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54	TITLE OF INVENTION

Medical device for dispensing medicaments

57	ABSTRACT (NOT MORE THAN 150 WORDS)

NUMBER OF SHEETS	51

The sheet(s) containing the abstract is/are attached.

If no classification is furnished, Form P.9 should accompany this form.
~~The figure of the drawing to which the abstract refers is attached.~~

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(57) **Abstract:** For selective treatment of diseased tissue sections or organ parts, the surface of medical devices entering into contact with areas thereof under pressure is coated with lipophilic substantially water-insoluble medicaments binding to various tissue components with good adherence thereto, said medicaments having an effect thereupon a short time after entering into contact therewith without exerting a harmful influence upon adjacent healthy tissue.

Description

Medical device for dispersing medicaments

This invention relates to a medical apparatus that releases drugs for the selective therapy of specific tissues or organ parts and to a method of manufacturing such drug-coated devices.

Numerous diseases do not affect the entire organism at the same time but are restricted to specific tissues, often even to very limited individual tissue areas or organ parts. Examples can be found among tumor, joint and vascular diseases.

Pharmacotherapy of such diseases generally is effected by oral or intravenous administration of drugs that spread throughout the body and cause undesirable side effects in healthy tissues and organs, especially when the disease to be treated is in a severe stage, which limit the therapeutic application. The diseased tissues could be treated either selectively using drugs that specifically bind to diseased tissue (e.g. antibodies) while the administration path is maintained, or by selective administration, e.g. direct injection into the diseased tissue or supply via a catheter to the blood vessels that feed the diseased tissue. In case of selective administration may problems arise due to the short period of time during which the drugs are efficacious and the invasive administration paths, as repeated administration is not an option. When drugs are selectively administered via the bloodstream that feeds the diseased tissue, there

is the additional problem that the drugs are insufficiently extracted when the blood or active agent solution swiftly flows through the blood vessels.

These problems used to be addressed by various pharmaceutical preparations with sustained release of the active agent, drug-releasing implants or selective access paths that stay operational for a longer period of time such as implanted catheters, etc.

It is known that the surface of medical equipment inserted into the body, in particular, of catheters, can be coated with agents that enhance gliding quality or prevent blood coagulation but have no therapeutic effect.

In addition, catheters are equipped with special devices for injecting drugs into the arterial wall, for example, using needles or a perforation of the catheter wall that sits adjacent to the vessel wall and through which the drug is injected at high pressure.

Other principles are based on extending the contact time between the arterial wall and an active agent preparation administered via the catheter by either blocking the blood flow for a sufficient period of time, e. g. using dual balloon catheters in which the active agent solution is contained in a chamber between the balloons, or by voids between a toric outer wall of the balloon allowing a limited flow of blood through a canal that passes through the balloon.

According to US 5 102 402, drugs in the form of microcapsules are inserted into preformed recesses of balloon catheters for delayed release of the active agent. When the balloon is inflated, the microcapsules are to be pressed against the vessel wall, remain there and slowly release the active agent(s). Many authors propose to apply drugs embedded in hydrogel onto balloon catheters while they do not specify the function of the hydrogel, i. e. to act as an adhesive, to improve the gliding quality, or for controlled drug release.

A disadvantage of the products mentioned above is their complex structure, which causes production, quality control, and cost problems and forces additional aggravating working steps on doctors and patients when applied. Some of the methods mentioned may result in undesirable vascular damage in excess of the intended dilatation of the vessel. Another setback is that each measure aimed at extending contact time entails another reduction in blood and oxygen supply to the downstream tissues.

For the sake of completeness, we also refer to a device for preventing restenosis as described in WO 01/24866 that is coated with a lipid ceramide substance derived from natural cell membranes. This substance is used because of its affinity to cell walls that is not found in common drugs. Experts in the field continue to state that restenosis prevention using drugs requires release of the active agent over a period of several days.

The problem underlying the present invention is to provide a device for the release of drugs into specific tissue areas or organ parts that has a strong therapeutic effect without damaging healthy tissue, which is sufficiently well tolerated, and can be produced and applied with a minimal effort.

This problem is solved according to the invention by a device designed or produced in accordance with the characteristics of claims 1 and 15. The subordinate claims disclose further characteristics and advantageous improvements of the invention.

