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(71) Applicant *(for all designated States except US)*: WILLIAM COOK EUROPE A/S [DK/DK]; No. 6 Sandet, DK-4632 Bjaeverskov (DK).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : LEONI, Gianni [DK/DK]; 10 Ulvefodvej, DK-2670 Greve (DK).

(74) Agents: SIMONSEN, Christian, Rosendal et al.; Internationalt Patent-Bureau, Høje Taastrup Boulevard 23, DK-2630 Taastrup (DK).

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(54) Title: A PROCESS FOR HYDROPHILIC COATING OF METAL SURFACES

(57) Abstract

Medical utensils, especially exploring or guiding threads, called guide wires, are coated with a hydrophilic, biocompatible, friction reducing, protein-based coating by application of a protein-containing solution, which has been pretreated by ebullition and addition of auxiliary substances, preferably tanning and sodium chloride, whereupon the coating undergoes a thermal treatment for partial denaturation of the proteins, whereby a thin coating with a good attachment is obtained, which will not harm the patient in case it should be scraped-off during use of the utensils.

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A process for hydrophilic coating of metal surfaces

The invention concerns a process for producing a hydrophilic, biocompatible, friction reducing protein-based coating on a metal surface and an exploring and guiding thread for medical use coated by the process.

The invention relates to the application of coatings on medical utensils, such as catheters and other instruments, but is especially developed for coating of exploring and guiding threads for medical purposes, termed "guide wires" in English medical terminology, and, therefore, the invention will henceforth be explained particularly in connection with application on such wires, even if the invention is not limited to that use.

Although the guide wires may have different designs, they typically have a spiral part, which wholly or partially encloses a core portion made of a noble metal. The spiral portion is formed by winding up a fine thread of for instance stainless steel or a noble metal. A typical standard guide wire has a length of, for instance, around 1 1/2 metres and with the last centimetres in the one end being especially flexible in order to facilitate the steering of the thread in the patient's vascular system. Guide wires are sold in many different thicknesses being adapted to the various forms of application. These include both diagnostic and curative forms of application.

In order to ensure that such a guide wire may be applied with a minimum of damage to the blood vessels etc. through which it is conducted inside the patient it should be compatible with the tissue which it contacts by the application. Moreover, in order to being able to manoeuvre the guide wire at all in the desired way through various vessels in human body the friction has to be low. When inserting catheters it is imperative that the wire has

a low friction against the material of which the catheter is made.

Several methods have been suggested for providing such medical utensils or tools with a friction reducing coating.

The known coatings for this purpose may be divided into two main groups, namely hydrophobic coatings, which may typically be plastic-like polymeric and especially polymeric fluorocarbonhydrids such as teflon and hydrophilic coatings for which several different materials have been suggested.

Interest has particularly centered around the hydrophilic materials as they display a greater gliding ability than the hydrophobic coatings in the environment that prevails in blood vessels.

Desirable qualities for coatings on guide wire and the like can be summed up in the following points:

(i) low friction in a wet environment

(ii) bio compatibility so that application of the coated guide wire does not lead to tissue reactions or thrombosis

(iii) good resistance to abrasion

(iv) harmless if scraped off parts are nevertheless left in the body

(v) resistance to swelling under the prevailing conditions of the body, or such a small thickness that any possible swelling does not cause any substantial increase of the outer diameter of the coated guide wire, as such an increase of the diameter during usage would impede an abrasion-free removal of the wire from a catheter, for the insertion of which the wire has been used. Moreover, it is vital that the wire dimension remains the same in certain applications in narrow vessels and

(vi) Suitable for being manufactured by industrial methods achieving uniform results with acceptable costs for materials, manpower and investment.

Prior art coatings for guide wires and other utensils only partly satisfy the above combination of desired properties.

It has thus been described that with both hydrophobic coatings of the teflon type and with hydrophilic polymer coatings, parts of the coating are prone to be scraped off when using the guide wire. And the scraped-off material may cause thrombosis. Moreover, it has been reported that swelling of hydrophilic polymer coatings after moistening may cause problems in connection with steering the wire in and out of a catheter. These kinds of problems were described in Else Tønnesen (M.D.)'s dissertation, Odense University, 1989.

