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METHOD FOR COATING IMPLANTS BY WAY OF A PRINTING METHOD

The present invention relates to a process and a device for applying a defined amount of a coating material onto the surface of an implant by way of a printing method, in particular using a printing roller. The invention also relates to the use of a printing method, in particular a printing roller, for applying a defined amount of a coating material onto the surface of the implant to be coated and to correspondingly produced coated implants.

In order to reduce the body's own defence reactions against foreign implants or to avoid them as far as possible, coated implants are being increasingly used in the field of medicine in order to improve the biological compatibility of the implant materials used, to permit a better integration into the surrounding tissue and to "camouflage" the material of the implant foreign to the body vis-à-vis the immune system. Moreover, implants coated or impregnated with pharmacologically effective substances are being increasingly used which allow a targeted release of the active principle locally at the site of the use of the implant.

Numerous processes for coating implants are known in the prior art. Commonly used methods for applying coatings onto implants are, for example, brush application, varnishing and, in particular, dipping and similar processes.

Coating of medical implants of complex form such as e.g. coronary stents, joint prostheses and, in particular, also surgical implants require increasingly a high application accuracy with respect to the exact determination of the quantity of the coating and/or the coating material to be applied, in particular if medicinal active principles are



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applied, but also with a view to the quality and durability of the coating.

Dipping or dip impregnation processes are frequently used. These processes have the disadvantage that the exact quantity of the pharmacologically active agent absorbed depends to a large extent on the absorption or adsorption characteristics and the coating conditions chosen. This makes the accurate determination of the quantity of pharmacologically active agent actually applied difficult and/or it is subject to process-related variations. Thus, there are usually discrepancies between the theoretical and the practical absorption capacity of porous implant surfaces for each individual active agent to be applied, which can be considerable in some cases.

From DE 198 49 467, it is known that stents coated with carrier polymers can be derivatised with cyclodextrins into which pharmacologically active agents can then be incorporated. In this case, the amount of the cyclodextrins applied on the surface determines the absorbable amount of the active agent in a manner that is relatively satisfactory to reproduce. As a result, the maximum dose of the active agent to be absorbed into the coating can be determined.

A disadvantage of the process of DE 198 49 467, however, consists of the fact that the surface of the stents needs to be coated with a carrier polymer which is capable of binding cyclodextrins. Moreover, measurements are required in the case of this process following the manufacture of the cyclodextrin-derivatised stent surface, which measurements determine the exact absorption capacity of the cyclodextrin portion for

pharmacologically active agents. On actual introduction of active agents into the cyclodextrins, discrepancies arise also here, as is the case with other absorptive systems, between the theoretical and practical absorption capacity as a function of the active agents used.

In view of the inaccuracies of the dosage of active principles when coating medical implants according to known processes, a requirement exists for simple and variedly usable coating methods which permit an accurate dosage of active agents when coating foreign bodies, in particular medical implants.

It is, consequently, an object of the present invention to provide a method for applying a coating material onto the surface of any desired implant, which method permits an exact control of the amount of the coating material applied.

It is a further object of the invention to provide a corresponding application method by means of which implants can be coated singly or multiply, i.e. with one or several layers of one or different coating materials in an exact and reproducible manner.

A further object of the present invention consists of providing a device for carrying out the application method according to the invention.

The solution, according to the invention, to the above-mentioned objects follows from the independent method and device claims.

Preferred embodiments are obtained by combination with the characteristic features of the dependent claims.

A solution, according to the invention, to the process-related object of the present invention consists of a method for applying a defined amount of a coating material onto the surface of an implant to be coated by means of a printing method comprising the steps of:

- charging the recesses formed in the jacket surface of a printing roller with a defined amount of the coating material;
- arranging the printing roller at the implant to be coated in such a way that the adsorption and/or adhesion forces which are intrinsic to the surface properties of the implant to be coated suffice to be able to attract the coating material present in the recesses of the jacket surface of the printing roller;
- applying the coating material present in the recesses of the jacket surface of the printing roller by moving along the jacket surface of the printing roller and the surface of the implant to be coated.

A device-related solution to the above-mentioned objects, according to the invention, consists of a device for applying a defined quantity of a coating material onto the surface of an implant to be coated using a printing roller in whose jacket surface a number of recesses have been formed in order to be able to take up a defined quantity of coating material, the printing roller being always arranged regarding the

implant to be coated in such a way that the suction and/or adsorption forces which are intrinsic regarding the surface properties of the implant to be coated suffice to be able to attract the coating material present in the recesses of the jacket surface of the printing roller, in order to apply, by moving along the jacket surface of the printing roller and the surface of the body to be coated, the coating material present in the recesses of the jacket surface of the printing roller onto the surface of the implant to be coated. Preferably, moving along of the jacket surface of the printing roller and the surface of body to be coated takes place in an essentially slip-free manner.

According to the invention, it has been found that printing processes are particularly suitable for applying coating materials onto the surface of an implant to be coated in a defined and, regarding the quantity, accurately metered manner.

Preferably, printing rollers with a defined surface structure are used for this purpose which exhibit recesses in the jacket surface of the printing roller which allow an exact determination of the volume of the coating material per surface unit of the printing roller.

The term printing roller is intended to mean in the case of the present invention, all printing rollers whose jacket surface contains numerous recesses of defined geometry and arrangement. The recesses in the jacket surface of the printing roller may have any desired three-dimensional geometrical forms such as e.g. small cups, groove structures,

pointed pyramids, flat pyramids, grids, semi-spherical grids, cylinder-shaped recesses and such like.

The recesses formed in the jacket surface of the printing roller make it possible, as a result of their known dimensions, to clearly and highly accurately determine the volume of a coating material which is being applied onto the printing roller, based on the surface unit of the jacket surface of the printing roller. The recess volume per surface unit of the jacket surface of the printing roller thus provides an exact measure of the maximum dosage of the coating material which can be released on applying the coating material present in the recesses of the jacket surface of the printing roller onto the surface of the implant to be coated.

In this way it is possible to accurately determine, from the recess volume of the printing roller per surface unit, the maximum coating material amount which is transferred onto the surface of the implant to be determined on moving the implant along the jacket surface of the printing roller or on moving the printing roller along the surface of the implant to be coated. By repeatedly moving along the jacket surface of the printing roller and the surface of the implant to be coated, the dosage of the coating material can be multiplied as desired.

Printing rollers suitable for use according to the invention can be selected from gravure rollers, anilox rollers, rotogravure rollers, ceramic rollers, ceramic anilox rollers, ceramic-coated anilox rollers, flexographic printing rollers, embossing rollers, calendar rollers and other printing rollers

whose jacket surfaces exhibit recesses for receiving coating material, particularly preferably anilox rollers.

According to a further aspect of the present invention, the possibility additionally exists of using printing rollers without recesses, i.e. with a smooth surface structure onto which the coating material is applied by means of suitable processes in a defined layer thickness. Such processes for charging printing rollers with defined layer thicknesses of coating material are known in the state of the art and familiar to the expert. All the characteristics described so far and in the following in connection with printing rollers containing recesses apply basically, if necessary after corresponding adaptation, also to printing rollers free from recesses and to application methods carried out therewith.

The coating thickness on the printing roller free from recesses can be adjusted by methods known to the skilled artisan, for example by using precision spray technology or ultrasound atomisation methods for extremely finely distributed and homogenous spray images.

According to the application method of the invention, the recesses formed in the jacket surface of the printing roller or the jacket surface of the printing roller itself are first charged with a defined amount of the coating material. This can take place in diverse ways, depending on the state of aggregation of the coating material, for example by partially or completely dipping the surface of the printing roller into liquid or powdery coating materials, spraying liquid, dissolved or powdery coating materials onto the surface of the printing roller and the like. In particularly preferred

embodiments, powdery coating materials can also be applied by electrostatic attraction onto the jacket surface and into the recesses.

In order to adjust the volume of the coating material in the recesses in the jacket surface of the printing roller as accurately as possible, possible excess coating material is preferably removed from the jacket surface after applying the coating material onto the printing roller. In the simplest case, this can be effected by using a slit bar or similar devices to doctor-blade or scrape the recesses back to the level of the roller surface.

It is also possible to ensure an accurate, reproducible dosage of the substance to be applied by way of a very fine pattern of the recesses and their anilox formation. In preferred embodiments of the process of the invention, the top surface of the recesses is smaller than the surface of the implant to be coated. The ratio of the top surface of the recesses in the printing roller to the surface of the implant to be coated is preferably 1:10, particularly preferably 1:100, especially preferably 1:1000, 1:5000, 1:10000 or more.