The invention provides improved drug-carrying balloon catheters or similar medical devices manufactured in a simple process that are highly versatile and facilitate the immediate release of active agents. Surprisingly, and contrary to the currently acknowledged opinion, no continuing release of the active agent from an inert matrix (polymer, hydrogel, microcapsule, etc.) and no special chemical or physical state of the active ingredients is required or useful. Therefore, no sophisticated techniques for producing or controlling depot formulations are required.

Coating balloons on catheters with drugs according to this invention is particularly useful because there is a frequent need for treatment after blood vessels or other passages in the body were dilated with balloons to prevent stenosis or an occlusion of the lumen created by the pressure of the balloon, to limit tumor growth or to enhance healing processes including the formation of

collateral circulation. This can be achieved by drugs that become effective in the immediate vicinity of the balloon surface. The drugs firmly adhere to the balloon while passing through arteries with an intense blood flow on their way to their target until the balloon is inflated, and an effective dose is released in the short time (sometimes just a few seconds) during which the inflated balloon is in contact with the tissue, absorbed by the tissue in such a way that the blood flow that resumes immediately after the balloon is deflated does not rinse it off.

The subjects for coating are wires of the invention used to guide catheters, needles and catheters or catheter parts that are pressed against the diseased tissue at least for a short time. Preferred catheter materials are polyamides, polyamide mixtures and copolymers, polyethylene terephthalate, polyethylene and copolymers, polyurethane, natural rubber and its derivatives. The lengths and diameters of the catheter or balloon areas designated for pharmacological treatment are not of any decisive importance for their application as the dosage is calculated in µg of active agent / mm^2 of surface area. For example, balloons with diameters ranging from 2 to 4 mm and lengths ranging from 1.0 to 4.0 cm are commonly used for coronary dilatation. Balloons up to > 20 mm in diameter and up to > 10 cm in length can be used for other vessels. The surfaces to be coated may be smooth (i.e. without a special structure for absorbing the active agents), roughed up or comprise any structure; while no special surface structures are required for the active agents to adhere, such structures also do not

impede adhesion. Adhesion of the active agents to the balloon surfaces is exclusively caused by selecting suitable solvents and, optionally, adding substances that influence adhesion. It is even surprisingly strong on completely smooth balloon surfaces.

All surfaces can additionally be coated with substances that improve the gliding quality of the products, prevent blood from coagulating on the surface or improve any other properties of these medical products have but the materials used for coating do not have to be released into the environment and this additional coating does not noticeably reduce the release of the active agents for treatment of the target tissue and thus the product's efficacy.

Balloon catheters are formed by dilating a segment of 1 cm to ca. 10 cm length of very thin plastic tubes. The dilated, very thin-walled balloon membrane is then folded several times along the catheter axis and wrapped tightly around the catheter axis so that the dilated area, when folded, is only slightly greater in diameter than the rest of the catheter. The tight folding of the balloon membrane is required for passing the balloon catheter through access ports, guiding catheters and heavily stenosed sections of blood vessels.

The balloons of catheters can be coated when folded or when unfolded. The process always provides an intact and sufficiently uniform surface coating, and the active agents adhere to the surface of the balloon catheter even when it is refolded after being coated when unfolded.

A balloon that was coated when unfolded is produced without any impact on the coating, for example by using balloon membranes with preformed folds and bends whose structure is not lost due to dilatation and which allow the balloon membrane to refold at least loosely when the pressure is discharged from the balloon without requiring an external force as primary cause. It is only after this prefolding that the preformed folds are compressed by external pressure or by a vacuum. Folds are in no way required to hold the active agent. In addition refolding can be achieved using minor mechanical force by very smooth materials, and the tools used may also be wetted by slippery biocompatible liquids in which the active ingredients do not or, at least, do not well dissolve.

In accordance with another variant of the invention, the balloons of readily folded balloon catheters are coated by dipping them into low-viscosity active agent solutions. Solvent and active agent penetrate into the extremely dense folds where they form a surprisingly uniform coat that contains a reproducible dose and is not damaged by any subsequent step. The solution or, after the solvent has dried, the coat that adheres to the outer surface may be left there or may be removed in another step so that only the active agent portion that sits inside the folds of the balloon is retained.

After coating, when the balloon is folded, a stent can be pulled over the balloon catheter and firmly pressed onto it. The only step still required is sterilization, e. g. using ethylene oxide.

The work cycle laid out like this is extremely simple, hardly susceptible to failures, and can be carried out even with mechanically, chemically and physically sensitive coating materials. It was found that coating using this method does not result in any undesirable loosening or sticking together of the folds and that the active agent applied in this way adheres firmly enough to not be rinsed off by the bloodstream but releases most of the active agent when the balloon is inflated in the target tissue.

