% of polyvinyl pyrrolidone iodine (PVPI) which was an iodine compound in pure water and the test piece was settled on the anode side and a pure Ti plate was settled on the cathode side to perform electrolysis at a constant voltage of 120 V (direct current (DC)) for 5 minutes to cause electrophoresis, thereby carrying out iodine-impregnation treatment to impregnate the oxide film formed on the surface of the test piece with the iodine compound. In the iodine-impregnation treatment, the initial current density shown was about 0.2 A/dm².

With regard to the test pieces which were only anodically oxidized or treated using a medicine and test pieces subjected to iodine-impregnation treatment after anodically oxidized or treated using a medicine, an antimicrobial activity test was made by the film covering method according to the provisions of JIS Z 2801. As the pathogenic organ, Escherichia coli (JCM 1649 strain) was used and cells number left after a predetermined time (24 h) passed was measured to evaluate the antimicrobial activity. As the cells number left after a predetermined time passed is smaller, the test piece is evaluated to be superior in antimicrobial activity. When cells number which was 42000/ml (4.2×10^4 /ml) at first was measured after a predetermined time (24 h)

passed, the case where the cells number was reduced to less than 10/ml was rated as 4 (antimicrobial activity value), the case where the cells number was reduced to 10/ml or more and less than 100/ml was rated as 3 (antimicrobial activity value), the case where the
5 cells number was reduced to 100/ml or more and less than 1000/ml was rated as 2 (antimicrobial activity value), the case where the cells number was reduced to 1000/ml or more and less than 10000/ml was rated as 1 (antimicrobial activity value), and the case where the cells number was 10000/ml or more was rated as 0 (antimicrobial
10 activity value).

The results obtained are shown in Table 3.

[Table 3]

Test piece No.	Base material *	Anodic oxidation treatment		Medicine treatment	Film			Iodine-impregnation treatment	Evaluation of antimicrobial activity Cells number after holding for 24 hr	Remarks
		Type **	Current load Frequency Hz		Presence or absence of micro pores or micro unevennesses	Number of micro pores (number/mm ²)	Film thickness (μm)			
21	B	A	3000	-	Present	16×10^3	4.9	Untreated	0	Comparative Example
22								Treated	4	Example of the present invention
23	B	-	-	High-temperature mixture solution***	Present	8.6×10^4	1.2	Untreated	0	Comparative Example
24								Treated	4	Example of the present invention

*) B: SUS304

**) a: pulsed

***) Oxalic acid-aqueous hydrogen peroxide-water (liquid temperature: 30°C)

It is found that all Examples of the present invention exhibit the rate 4 (antimicrobial activity value), so that they each keep excellent antimicrobial activity. With regard to Comparative Examples in which no iodine-impregnation treatment is performed, the antimicrobial activity value is 0, that is, these Comparative Examples do not exhibit any antimicrobial activity. (Example 3)

A Co-Cr alloy (mass% basis, 63.0% Co-6.0% Mo-2.0% Ni-0.25% C-rest Cr) was used as a base material to manufacture disc-like test pieces (plate thickness: 5.0 mm) for antimicrobial test. These test pieces were each washed with an acid and then subjected to anodic oxidation treatment.

In the anodic oxidation treatment, the test piece was electrolyzed at a constant voltage (150 V, direct current (DC)) for 15 minutes by using the test piece as the anode and pure Ti plate as the cathode in an alkali electrolytic solution (solution temperature: room temperature) of a mixture bath containing potassium hydroxide (165 g/l)-potassium fluoride (35 g/l)-sodium phosphate (35 g/l)-aluminum hydroxide (35 g/l)-water. As the current load, pulsed current having a frequency of 5000 Hz was used. The initial current value was 8 A/dm².

The obtained test pieces were subjected to a scanning electron microscope (magnification: 2500 times) to observe the surface structure of the film (oxide film) formed on the surface of each test piece, thereby determining the number of pores formed on the surface of each test piece and the average thickness of the film in the same manner as in Example 2.

Then, a part of the test pieces subjected to these treatments were cleaned with water. Then, the test piece was dipped in an

aqueous iodine compound solution prepared by dissolving 0.5 mass% of polyvinyl pyrrolidone iodine (PVPI) which was an iodine compound in pure water and the test piece was settled on the anode side and a pure Ti plate was settled on the cathode side to perform
5 electrolysis at a constant voltage of 150 V (direct current (DC)) for 5 minutes to cause electrophoresis, thereby carrying out iodine-impregnation treatment to impregnate the oxide film formed on the surface of the test piece with the iodine compound. In the iodine-impregnation treatment, the initial current density was
10 about 0.2 A/dm².

