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(54) **MEDICAL PRODUCT WITH A PARTICLE-FREE COATING RELEASING AN ACTIVE SUBSTANCE**

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(57) **ABSTRACT**

Embodiments described herein concern medical products, which come into contact with the organism, such as short-term implants and long-term implants, coated with at least one layer, containing a molecular-disperse distributed or dissolved active substance in at least one carrier and optionally one or more adjuvants, wherein the at least one layer forms a stably spreadable solution, methods for making this coating of stably spreadable solution and use of the medical products coated with the stably spreadable solution.

MEDICAL PRODUCT WITH A PARTICLE-FREE COATING RELEASING AN ACTIVE SUBSTANCE

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] The present invention concerns medical products, which come into contact with the organism, such as short-term implants and long-term implants, coated with at least one layer, containing a molecular-disperse distributed or dissolved active substance in at least one carrier and optionally one or more adjuvants, wherein the at least one layer forms a stably spreadable solution, methods for making this coating of stably spreadable solutions and use of the medical products coated with the stably spreadable solution.

[0003] 2. Description of the Relevant Art

[0004] In the past, improvements concerning balloon catheters related primarily on their ability to place a stent precisely and safely. The PTCA as an independent method was—and is still—used primarily to remove existing stenosis by temporary dilatation and thereby widening of the vessel, but was largely replaced in the coronary field by stent implantation as permanent vessel support. Use of PTCA for prophylaxis of restenosis is still in its infancy.

[0005] However, use of PTCA shows clear advantages in comparison to the stent, not least because there is at no time after treatment a foreign body in the organism, resulting in additional stress or being the starting point of after-effects, such as restenosis. Therefore there exist linkages to work done in the late 80 s concerning an active substance releasing balloon catheter.

[0006] For example, different embodiments of balloon catheters are described, where holes are disposed over parts of the hull in direct contact with the surrounding area and during dilatation, solubilized or liquid active substances are pressed under pressure to the vessel walls (e.g. in U.S. Pat. No. 5,087,244, U.S. Pat. No. 4,994,033, U.S. Pat. No. 4,186,745). EP 0 383 429 A discloses, for instance, a balloon catheter with tiny holes, whereby during dilatation heparin solution is delivered.

[0007] Of those few drug-eluting balloons (DEB) available on the market today, some have the disadvantage that, although the balloons are coated with the active substance paclitaxel, they are not able to release it during dilatation and hence are not more effective than an uncoated balloon catheter. Others show the disadvantage that during dilatation the active substance paclitaxel is delivered in form of hardly soluble particles, raising the risk of vessel occlusion, distal from the site of dilatation and thereby presenting a considerable danger to the patient, which gave also reason for criticism by the FDA and European regulators.

[0008] These examples already show the difficulties that arise for the applicability of effective active substances especially for PTCA. As the effectiveness of these active substances is not only determined by their chemical and physiological properties, but also by their physical properties the state of matter, solubility, viscosity, density, boiling- or melting-point also have to be considered. They have a determining influence on processing and practicability of the substance and hence influence the possible applications to a significant degree. As a consequence, the successful use of an active agent is connected to its processability and attainable availability at the target site.

[0009] As an example, it is referred to the strong lipophil and water-insoluble chemotherapeutic agent paclitaxel, which is used in form of an emulsion as injection solution or infusion solution. The solvent used is ethanol (with approximately 50 volume percent) and a mixture of macrogolricinoleate (Cremophor EL) as emulgator, thereby improving the solubility in the aqueous blood system. It is a proven fact that the addition of Cremophor EL is responsible for diverse, partially serious acceptance problems (New Engl J of Medicine, Vol 332 No 15, 1995:1004). Nonetheless, Cremophor is a necessary and therefore often used additive to enhance the solubility of water-insoluble active substances, such as paclitaxel, cyclosporine, vitamin K, propofol, diazepam etc. To extend the applicability of paclitaxel to water-soluble systems, paclitaxel derivatives were manufactured e.g. by covalent binding of water-soluble polymers, thereby trying to enhance the availability without loss of effectiveness in the vessel system of the organism (U.S. Pat. No. 5,648,506A; U.S. Pat. No. 6,262,107B1, U.S. Pat. No. 6,441,025B2); however with no success.