Suitable drugs are lipophilic, mostly water-insoluble and strongly acting drugs that bind to any tissue components. Drugs are called lipophilic when their butanol to aqueous buffer solution (pH 7) distribution ratio is 0.5, preferably 1 and particularly preferred 5, or when their octanol to aqueous buffer solution (pH 7) distribution ratio is 1, preferably 10, and particularly preferred greater than 50. Alternatively, or in addition to this, the drugs should reversibly and/or irreversibly bond to cell components at percentages greater than 10%, preferably greater than 50%, and particularly preferred greater than 80%. Preferred are substances that inhibit cell proliferation or inflammatory processes, or antioxidants such as Paclitaxel and other taxanes, Rapamycin and related substances, tacrolimus and related substances, corticoids, sexual hormones (estrogen, estradiol, antiandrogens) and related substances, statins, epothilones, probucol, prostacyclins, angiogenesis inducers, etc.

These substances are preferably present as a dry solid or as an oil on the surfaces of the various medical products. Preferred are the smallest particle sizes (mostly < 5 microns, preferably < 1 microns, particularly preferred < 0.1 microns), particularly preferred are amorphous non-crystalline structures of the finest particle size that dissolve fast upon contact with tissue due to their large surface area and despite the generally poor water-solubility of the drugs and do not function as microcapsules, i. e. dissolve spontaneously and fast. It is sufficient that an effective dose is present in the form of smallest or amorphous particles; larger particles hardly contribute to the active agent concentration in the tissue but do not cause any interference. The dosage depends on the desired effect and the efficacy of the drug used. It may be up to 5 µg/ mm² and this value does not even constitute an upper limit. It is easier to handle smaller dosages.

Good adhesion to the surfaces of catheters, needles or wires on an improved absorption by the tissues is achieved by embedding strongly lipophilic active agents with poor water solubility in a readily water-soluble matrix substance. Suitable matrix substances are low-molecular (molecular weight < 5000 D, preferably < 2000 D) hydrophilic substances such as contrast agents and dyes used in vivo for various diagnostic procedures in medicine, sugar and related substances such as sugar alcohols, low-molecular polyethylene glycols, biocompatible organic and inorganic salts such as, for example, benzoates, salts and other derivatives of salicylic acid, etc. Examples of contrast agents are

iodinated X-ray contrast agents and paramagnetic chelates, examples of dyes are indocyanine green, fluorescein, and methylene blue. Excipients may also improve shelf life of the products, cause specific additional pharmacological effects or be instrumental for quality control.

In another embodiment of the invention, the pharmaceutical active agents can be adsorbed to particles or applied to the surfaces of suitable medical products with a low-molecular matrix. Suitable particles once again are diagnostics known to be biocompatible such as ferrites and various contrast agents for sonography.

Excipients of any kind can be used at lower or higher doses than the active ingredients.

The medical products are coated using solutions, suspensions, or emulsions of the drugs and excipients mentioned above. Suitable media for solution, suspension or emulsion are, for example, ethanol, isopropanol, ethyl acetate, diethyl ether, acetone, dimethyl sulfoxide, dimethyl formamide, glycerin, water or mixtures thereof. Solvent selection is based on the solubility of the active agents and adjuvants, the wetting of the surfaces to be coated and the effect on the structure of the coating and particles remaining after evaporation of the solvent, their adhesion to the surface and active agent transfer to the tissue in very short contact times.

Coating can be carried out by immersing, spreading, applying with devices which deliver a defined volume to

the surface or spraying at various temperatures and, optionally, vapor saturation of the solvents in the atmosphere. The procedure can be repeated several times using different solvents and excipients as may be required.

The balloons of folded balloon catheters ready for use can be given a surprisingly uniform, reproducible, dose-controllable coating without impairing catheter functionality by immersing them in solutions containing the active agent(s) or by other measures. When the balloons are repeatedly immersed in unsaturated active agent solutions, the active agent applied previously is not completely stripped off; instead, the active agent content of the balloons is increased in a reproducible manner.

Excess solution or excess substances from the coating solution that are loosely attached to the exterior can be removed with simple methods without impairing the efficacy of the coating.