The use of gravure rollers/anilox rollers, in particular ceramic anilox rollers or ceramic-coated anilox rollers and the use of gravure rollers of metal, in particular stainless steel, is particularly preferred. Moreover, gravure/anilox rollers of steel, if necessary chromium-plated, or stainless steel, are particularly preferred rollers. In preferred embodiments, stainless steel anilox or gravure rollers or chromium-plated steel anilox rollers with a pattern of 120, 240 and up to 300, i.e. 120 x 120, 240 x 240 or 300 x 300

recesses per cm^3 of the printing roller jacket surface are used in particular. The volume of the recesses usually amounts to $1 \times 10^{-6} \text{mm}^3$ to $1 \times 10^{-4} \text{mm}^3$, but can be chosen larger or smaller by the skilled person, depending on the desired application, by using e.g. a more dense pattern of recesses or deeper or larger recesses. The recess volume of a stainless steel anilox roller suitable for use according to the invention is preferably approximately $2 \times 10^{-5} \text{mm}^3$ with a 240 pattern.

In the case of ceramic anilox rollers or ceramic-coated anilox rollers, preferred pattern densities are of the type 120, 450 up to 700 with recess volumes of $1 \times 10^{-7} \text{mm}^3$ to $1 \times 10^{-4} \text{mm}^3$ each, preferably $5.7 \times 10^{-6} \text{mm}^3$ each, wherein the skilled person may also select larger or smaller recess volumes, depending on the desired application, by using e.g. a more dense recess patterns or deeper and/or larger recesses.

According to a preferred embodiment of the invention, charging of the recesses formed in the jacket surface of the printing roller with a coating material takes place via a rotating scoop roller (fountain roller), wherein at least one cylinder segment of the scoop roller is continually present in a coating material bath during rotation, as a result of which the scoop roller is wetted circumferentially with coating material and the scoop roller transferring the coating material thus received subsequently onto the printing roller. Preferably, the scoop roller touches the printing roller during this process such that excess coating material is squeezed off essentially from the surface of the printing roller. If necessary, the surface of the scoop roller can, as a substitute or additionally, also be doctored by using a slitter bar or such like.

The printing roller charged with the coating material in a defined quantity is arranged vis-à-vis the implant to be coated in such a way that the adsorption and/or adhesion forces which are intrinsic to the surface properties of the implant to be coated suffice to be able to attract the coating material present in the recesses of the jacket surface of the printing roller, i.e. to remove it from the recesses of the printing roller jacket surface and to attach it to and/or fix it on the surface of the implant to be coated or to absorb it in the pore system of a porous implant surface.

According to one embodiment of the invention, positioning of the charged printing roller vis-à-vis the implant to be coated takes place in such a way that a direct contact is established between the implant and the printing roller.

According to an alternative embodiment of the present invention which is at present preferred, positioning of the charged printing roller vis-à-vis the implant to be coated takes place without direct contact. In this case, the printing roller and the implant to be coated approach each other sufficiently closely such that the coating material volumes present in the recesses of the jacket surface of the printing roller can pass from the printing roller onto the implant to be coated, preferably essentially completely. The skilled person will be able to determine the best geometry for a contact-free application process simply by routine trials, as a function of the specific properties of the coating material used in each case and the surface properties of the implant.

In the case of liquid coating materials, distances between the printing roller and the implant of $1\mu\text{m}$ to 10mm , preferably approximately $100\mu\text{m}$, for example, are possible.

To apply the coating material present in the recesses of the jacket surface of the printing roller, it is preferable that the movement between the jacket surface of the printing roller and the surface of the implant to be coated is effected in a slip-free manner. The process according to the invention can be carried out in such a way that the surface of the implant to be coated is moved in a slip-free manner along the jacket surface of the printing roller or that the jacket surface of the printing roller is moved in a slip-free manner along the surface of the implant to be coated. A preferably slip-free counter-movement between the jacket surface of the printing roller and the surface of the implant to be coated is also possible according to the invention, and particularly preferred in certain embodiments of the method of the invention.

For as long as moving along of the jacket surface of the printing roller and the surface of the body to be coated is not effected in a slip-free manner, the conditions of the transfer of coating material from the printing roller onto the implant should be adjusted in such a way that a reproducible amount of coating material is transferred per movement process. For this purpose, the hydrodynamic conditions should be appropriately adjusted in the case of liquid systems.

In a particularly preferred embodiment of the invention, the implant to be coated itself has a cylindrical form such that the preferably slip-free movement of the jacket surface of the

printing roller and the surface of the implant to be coated along each other takes place in such a way that the printing roller and the implant to be coated are rotated in opposite directions around two axes lying essentially parallel to each other.

In the case of non-cylindrical geometries of the implant to be coated, the preferably slip-free movement of the jacket surface of the printing roller and the surface of the implant to be coated along each other can take place in such a way that the axis of the printing roller is moved in an equidistant manner along the surface of the implant to be coated. In this way, a quasi scanning of the surface of the implant to be coated with the charged roller takes place.

The implant to be coated according to the method of the invention can, basically, adopt any desired forms, provided the method is adjusted in terms of the device technology. For this purpose, the skilled person knows several possible arrangements of the printing roller and the charging system for the recesses in the jacket surface of the printing roller, which he will select as required.

The term "implant" is used within the present description in such a way that it comprises in general medical, diagnostic and therapeutic implants such as e.g. vascular endoprostheses, intraluminal endoprostheses, stents, coronary stents, peripheral stents, surgical and/or orthopaedic implants for temporary purposes such as surgical screws, plates, nails and other fixing means, permanent surgical or orthopaedic implants such as bone or joint prostheses, e.g. artificial hip or knee joints, joint cavity inserts, screws, plates, nails,

implantable orthopaedic fixing means, vertebral body substitutes as well as artificial hearts and parts thereof, artificial heart valves, pacemaker housings, implants for percutaneous, subcutaneous and/or intramuscular use, slow release active principles and microchips and such like which are intended to be used in the human or animal body and/or are intended for application on or in the human or animal body.

According to the invention, the implant to be coated consists preferably of medical, diagnostic or therapeutic implants such as vascular endoprostheses, stents, coronary stents, peripheral stents, orthopaedic implants, bone or joint prostheses, artificial hearts, artificial heart valves, pacemaker electrodes, subcutaneous, percutaneous and/or intramuscular implants, surgical nails, screws, fixing agents, pins and the like.

However, basically any desired body form can be coated by means of the method/device of the invention, the method of the invention being characterised in particular in that the quantity of the coating material applied can be determined and predetermined with great accuracy.

According to a particularly preferred embodiment of the invention, the implant to be coated is a stent, in particular preferably of a generally cylindrical form, particularly preferably a carbon-coated stent, for example as described in DE 103 33 098, and manufactured according to the method described therein.

The implants coatable reproducibly by means of the method of the present invention can consist of almost any desired

material, in particular of all materials of which implants can be made.

Examples in this respect are amorphous and/or (partially) crystalline carbon, bulk carbon material, porous carbon, graphite, carbon composite materials, carbon fibers, plastics, polymer material, synthetic resin fibers, ceramics such as e.g. zeolites, silicates, aluminum oxides, aluminosilicates, silicon carbide, silicon nitride; metal carbides, metal oxides, metal nitrides, metal carbonitrides, metal oxycarbides, metal oxynitrides and metal oxycarbonitrides of the transition metals such as titanium, zirconium, hafnium, vanadium, niobium, tantalum, chromium, molybdenum, tungsten, manganese, rhenium, iron, cobalt, nickel; metals and metal alloys, in particular of the noble metals gold, silver, ruthenium, rhodium, palladium, osmium, iridium, platinum; metals and metal alloys of titanium, zirconium, hafnium, vanadium, niobium, tantalum, chromium, molybdenum, tungsten, manganese, rhenium, iron, cobalt, nickel, copper; steel, in particular stainless steel, shape retention alloys such as nitinol, nickel-titanium alloy, glass, stone, glass fibers, minerals, natural or synthetic bone substance, bone imitates based on alkaline earth metal carbonates such as calcium carbonate, magnesium carbonate, strontium carbonate and any desired combinations of the above-mentioned materials.

Depending on the coating material to be applied, the implant to be coated can consist of any desired substances provided the material is able to absorb and/or bind the coating material or fix it at the surface.

