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(54) BIOCOMPATIBLE ARTICLE

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(57) ABSTRACT

The invention relates to an article, in particular an implant, comprising a substrate which is coated at least partly with at least one layer, and on which there is at least partly a protein-, peptide- and/or saccharide-containing substance, where the layer directly adjacent to the substance comprises at least one metal selected from titanium, zirconium and hafnium, or a compound thereof with one or more non-metals and/or semiconductors, or an alloy thereof with one or more other metals, and has been applied by means of a vacuum coating process. Also provided is a process for producing the article, in which the layer is applied to the substrate under vacuum, and the use of the article.

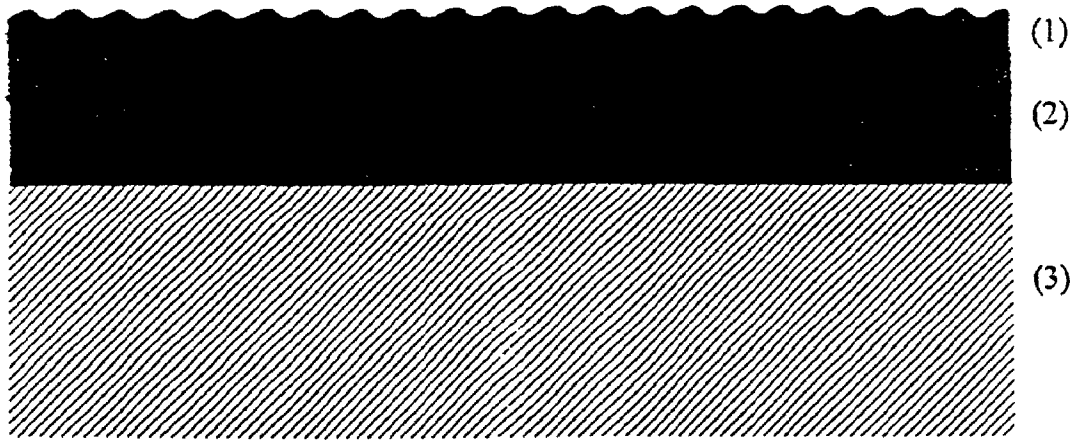
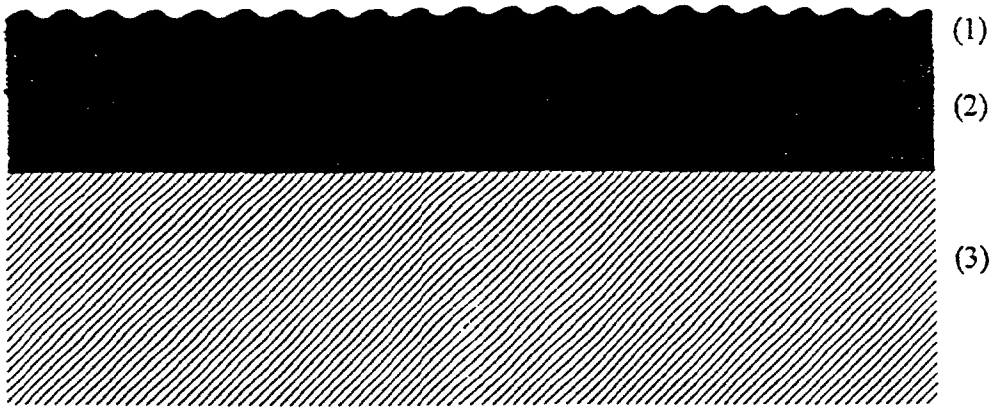