With regard to the test pieces which were only anodically oxidized and test pieces subjected to iodine-impregnation treatment after anodically oxidized, an antimicrobial activity test was made by the film covering method according to the
15 provisions of JIS Z 2801 to evaluate the antimicrobial activity of each test piece in the same manner as in Example 2. The method of evaluation was the same as that of Example 2.

The results obtained are shown in Table 4.

[Table 4]

Test piece No.	Base material *	Anodic oxidation treatment		Film		Iodine-impregnation treatment	Evaluation of antimicrobial activity	Remarks	
		Current load	Frequency	Presence or absence of micro pores or micro unevennesses	Number of micro pores (number/mm ²)				Film thickness (μm)
31	C	a	3000	Present	7.6x10 ⁴	3.6	Untreated	Comparative Example	
32							Treated	Example of the present invention	

*) C: Co-Cr alloy

**) a: pulsed

It is found that all Examples of the present invention exhibit the rate 4 as the antimicrobial activity value, so that they each keep excellent antimicrobial activity. With regard to Comparative Examples in which no iodine-impregnation treatment is performed, the antimicrobial activity value is 0, that is, these Comparative Examples do not exhibit any antimicrobial activity. (Example 4)

Stainless steel (SUS 304) was used as a base material to manufacture disc-test pieces for antimicrobial test (plate thickness: 2 mm). These test pieces were first subjected to shot blasting as mechanical processing treatment of mechanical treatment. The shot blasting was performed using four types of alumina shots one by one. In treatment in a first stage, a #60-mesh alumina shot was used to perform shot blasting under a pressure of 3.5 kg/cm² for about 2 minutes carefully from all directions so as not to leave non-blasted part. Then, in a second stage, the surface treated by shot blasting using #60 mesh shot was carefully shot-blasted using a #100-mesh alumina shot in the same pressure and time condition as in the first stage in such a manner as to be equally shot-blasted. Then, in a third stage, the surface treated by shot blasting using #100 mesh shot was carefully shot-blasted using a #150-mesh alumina shot in the same pressure and time condition as in the first and second stage in such a manner as to be equally shot-blasted. Then, in a fourth stage, the surface treated by shot blasting using #150-mesh shot was shot-blasted using a #200-mesh alumina shot in the same pressure and time condition as above. Accordingly, macro unevenness was provided to the surface of the test piece. The surface roughness in the shot-blasted state when measured according to the

provisions of JIS B 0601-1994 was as follows: arithmetic average roughness Ra was 2 μm , maximum height of roughness profile Ry was 55 μm and ten-point height Rz of roughness profile was 3.5 μm .

Then, the test piece having the surface properties mentioned
5 above was further subjected to medicine treatment which was chemical treatment. In this medicine treatment, the above test piece was treated by dipping the test piece in a mixture bath containing sulfuric acid (50 g)-oxalic acid (50 g)-water (400 g) at a liquid temperature of 60°C for one hour. The shot-blasted
10 surface was chemically oxidized into a micronized etching surface having an oxide film on the surface thereof. The surface roughness at this time was as follows: arithmetic average roughness Ra was 2.5 μm , maximum height of roughness profile Ry was 65 μm and ten-point height Rz of roughness profile was 4.3 μm .

15 The obtained test pieces were subjected to a scanning electron microscope (magnification: 2500 times) to observe the surface structure of the film (oxide film) formed on the surface of each test piece, thereby observing the number of micro unevennesses of the film formed on the surface of each test piece
20 in the same manner as in Example 2.

Then, a part of the test pieces subjected to these treatments were thoroughly cleaned with water. Then, the test piece was dipped in an aqueous iodine compound solution (liquid temperature: 25°C) prepared by dissolving 0.5 mass% of β -Cyclodextrin iodine
25 (BCDI) which was an iodine compound in pure water and the test piece was settled on the anode side and a pure Ti plate was settled on the cathode side to perform electrolysis at a constant voltage of 150 V (direct current (DC)) for 3 minutes to cause electrophoresis, thereby carrying out iodine-impregnation

treatment to electro-deposit the iodine compound on the micro unevennesses of the oxide film formed on the surface of the test piece. In the iodine-impregnation treatment, the initial current density was about 12 A/dm² and the current density was decreased gradually with passage of time.

With regard to the test pieces which were only mechanically treated and treated using a medicine and test pieces subjected to iodine-impregnation treatment after mechanically treated and treated using a medicine, an antimicrobial activity test was made by the film covering method according to the provisions of JIS Z 2801 to evaluate the antimicrobial activity of each test piece in the same manner as in Example 2. The cells number at the start of the test was 56000/ml (5.6×10^4 /ml). The method of evaluation was the same as that of Example 2.

The results obtained are shown in Table 5.