Preferred materials from the field of medical, diagnostic or therapeutic implants which can be coated with the method of the invention, are, for example, carbon, carbon fibers, bulk carbon material, carbon composite material, carbon fiber, plastics, polymer material, synthetic resin fibers, ceramic, glass or glass fibers, metals such as stainless steel, titanium, tantalum, platinum; alloys such as nitinol, nickel-titanium alloy; bone, stone, mineral or combinations of these materials of which the implant to be coated consists. If necessary, the implants to be coated consisting of the above-mentioned materials can also be coated already with one or several layers of one or several of the above-mentioned materials.

The coating material for use in the method of the invention can be a solution, suspension or emulsion of one or several active agents or active agent precursors in a suitable carrier material, an undiluted liquid active agent or also one or several active agents and active agent precursors in powder form.

The term "active agent" should be understood to mean, according to the invention, pharmacologically effective substances such as medicines, medicaments, pharmaceuticals but also micro-organisms, living organic cell material, and enzymes as well as biocompatible inorganic or organic substances. The term "active agent precursors" refers to substances or mixtures of substances, which, after application onto an implant to be coated, are converted by thermal, mechanical or chemical and/or biological processes into active agents of the above-mentioned type.

The active agents or active agent precursors of an organic type that can be used in the coating materials of the method of the invention can be biodegradable and/or resorbable polymers such as collagen, albumin, gelatin, hyaluronic acid, starch, celluloses such as methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose phthalate, casein, dextrans, polysaccharides, fibrinogen, poly(D,L-lactides), poly(D,L-lactide coglycolides), poly(glycolides), poly(hydroxybutylates), poly(alkyl carbonates), poly(orthoesters), polyesters, poly(hydroxyvaleric acid), polydioxanones, poly(ethyl enterephthalates), poly(malatic acid), poly(tartronic acid), polyanhydrides, polyphosphazenes, poly(amino acids), and their copolymers or non-biodegradable and/or resorbable polymers. Anionic, cationic or amphoteric coatings such as alginate, carrageenan, carboxymethylcellulose; chitosan, poly-L-lysine; and/or phosphoryl choline are particularly preferred.

Active agents or active agent precursors that can be used as coating material according to the present invention can also be markers, contrast agents or the like which can be used to locate coated implants in the body, e.g. therapeutic or diagnostic amounts of radioactive sources of radiation and the like.

In certain embodiments, in particular in the case of subcutaneous/intramuscular active agent depots or stents, the charge of active agent can also be temporary, i.e. the active agent is released after implanting of the implant, or the active agent is immobilised permanently in or on the implant. In this way, medical implants containing active agents can be

produced with static, dynamic or combined static and dynamic charges of active agents. In this way, multifunctional coatings may be obtained on the implants coated according to the invention.

In the case of static charging with active agents, the active agents are essentially permanently immobilised on the implant. Active agents suitable for use for this purpose are biocompatible inorganic substances, e.g. hydroxyl apatite (HAP), fluoroapatite, tricalcium phosphate (TCP), zinc; and/or organic substances such as peptides, proteins, carbohydrates such as monosaccharides, oligosaccharides and polysaccharides, lipids, phospholipids, steroids, lipoproteins, glycoproteins, glycolipids, proteoglycans, DNA, RNA, signal peptides or antibodies or antibody fragments, bioresorbable polymers, e.g. polylactonic acid, chitosan and pharmacologically effective substances or mixtures of substances and combinations thereof.

In the case of dynamic charging with active agents, the applied active agents should be released after inserting the implant in the body. In this way, it is possible to use the coated implants for therapeutic purposes, wherein the active agents applied onto the implant are released locally, successively at the site of use of the implant. Active agents suitable for use in dynamic charges of active agents for release of active agents are, for example, hydroxyl apatite (HAP), fluoroapatite, tricalcium phosphate (TCP), zinc; and/or organic substances such as peptides, proteins, carbohydrates such as monosaccharides, oligosaccharides and polysaccharides, lipids, phospholipids, steroids, lipoproteins, glycoproteins, glycolipids, proteoglycans, DNA, RNA, signal peptides or antibodies or antibody fragments, bioresorbable polymers, e.g.

polylactonic acid, chitosan and the like and pharmacologically effective substances or mixtures of substances.

Suitable pharmacologically effective substances or mixtures of substances for static and/or dynamic charging of implants coated according to the invention comprise active agents or active agent combinations which are selected from heparin, synthetic heparin analogues (e.g. fondaparinux), hirudin, antithrombin III, drotrecogin alpha; fibrinolytics such as alteplase, plasmin, lysokinases, factor XIIa, prourokinase, urokinase, anistreplase, streptokinase; thrombocyte aggregation inhibitors such as acetyl salicylic acid, ticlopidins, clopidogrel, abciximab, dextrans; corticosteroids such as alclometasones, amcinonides, augmented betamethasones, beclomethasones, betamethasones, budesonides, cortisones, clobetasol, clocortolones, desonides, desoximetasones, dexamethasones, flucinolones, fluocinonides, flurandrenolides, flunisolides, fluticasones, halcinonides, halobetasol, hydrocortisones, methyl prednisolones, mometasones, prednicarbates, prednisones, prednisolones, triamcinolones; so-called non-steroidal anti-inflammatory drugs such as diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumethones, naproxen, oxaprozin, piroxicam, salsalates, sulindac, tolmetin, celecoxib, rofecoxib; cytostatics such as alkaloids and podophyllum toxins such as vinblastin, vincristin; alkylants such as nitroso ureas, nitrogen dichlorodiethyl sulphide analogues; cytotoxic antibiotics such as daunorubicin, doxorubicin and other anthracyclins and allied substances, bleomycin, mitomycin; antimetabolites such as folic acid, purine analogues or pyrimidine analogues; paclitaxel, docetaxel,

sirolimus; platinum compounds such as carboplatin, cisplatin or oxaliplatin; amsacrin, irinotecan, imatinib, topotecan, interferon-alpha 2a, interferon-alpha 2b, hydroxycarbamide, miltefosin, pentostatin, porfimer, aldesleukin, bexarotene, tretinoin; antiandrogens and antiestrogens; antiarrhythmics, in particular antiarrhythmics of class I such as antiarrhythmics of the quinidine type, e.g. quinidine, dysopyramid, ajmalin, prajmalium bitartrate, detajmium bitartrate; antiarrhythmics of the lidocain type, e.g. lidocain, mexiletin, phenytoin, tocainid; antiarrhythmics of class I C, e.g. propafenon, flecainid (acetate); antiarrhythmics of class II, beta-receptor blockers such as metoprolol, esmolol, propranolol, metoprolol, atenolol, oxprenolol; antiarrhythmics of class III such as amiodaron, sotalol; antiarrhythmics of class IV such as diltiazem, verapamil, gallopamil; other antiarrhythmics such as adenosine, orciprenaline, ipratropium bromide; agents for stimulating angiogenesis in the myocardium such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), non-viral DNA, viral DNA, endothelial growth factors; FGF-1, FGF-2, VEGF, TGF; antibodies, monoclonal antibodies, anticalines; stem cells, endothelial progenitor cells (EPC); digitalis glycosides such as acetyl digoxin/methyl digoxin, digitoxin, digoxin; heart glycosides such as ouabain, proscillaridin; antihypertensives such as centrally acting anti-adrenergic substances e.g. methyl dopa, imidazoline receptor agonists; calcium channel blockers of the dihydropyridine-type such as nifedipine, nitrendipine; ACE blockers: quinaprilat, cilazapril, moexipril, trandolapril, spirapril, imidapril, trandolapril; angiotensin-II antagonists; candesartan cilexetil, valsartan, telmisartan, olmesartan medoxomil, eprosartan; peripherally effective alpha-receptor blockers such as prazosin, urapidil, doxazosin,

bunazosin, terazosin, indoramin; vasodilators such as dihydralazin, diisopropyl amine dichloroacetate, minoxidil, nitroprussid sodium; other antihypertensives such as indapamid, co-dergocrinmesilate, dihydroergotoxin methane sulphonate, cicletanin, bosentan, fludrocortisone; phosphodiesterase inhibitors such as milrinone, enoximon and antihypertensives such as, in particular, adrenergic and dopaminergic substances such as dobutamine, epinephrine, etilefrine, norfenefrine, norepinephrine, oxilofrine, dopamine, midodrine, pholedrine, amexinium methyl; and partial adrenoreceptor agonists such as dihydroergotamine; fibronectin, polylysines, ethylene vinyl acetates, inflammatory cytokines such as TGF β , PDGF, VEGF, bFGF, TNF α , NGF, GM-CSF, IGF-a, IL-1, IL-8, IL-6, growth hormones; as well as adhesive substances such as cyanacrylates, beryllium, silica; and growth factors such as erythropoietin, hormones such as corticotrophins, gonadotropins, somatropin, thyrotrophin, desmopressin, terlipressin, oxytocin, cetorelix, corticorelin, leuprorelin, triptorelin, gonadorelin, ganirelix, buserelin, nafarelin, goserelin and regulatory peptides such as somatostatin, octreotide; bone and cartilage stimulating peptides, so-called "bone morphogenic proteins" (BMPs), in particular recombinant BMPs such as e.g. recombinant human BMP-2 (rhBMP-2), bisphosphonate (e.g. risedronates, pamidronates, ibandronates, zoledronic acid, clodronic acid, etidronic acid, alendronic acid, tiludronic acid), fluorides such as disodium fluorophosphate, sodium fluoride; calcitonin, dihydrotachystyrene; growth factors and cytokines such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), transforming growth factors-b (TGFs-b), transforming growth factor-a (TGF-a), erythropoietin (Epo), insulin-like growth factor-I (IGF-I),