Figure 1



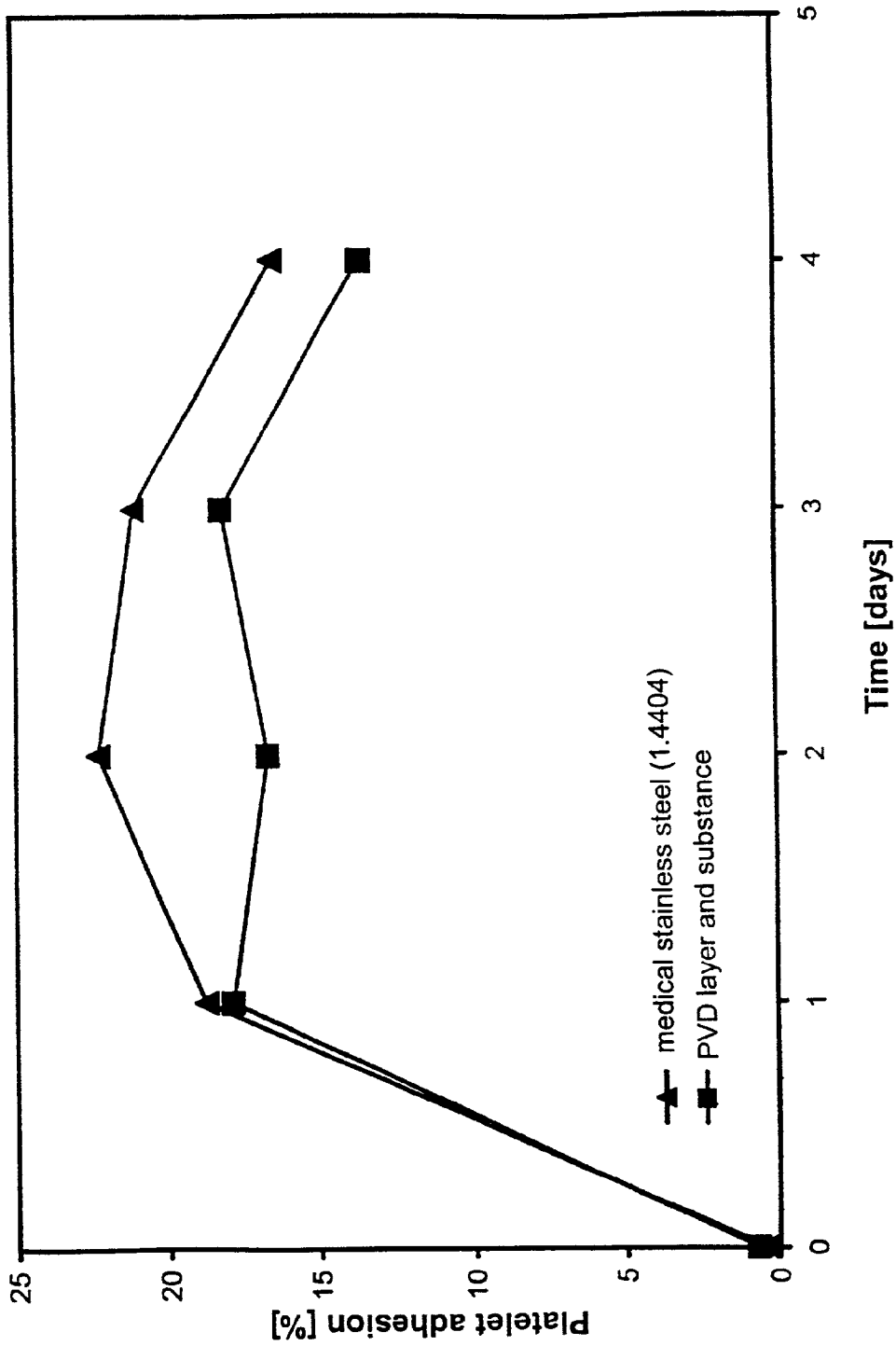

Platelet adhesion [%]
25
20
15
10
5
0
0
1
2
3
4
5
Time [days]
medical stainless steel (1.4404)
PVD layer and substance