[0010] In particular, the antiproliferative active substances paclitaxel and rapamycin were not only effective in antitumor therapy but proved to be generally effective against excessive cell growth. To this end the active substances are brought into direct contact with the area to be treated, either systemically or with the aid of a medical product without a polymer matrix or embedded in a solid and preferably polymer matrix. The advantage of a non-systemic application is apparent, given that by means of a medical product, the applicated active substance concentrations are so low, that toxic side effects, as known from systemic administrations, do not occur and no further stress is placed on the organism.

[0011] However, the non-systemic and far less strenuous direct treatment of the affected area and in particular of narrowed areas in blood vessels with hydrophobic and effective active substances is restricted due to physical properties, causing handling- and availability-bottlenecks or rather imposing massive restrictions.

[0012] Consequently, there is a need for special coatings, allowing, in a relative short time frame, a controlled release of a therapeutically sufficient concentration of active substances into the cell.

SUMMARY OF THE INVENTION

[0013] Active substances, such as paclitaxel and rapamycin proved to be especially suitable against hyperproliferative cells. Exactly these highly effective active substances show the above described disadvantages concerning the particle release during dilatation and insolubility in water. Therefore, among other things the applicant was faced with the task to apply effective substances on a catheter ballon resulting in a hydrophil coating, which detaches easily from the balloon during dilatation of the vessel, releases the active substance in colloidal or solubilized form and above all, transfers to the vessel wall without formation of particles.

[0014] This problem is solved by the technical teaching of the independent claims of the present invention. Further preferred embodiments of the invention result from the dependent claims, the description and the examples.

[0015] The present invention is directed to medical devices, wherein the surface of the device is coated completely or partially with a stably spreadable solution containing at least one active substance and at least one carrier.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0016] The medical products or medical devices, as described herein, which come into contact with the organism, are implants, which remain permanently in the body, such as stents and vessel prosthesis and therefore are termed herein as long-term implants, but also removable, for a limited time period implanted devices, such as catheters, e.g. bladder catheters, ventilation tubes, venous catheter, balloon catheter, dilatation catheter, PTCA- and PTA-catheter, embolectomy catheter, valvuloplasty catheter and cannulas. Of the aforementioned catheters, the balloon, the catheter balloon or the dilatable area of the catheter is provided with a coating in form of a stably spreadable solution.

[0017] Preferred are coatings that are not a suspension and are not a solid dispersion, since solid dispersions are too fragile and flake with high probability during implantation or introduction of the catheter balloon. Particular severe risks come off fragile or brittle coatings, applied to expandable medical devices. This is in particular harmful for implants in hollow organs (stents, balloon catheters), since the fragments can cause an occlusion. Especially in the blood vessel system coating fragments must be prevented, because in the increasingly smaller vessels, already the smallest fragments bring the danger of stenosis and of acute injury of the respective tissue, even up to a heart infarct. These fragments can be crystalline particles of the active substance or particles of the solid coating, which detach during introduction of the catheter and/or during dilatation of the catheter balloon.

[0018] The term solid dispersion describes systems in a solid state, containing at least one active substance in an inert carrier. The generic term solid dispersion covers solid suspensions as well as solid solutions. In a solid suspension the active substance is contained in particulate form in the carrier. In contrast, in solid solutions, the active substance is molecular-disperse distributed, i.e. it is dissolved in the basis structure of the carrier.

[0019] In solid solutions, a carrier in the solid state functions as solid solvent for the active substance molecules. In crystalline solid solutions, the active substance is either integrated in the crystal lattice or is located in the space between the lattice molecules of the carrier. If the carrier with the dissolved active substance molecules is amorphous, these are known as glass-like solid solutions.

[0020] The term "stably spreadable solution", as used herein, describes a system of at least one active substance, molecular-disperse distributed in a viscous carrier, which is not a solid but a liquid. As with any liquid, the active substance molecules are dissolved in the carrier. The stably spreadable solution, as defined herein, is no longer capable of flowing. The term "molecular-disperse", as used herein, implies that the active substance is contained in the carrier as single molecules, dispersed in the carrier, i.e. the particle size of the active substance is on the level of single active substance molecules.

[0021] In particular, it is known for the active substance paclitaxel, that bigger particles, consisting of or comprising the active substance paclitaxel are considerably less effective or even uneffective for prophlyaxis of restenosis, when compared to very fine active substance crystals. The applicant has found that this is also true for rapamycin and for other indications than restenosis.