insulin-like growth factor-II (IGF-II), interleukin-I (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), tumour necrosis factor-a (TNF-a), tumour necrosis factor-b (TNF-b), interferon-g (INF-g), colony stimulating factors (CSFs); monocyte chemotactic protein, fibroblast stimulating factor 1, histamine, fibrin or fibrinogen, endothelin-1, angiotensin II, collagens, bromocriptin, methyl sergide, methotrexate, carbon tetrachloride, thioacetamide and ethanol; also silver (ions), titanium dioxide, antibiotics and anti-infectives such as, in particular, β -lactam antibiotics, e.g. β -lactamase-sensitive penicillins, such as benzyl penicillins (penicillin G), phenoxymethyl penicillin (penicillin V); β -lactamase-resistant penicillins such as aminopenicillins such as amoxicillin, ampicillin, bacampicillin; acyl aminopenicillins such as mezlocillin, piperacillin; carboxypenicillins, cephalosporins such as cefazolin, cefuroxim, cefoxitin, cefotiam, cefaclor, cefadroxil, cefalexin, loracarbef, cefixim, cefuroximaxetil, ceftibuten, cefpodoximproxetil, cefpodoximproxetil; aztreonam, ertrapenem, meropenem; β -lactamase-inhibitors such as sulbactam, sultamicillin tosilat; tetracyclines such as doxycycline, minocycline, tetracycline, chlorotetracycline, oxytetracycline; aminoglycosides such as gentamicin, neomycin, streptomycin, tobramycin, amikacin, netilmicin, paromomycin, framycetin, spectinomycin; macrolide antibiotics such as azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin, josamycin; lincosamides such as clindamycin, lincomycin, gyrase inhibitors such as fluoroquinolones such as ciprofloxacin, ofloxacin, moxifloxacin, norfloxacin, gatifloxacin, enoxacin, fleroxacin, levofloxacin; quinolones such as pipemidic acid; sulphonamides, trimethoprim, sulphadiazine, sulphalene; glycopeptide antibiotics such as

vancomycin, teicoplanin; polypeptide antibiotics such as polymyxines such as colistin, polymyxin-B, nitroimidazol derivatives such as metronidazol, tinidazol; aminoquinolones such as chloroquin, mefloquin, hydroxychloroquin; biguanides such as proguanil; quinine alkaloids and diamino pyrimidines such as pyrimethamine; amphenicols such as chloramphenicol; rifabutin, dapson, fusidinic acid, fosfomycin, nifuratel, telithromycin, fusafungin, fosfomycin, pentamidine diisethionate, rifampicin, taurolidine, atovaquone, linezolid; virustatics such as aciclovir, ganciclovir, famciclovir, foscarnet, inosine (dimepranol-4-acetamidobenzoate), valganciclovir, valaciclovir, cidofovir, brivudin; antiretroviral active principles (nucleoside analogous reverse transcriptase inhibitors and derivatives) such as lamivudin, zalcitabin, didanosin, zidovudin, tenofovir, stavudin, abacavir; non-nucleoside analogous reverse transcriptase inhibitors: amprenavir, indinavir, saquinavir, lopinavir, ritonavir, nelfinavir; amantadin, ribavirin, zanamivir, oseltamivir and lamivudin as well as any desired combinations and mixtures thereof.

In particularly preferred embodiments of the process according to the invention, pharmacologically effective substances incorporated into microcapsules, liposomes, nanocapsules, nanoparticles, micelles, synthetic phospholipids, gas dispersions, emulsions, microemulsions or nanospheres can be used as the coating material.

Suitable solvents can be used as a carrier medium for coating material solutions, suspensions or emulsions. Examples in this respect are methanol, ethanol, n-propanol, isopropanol, butoxydiglycol, butoxy ethanol, butoxy isopropanol, butoxy

propanol, n-butyl alcohol, t-butyl alcohol, butylene glycol, butyl octanol, diethylene glycol, dimethoxydiglycol, dimethylether, dipropylene glycol, ethoxydiglycol, ethoxyethanol, ethyl hexane diol, glycol, hexane diol, 1,2,6-hexane triol, hexyl alcohol, hexylene glycol, isobutoxy propanol, isopentyl diol, 3-methoxy butanol, methoxy diglycol, methoxy ethanol, methoxy isopropanol, methoxy methyl butanol, methoxy PEG-10, methylal, methyl hexyl ether, methyl propane diol, neopentyl glycol, PEG-4, PET-6, PET-7, PEG-8, PEG-9, PEG-6-methyl ether, pentylene glycol, PPG-7, PPG-2-buteth-3, PPG-2 butyl ether, PPG-3 butyl ether, PPG-2 methyl ether, PPG-3 methyl ether, PPG-2 propyl ether, propane diol, propylene glycol, propylene glycol butyl ether, propylene glycol propyl ether, tetrahydrofuran, trimethyl hexanol, phenol, benzene, toluene, xylene; and water, if necessary in mixture with dispersing agents and mixtures thereof.

According to the method of the invention, the surface of the implant to be coated can be coated partially, essentially completely and also multiply. A multiple coating is effected by multiply moving along the jacket surface of the printing roller and the surface to be coated in a slip-free manner, wherein drying steps may be applied, if necessary, after each coating step.

It is particularly preferred to coat the implant to be coated with one or several pharmacologically effective substances and subsequently with one or several coatings of one or several, if necessary, different materials modifying the release of the pharmacologically effective substance or substances. Release-modifying materials suitable for this purpose are, for example, cellulose and cellulose derivatives such as

hydroxypropyl methylcellulose, hydroxypropyl cellulose, poly(meth)acrylates, carbomers, polyvinyl pyrrolidone and the like.

Particularly preferred embodiments of the present invention are coated vascular endoprostheses (intraluminal endoprostheses) such as stents, coronary stents, intravascular stents, peripheral stents and such like.

These can be biocompatibles charged in a simple manner by the method of the invention, as a result of which the restenoses frequently occurring in the case of percutaneous transluminal angioplasty using conventional stents, for example, can be prevented.

In particularly preferred embodiments, stents, in particular stents provided with a carbon-containing surface layer, can be charged with pharmacologically effective substances or mixtures of substances. The stent surfaces can, for example, be equipped with the following active principles for the local suppression of cell adhesion, thrombocyte aggregation, complement activation and/or inflammatory tissue reactions or cell proliferation:

Heparin, synthetic heparin analogues (e.g. fondaparinux), hirudin, antithrombin III, drotrecogin alpha; fibrinolytics (alteplase, plasmin, lysokinases, factor XIIa, prourokinase, urokinase, anistreplase, streptokinase) thrombocyte aggregation inhibitors (acetyl salicylic acid, ticlopidins, clopidogrel, abciximab, dextrans), corticosteroids (alclometasones, amcinonides, augmented betamethasones, beclomethasones, betamethasones, budesonides, cortisones,

clobetasol, clocortolones, desonides, desoximetasones, dexamethasones, flucinolones, fluocinonides, flurandrenolides, flunisolides, fluticasones, halcinonides, halobetasol, hydrocortisones, methyl prednisolones, mometasones, prednicarbates, prednisones, prednisolones, triamcinolones), so-called non-steroidal anti-inflammatory drugs (diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumethones, naproxen, oxaprozin, piroxicam, salsalates, sulindac, tolmetin, celecoxib, rofecoxib), cytostatics (alkaloids and podophyllum toxins such as vinblastin, vincristin; alkylants such as nitroso ureas, nitrogen dichlorodiethyl sulphide analogues; cytotoxic antibiotics such as daunorubicin, doxorubicin and other anthracyclins and allied substances, bleomycin, mitomycin; antimetabolites such as folic acid, purine analogues or pyrimidine analogues; paclitaxel, docetaxel, sirolimus; platinum compounds such as carboplatin, cisplatin or oxaliplatin; amsacrin, irinotecan, imatinib, topotecan, interferon-alpha 2a, interferon-alpha 2b, hydroxycarbamide, miltefosin, pentostatin, porfimer, aldesleukin, bexarotene, tretinoin; antiandrogens and antiestrogens).