The various types of medical devices designed and manufactured according to the invention come into short-term contact with the tissue, i. e. for a few seconds, minutes, or hours. It is desirable in some cases to pharmacologically treat the tissue with drugs in the immediate vicinity of the medical product, e. g. to prevent excess growth as a response to an injury or to reduce tumor growth, to enhance neovascularization or diminish inflammatory reactions. In all these cases, high local drug concentrations can be achieved for an

astonishingly long time using the method described above. A major advantage is the extraordinary versatility of uses of the products and methods described.

A preferred application is to reduce hyperproliferation of vessel walls induced by dilatation with balloon catheters. This can be achieved when stents are implanted by coating these stents with drugs, but only for the vessel section covered by the stent. The coated balloon catheters also treat any areas at short distance in front of and just behind the stent that need treatment, they can treat the section where a stent has been implanted without requiring another stent implantation and vessels in which no stent is to be or can be implanted. An advantage as compared to the stents that release a drug over a long period of time is improved healing and simultaneous good inhibition of hyperproliferation and a reduced risk of thrombosis.

Several embodiments of the invention will be described below with reference to examples regarding the coating of balloon catheters, adhesion of the coating in the bloodstream, restenosis inhibition and active agent content of the catheters.

Example 1:
Coating an expanded balloon catheter with Paclitaxel in ethyl acetate

Balloon catheters made by BMT, Oberpfaffenhofen/ Munich, Germany, product name Joker Lite, balloon dimensions

2.5 mm by 20 mm, are inflated to the maximum and immersed full length for 1 minute in ethyl acetate, 18.8 mg Paclitaxel per ml, + 1% pharmaceutical olive oil, dried: Paclitaxel content 39 micrograms (after extraction with ethanol, HPLC).

Example 2:
Coating a folded balloon catheter with Paclitaxel in ethyl acetate

Balloon catheters made by BMT, Oberpfaffenhofen/ Munich, Germany, product name Joker Lite, balloon dimensions 2.5 mm by 20 mm, are immersed full length in folded condition for 1 minute in ethyl acetate, 18.8 mg Paclitaxel per ml, + 1% pharmaceutical olive oil, and dried:

Paclitaxel content 69 micrograms.

Example 3:
Coating a folded balloon catheter with Paclitaxel in ethyl acetate

a) Balloon catheters made by BMT, Oberpfaffenhofen/ Munich, Germany, product name Joker Lite, balloon dimensions 2.5 mm by 20 mm, are immersed full length in folded condition for 1 minute in ethyl acetate, 16.6 mg Paclitaxel per ml, and dried for 4 hours: Paclitaxel content 54 micrograms.

b) Same procedure, but additional two times immersed for 5 seconds with 1 hour drying time after each immersion process in solution A (= 3.33 ml

ethyl acetate + 100.0 mg of Paclitaxel): Paclitaxel content 126 micrograms.

c) Same procedure, but additional four times immersed for 5 seconds with 1 hour drying time after each immersion process in the same solution:
Paclitaxel content 158 micrograms.

Example 4:
Coating a balloon catheter with Paclitaxel in acetone

Dissolve 350 mg of Paclitaxel in 9.0 ml of acetone; balloon catheters made by BMT, Oberpfaffenhofen/ Munich, Germany, product name Joker Lite, balloon dimensions 2.5 mm by 20 mm, are inflated to the maximum and immersed full length for 1 minute and removed. The solvent is dried for 12 hours at room temperature. Then the balloon is deflated and folded in the common way using a PTFE-coated tool. Optionally, one can crimp a stent of suitable dimensions onto the balloon: 29 micrograms of Paclitaxel on the balloon.

Example 5:
Coating a balloon catheter with Paclitaxel in acetone

a) Immersion of folded balloon catheters made by BMT, product name Allegro, balloon dimensions 2.5 by 20 mm in a mixture of 0.15 ml ethanol + 4.5 µl of Ultravist 300 (an X-ray contrast agent made by Schering AG,

Berlin, Germany) + 1.35 ml of acetone + 0.8 mg of Sudan red + 30.0 mg of Paclitaxel:
The folded balloon sections of the catheters are immersed 5 times, the first time for one minute, then dried for 3 hours, then 4 times at 1 hour intervals for 5 seconds each; subsequently, a stent was crimped on and the catheter was sterilized in the common way using ethylene oxide: Paclitaxel content 172 micrograms, no decomposition products of the active agent were determined using HPLC

b) A saturated aqueous mannitol solution is used instead of Ultravist 300

c) A saturated aqueous sodium salicylate solution (pH 7.5) is used instead of Ultravist 300

d) 5 mg of acetylsalicylic acid are added to the completed solution according to (5a).

e) 5 mg of glycerin are added to the completed solution according to (5a).