[Table 5]

Test piece No.	Base material *	Mechanical treatment	Medicine treatment	Film			Iodine-impregnation treatment	Evaluation of antimicrobial activity	Remarks
					Presence or absence of micro pores or micro unevennesses	Number of micro unevennesses (number/mm ²)			
41	B	a	α		Present	9.2×10^4	Untreated	0	Comparative Example
42	B	a	α		Present	9.5×10^4	Treated	4	Example of the present invention

*) B: SUS304

**) a: shot blasting using an alumina shot

***) α : dipping in 60°C sulfuric acid-oxalic acid-water mixture solution

It is found that all Examples of the present invention exhibit the rate 4 as the antimicrobial activity value, so that they each keep excellent antimicrobial activity. With regard to Comparative Examples in which no iodine-impregnation treatment
5 is performed, the antimicrobial activity value is 0, that is, these Comparative Examples do not exhibit any antimicrobial activity.

CLAIMS

1. Metallic medical supplies using a metallic material as a base material, the medical supplies comprising a film having micro pores and/or micro unevennesses on the surface of the base material,
5 pores and/or micro unevennesses on the surface of the base material, wherein the micro pores and/or micro unevennesses are impregnated with iodine or iodine compounds.
2. The metallic medical supplies according to Claim 1, wherein
10 the film comprises the micro pores and/or micro unevennesses having a density of at least $5 \times 10^4/\text{mm}^2$ or more.
3. The metallic medical supplies according to Claim 1 or 2, wherein the film is formed by any one of electrochemical treatment,
15 chemical treatment, thermal and/or mechanical treatment or a combination of two or more of these treatments.
4. The metallic medical supplies according to Claim 3, wherein the electrochemical treatment is anodic oxidation treatment, the
20 chemical treatment is medicine treatment, the thermal and/or mechanical treatment is any one of heating treatment, thermal processing treatment and mechanical processing treatment.
5. The metallic medical supplies according to any one of Claims
25 1 to 4, wherein the iodine compound is polyvinyl pyrrolidone iodine, β -cyclodextrin iodine or silver iodide.
6. The metallic medical supplies according to any one of Claims 1 to 5, wherein the metallic material is a pure metal selected

from the group consisting of Ti and Co or an alloy selected from the group consisting of a Ti alloy, a Co alloy, stainless steel and a Co-Cr alloy.

- 5 7. Metallic medical supplies using a metallic material as a base material, the medical supplies comprising a film subjected to anodic oxidation treatment having micro pores having a density of at least $5 \times 10^4/\text{mm}^2$ on the surface of the base material, wherein the micro pores are impregnated with iodine or iodine compounds.

10

8. The metallic medical supplies according to Claim 7, wherein the iodine compound is polyvinyl pyrrolidone iodine, β -cyclodextrin iodine or silver iodide.

- 15 9. The metallic medical supplies according to Claim 7 or 8, wherein the film has a thickness of 3 μm or more.

10. The metallic medical supplies according to any one of Claims 7 to 9, wherein the base material is made of any one of Ti or Ti alloy, stainless steel, and a Co-Cr alloy.

20

11. A method of producing metallic medical supplies, the method comprising using a metallic material as a base material, treating the base material by carrying out any one of electrochemical treatment, chemical treatment, thermal and/or mechanical treatment or a combination of two or more of these treatments to form a film having micro pores and/or micro unevennesses having a density of at least $5 \times 10^4/\text{mm}^2$ or more on the surface of the base material, and carrying out iodine-impregnation treatment to

25

impregnate the film with iodine or iodine compounds, to make medical supplies.

12. The method of producing metallic medical supplies according to Claim 11, wherein the electrochemical treatment is anodic oxidation treatment, the chemical treatment is medicine treatment, the thermal and/or mechanical treatment is any one of heating treatment, thermal processing treatment and mechanical processing treatment.

10

13. The method of producing metallic medical supplies according to Claim 12, wherein the anodic oxidation treatment is a treatment in which an acid electrolytic bath or an alkali electrolytic bath is used as an electrolytic solution, and pulsed current having a frequency of 50 to 10000 Hz is applied to the base material in the electrolytic solution to carry out electrolysis treatment.

14. The method of producing metallic medical supplies according to Claim 12, wherein the medicine treatment is a treatment in which an alkali bath or acid bath having a liquid temperature of 30°C or more is used and the base material is dipped in the alkali bath or acid bath.

15. The method of producing metallic medical supplies according to Claim 12, wherein the mechanical processing treatment is a shot blasting.

16. The method of producing metallic medical supplies according to any one of Claims 11 to 15, wherein the iodine compound is

polyvinyl pyrrolidone iodine, β -cyclodextrin iodine or silver iodide.

17. The method of producing metallic medical supplies according
5 to any one of Claims 11 to 16, wherein the base material is made
of any one of Ti or Ti alloy, stainless steel, and a Co-Cr alloy.