[0022] The stably spreadable solution or rather the coating on the medical device, the stent, the catheter balloon without a stent or the catheter balloon with a stent, has preferably a dynamic viscosity between 105 mPa·s and 1018 mPa·s, further preferred between 1,5·105 mPa·s and 1013 mPa·s, more preferred between 2,5·105 mPa·s and 1012 mPa·s and in particular preferred between 106 mPa·s and 109 mPa·s. The stably spreadable solution or the coating of the inventive device has preferably a viscosity >250 Pa·s and more preferred >1000 Pa·s. All herein mentioned values refer to a viscosity at 20° C.

[0023] The viscosity is a measure for the thickness of a liquid or a gas. The reciprocal value of viscosity is fluidity, which is a measure for the flowability of a liquid or a solution. The higher the viscosity, the thicker (less capable of flowing) is the liquid; the lower the viscosity, the thinner (more capable of flowing) is the liquid.

[0024] Usually, the term viscosity is associated with shearing viscosity however it is also possible to measure the extensional viscosity. It is known to the skilled artisan that several types of viscometers, measuring devices for measurement of tenacity (viscosity) exist, wherein usage of them is common knowledge to the skilled artisan.

[0025] Solids are in a solid state of matter. A particular characteristic of solids is the stability of order of its components (amorphous or crystalline). A liquid is matter in the liquid state of matter. A liquid is a substance, wherein a dimensional change (i.e. a deformation or change in shape) is not resisted, while a change of volume is greatly resisted. Hence, liquids are volume-retaining, variable in shape and are liable to a constant Brownian movement.

[0026] The term "stably spreadable solution", as used herein, preferably also comprises melts and in particular undercooled melts. An undercooled melt is a state, wherein the substance remains in a state of matter, which usually should not exist under the transition point. An undercooled melt or liquid has a lower temperature at a given pressure, than would be adequate for its state of matter.

[0027] Assuming a liquid state of a substance above its melting temperature Tm (melt), crystallization of the substance usually occurs on falling below Tm. On the other hand, if during cooling of the melt, no crystallization occurs after falling below Tm, the result is a so called undercooled melt. In such a scenario either the cooling process is too rapid for the crystallization process due to a high cooling rate, or the molecules of the investigated substance have unfavourable properties for a fast crystallization. The sudden change in enthalpy or of the free volume, which is common to phase transitions of the first order, does not occur if no crystallization happens after falling below Tm.

[0028] The molecular mobility of the undercooled melt is reduced so far at the glass transition, that further lowering of temperature cannot establish a state of equilibrium of the undercooled melt as fast as thermal energy is withdrawn from the system. The molecules of the undercooled liquid become kinetic frozen at glass transition and therefore have a similar random distribution pattern as in the liquid state. However, contrary to the undercooled melt, the molecular mobility in the glass-like state is significantly reduced.

[0029] The state of the undercooled melt (rubberelastic state) and the glass-like state of a substance are separated by the glass transition temperature T_g. Above this temperature the substance is in the state of undercooled melt and below in a glass-like solid state, which is characterized by a viscosity greater than 10^{12} Pa·s.

[0030] At the glass transition temperature T_g a sudden change of the thermal capacity value c_p occurs. In the glass-like state, i.e. below T_g the value of the thermal capacity is significantly reduced and the loss of thermal energy is considerably slower at further decreasing temperatures. The transition from undercooled melt to a glass-like solid solution is therefore characterized by a sudden change of the thermal capacity. A transition into the glass-like state is not associated with a change in enthalpy. The skilled artisan knows how to determine the glass transition temperature T_g, so that by determination of the glass transition temperature T_g, the inventive embodiments with a coating in form of an undercooled melt (state above of T_g) can be distinguished from such with a coating in form of a glass-like solid solution.

[0031] The inventive coatings in form of an undercooled melt have a glass transition temperature T_g preferably below 30° C., further preferred below 20° C., even further preferred below 10° C. and in particular preferred below 0° C. Furthermore, it is to be noted, that it is not crucial, whether the temperature falls below the glass transition temperature T_g during storage of the inventive coated medical device or the inventive coated catheter balloon or the inventive coated stent. It is important that during introduction or implantation of the inventive coated medical device or the inventive coated catheter balloon or the inventive coated stent, the temperature is above of T_g. Since the body temperature is usually 37° C., T_g must be below 37° C., preferably below 30° C., further preferred under 20° C., even further preferred below 10° C. and in particular preferred below 0° C.