Figure 2

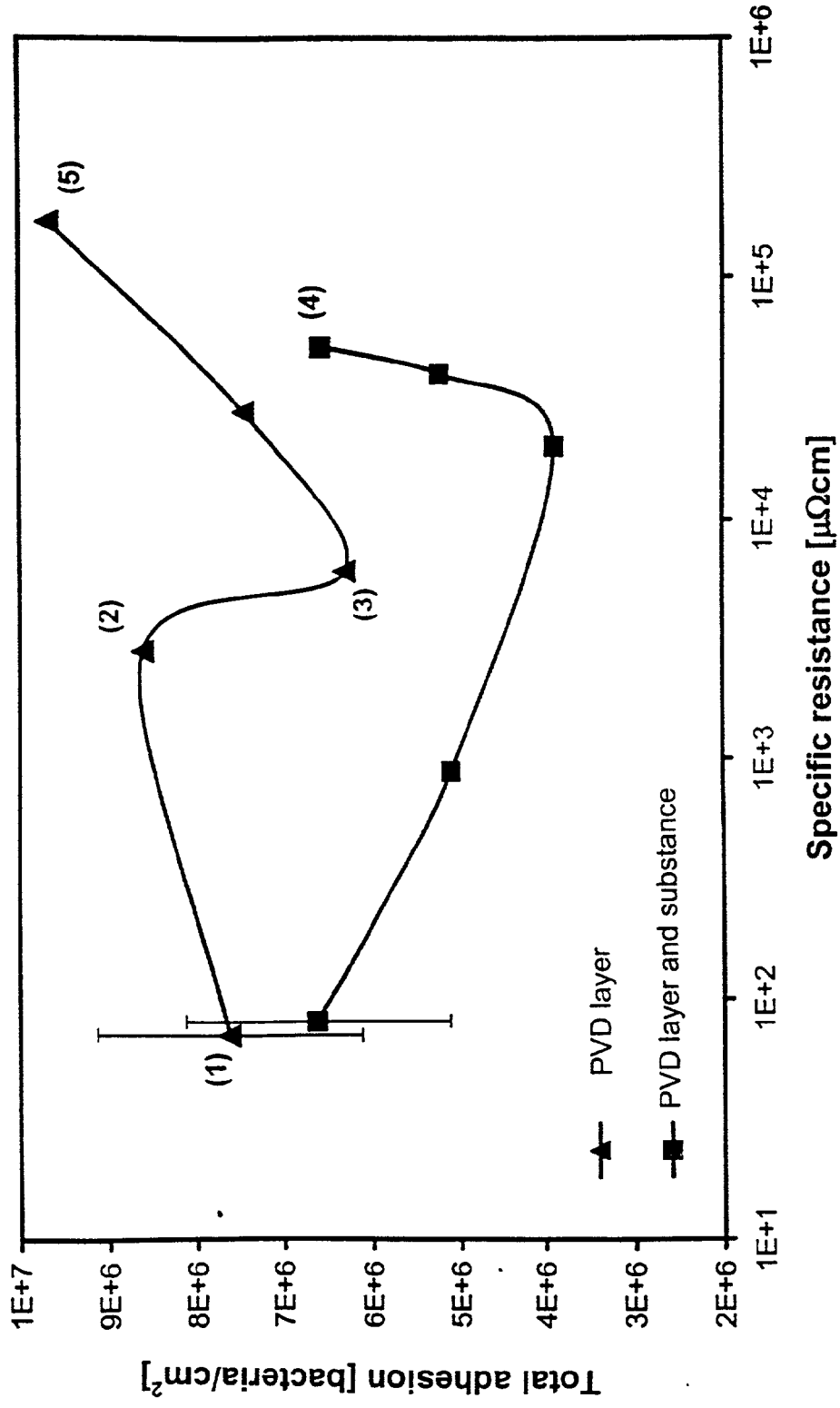

Total adhesion [bacteria/cm²]
1E+7
9E+6
8E+6
7E+6
6E+6
5E+6
4E+6
3E+6
2E+6
1E+1
1E+2
1E+3
1E+4
1E+5
1E+6
Specific resistance [μΩcm]
PVD layer
PVD layer and substance
(1)
(2)
(3)
(4)
(5)

Figure 3

BIOCOMPATIBLE ARTICLE

[0001] The invention relates to an, in particular biocompatible, article, in particular an implant such as a stent, to a process for its production and to its use.

[0002] Modern biomedical science is distinguished by bringing natural organic fluids and tissues into contact with synthetic articles in order to imitate or influence defined physiological processes. Examples include the insertion of implants, extracorporeally used medical appliances or the in vitro cultivation of particular cell cultures in an artificial environment.

[0003] The principle applying in these cases is that greater compatibility between the natural and the synthetic substances leads to a better result. Bio-compatibility thus relates to the specific use of a technically defined material in a physiologically defined environment with the aim of assisting or replacing specific physiological functions. Thus, for example, the surface for an orthopedic prosthesis would ideally be designed so that it is able to become incorporated in the bone as quickly as possible, but at the same time the risk of infection should be low. The biological compatibility of a stent for coronary arteries would be optimal if its thrombogenicity is only slight or absent and there is minimal or absolutely no influence on the function of the cells in the direct vicinity, for example the endothelial cells; in particular, proliferation of cells of the so-called intimal layer of the vessel wall should be avoided.

[0004] Another success of modern medicine is the temporary replacement of organs or their functions by medical appliances, for example hemodialysis, cardiac bypass or extracorporeal membrane oxygenation (ECMO). In these cases too there is a direct relation between biocompatibility and the incidence of complications, some of which are life-threatening, such as hemolysis or hemorrhagic complications as a result of iatrogenic anticoagulation induction.

[0005] In the past there have been many approaches to solving the problems described, at least in part. Thus, the research group of Dunn et al. attempted in 1994 (Ciprofloxacin Attachment to Porous-Coated Titanium Surfaces, D. S. Dunn, S. Raghavan, R. G. Volz, Journal of Applied Biomaterials, Vol. 5, 325-331, 1994) to modify a titanium surface in order to deposit the antibiotic ciprofloxacin thereon.

[0006] Constrictions in the coronary vessels of the heart in particular are nowadays treated to an increasing extent by the implantation of stents. These stents consist of medical stainless steel, tantalum, Nitinol or titanium (see DE-A-195 33 682, DE-A-196 53 708, Characteristics of metals used in implants, I. Gotman, J. Endourol., 11(6):383-389; and U.S. Pat. No. 5,356,433). However, two serious complications may occur when they are used. On the one hand, blood coagulation is activated by the metal. This may lead to blockage of the stent by a thrombosis especially within the first four days after implantation. The second problem on use of coronary stents is restenosis due to intimal hyperplasia. The coronary vessel of the heart is composed of three layers of tissue, the intima, media and adventitia. The intima consists of endothelial cells which line the lumen of the vessel and are in direct contact with the bloodstream. The boundary between it and the media, which consists of smooth muscle cells, is formed by the so-called internal elastic lamina. The outer layer, adventitia, then forms the connection between the vessel and surrounding tissue. Histological investigations show that introduction of stents leads to a lesion of the endothelial layer of the intima and, in particular, of the internal elastic lamina. The body reacts to this irritation with a proliferation of intimal cells, which is called intimal hyperplasia, which may be so extensive that renewed blockage of the lumen of the vessel takes place inside the stent.