For systemic, cardiological effects, the stents according to the invention can be charged with:

Antiarrhythmics, in particular antiarrhythmics of class I (antiarrhythmics of the quinidine type: quinidine, dysopyramid, ajmalin, prajmalium bitartrate, detajmium bitartrate; antiarrhythmics of the lidocain type: lidocain, mexiletin, phenytoin, tocainid; antiarrhythmics of class I C: propafenon, flecainid (acetate); antiarrhythmics of class II

(beta-receptor blockers (metoprolol, esmolol, propranolol, metoprolol, atenolol, oxprenolol), antiarrhythmics of class III (amiodaron, sotalol), antiarrhythmics of class IV (diltiazem, verapamil, gallopamil), other antiarrhythmics such as adenosine, orciprenaline, ipratropium bromide; agents for stimulating angiogenesis in the myocardium: vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), non-viral DNA, viral DNA, endothelial growth factors, FGF-1, FGF-2, VEGF, TGF; antibodies, monoclonal antibodies, anticalines; stem cells, endothelial progenitor cells (EPC). Further cardials are: digitalis glycosides (acetyl digoxin/methyl digoxin, digitoxin, digoxin), further heart glycosides (ouabain, proscillaridin). Also antihypertensives (centrally acting anti-adrenergic substances: methyl dopa, imidazoline receptor agonists; calcium channel blockers: of the dihydropyridine type such as nifedipine, nitrendipine; ACE blockers: quinaprilate, cilazapril, moexipril, trandolapril, spirapril, imidapril, trandolapril; angiotensin-II antagonists: candesartan cilexetil, valsartan, telmisartan, olmesartan medoxomil, eprosartan; peripherally effective alpha-receptor blockers: prazosin, urapidil, doxazosin, bunazosin, terazosin, indoramin; vasodilators: dihydralazin, diisopropyl amine dichloroacetate, minoxidil, nitroprussid sodium), other antihypertensives such as indapamid, co-dergocrinmesilate, dihydroergotoxin methane sulphonate, cicletanin, bosentan. Further phosphodiesterase inhibitors (milrinon, enoximon) and antihypotonics, in this case in particular adrenergic and dopaminergic substances (dobutamine, epinephrine, etilefrine, norfenefrine, norepinephrine, oxilofrine, dopamine, midodrine, pholedrine, amexinium methyl), partial adrenoreceptor agonists (dihydroergotamin) and finally other antihypotonics such as fludrocortisone.

To increase the tissue adhesion, in particular in the case of peripheral stents, components of the extracellular matrix, fibronectin, polylysines, ethylene vinyl acetate, inflammatory cytokines such as: TGF β , PDGF, VEGF, bFGF, TNF α , NGF, GM-CSF, IGF-a, IL-1, IL-8, IL-6, growth hormones; as well as adhesive substances such as: cyanoacrylates, beryllium or silica can be used.

Further substances suitable for this purpose which have a systemic and/or local effect, are growth factors, erythropoietin.

Hormones, too, can be provided in the stent charges such as e.g. corticotropins, gonadotropins, somatropin, thyrotrophin, desmopressin, terlipressin, oxytocin, cetorelix, corticorelin, leuprorelin, triptorelin, gonadorelin, ganirelix, buserelin, nafarelin, goserelin as well as regulatory peptides such as somatostatin and/or octreotide.

In the case of surgical and orthopaedic implants, implants with macroporous surface layers are frequently used. Their pore sizes are in the region of 0.1 to 1000 μ m, preferably 1 to 400 μ m, in order to support better integration of the implants by in-growing into the surrounding cell or bone tissue. These implants are particularly suitable for application and impregnation with a wide variety of different active agents and active agent precursors.

For orthopaedic and non-orthopaedic implants and heart valves, pacemaker electrodes or artificial heart parts, essentially the same active agents can, moreover, be used for the local

suppression of cell adhesion, thrombocyte aggregation, complement activation and/or inflammatory tissue reaction or cell proliferation as in the stent applications described above.

Moreover, to stimulate tissue growth, in particular in the case of orthopaedic implants, the following active agents can be used for a better implant integration:

bone and cartilage stimulating peptides, bone morphogenic proteins (BMPs), in particular recombinant BMPs (recombinant human BMP-2 (rhBMP-2), bisphosphonates (e.g. risedronates, pamidronates, ibandronates, zoledronic acid, clodronic acid, etidronic acid, alendronic acid, tiludronic acid), fluorides (disodium fluorophosphate, sodium fluoride); calcitonin, dihydrotachystyrene. The all growth factors and cytokines (epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), transforming growth factors-b (TGFs-b), transforming growth factor-a (TGF-a), erythropoietin (Epo), insulin-like growth factor-I (IGF-I), insulin-like growth factor-II (IGF-II), interleukin-I (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), tumour necrosis factor-a (TNF-a), tumour necrosis factor-b (TNF-b), interferon-g (INF-g), colony stimulating factors (CSFs). Further adhesion and integration promoting substances, apart from the inflammatory cytokines already mentioned, are the monocyte chemotactic protein, fibroblast stimulating factor 1, histamine, fibrin or fibrinogen, endothelin-1, angiotensin II, collagens, bromocriptin, methyl sergide, methotrexate, carbon tetrachloride, thioacetamide, ethanol.

In addition, the implants can be provided also with antibacterial anti-infectious coatings by means of the

printing method of the invention, the following substances or substance mixtures being suitable for use as coating material: silver (ions), titanium dioxide, antibiotics and anti-infectives. In particular β -lactam antibiotics, (β -lactamase-sensitive penicillins, such as benzyl penicillins (penicillin G), phenoxymethyl penicillin (penicillin V); β -lactamase-resistant penicillins such as aminopenicillins such as amoxicillin, ampicillin, bacampicillin; acyl aminopenicillins such as mezlocillin, piperacillin; carboxypenicillins, cephalosporins (cefazolin, cefuroxim, cefoxitin, cefotiam, cefaclor, cefadroxil, cefalexin, loracarbef, cefixim, cefuroximaxetil, ceftibuten, cefpodoximproxetil, cefpodoximproxetil), or others such as aztreonam, ertrapenem, meropenem. Further antibiotics are β -lactamase inhibitors (sulbactam, sultamicillin tosilat), tetracyclines (doxycycline, minocycline, tetracycline, chlorotetracycline, oxytetracycline), aminoglycosides (gentamicin, neomycin, streptomycin, tobramycin, amikacin, netilmicin, paromomycin, framycetin, spectinomycin), macrolide antibiotics (azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin, josamycin), lincosamides (clindamycin, lincomycin), gyrase inhibitors (fluoroquinolones such as ciprofloxacin, ofloxacin, moxifloxacin, norfloxacin, gatifloxacin, enoxacin, fleroxacin, levofloxacin; other quinolones such as pipemidic acid), sulphonamides and trimethoprim (sulphadiazine, sulphalene, trimethoprim), glycopeptide antibiotics (vancomycin, teicoplanin), polypeptide antibiotics (polymyxines such as colistin, polymyxin-B), nitroimidazol derivatives (metronidazol, tinidazol), aminoquinolones (chloroquin, mefloquin, hydroxychloroquin), biguanides (proguanil), quinine alkaloids and diamino pyrimidines (pyrimethamine), amphenicols

(chloramphenicol), and other antibiotics (rifabutin, dapson, fusidinic acid, fosfomycin, nifuratel, telithromycin, fusafungin, fosfomycin, pentamidine diisethionate, rifampicin, tauroloidine, atovaquone, linezolid). The following need to be mentioned among the virustatics aciclovir, ganciclovir, famciclovir, foscarnet, inosine (dimepranol-4-acetamidobenzoate), valganciclovir, valaciclovir, cidofovir, brivudin. Counted among these are also santiretroviral active principles (nucleoside analogous reverse transcriptase inhibitors and derivatives): lamivudin, zalcitabin, didanosin, zidovudin, tenofovir, stavudin, abacavir; non-nucleoside analogous reverse transcriptase inhibitors: amprenavir, indinavir, saquinavir, lopinavir, ritonavir, nelfinavir), and other virustatics such as amantadin, ribavirin, zanamivir, oseltamivir and lamivudin.