Examples of known procedures for making hydrophilic coatings for medical instruments may be those outlined in EP-A-0166 998. According to this application a hydrophilic surface is achieved by binding water-soluble polymers, which have been chosen among cellulose polymers, maleic acid anhydride polymers, polyacrylamide and water-soluble nylon or derivates thereof co-valently to functional groups, which have previously been provided on the surface of the substrate. The method is alleged to be suited for a guide wire, but the resultant coating does not satisfy all the above requirements as there is a marked tendency for swelling causing an increase in volume and a decrease in strength. Consequently, there is a substantial risk that the swelled coating will be partly scraped off. The scraped-off material consisting of cross-linked reaction products comprising functional groups from the pretreatment agent, such as aldehyde, epoxy, isocyanate and amino groups, will not immediately dissolve inside the body, but constitute a risk of thrombosis.

Also WO 89/09246 describes the manufacture of hydrophilic coatings having low friction when wet. Several mutually very different substances are mentioned as components in the coating material consisting of a cross-linked hydrophilic polymer. The layer is typically based on

polyvinylpyrolidone, and the same applies to several of the coatings dealt with in the US patent publications mentioned in the introduction of the specification of said WO-application.

These known coatings seem not to be described as being suitable for application on, for instance, a guide wire, and they will hardly satisfy the above requirements (iv) and (v).

Methods are also known for protein coating of objects which are to be inserted or more permanently fitted in the human organism or are contacting a bloodstream by extra corporal treatments.

In the Danish patent application 4270/79 (equivalent to PCT/SE79/00035) a method is described for producing a coating which does not lead to thrombosis. The coating in question is stated to be made by peptidehydrogen-ionisation of heparin, hirudin and other anticoagulant proteins with a metal salt. By liberating the anticoagulant components the desired effect is achieved. Apparently, the resultant coating is so strong that it cannot be removed by blood streams. However, it does not seem likely that it is strong enough to be used on guide wires, and in the application no friction reducing properties are mentioned.

DE-A-2139455 describes how to make a collagenous layer on medical utensils of polymer materials. It is essential that a denaturation of the collagen is avoided and it is hardened by being exposed to radioactive treatment, cathode-rays or ultraviolet light. Simultaneously, it is taken care that the water content in the collagen constitutes more than 20 percentage by weight.

According to the specification the treatment seems primarily to be intended for blood vessel prosthesis where the bio-compatibility certainly is important but where the other above mentioned requirements seem to play a minor role. Thus, nothing is mentioned regarding a property which is crucial for this invention, namely that in wet states a substantial friction reduction should take place.

It has now turned out that by the below defined procedure it is possible to make a coating which satisfies the above defined requirements (i) - (vi), to a high extend than is the case for known coatings for similar purposes.

The invention thus concerns a process for producing a hydrophilic, bio-compatible, friction reducing, protein-based coating on a metal surface of an object which is intended for being introduced into the human body, which process according to the invention is characterized in

(a) an aqueous protein-containing solution is produced

(b) after cleaning the metal surface it is wetted with the solution

(c) the wet metal surface is dried in order to produce a protein-containing coating thereon, and

(d) the coating is subjected to a thermal treatment using a temperature and a duration which in each case depend on the composition of the solution, and is determined so as to denaturate the protein in the coating to such an extent that reduction a solubility in water of the coating is reduced sufficiently to ensure a stable coating for the purpose in question.

In this specification and claims the word "protein" is used as not only comprising proper proteins, but also decomposition and hydrolysis products derived herefrom, such as polypeptides and oligopeptides including protein derivates.

It has surprisingly turned out that just by a thermal treatment, the intensity and duration of which can easily be determined experimentally by simple initial tests, it is possible to make a coating which essentially meets the above six requirements, including substantial, unforeseeable resistance to abrasion when used in a moist environment.

When performing the process it is prefered at step (a) to boil the aqueous solution to partial hydrolyzation of the protein, preferably from 1 to 10 hours, more prefered from 2 to 6 hours.