[0007] Technical attempts have been made to reduce the tendency to thrombosis and/or intimal hyperplasia by various coatings on stents. Thus, EP-A-0 836 839 discloses a gold layer on a stent. Antithrombogenic Coating of Stents Using a Biodegradable Drug Delivery Technology, R. Herrmann, G. Schmidmaier, B. Märkl, A. Resch, I. Hähnel, A. Stemberger, E. Alt; Thromb. Haemost., 82, 51-57, 1999 discloses stents with steel or gold surfaces coated with biodegradable polylactic acid. The article "Local drug delivery of argatroban from a polymeric-metallic composite stent reduces platelet deposition in a swine coronary model", K. R. Kruse, J. J. Crowley, J. F. Tanguay, R. M. Santos, D. S. Millare, H. R. Phillips, J. P. Zidar, R. S. Stack, Catheter Cardiovasc. Interv., 46(4), 503-7, 1999 relates to a polymer-metal stent which is provided with argatroban. The antiproliferative agent Taxol and the antiinflammatory substance dexamethasone have, besides the anticoagulant medicament heparin (DE-A-195 33 682), been applied to stents, cf. Antiproliferative stent coatings: Taxol and related compounds, C. Herdeg, M. Oberhoff, K. R. Karsch, Semin. Interv. Cardiol., 3, (3-4), 179-9, 1998; and Anti-inflammatory Stent Coatings. Dexamethasone and Relates Compounds, S. H. Park, A. M. Lincoff, Semin. Interv. Cardiol., 3(3-4):191-5, 1998. A stent provided with a coating of silicon carbide has also been investigated in clinical studies on the reduction of endothelial proliferation and platelet activation, cf. Silicon carbide-coated stents: clinical experience in coronary lesions with increased thrombotic risk, B. Heublein, C. Ozbek, K. Pethig, J. Endovasc. Surg., 5(1), 32-6, 1998; and Silicon-carbide coated coronary stents have low platelet and leukocyte adhesion during platelet activation, S. H. Monnink, A. J. van Boven, H. O. Peels, I. Tigchelaar, P. J. deKam, H. J. Crijns, W. van Oeveren, J. Investig. Med., 47(6), 304-10, 1999.

[0008] Coated stents are also described in Coated stents: local pharmacology, V. K. Raman, E. R. Edelman, Semin. Interv. Cardol., 3(3-4), 133-7, 1998; In vivo evaluation of a fluorine-acryl-stylene-urethane-silicone antithrombogenic coating material copolymer for intravascular stents, T. Matsuhashi, H. Miyachi, T. Ishibashi, K. Sakamoto, A. Yamaddera, Acad. Radiol., 3(7), 581-8, 1996; and Antithrombogenic coating of stents using a biodegradable drug delivery technology, R. Herrmann, G. Schmidmaier, B. Markl, A. Resch, I. Hahnel, A. Stemberger, E. Alt, Thromb. Haemost., 82(1), 51-7, 1999.

[0009] Besides these approaches, attempts have also been made to cover surfaces with covalently modified albumin, cf. The Potent Platelet Inhibitory Effects of S-Nitrosated Albumin Coating of Artificial Surfaces, N. Maalej, R. Albrecht, J. Loscalzo, J. D. Folts, J.A.C.C., 33(5), 1408-1414, 1999; and Adherence and Proliferation of Endothelial Cells on Surface-Immobilized Albumin-Heparin Conjugate, G. W. Bos, N. M. Scharenborg, A. A. Poot, G. H. M. Engbers, J. G. A. Terlingen, T. Beugeling, W. G. Van Aken, J. Feijen,

Tissue Engineering, 4(3), 267-279, 1998. In Hydration and preferential molecular adsorption on titanium in vitro, K. E. Healy and P. Bucheyne, Biomaterials 1992, Vol. 13, No. 8, 553-561, the behavior of titanium towards human serum was investigated by surface spectroscopy.

[0010] None of the developed methods has yet led to a convincing product on the market. Whereas the occurrence of stent thromboses can at present be treated sufficiently well by systemically administered medicaments, called platelet aggregation inhibitors, there is as yet no satisfactory therapy for restenosis due to intimal hyperplasia.

[0011] The problems described above are solved according to the invention by an article comprising a substrate which is coated at least partly with at least one layer, and on which there is at least partly a protein-, peptide- and/or saccharide-containing substance, where the layer directly adjacent to the substance comprises at least one metal selected from titanium, zirconium and hafnium, or a compound thereof with one or more nonmetals and/or semiconductors, or an alloy thereof with one or more other metals, and has been applied by means of a vacuum coating process. The invention additionally relates to a process for producing the article, in which a substrate is at least partly coated with at least one layer, and subsequently a protein-, peptide- and/or saccharide-containing substance is applied at least partly to the coated substrate, where the layer directly adjacent to the substance is applied using at least one metal selected from titanium, zirconium and hafnium, or a compound thereof with one or more nonmetals and/or semiconductors, or an alloy thereof with one or more other metals at a temperature of from 20 to 500° C. under vacuum. The invention moreover relates to the use of the article for implantation, insertion or attachment in or on the animal or human body or for bringing into contact with animal or human blood or tissue or animal or human cells. The invention further comprises the use of a protein-, peptide- and/or saccharide-containing substance for application to a layer as defined above.

[0012] Preferred embodiments of the invention are described in the following description, the figures, the examples and the dependent claims.

[0013] In the figures,

[0014] **FIG. 1** shows a diagrammatic representation of a preferred article according to the invention;

[0015] **FIG. 2** shows a graphical depiction of the results obtained in Example 1 described hereinafter; and

[0016] **FIG. 3** shows a graphical depiction of the results obtained in Example 2 described hereinafter.