In particularly preferred embodiments of the present invention, the implants can be suitably modified regarding their chemical or physical properties by means of further agents, e.g. in order to modify the hydrophilicity, hydrophobicity, electric conductivity, adhesion or other surface properties. Substances suitable for use as coating material for this purpose are biodegradable or non-degradable polymers such as e.g. regarding the biodegradables: collagen, albumin, gelatin, hyaluronic acid, starch, celluloses (methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose phthalate; also casein, dextrans, polysaccharides, fibrinogen, poly(D,L-lactides), poly(D,L-lactide coglycolides), poly(glycolides), poly(hydroxybutylates), poly(alkyl carbonates), poly(orthoesters), polyesters, poly(hydroxyvaleric acid), polydioxanones, poly(ethyl enterophthalates), poly(malatic

acid), poly(tartronic acid), polyanhydrides, polyphosphazenes, poly(amino acids), and all their copolymers.

The non-biodegradables include: poly(ethylene vinyl acetates), silicones, acrylic polymers such as polyacrylic acid, polymethyl acrylic acid, polyacrylocynoacrylate; polyethylenes, polypropylenes, polyamides, polyurethanes, poly(ester urethanes), poly(ether urethanes), poly(ester ureas), polyethers such as polyethylene oxide, polypropylene oxide, pluronics, polytetramethylene glycol; vinyl polymers such as polyvinyl pyrrolidones, poly(vinyl alcohols), poly(vinyl acetate phthalate).

It is generally applicable that polymers with anionic (e.g. alginate, carrageenan, carboxymethylcellulose) or cationic (e.g. chitosan, poly-L-lysines etc.) or both properties (phosphoryl choline) can be advantageously used.

To modify the release properties of active agent-containing coated implants according to the invention, specific pH-dependent or temperature-dependent release properties can be produced by applying further polymers, for example. pH-sensitive polymers are, for example, poly(acrylic acid) and derivatives, for example: homopolymers, such as poly(aminocarboxylic acid), poly(acrylic acid), poly(methyl acrylic acid) and their copolymers. This also applies to polysaccharides such as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxylpropyl methylcellulose succinate, cellulose acetate trimellitate and chitosan. Heat sensitive polymers are for example poly(N-isopropyl acrylamide) cosodium acrylate co-n-N-alkyl acrylamide), poly(N-methyl N-n-propyl acrylamide), poly(N-

methyl N-isopropyl acrylamide), poly(N-n-propyl methacrylamide), poly(N-isopropyl acrylamide), poly(N,n-diethyl acrylamide), poly(N-isopropyl methacrylamide), poly(N-cyclopropyl acrylamide), poly(N-ethyl acrylamide), poly(N-ethyl methyl acrylamide), poly(N-methyl-N-ethyl acrylamide), poly(N-cyclopropyl acrylamide). Further polymers with thermogel characteristics are hydroxypropylcellulose, methylcellulose, hydroxypropyl methylcellulose, ethyl hydroxy ethyl-cellulose and pluronics such as F-127, L-122, L-92, L-81, L-61.

In the case of the additional coatings of the implants charged according to the invention, a distinction can consequently be made between physical barriers such as inert biodegradable substances (poly-L-lysine, fibronectin, chitosan, heparin etc.) and biologically active barriers. The latter can be sterically hindered molecules which are bioactivated physiologically and permit the release of active principles and/or their carriers. Enzymes, for example, which mediate the release, activate biologically active substances or bind non-active coatings and lead to the exposure of active principles.

The implants coated according to the invention may also be charged, in particular applications with living cells or micro-organisms. These can settle in suitable porous surfaces of the implants, it then being possible to provide the implant thus colonised with a suitable membrane or membrane-type coating which is permeable to nutrients and active principles produced by the cells or micro-organisms, but not to the cells themselves.

In this way, it is possible, by using the technology according to the invention, to produce, for example, by printing with suspensions of insulin-producing cells, implants containing insulin-producing cells, which, after implanting into the body, produce and release insulin as a function of the glucose level of the surrounding.

In the following, a preferred embodiment of the method of the invention and of the device of the invention for applying active agents onto the surface of stents are described as an example. These details regarding the explanation of an exemplary embodiment are intended merely for further illustration of the principles of the invention and do not represent a restriction of the general inventive thought to a certain embodiment.

Figure 1 shows two views A and B of an embodiment of a device of the invention for applying a defined amount of a coating material onto the surface of an implant to be coated by means of a printing roller.

As shown in 1, an implant, in this case a cylindrical stent, which is arranged on a drive shaft which is driven in a slip-free manner against the printing roller 2. In the embodiment of Figure 1, the printing roller 2 is a precision anilox/gravure roller with a drive 7 which permits a slip-free movement with respect to the drive shaft of the stent 1 in the form of a movement counter-current to the precision anilox/gravure roller 2. In the preferred embodiment of the device according to figure 1, the transfer of the coating material from the precision anilox/gravure roller 2 to the stent 1 takes place in a contact-free manner.

As can be seen in the side view **A** of Figure 1, the precision anilox/gravure roller 2 is in direct contact with a scoop roller 4 which dips at least partially into a storage vessel 10 which is filled with coating material or coating material solution. The movement of the scoop roller 4 takes place counter-currently to the precision anilox/gravure roller 2. The level of fill of the coating material in the storage vessel 10 can, as indicated in the side view **A** of Figure 1, be equipped by filling level sensors 5 and 6 for the determination of the upper and lower level of fill in the storage vessel. The filling level sensors 5 and 6 can be capacitive or conductivity sensors, for example, and in automated operation, they permit regular making up of the storage vessel 10 with coating material, the level of the coating material in the storage vessel being maintained between the levels of fill indicated by the filling level sensors 5 and 6 by way of a suitable automated control.

The coating material taken up by the scoop roller 4 is transferred to the precision anilox/gravure roller 2 by contact, the recesses in the anilox/gravure roller being filled with coating material. Excess coating material on the precision anilox/gravure roller 2 is doctored with a doctoring device 3 such as a slit bar, in order to obtain a defined quantity of coating material pre-indicated by the volume of the recesses of the precision anilox/gravure roller 2. The precision anilox/gravure roller 2 rotates counter-currently in a slip-free manner to the stent drive shaft 1 in such a way that, defined by the number of rotations, a certain amount of coating material is transferred from the precision anilox/gravure roller 2 to the stent 1 with every complete

rotation. In the contact-free process, this takes place by transfer of the coating material from the precision anilox/gravure roller 2 onto the stent 1 as a result of the adsorption and/or adhesion forces which are intrinsic to the surface properties of the implant to be coated which suffice, due to a suitable arrangement of the printing roller 2 vis-à-vis the stent 1 to be coated to be able to attract the coating material present in the recesses of the jacket surface of the printing roller 2.

As can be seen in the front view B, the stent 1 is held on a shaft in shaft bearing blocks 8 and the stent shaft 1 or the anilox/gravure roller 2 are moved against each other in a slip-free manner via a corresponding precision drive 7.

In the embodiment of Figure 1 described, the shaft bearing blocks 8 are accommodated in a housing in which the storage vessel for active principle 10 is also provided as an integral structural component, resulting in a compact construction.

In a particularly preferred embodiment of the present invention, a suitable drying device 9, such as an air nozzle, for example, can be provided in spatial vicinity to the stent 1 in order to subject the stent to a flow of heated inert gas in order to evaporate solvent or to dry the coating material. As an alternative, the drying device 9 can also be a thermal radiation device such as an infrared lamp or the like.

CLAIMS

1. A method for applying a defined amount of a coating material onto the surface of a medical implant to be coated by means of a printing method comprising the steps of:
 - charging the recesses formed in the jacket surface of a printing roller with a defined amount of the coating material;
 - arranging the printing roller at the implant to be coated in such a way that the adsorption and/or adhesion forces which are intrinsic to the surface properties of the implant to be coated suffice to be able to attract the coating material present in the recesses of the jacket surface of the printing roller;
 - applying the coating material present in the recesses of the jacket surface of the printing roller by moving along the jacket surface of the printing roller and the surface of the implant to be coated.
2. The method of claim 1,
characterised in that the recesses formed in the jacket surface of the printing roller are charged with a defined amount of coating material by filling the recesses with coating material and subsequently removing possible coating material excesses from the jacket surface.