The invention is not bound by any special theory as to the resultant chemical reactions, but it is assumed that this ebullition causes a hydrolyzation and a shortening of the peptide chains so that a great number of reactive groups including SH groups are available for the creation of the interconnecting structure at the final thermal treatment in step (d).

The best results as to the friction reducing ability and other desirable properties of the coating is achieved when a substance promoting the hydrolysis, preferably a weak organic acid, is added when making the solution. Good results have especially been achieved when tannic acid is added.

As protein for making the protein-containing solution protease-free gelatin, collagen, fribinogen, albumin, glubulin, keratin or mixtures thereof are preferably used.

It has turned out that the structure of the finished coating becomes the most suitable if during the preparation of the solution in step (a) an alkaline or alkaline earth metal salt acceptable to the human body is added, in a quantity of 0,1 to 2 weight-% calculated on the dry solids of the solution. Sodium chloride is primarily used as an alkaline metal or alkaline earth metal salt.

In order to modify the properties of the coating one or several water soluble polysaccaharides, especially caragenan or agar-agar may be added in connection with or after preparing the protein solution.

The thermal treatment in step (d) depends as already mentioned on the composition of the solution applied, in other words on the chosen protein and the various additives. However, the treatment is undertaken most expediently at a temperature between 100 and 260°C, preferably between 140 and 200°C and most preferably between 160 and 180°C in a period of time lasting from half an hour to 10 hours, preferably from 1 to 4 hours.

It has turned out that when using 0.2-0.8 g, preferably around 0.4 g gelatin, 0.001-0.01 g, preferably

about 0.004 g tannin and 0.0008-0.008, preferably about 0.002 g sodium chloride per millilitre water particularly satisfactory results can be achieved for the coating of guided wires.

When the process is carried out in practice the metal surface to be coated has to be cleaned and degreased as conventional, and the aqueous protein-containing solution may be applied in any suitable way, for instance by immersion. The thus wetted metal surface is then dried appropriately in a stream of hot air, whereupon the coated or partially coated object is placed in an oven, optionally after having been placed in a protective tube or the like, to performe the thermal treatment.

Consequently, the method does not call for any big investment regarding necessary equipment and relatively cheap starting materials are needed, and in these respects the method is superior to most of the above mentioned known methods.

It is a characteristic of the method according to the invention that it enables the production of very thin coatings having a dimension of a few µm which together with the fact that the coating does not show any tendency to swell ensure that the above requirement (v) is totally met.

As appears above, the method is especially suited for the coating of guide wires, i.e. exploring and guiding threads for medical use and consequently the invention also deals with an exploring or guiding thread for medical use which is characteristic in that it is wholly or partially coated by the method according to the invention.

The method of the invention is further illustrated below by means of the following examples:

E X A M P L E 1

Guide wires having a spiral exterior of stainless steel were freed of solid particles in an ultra-sound bath and purified of lubricants by washing with sulfo soap and 10 per cent acetic acid by boiling for 15 minutes. Then

they were rinsed in running water and desiccated in an oven at 105°C for 30 minutes.

The coating solution was prepared from the following components:

10 g	gelatin (type A prepared from pig skin, protease-free electrophoresis quality)
0.10 g	tannin, analysis quality
0.056 g	sodium chloride, analysis quality
25 ml	ice cold non-pyrogenic water

The components were mixed into a mass which was transferred to a flask and placed in a microwave oven. After having been heated to such an extent that a liquid phase was formed the flask was provided with a water cooled reflux and placed on a thermostatic hotplate. Then it was boiling carefully for 4 hours.

The compound thereby achieved was filtered through a 0.45 µm filter and the ensuing clear yellow liquid was stored in a refrigerator at 5°C.

The application on the guide wire was done by immersion, whereupon the coating was dried and the guide wire was placed in an oven at 170°C +/- 3°C for two hours. Then it was taken out and put in a protective glas tube.

E X A M P L E 2

The same procedure as in example 1 was used except that the tannin was omitted.

TESTING THE COATING

Determining the friction

A hose made of polyurethane, with a degree of hardness of 80 shore A, with an inner diameter of 2.5 mm and an outer diameter of 3.3 mm was used as testing equipment at these examinations. The hose was wound up on a reel having a diameter of 10 cm and was fixed to it in such a way that a coil was formed. This spirally coiled hose was filled with 37°C warm water in a bath and closed

in one end and any air bubbles were removed.