Example 6:
Adhesion of the active agent in the bloodstream

12 balloon catheters made by BMT, product name Allegro, balloon dimensions 2.5 by 20 mm, were used. The folded balloon sections of 6 catheters each were either 5 times immersed in [0.15 ml of ethanol + 4.5 µl of Ultravist 300 + 1.35 ml of acetone + 0.8 mg of Sudan red + 30.0 mg Paclitaxel] or 5 times in [1.5 ml of ethyl acetate + 0.8 mg Sudan red + 31.0 mg Paclitaxel], the first time for 1 minute each with 3 hours of drying time, then 4 times for 5 seconds each at 1 hour intervals; then 3 of

the folded balloons of each group were gently moved for 5 minutes at 37°C in 50 ml of human blood and removed to determine the Paclitaxel content: Reduction of mean values (n=3 per coating method) by 5 minutes of movement in blood as compared to 3 control catheters that were not incubated in blood.

Acetone:	12 %
Ethyl acetate:	10 %

Example 7:

Examination of restenosis inhibition after angioplasty and stent implantation in coronary arteries of pigs.

Folded balloon catheters of the Joker Lite type made by BMT, 3.5 by 20 mm or 3.0 by 20 mm were immersed for 1 minute either in

solution A) 3.33 ml of ethyl acetate (EA)+ 100.0 mg of Paclitaxel, or in

solution B) 0.45 ml of ethanol + 100 µl of Ultravist-370 + 4.5 ml acetone (ac) + 150.0 mg Paclitaxel

and dried over night at room temperature. One more (low dose = L) or 4 more (high dose = H) immersion process(es), respectively, were carried out for just five seconds at 1 hour intervals on the next day.

Active agent content after 2 immersions in solution (B) averaged 250 µg, after 5 immersions in solution (B) 500 µg, in solution (A) 400 µg.

The catheters coated with Paclitaxel or uncoated were used to implant stents into the left anterior or lateral

coronary artery of a total of 22 pigs, and the vessels were slightly overdilated to stimulate restenosis by tissue hyperplasia. The animals were reangiographed after 5 weeks, and the vessel stenosis shown in the angiograms was measured using an automatic computer program.

Group	Stenosis (%)
Uncoated	50.49
AcL	20.22
EAH	36.01
AcH	0.86
P	.004

Quantitative coronary angiography 5 weeks after stent implantation with uncoated and coated catheters; stenosis = reduction of lumen diameter in percent in the area of the stent as compared to the lumen diameter immediately after stent implantation; mean value and statistical significance of the effect of treatment.

Example 8:

Active agent content of the catheters after vessel dilatation and stent implantation

After stent implantation and removal from the animals, the balloons from Example 8 ca. 3 cm in length were cut off the balloon catheters and placed in 1.5 ml of ethanol. Paclitaxel content was determined using HPLC. All available coated balloons and a selection of uncoated balloons were examined.

Coronary,

3.0 by 20 mm, coating:	Ac high	38 ± 4 µg (n=4)
	Ac low	22 ± 5 µg (n=2)
	EEE high	41 (n=1)
3.5 by 20 mm, coating:	Ac high	37 ±10 µg (n=8)
	Ac low	26 ± 6 µg (n=8)
	EEE high	53 ± 9 µg (n=9)

Uncoated (independent of size and vessel area)

0.9 ± 1.0 µg (n=7)

It follows from Example 6 that a maximum of 10% of the dose is lost before the balloon is inflated and about 10% of the dose remain on the balloon.

Example 9:

Probucol is added to acetone at a concentration of 100 mg per ml; the solution is used to coat balloon catheters as described in the above examples.

Example 10:

Rapamycin is dissolved at a concentration of 10 mg/ml in diethyl ether. The balloon sections of the catheters are coated as described in the above examples; after removal from the coating solution, the balloons should be brought into a horizontal position and continuously be turned around their longitudinal axis as soon as possible.

Example 11:

Epothilone B is dissolved in ethyl acetate at a concentration of 2 mg/ml; the solution is used to coat balloon catheters as described in the above examples.

Claims:

1. A medical device that releases drugs for the selective therapy of specific diseased tissues or organ parts, characterized in that lipophilic, largely water-insoluble drugs that bind to any tissue components adhere to the surfaces of devices that come into contact with the diseased tissue by being pressed against it at least for a short time and immediately release the active agent when in contact with tissue.