[0017] An article is intended to mean for the purpose of the invention every appliance or every device which comes into contact, even for a short time, with human or animal blood or tissue or with human or animal cells, or can be implanted into the human or animal body or inserted or attached for a longer or shorter period. Examples which may be mentioned are: catheters, tubes, sensors, stents, artificial heart valves, endotracheal tubes or cardiac pacemakers.

[0018] The metal in the layer is preferably titanium. Besides this, a compound or alloy of titanium is also preferred. Preferred compounds, in particular ceramic compounds, have the formula $MC_xN_yO_z$, where M=Ti, Zr and/or Hf; x, y, z=0 to 2.1; x+y+z=0.01 to 4, in particular x+y+z=0.01 to 2, particularly preferably x+y+z=0.05 to 1.5. Moreover the ratio of metal to nitrogen to oxygen to carbon is 1:(0 to 2.1):(0 to 2.1): (0 to 2.1), preferably 1:(0 to 1.0): (0 to 2.0): (0 to 1.0), particularly preferably 1:(0 to 0.8):(0 to 1.5): (0 to 0.3). The above ratios refer to the number of particles or molar ratios. M is preferably titanium or a zirconium/titanium alloy. Besides titanium, zirconium and/or hafnium, the layer may also contain as additional metals niobium, tantalum, tungsten, molybdenum or alloys thereof, which has advantageous effects for the resistance of the layer to corrosion. Such alloys may furthermore have beneficial mechanical properties. Preferred alloys are a titanium/aluminum/vanadium alloy, titanium/aluminum/niobium alloy, titanium/aluminum/iron alloy and a titanium/niobium/zirconium alloy. It is also possible for the layer to contain hydrogen (dissolved or preferably bound). Suitable as material for the layer are also materials like those described in DE-C-4 3 44 258 and DE-A-196 06 188. It is also possible to use a layer system in which a TiN layer, which is preferably about 0.5 μm thick, is applied to an electrically conducting intermediate layer of titanium suboxide, in particular of the composition $TiO_{1.7}$. This layer system is particularly corrosion-resistant.

[0019] The thickness of the layer is preferably in the range between 0 and 5 μm, more preferably from 50 to 3000 nm, very preferably from 100 to 1000 nm. Such a layer thickness ensures that flexing of the particular article can also be tolerated without damage.

[0020] The layer preferably has a specific resistance in the range from 10 to 10^7 μΩcm, preferably from 50 to 100,000 μΩcm, particularly preferably from 50 to 10,000 μΩcm. The specific resistance can easily be adjusted by the skilled person by altering the content of oxygen, nitrogen and/or carbon within the scope of experiments customary in the art. Measurements have shown that blood platelet adhesion has a maximum at 1000-10,000 μΩcm. The article can be adapted to the electrophysiological conditions by altering the electrical conductivity. The article can be adapted to the physicochemical conditions by supplementing the layer with the protein-, peptide- and/or saccharide-containing substances provided according to the invention, which are also assisted where appropriate by agents with an antibiotic or pharmacological action.

[0021] The layer is present as a thin layer on a substrate. Suitable substrates are made of a metal such as molybdenum, silver, gold, copper, aluminum, tungsten, nickel, chromium, zirconium, titanium, hafnium, tantalum, niobium, vanadium, iron or mixtures or alloys thereof, in particular stainless steel or Nitinol, or of a polymer such as polyester, polyamide, polyurethane (PU), polyethylene (PE), polytetrafluoroethylene (PTFE) or DACRON®. The substrate preferably consists of stainless steel, in particular medical stainless steel, tantalum, Nitinol, titanium, gold or polymer. The layer is preferably applied to a rough substrate surface whose roughness is characterized by a random distribution of the deviations from the average level, and the standard deviation of this distribution is in the range 0.5-50,000 nm, preferably 40-1200 nm. The substrate is at least partly, preferably completely, coated with the layer.

[0022] A layer which is directly adjacent to the substance and has been applied by a vacuum coating process is also

intended to mean for the purpose of the invention a layer which, after its application by a vacuum coating process, has been subjected to a natural aging process by breaking the vacuum, preferably in air or storage under normal conditions.

[0023] In a preferred embodiment, an intermediate layer is provided between substrate and layer, which has a greater adhesive strength. This intermediate layer consists of a metal, preferably of chromium, copper, nickel, molybdenum, tantalum, niobium, silver or alloys of these metals or a semiconductor, for example silicon.