The level of friction in the guide wires to be tested was determined by introducing the guide wire in question into the hose and measuring how far the guide wire could be introduced while exerting a given pushing power.

In all the tests a stainless steel guide wire was used having a diameter of 0.90 mm, a length of 130 cm and a special flexible tip of 5 cm.

Tests were made with commercially available guide wires which were coated with teflon, or with guide wires without any coating, with guide wires produced pursuant to example 1 and with guide wires produced according to example 2. The ensuing results appear on table 1 below where each number represents an average of tests made with six different pieces. The statistical uncertainty of the tests equals a variation in the introduction length of +/- 2 cm.

TABEL 1

INTRODUCTION (cm)

	1. introduction force (N)	2. introduction force (N)	3. introduction force (N)
Teflon coating	18 cm (0.08)	25 cm (0.08)	37 cm (2.3)
Without coating	18 cm (0.08)	23 cm (0.8)	26 cm (2.3)
Coated acc.to example 1	125 cm (0.08)	126 cm (0.08)	124 cm (0.32)
Coated acc.to example 2	95 cm (0.08)	98 cm (0.08)	

It appears from table 1 that the wires coated according to the invention have a much greater sliding ability than teflon-coated wires and wires having free metal surface, and this corresponds with the method described in the invention.

When carefully examination of the water which had been present in the coiled hose during the three introductions and following withdrawals of wires coated according to examples 1 and 2, no trace of scraped-off coating material was noticed.

COATING THICKNESS

The thickness of the coating which was applied according to example 1 equals less than 9 mg per m guide wire having an outer diameter of 0.9 mm and less than 10 mg per m for a wire having an outer diameter of 0.96 mm.

As the surface of the guide wire reflects that the wire is made of a spirally wounded thread the coating cannot be expected to be totally even on "tops" and "bottoms" respectively. But despite these uncertainties it can be estimated that the quantities in question are equivalent to a thickness of the "tops"of 1 µm.

THE IMPORTANCE OF THE DURATION OF THE THERMAL TREATMENT AND THE STABILITY OF THE COATING IN WATER

7 guide wires each having a length of 130 cm were weighed and coated according to the method described in example 1. As far as the 3 wires were concerned, the thermal treatment was prolonged to 3 or 4 hours.

The treated wires were weighed and the weight of the coating ΔW calculated. The results appear in table 2.

TABLE

No.	Wo gr.	time min.	Wl gr.	ΔW gr.
1	4,392	120	4,403	0,011
2	4,393	120	4,405	0,012
3	4,370	120	4,381	0,011
4	4,391	120	4,403	0,012
5	4,360	180	4,371	0,011
6	4,387	180	4,398	0,011
7	4,398	240	4,410	0,012

Table 2 shows partly that the weight increase by the 7 treatments is very similar as the differences fall within the discrepancy level of the test results, partly that an extension of the thermal treatment does not lead to additional reactions resulting in the formation of volatile substances.

After being weighed each guide wire was put into a 150 cm long glass tube having an inner diameter of 11 mm filled with 138 ml non-pyrogenic water and placed horizontally in an oven at a temperature of 37°C. The duration of the water immersion varied as it appears from table 3 below. Afterwards the wires were taken out and dried at 105°C for an hour. Then they were weighed in order to estimate the weight loss ΔW.

The results obtained appear from table 3.

TABLE 3

No.	Time (min.) 37°C (H_2O)	ΔW mg
1	1	0.004
2	5.13"	0.004
3	18.05"	0.005
4	34.00"	0.004
5	60.00"	0.002
6	60.00"	0.002
7	30.00"	0.000

It appears from the table that the four coatings which had received a thermal treatment for 120 minutes lost 1/3 of their weight to the water, and this was more or less irrespective of the duration. The coatings which had received a more lengthy thermal treatment lost less weight to the water.

A moderate dissolution of the coating during the use of the guide wire is not regarded to be unfortunate as the liberated substances will be amino acids or lower polypeptides which are harmless to the human body. On the contrary a moderate solution from the surface of the coating may prevent that the coated wire gets caught in a catheter or the like when it is used.