2. The device according to claim 1, characterized in that balloon catheters without stents or in conjunction with stents, catheters and/or parts thereof, needles and guiding wires as well as stents are used as carriers of the active agent(s).

3. The device according to claim 2, characterized in that balloons with preformed longitudinal folds are used for drug coating, and that their inclination to refold is not lost due to inflation.

4. The device according to claim 2, characterized in that the balloons consist of a very smooth material to which drugs adhere sufficiently well to resist the forces required for folding essentially without damage.

5. The device according to claim 2, characterized in that balloons coated by immersion in a low-viscosity active agent solution in fully folded condition are used.

6. The device according to any one of claims 2 to 5, characterized in that only the area covered by the folds is covered with the drug that was dried after application.

7. The device according to claim 1, characterized in that the lipophilic drugs are inhibitors of cell proliferation or inflammatory processes, or antioxidants.

8. The device according to claim 7, characterized in that the drugs used are Paclitaxel and other taxanes, Rapamycin and related substances, tacrolimus and related substances, corticoids, sexual hormones and related substances, statins, epothilones, probucol, prostacyclins, angiogenesis inducers.

9. The device according to claim 7 or 8, characterized in that the lipophilic drugs are present as dry solids or oils on the surface of the respective product.

10. The device according to claim 9, characterized in that the effective dose of the drug includes amorphous structures with particle sizes ranging from

<0.1 microns to 5 microns that dissolve fast due to their large surface area and despite the poor water-solubility of the active ingredients.

11. The device according to claim 1, characterized in that said lipophilic drugs are embedded in a readily water-soluble matrix substance to achieve good adhesion to the surface of the device and improve absorption by the tissue.

12. The device according to claim 11, characterized in that said matrix substance consists of a low-molecular hydrophilic substance with a molecular weight <5000 D.

13. The device according to claim 1, characterized in that said lipophilic drugs are absorbed to particles or applied to the surface of the device with a low-molecular matrix.

14. The device according to claim 1, characterized in that the surfaces are additionally coated with substances that influence specific properties such as the gliding quality of the device or that prevent blood coagulation.

15. A method for producing the device according to claims 1 through 14, characterized in that the lipophilic drugs and excipients in a solution, suspension or emulsion medium are applied using an immersion,

spreading, or spraying process or an instrument which delivers a defined volume to the surface of the device while excess media and substances that adhere loosely to the surface are removed.

16. The method according to claim 15, characterized in that the coating process is carried out repeatedly for a reproducible increase of the active agent content with the same or different solution, suspension, or emulsion media and/or excipients.

17. The method according to claim 16, characterized in that ethanol, isopropanol, ethyl acetate, diethyl ether, acetone, dimethyl sulfoxide, dimethyl formamide, glycerin, water or mixtures thereof are used as solution, suspension, and emulsion media.

18. The method according to one of claims 15 to 17, characterized in that balloons folded ready for use that are provided as drug carrier to be coated prior to or after sterilization with or without a crimped-on stent.

19. The method according to claim 18, characterized in that the balloons are coated with the respective lipophilic drugs in unfolded condition and that the balloons are folded with a particularly lubricating tool optionally wetted with biocompatible, gliding agents.

20. The method according to claim 15, characterized in that stents connected with a balloon catheter are attached prior to or after coating.

21. The method according to claim 15, characterized in that the completely coated device is sterilized using ethylene oxide.

22. Use of a medical device according to any one of claims 1 to 14 in the manufacture of a means for treating vascular diseases or circulation disturbances.

23. Use of a medical device according to any one of claims 1 to 14 in the manufacture of a means for creating open passages in the body.

24. A device for use in a method for treating vascular diseases or circulation disturbances, said device comprising a medical device according to any one of claims 1 to 14, and said method comprising using said device.

25. A device for use in a method for creating open passages in the body, said device comprising a medical device according to any one of claims 1 to 14, and said method comprising using said device.

26. A device according to any one of claims 1 to 14, substantially as herein described and illustrated.

27. A method according to any one of claims 14 to 21, substantially as herein described and illustrated.

28. Use according to claim 22 or claim 23, substantially as herein described and illustrated.

29. A device for use in a method of treatment according to claim 24 or claim 25, substantially as herein described and illustrated.

30. A new device, a new method for producing a device, a new use of a device according to any one of claims 1 to 14, or a device for a new use in a method of treatment, substantially as herein described.