[0024] Suitable protein-, peptide- and saccharide-containing substances are albumin; fibrinogen; heparins; collagen; blood proteins, for example alpha-2 globulin; immunoglobulins such as IgG, IgM, IgE IgA and proteins of the complement system, cytokines, interleukins and interferons; glycoproteins such as ferritin and lactoferrin; salivary proteins such as lysozyme, IgA2, mucin and glandulin; and/or alpha-1 proteinase inhibitors. These substances may be present either alone or in a mixture thereof. The preferred substances are albumin, fibrinogen, heparin or a mixture thereof. Albumin is most preferred, especially a mixture of albumin with fibrinogen, heparin and/or one or more of the other abovementioned substances, in particular albumin with fibrinogen. Albumin is a protein which is very soluble in water, is highly hydrated, is difficult to salt out, has an elliptical shape and a molecular weight of about 660,000, and has a content of sulfur-containing amino acids, an isoelectric point of 4.6 and ampholytic behavior. Particularly suitable albumins are human albumin, bovine albumin, pig albumin, chicken albumin, dog albumin, or albumin from cats, monkeys, guinea pigs, mice, turkeys, hamsters, rhesus monkeys or sheep. Human albumin is most preferred.

[0025] The substance is present on the layer at least in part, preferably completely.

[0026] The article according to the invention reduces foreign-body reactions and allows a wide variety of desired properties to be generated. Thus, for example, the restenosis rate is reduced to 53% by combining albumin, preferably human albumin, with a TiN_xO_y layer on a stent substrate of medical stainless steel, where x and y are as defined above (cf. Example 3 hereinafter). Other proteins, such as fibrinogen, reduce the adhesion of certain bacterial strains (cf. Example 2 hereinafter). This is particularly relevant for example to various catheters in the region of urogenital tract or blood system or to implants in the region of the respiratory tract.

[0027] To produce the article, the layer is applied by a vacuum coating process to the substrate. This expediently takes place by PVD (physical vapor deposition), CVD (chemical vapor deposition), PECVD (plasma enhanced chemical vapor deposition) or ion plating, in particular by PVD processes such as reactive vapor deposition, sputtering, reactive plasma processes or the process described in DE-A-195 06 188. Particularly suitable for applying the layer to the substrate is the following process: the substrate is positioned in a vacuum chamber and heated to 20 to 500° C., preferably to 100 to 400° C., particularly preferably 200 to 350° C. For the coating, the metal or the alloy as defined above is vaporized in the chamber via vaporization, preferably electron beam vaporization, under a vacuum of from 10^{-5} to 10^{-2} mbar, preferably from 10^{-4} to 10^{-2} mbar, particularly preferably from 10^{-4} to 5×10^{-3} mbar. If compounds are to be applied, the corresponding gases, oxygen, nitrogen and/or carbon-containing gases such as, for example, ethyne or carbon dioxide, are introduced into the vacuum chamber. The procedure in this case for generating the required chemical composition of the compound is preferably as follows:

[0028] The chemical composition is generally determined by the parameters:

[0029] r_M—rate of vaporization of metal M

[0030] a_{GM}—affinity of gas type G for metal M

[0031] $U_{pi}I_p$—voltage and current of any plasma which has been ignited

[0032] T_s—substrate temperature

[0033] I—vaporizer-substrate distance

[0034] P_{tot}—total gas pressure and

[0035] P_G—partial pressure of gas type G where the latter variable is determined by

[0036] f_G—mass flux of gas type G

[0037] L_G—pumping capacity of the vacuum pump for gas type G

[0038] The skilled person can determine from this experimentally the function "process composition" for each vacuum chamber and for each use. If a metal M and a gas G are involved (for example titanium and oxygen), the multidimensional parameter space described above can be reduced to a linear two-dimensional problem. For example, for the titanium/oxygen system in the parameter range

[0039] r_{titan}=0.1-10 mm/s

[0040] T_s=20° C.-500° C.

[0041] I=20-120 cm

[0042] $P_{tot}=10^{-5}$-10^{-2} mbar

[0043] the chemical composition is a linear function of the oxygen flux f_{02} controlled by a flow control device. This relationship can be described by a parameterized family of curves

$$v=0.0245\times(f_{02}+t)-0.879$$

[0044] where v describes the particle ratio of oxygen to titanium in the layer, f_{02} describes the oxygen flux which has been made dimensionless (oxygen flux without dimension) and t describes a family of curves parameter which described the pump capacity of the chamber and geometry. In this system, the specific resistance p (without dimension) of the layer can also be described as a function of the chemical composition:

$$v=0.357\ ln(p)-2.1987$$

[0045] On addition of a second gas, the different affinities (a_{GM1}, a_{GM2}) between the metal M and the two gas types G1 and G2 are taken into account. The ratio of a_{GM1} to a_{GM2} determines the parameter space in which there is a linear relation between chemical composition in the layer and the fluxes of the two gas types. On use of more than two gas types and/or more than one metal type it is possible by stochastic optimization algorithms, for example genetic algorithms, to examine the parameter space experimentally

in order to find parameter space regions which lead to the desired properties. In this case, the adjustment of the required ratio of amounts of the gases preferably takes place by flow control devices, for example so-called mass flow controllers. It may in some cases be advantageous to ignite a plasma. Deposition of the layer on the substrate takes place in a conventional vacuum deposition apparatus familiar to the person skilled this art.

[0046] The layers applied to the substrate may still be chemically unstable and undergo an aging process shortly after the application and removal from the vacuum chamber. Thus, for example, titanium undergoes passivation to titanium oxide or TiO_2, and this process may take hours or even days.