3. The method of claim 1 or 2,
characterised in that charging of the recesses formed in the jacket surface of the printing roller is effected with coating material via a rotating scoop roller, at least one cylinder segment of the scoop roller being continually present in the coating material bath during rotation, as a result of which the scoop roller is wetted circumferentially with coating material and the scoop roller transferring the coating material thus taken up onto the printing roller.
4. The method of any one of claims 1 to 3,
characterised in that the positioning of the printing roller vis-à-vis the coated implant allows direct contact.
5. The method of any one of claims 1 to 3,
characterised in that the positioning of the printing roller vis-à-vis the coated implant takes place in a contact-free manner.
6. The method of any one of claims 1 to 5,
characterised in that the moving along of the jacket surface of the printing roller and the surface of the implant to be coated takes place in an essentially slip-free manner.
7. The method of any one of claims 1 to 6,
characterised in that moving along of the jacket surface of the printing roller and the surface of the coated implant takes place by the printing roller and the implant to be coated being rotated in the opposite direction around two essentially parallel axes.

8. The method of any one of claims 1 to 6,
characterised in that the slip-free moving along of the jacket surface of the printing roller and the surface of the implant to be coated takes place by moving the axis of the printing roller in an equidistant manner to the surface of the implant to be coated.
9. The method of one of the preceding claims,
characterised in that the implant to be coated is selected from medical or therapeutic implants such as vascular endoprostheses, stents, coronary stents, peripheral stents, orthopaedic implants, bone or joint prostheses, artificial hearts, artificial heart valves, pacemaker electrodes, subcutaneous and/or intramuscular implants and the like.
10. The method of one of the preceding claims,
characterised in that the implant to be coated consists of carbon, carbon fiber, bulk carbon material, carbon composite material, carbon fibers, plastics, polymer material, synthetic fibers, ceramics, glass or glass fibres, metals such as stainless steel, titanium, tantalum, platinum; alloys such as nitinol, nickel-titanium alloy; bone, stone, mineral or combinations of these materials, which, if necessary, can be coated on the surface with one or several of the above-mentioned materials.
11. The method of claim 9,
characterised in that the implant to be coated is a stent, in particular a carbon-coated stent.

12. The method of any one of the preceding claims,
characterised in that the printing roller is selected from from gravure rollers, anilox rollers, rotogravure rollers, ceramic rollers, ceramic anilox rollers, ceramic-coated anilox rollers, flexographic printing rollers, embossing rollers, calendar rollers and other printing rollers whose jacket surfaces exhibit recesses for receiving coating material, particularly preferably anilox/gravure rollers.
13. The method of any one of the preceding claims,
characterised in that the coating material is a solution, suspension or emulsion of one or several active agents or active agent precursors in a suitable carrier medium.
14. The method of claim 13,
characterised in that the active agents or active agent precursors are selected from pharmacologically effective substances, micro-organisms, living organic cell material as well as biocompatible inorganic or organic substances.
15. The method of any one of claims 13 or 14,
characterised in that the active agents or active agent precursors are selected from organic substances such as hydroxyl apatite (HAP), fluoroapatite, tricalcium phosphate (TCP), zinc; organic substances such as peptides, proteins, carbohydrates such as monosaccharides, oligosaccharides and polysaccharides, lipids, phospholipids, steroids, lipoproteins, glycoproteins, glycolipids, proteoglycans, DNA, RNA, signal peptides or antibodies and/or antibody fragments, bioresorbable

polymers, e.g. polylactonic acid, chitosan; pharmacologically effective substances or mixtures of substances such as heparin, synthetic heparin analogues (e.g. fondaparinux), hirudin, antithrombin III, drotrecogin alpha; fibrinolytics such as alteplase, plasmin, lysokinases, factor XIIa, prourokinase, urokinase, anistreplase, streptokinase; thrombocyte aggregation inhibitors such as acetyl salicylic acid, ticlopidins, clopidogrel, abciximab, dextrans; corticosteroids such as alclometasones, amcinonides, augmented betamethasones, beclomethasones, betamethasones, budesonides, cortisones, clobetasol, clocortolones, desonides, desoximetasones, dexamethasones, flucinolones, fluocinonides, flurandrenolides, flunisolides, fluticasones, halcinonides, halobetasol, hydrocortisones, methyl prednisolones, mometasones, prednicarbates, prednisones, prednisolones, triamcinolones; so-called non-steroidal anti-inflammatory drugs such as diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumethones, naproxen, oxaprozin, piroxicam, salsalates, sulindac, tolmetin, celecoxib, rofecoxib; cytostatics such as alkaloids and podophyllum toxins such as vinblastin, vincristin; alkylants such as nitroso ureas, nitrogen dichlorodiethyl sulphide analogues; cytotoxic antibiotics such as daunorubicin, doxorubicin and other anthracyclins and allied substances, bleomycin, mitomycin; antimetabolites such as folic acid, purine analogues or pyrimidine analogues; paclitaxel, docetaxel, sirolimus; platinum compounds such as carboplatin, cisplatin or oxaliplatin; amsacrin, irinotecan, imatinib, topotecan, interferon-

alpha 2a, interferon-alpha 2b, hydroxycarbamide, miltefosin, pentostatin, porfimer, aldesleukin, bexarotene, tretinoin; antiandrogens and antiestrogens; antiarrhythmics, in particular antiarrhythmics of class I such as antiarrhythmics of the quinidine type, e.g. quinidine, dysopyramid, ajmalin, prajmalium bitartrate, detajmium bitartrate; antiarrhythmics of the lidocain type, e.g. lidocain, mexiletin, phenytoin, tocainid; antiarrhythmics of class I C, e.g. propafenon, flecainid (acetate); antiarrhythmics of class II, beta-receptor blockers such as metoprolol, esmolol, propranolol, metoprolol, atenolol, oxprenolol; antiarrhythmics of class III such as amiodaron, sotalol; antiarrhythmics of class IV such as diltiazem, verapamil, gallopamil; other antiarrhythmics such as adenosine, orciprenaline, ipratropium bromide; agents for stimulating angiogenesis in the myocardium such as vascular endothelial growth factor (VEGF), basic fibroblast growth Factor (bFGF), non-viral DNA, viral DNA, endothelial growth factors; FGF-1, FGF-2, VEGF, TGF; antibodies, monoclonal antibodies, anticalines; stem cells, endothelial progenitor cells (EPC); digitalis glycosides such as acetyl digoxin/methyl digoxin, digitoxin, digoxin; heart glycosides such as ouabain, proscillaridin; antihypertonics such as centrally acting anti-adrenergic substances e.g. methyl dopa, imidazoline receptor agonists; calcium channel blockers of the dihydropyridine-type such as nifedipine, nitrendipine; ACE blockers: quinaprilat, cilazapril, moexipril, trandolapril, spirapril, imidapril, trandolapril; angiotensin-II antagonists; candesartan cilexetil, valsartan, telmisartan, olmesartan medoxomil, eprosartan; peripherally effective alpha-receptor blockers such as

prazosin, urapidil, doxazosin, bunazosin, terazosin, indoramin; vasodilators such as dihydralazin, diisopropyl amine dichloroacetate, minoxidil, nitroprussid sodium; other antihypertotics such as indapamid, co-dergocrinmesilate, dihydroergotoxin methane sulphonate, cicletanin, bosentan, fludrocortisone; phosphodiesterase inhibitors such as milrinon, enoximon and antihypotonics such as, in particular, adrenergic and dopaminergic substances such as dobutamine, epinephrine, etilefrine, norfenefrine, norepinephrine, oxilofrine, dopamine, midodrine, pholedrine, amexinium methyl; and partial adrenoreceptor agonists such as dihydroergotamin; fibronectin, polylysines, ethylene vinyl acetates, inflammatory cytokines such as TGF β , PDGF, VEGF, bFGF, TNF α , NGF, GM-CSF, IGF-a, IL-1, IL-8, IL-6, growth hormones; as well as adhesive substances such as cyanacrylates, beryllium, silica; and growth factors such as erythropoietin, hormones such as corticotropins, gonadotropins, somatropin, thyrotrophin, desmopressin, terlipressin, oxytocin, cetorelix, corticorelin, leuprorelin, triptorelin, gonadorelin, ganirelix, buserelin, nafarelin, goserelin and regulatory peptides such as somatostatin, octreotid; bone and cartilage stimulating peptides, bone morphogenic proteins (BMPs), in particular recombinant BMPs such as e.g. recombinant human BMP-2 (rhBMP-2), bisphosphonate (e.g. risedronates, pamidronates, ibandronates, zoledronic acid, clodronic acid, etidronic acid, alendronic acid, tiludronic acid), fluorides such as disodium fluorophosphate, sodium fluoride; calcitonin, dihydrotachystyrene; growth factors and cytokines such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth

factors (FGFs), transforming growth factors-b (TGFs-b), transforming growth factor-a (TGF-a), erythropoietin (Epo), insulin-like growth factor-I (IGF-I), insulin-like growth factor-II (IGF-II), interleukin-I (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), tumour necrosis factor-a (TNF-a), tumour necrosis factor-b (TNF-b), interferon-g (INF-g), colony stimulating factors (CSFs); monocyte chemotactic protein, fibroblast stimulating factor 1, histamine, fibrin or fibrinogen, endothelin-1, angiotensin II, collagens, bromocriptin, methyl sergide, methotrexate, carbon tetrachloride, thioacetamide and ethanol; also silver (ions), titanium dioxide, antibiotics and anti-infectives such as, in particular, β -lactam antibiotics, e.g. β -lactamase-sensitive penicillins, such as benzyl penicillins (penicillin G), phenoxymethyl penicillin (penicillin V); β -lactamase-resistant penicillins such as aminopenicillins such as amoxicillin, ampicillin, bacampicillin; acyl aminopenicillins such as mezlocillin, piperacillin; carboxypenicillins, cephalosporins such as cefazolin, cefuroxim, cefoxitin, cefotiam, cefaclor, cefadroxil, cefalexin, loracarbef, cefixim, cefuroximaxetil, ceftibuten, cefpodoximproxetil, cefpodoximproxetil; aztreonam, ertrapenem, meropenem; β -lactamase-inhibitors such as sulbactam, sultamicillin tosilat; tetracyclines such as doxycycline, minocycline, tetracycline, chlorotetracycline, oxytetracycline; aminoglycosides such as gentamicin, neomycin, streptomycin, tobramycin, amikacin, netilmicin, paromomycin, framycetin, spectinomycin; macrolide antibiotics such as azithromycin, clarithromycin, erythromycin, roxithromycin, spiramycin, josamycin; lincosamides such as clindamycin, lincomycin,

gyrase inhibitors such as fluoroquinolones such as ciprofloxacin, ofloxacin, moxifloxacin, norfloxacin, gatifloxacin, enoxacin, fleroxacin, levofloxacin; quinolones such as pipemidic acid; sulphonamides, trimethoprim, sulphadiazine, sulphalene; glycopeptide antibiotics such as vancomycin, teicoplanin; polypeptide antibiotics such as polymyxines such as colistin, polymyxin-B, nitroimidazol derivatives such as metronidazol, tinidazol; aminoquinolones such as chloroquin, mefloquin, hydroxychloroquin; biguanides such as proguanil; quinine alkaloids and diamino pyrimidines such as pyrimethamine; amphenicols such as chloramphenicol; rifabutin, dapson, fusidinic acid, fosfomicin, nifuratel, telithromycin, fusafungin, fosfomicin, pentamidine diisethionate, rifampicin, taurolidine, atovaquone, linezolid; virustatics such as aciclovir, ganciclovir, famciclovir, foscarnet, inosine (dimepranol-4-acetamidobenzoate), valganciclovir, valaciclovir, cidofovir, brivudin; antiretroviral active principles (nucleoside analogous reverse transcriptase inhibitors and derivatives) such as lamivudin, zalcitabin, didanosin, zidovudin, tenofovir, stavudin, abacavir; non-nucleoside analogous reverse transcriptase inhibitors: amprenavir, indinavir, saquinavir, lopinavir, ritonavir, nelfinavir; amantadin, ribavirin, zanamivir, oseltamivir and lamivudin as well as any desired combinations and mixtures thereof.

16. The method of claim 15,
characterised in that the pharmacologically effective substances are incorporated into micro-capsules, liposomes, nanocapsules, nanoparticles, micelles,

synthetic phospholipids, gas dispersions, emulsions, micro-emulsions or nanospheres.

17. The method of claim 15,
characterised in that the biocompatible substances are selected from biodegradable and/or resorbable polymers such as collagen, albumin, gelatin, hyaluronic acid, starch, celluloses such as methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethylcellulose phthalate; casein, dextrans, polysaccharides, fibrinogen, poly(D,L-lactides), poly(D,L-lactide coglycolides), poly(glycolides), poly(hydroxybutylates), poly(alkyl carbonates), poly(orthoesters), polyesters, poly(hydroxyvaleric acid), polydioxanones, poly(ethyl enterephthalates), poly(malatic acid), poly(tartronic acid), polyanhydrides, polyphosphazenes, poly(amino acids), and their copolymers or of non-biodegradable and/or resorbable polymers such as poly(ethylene vinyl acetates), silicones, acrylic polymers such as polyacrylic acid, polymethyl acrylic acid, polyacrylocyanoacrylate; polyethylenes, polypropylenes, polyamides, polyurethanes, poly(ester urethanes), poly(ether urethanes), poly(ester ureas), polyethers, poly(ethylene oxide), poly(propylene oxide), pluronics, poly(tetramethylene glycol); vinyl polymers such as polyvinyl pyrrolidones, poly(vinyl alcohols), poly(vinyl acetate phthalate) as well as their copolymers; or of anionic or cationic or amphoteric substances such as alginate, carrageenan, carboxymethylcellulose, chitosan, poly-L-lysines; and/or phosphoryl choline.

18. The method of any one of claims 13 to 16,
characterised in that the carrier material is selected from methanol, ethanol, N-propanol, isopropanol, butoxydiglycol, butoxy ethanol, butoxy isopropanol, butoxy propanol, n-butyl alcohol, t-butyl alcohol, butylene glycol, butyl octanol, diethylene glycol, dimethoxydiglycol, dimethylether, dipropylene glycol, ethoxydiglycol, ethoxyethanol, ethyl hexane diol, glycol, hexane diol, 1,2,6-hexane triol, hexyl alcohol, hexylene glycol, isobutoxy propanol, isopentyl diol, 3-methoxy butanol, methoxy diglycol, methoxy ethanol, methoxy isopropanol, methoxy methyl butanol, methoxy PEG-10, methylal, methyl hexyl ether, methyl propane diol, neopentyl glycol, PEG-4, PET-6, PET-7, PEG-8, PEG-9, PEG-6-methyl ether, pentylene glycol, PPG-7, PPG-2-buteth-3, PPG-2 butyl ether, PPG-3 butyl ether, PPG-2 methyl ether, PPG-3 methyl ether, PPG-2 propyl ether, propane diol, propylene glycol, propylene glycol butyl ether, propylene glycol propyl ether, tetrahydrofuran, trimethyl hexanol, phenol, benzene, toluene, xylene; and water, if necessary in mixture with dispersing agents and mixtures thereof.
19. The method of any one of the preceding claims,
characterised in that the surface of the implant to be coated is coated partially, essentially completely and/or multiply.
20. The method of claim 19,
characterised in that the implant is coated with a layer of one or several pharmacologically effective substances and subsequently with one or several layers of one or several, if necessary, different materials modifying the

release of the pharmacologically effective substance or substances.

21. A device for applying a defined amount of a coating material onto the surface of an implant to be coated using a printing roller in whose jacket surface a plurality of recesses have been formed in order to be able to take up a defined amount of a coating material, the printing roller being arranged at the implant to be coated in such a way that the suction and/or adsorption forces which are intrinsic to the surface properties of the implant to be coated suffice to be able to attract the coating material present in the recesses of the jacket surface of the printing roller, in order to apply, by moving along, in a slip-free manner, the jacket surface of the printing roller and the surface of the body to be coated, the coating material present in the recesses of the jacket surface of the printing roller onto the surface of the implant to be coated.
22. A use of a printing process for applying a defined amount of a coating material onto an implant to be coated.
23. The use of claim 20,
characterised in that the application is effected with an anilox/gravure roller.
24. The use of claim 20,
characterised in that the application is effected with a printing roller with a smooth jacket surface.

25. The use of any one of claims 22 to 24,
characterised in that the implant to be coated is selected from medical or therapeutic implants such as vascular endoprostheses, stents, coronary stents, peripheral stents, orthopaedic implants, bone or joint prostheses, artificial hearts, artificial heart valves, pacemaker electrodes, subcutaneous and/or intramuscular implants and such like.
26. The use of any one of claims 22 to 25,
characterised in that the coating material is a solution, suspension or emulsion of one or several active agents or active agent precursors in a suitable carrier medium.
27. The use of claim 26,
characterised in that the active agents or active agent precursors are selected from pharmacologically effective substances, micro-organisms, living organic cell material as well as biocompatible inorganic or organic substances.
28. A coated implant, producible according to the method of any one of claims 1 to 19.