SWELLING PROPERTIES

In order to test the swelling properties a foil having a thickness of about 10 µm of the coating material was made by applying an aqueous dilution of a protein solution equivalent to the one which was made in Example 1 on a teflon surface, liberating the layer formed and heat-treating it for two hours at 170°C.

A sample of the thus produced foil was cut off and left in non-pyrogenic water at 37°C for 1 hour and then compared to the rest of the foil which had not been kept in the water.

By this comparative test the swelling was found to be only insignificant.

PATENT CLAIMS

1. A process for producing a hydrophilic, biocompatible, friction reducing, protein-based coating on a metal surface of an object which is intended for introduction into the human body, characterized in that

(a) an aqueous, protein-containing solution is prepared,

(b) after cleaning the metal surface it is wetted with the solution,

(c) the wetted metal surface is dried to form a protein-containing coating thereon, and

(d) the coating is subjected to a thermal treatment at a temperature and a duration which in each case is dependent on the composition of the solution, and is determined so as to denaturate the protein in the coating to such an extent that reduction solubility in water of the coating is reduced sufficiently to ensure a stable coating for the purpose in question.

2. A process according to claim 1, characterized in that in step (a) the aqueous solution is boiled to partial hydrolization of the protein, preferably in a period of 1-10 hours, more preferably from 2 to 6 hours.

3. A process according to claim 2, characterized in that a hydrolysis-promoting substance is added at the preparation of the solution, preferably a weak organic acid, most preferably tannin.

4. A process according to claim 1, 2 or 3, characterized in that the duration and/or the temperature of the thermal treatment in step (d) is determined by previous tests.

5. A process according to any previous claims, characterized in that in step (a) the protein-containing solution is prepared using protease-free gelatin, collagen, fibrinogen, albumin, glubolin, keratin or mixtures thereof.

6. A process according to any of the previous claims, characterized in that for the preparation of

the solution in step (a) an alkaline or alkaline earth metal salt acceptable to the human body is added in a quantity of 0.1 to 2 percentage by weight, calculated on the dry solids of the solution.

7. A process according to any of the previous claims, c h a r a c t e r i z e d in that when preparing the solution in step (a) one or several water-soluble polysaccaharides, preferably caragenan or agar-agar are additionally added.

8. A process according to any of the previous claims, c h a r a c t e r i z e d in that the thermal treatment in step (d) is undertaken at a temperature between 100 and 260°C, preferably between 140 and 200°C, and most preferably between 160 and 180°C in a period of time from half an hour to 10 hours, preferably from 1 to 4 hours.

9. A process according to any of claims 1-6 and 8, c h a r a c t e r i z e d in that when preparing the aqueous solution in step (a) 0.2-0.8 g, preferably about 0.4 g, gelatin, 0.001-0.01 g, preferably about 0.004 g, tannin and 0.0008-0.008 g, preferably about 0.002 g, sodium chloride is applied per ml water.

10. Exploring or guiding thread for medical use, c h a r a c t e r i z e d in that it partially or in all its length is coated by a method according to any of the previous claims.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 92/00354

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61L 27/00, A61L 29/00, A61L 33/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61L

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

SE,DK,FI,NO classes as above

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

WPI, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, A1, 0214392 (CYTOMED MEDIZINTECHNIK GMBH), 18 March 1987 (18.03.87), claim 1	1,10
A	EP, A2, 0366564 (TERUMO KABUSHIKI KAISHA), 2 May 1990 (02.05.90), claim 1	1,10
A	WO, A1, 7900638 (THIN CONDUCTIVE COATING ÖSTERMALM ET AL.), 6 Sept 1979 (06.09.79), claim 1	1,10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 March 1993	10 -03- 1993
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer INGA-KARIN PETERSSON Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A1, 8501507 (ALFA-LAVAL AGRI INTERNATIONAL AB ET AL.), 11 April 1985 (11.04.85), claims 1,9,12, 13	1,10

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INTERNATIONAL SEARCH REPORT

Information on patent family members

29/01/93

International application No.

PCT/DK 92/00354

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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