[0047] The protein-, peptide- and/or saccharide-containing substance is then applied to the coated substrate. In a preferred embodiment, the substance is applied immediately or soon after the application of the layer. This preferably takes place from 1 minute to 1 week, particularly preferably 1 minute to 5 hours, after the application of the layer or removal of the coated substrate from the vacuum chamber. Suitable processes for applying the substance in solution are dipping and spraying. The substance is expediently applied by introducing the coated substrate into a solution containing the substance. Suitable solutions contain 1-70% by weight, preferably 1 to 40% by weight, in particular 1 to 35% by weight, of the substance based on 100% by weight of solution. A solution containing 1-30% by weight of human albumin, in particular 1 to 15% by weight of human albumin, based on 100% by weight of solution, is preferably used. Besides the substance described above, the solution contains water and, where appropriate, salts, electrolytes and/or buffers. The albumin may be in the form not only of a solution for application but also of a powder produced, for example, by heat shock or (salt) crystallization. In the latter case, the powder is distributed on the layer and then the article is stored in a humidity chamber. It is also possible for parts of the substance to be denatured, which extends the range of applications. Thus, denatured fibrinogen may inhibit blood platelet aggregation on the surface. The substance can also be applied by bringing the coated substrate into contact with a gaseous mixture of the required substance. It is also possible to add depot agents, for example anticoagulant substances or antibiotics, to the substance, which are then released continuously.

[0048] When the substance is applied by dipping in a solution, the article is stored there for from a few seconds to several days at temperatures from −12 to +20° C., preferably from 0 to +7° C. The article can be marketed with the solution. In this form, it is stable for at least one month. In a preferred embodiment of the invention, the article is designed as an implant, in particular as a stent.

[0049] The article according to the invention can be used for implantation, insertion or attachment in or on the animal or human body or for bringing into contact with human or animal blood or tissue or human or animal cells. It is used in particular for implantation, insertion or attachment in or on the animal or human body.

[0050] The invention also relates to the use of a protein-, peptide- and/or saccharide-containing substance for application, in particular addition or deposition, to a layer which is defined as described above. The substance in this case is defined as described above. It is preferably selected from albumin, fibrinogen and heparin, with albumin being most preferred.

[0051] **FIG. 1** shows diagrammatically the structure of an article which is preferred according to the invention and has the substrate (3) which is coated with the PVD layer (2) and on which the substance (1) is located.

[0052] The invention is explained in detail by means of the following examples, which represent preferred embodiments of the invention.

EXAMPLE 1

[0053] Medical steel 1440 was mounted on a specially produced substrate holder and placed in a vacuum chamber. After evacuation of the chamber to 10^{-5} mbar, the substrate was heated to 400° C. Titanium was vaporized at a rate of 0.5 nm/s using an electron gun. A nitrogen flux of 150 scam (standard cm^3) and an oxygen flux of 35 scam were fed in using mass flow controllers. The pressure reached in the process was 10^{-3} mbar. A $TiN_{0.95}O_{0.15}$ layer with a specific resistance of 1000 $\mu\Omega$cm was applied in this way. The layer had a thickness of 1 μm.

[0054] The sample was then incubated with 1% human albumin solution (% by weight) at room temperature for 1 hour and subsequently dried. After the incubation with albumin, the sample was rinsed with phosphate buffer (PBS) and thus excess unbound albumin was washed off.

[0055] The sample was then cut into 5 rectangles (l×b×h=76×38×0.2 [mm]), of which 4 samples were incubated with filtered human plasma for 1, 2, 3 and 4 days respectively. The platelet adhesion on these 4 samples, and on the 5th sample which had been incubated only with the albumin (and not with the human plasma), was measured. This was done by flushing citrate-anticoagulated human blood over the particular sample in a flow chamber (0.6 mm×38 mm in size). The flow rate was 39.67 ml/min. Perfusion lasted 5 minutes in each case and took place at a temperature of 37° C. After the perfusion, the particular sample was rinsed with Hepes/NaCl. Comparative samples comprised untreated substrates, that is to say medical steel of the same size and incubated and measured in the same way as the sample with human plasma.

[0056] The samples and comparative samples treated in this way were then fixed and the amount of blood platelets adhering to the samples was quantified by fluorescence microscopy and stated as % of area covered relative to the total area.

[0057] The results are depicted in **FIG. 2**, where the platelet adhesion is plotted in [%] against the time in [days]. It is evident from **FIG. 2** that platelet adhesion to the article according to the invention is reduced even after 1 day.

EXAMPLE 2

[0058] The surface of medical steel 1440 was coated in a vacuum chamber as in Example 1, but the amounts of nitrogen and oxygen etc. fed in are indicated in the table below. The pressure reached in this process was 10^{-3} mbar. It was possible by altering the process parameters as specified in DE-A-195 06 188 to produce layers differing in conductivity. The layer thickness was 10^{-6} m. Coated substrates with the resistances stated in the following table were obtained in this way.

No.	Specific resistance ($\mu\Omega$cm)	Composition Ti:N:O	N_2 mass flux [sccm]	O_2 mass flux [sccm]
1	6×10^1	1:0:0.01	—	—
2	2×10^3	1:0.8:0.2	108	44
3	6×10^3	1:0.12:1.32	35	90
4	5×10^4	1:0.01:1.88	5	140
5	2×10^5	1:0:2.05	2	120

[0059] In addition, a further 5 coated substrates were produced with the resistances depicted in **FIG. 3**. Substance was deposited according to the invention on 5 samples, the samples being incubated in a solution containing purified human fibrinogen (grade L, KabiVitrum, 33 g of human fibrinogen/100 ml of potassium phosphate) for 30 min. The other 5 samples were not treated with the substance (fibrinogen) and acted as comparative samples.

[0060] The samples and comparative samples were then investigated in a flow chamber (dimensions: 1×b×h=76×38×0.6 mm) for adhesion of the bacterial strain *Staphylococcus epidermidis* 11047. This entailed the bacterial solution flowing over the samples and comparative samples at a flow rate of 2 ml/min for 5 hours and being quantified.

[0061] The results are depicted in **FIG. 3**, where the total adhesion in [bacteria/cm^2] is plotted against the specific resistance in [$\mu\Omega$cm] of the sample. It is evident from this that the samples according to the invention show distinctly reduced adhesion.

EXAMPLE 3

[0062] Commercially available coronary stents were coated as described in Example 1 to result in the same specific resistance and the same layer thickness. After venting the vacuum chamber with nitrogen, the stents were placed in a solution containing 5% by weight human albumin and sealed.

[0063] The stents were implanted into the coronary vessels of the hearts of 20 pigs. At the same time, untreated control stents, that is to say stents without coating and without substance, were implanted in the pigs. After six weeks, the intimal hyperplasia induced by the stents and control stents was measured. To do this, samples were taken from the vessel wall immediately upstream of the implanted stents and within the implanted stents, and histological specimens were prepared. The thickness of the intimal layer in the histological specimens was measured. Comparison between the stents according to the invention and the control stents showed a reduction in the intimal hyperplasia by 53% in the stents according to the invention. The result was significant with $p<0.04$.

1. An article comprising a substrate which is coated at least partly with at least one layer, and on which there is at least partly a protein-, peptide- and/or saccharide-containing substance, where the layer directly adjacent to the substance comprises at least one metal selected from titanium, zirconium and hafnium, or a compound thereof with one or more nonmetals and/or semiconductors, or an alloy thereof with one or more other metals, and has been applied by means of a vacuum coating process:

2. An article as claimed in claim 1, wherein the metal is titanium.

3. An article as claimed in claim 1 or **2**, wherein the layer comprises compounds of at least one metal selected from titanium, zirconium and hafnium with at least one element selected from nitrogen, oxygen and carbon, where the compounds have the formula $MC_xN_yO_z$, where M=Ti, Zr and/or Hf; x, y, z=0.0 to 2.1; and x+y+z=0.01 to 4.

4. An article as claimed in any of claims 1 to 3, wherein the layer has been applied by PVD, PECVD or CVD.

5. An article as claimed in any of the preceding claims, wherein the thickness of the layer is between 0 and 5 μm.

6. An article as claimed in any of the preceding claims, wherein the specific resistance of the layer is between 10 and 10^7 $\mu\Omega$cm.

7. An article as claimed in any of the preceding claims, wherein the layer which is directly adjacent to the substance and has been applied by the vacuum coating process has undergone an aging in air.

8. An article as claimed in any of the preceding claims, wherein the at least one substance is selected from albumin, fibrinogen and heparin.

9. An article as claimed in any of the preceding claims, wherein the substance comprises at least albumin.

10. An article as claimed in any of the preceding claims, wherein the substrate consists of stainless steel, tantalum, Nitinol, titanium, gold, and/or polymer.

11. An article as claimed in any of the preceding claims, which is designed as a stent.

12. A process for producing an article as claimed in any of the preceding claims, wherein a substrate is at least partly coated with at least one layer, and subsequently a protein-, peptide- and/or saccharide-containing substance is applied at least partly to the coated substrate, where the layer directly adjacent to the substance is applied using at least one metal selected from titanium, zirconium and hafnium, or a compound thereof with one or more nonmetals and/or semiconductors, or an alloy thereof with one or more other metals at a temperature of from 20 to 500° C. under vacuum.

13. A process as claimed in claim 12, wherein the substance is applied by introducing the coated substrate into a solution containing the substance.

14. A process as claimed in claim 13, wherein the solution contains from 0.5 to 40% by weight of the substance, based on 100% by weight of solution.

15. A process as claimed in any of claims 12 to 14, wherein the substrate is coated under a pressure of from 10^{-5} to 10^{-2} mbar.

16. A process as claimed in any of claims 12 to 15, wherein the substrate, the layer and the substance are as defined in any of claims 2 to 10.

17. The use of an article as claimed in any of claims 1 to 11 for implantation, insertion or attachment in or on the animal or human body or for bringing into contact with human or animal blood or tissue or human or animal cells.

18. The use of a protein-, peptide- and/or saccharide-containing substance for application to a layer, which comprises at least one metal selected from titanium, zirconium and hafnium, or a compound thereof with one or more nonmetal and/or semiconductors, or an alloy thereof with one or more other metals, and has been applied by a vacuum coating process.

19. The use as claimed in claim 17, wherein a substance as defined in claim 8 or **9** is used.

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