[0032] Surprisingly, stably spreadable solutions for coating of a medical device containing at least one active substance are in particular suitable to achieve a successful local application of an active substance and especially of hydrophobic active substances. Because of their structure (low degree of order), solutions show the advantage that there is no occurrence of strong lattice forces that would oppose a fast dissolution of the carrier and the release of the active substance. Stably spreadable solutions with strongly reduced flowing capabilities or strongly increased viscosity additionally show the property to remain on the medical device even during introduction through a distance of more than one meter of blood vessel. Furthermore, it could be shown that this is also true for implantation processes or during introduction by means of a catheter. The stably spreadable solution, as defined herein, can also be described as a solution with a rubber-like, gel-like, viscous, semisolid, thickly viscose or highly viscose consistency. This means, without disturbances, stably spreadable coatings are in a solid-like state, but they begin to deform and to flow under the influence of external forces. The pressure, building up during dilatation, can be seen as such an external force, which deforms the coating which is in form of a stably spreadable solution.

[0033] In the inventive stably spreadable solution, the active substance is molecular-disperse distributed in a carrier, so that it is already dissolved when coming into contact with the solvent (such as blood or other body liquids). Ideally, in a stably spreadable solution, the rate at which the active substance is released is solely determined by the dissolution rate of the carrier. The active substance is released more rapidly than any of its crystalline or colloidal forms during the dissolution procedure, because of the omission of the melting enthalpy.

[0034] Stably spreadable solutions can prevent recrystallization, which occurs frequently during storage of pure amorphous active substances. Recrystallization is hindered by dissolution of the active substance in the carrier, whereby the molecules are mainly separated from each other.

[0035] Medical devices are preferred, wherein the proportion of the at least one active substance and the at least one carrier ranges from 90% by weight of the active substance to 10% by weight of the carrier to 10% by weight of the active substance to 90% by weight of the carrier.

[0036] Preferred are in the present application all antirestenotic effective substances and active substances for treatment and prophylaxis of disorders of the blood and the blood-building organs, in particular antithrombotic and anticoagulating active substances. Further preferred are antiproliferative, antimicrotubuli, antimitotic and cytostatic active substances.

[0037] Medical devices are preferred, whereby the at least one active substance is selected from the group comprising or consisting of:

Taxanes such as paclitaxel, docetaxel, limus-compounds such as rapamycin (sirolimus), biolimus A9, zotarolimus, everolimus, myolimus, novolimus, pimecrolimus, tacrolimus, ridaforolimus, temsirolimus, lapachon, vitamin K, vitamin D, propofol, diazepam. Specifically preferred are taxanes and rapamycin and their derivatives (limus-compounds), cumarin, cumarin-derivatives, heparin, heparin-derivatives, dabigatran, fondaparinux, hirudin, lepirudin, rivaroxaban and calcium-complexing agents.

[0038] Thereby the following active substances are specifically preferred: taxanes such as paclitaxel, docetaxel also the limus-compounds such as rapamycin (sirolimus), biolimus A9, zotarolimus, everolimus, myolimus, novolimus, pimecrolimus, tacrolimus, ridaforolimus and temsirolimus. It is also preferred, when the active substance paclitaxel is applied in combination with one of the other herein mentioned active substances.

[0039] Suitable carriers are substances, in which the at least one active substance is soluble. Suitable carriers are furthermore compounds, which are able to prevent or impede crystallization in an undercooled melt or in a solution, because due to their great number of hydrogen bonds and at the same time allow a heating up to the melting temperature without degradation. An essential requirement for a suitable carrier is the miscibility of active substance and carrier in molten state, provided a stably spreadable solution shall be manufactured by melting method. Alternatively, the active substance and the carrier have to be soluble in the same solvent or solvent mixture, provided a stably spreadable solution shall be manufactured by solution method.

[0040] A suitable pure carrier can be solid as well as liquid at room temperature. It is common knowledge to every chemical lab technician, how to determine, which active substance is soluble in which carrier and/or solvent. If adjuvants are used, they should or they also have to be soluble in the carrier or solvent. Suitable systems of active substance, carrier and optionally adjuvant and/or optionally solvent or solvent mixture can be found with simple standard solubility experiments, which belong to the common repertoire of the skilled artisan and even of any lab technician.

[0041] Preferred are medical devices, wherein the at least one carrier is selected from the group comprising or consisting of polyether, polylactonic acid, polyethylene glycol (PEG), poly(N-vinyl) pyrrolidone, N-dodecyl pyrrolidone, N-decyl pyrrolidone, N-octyl pyrrolidone, polyvinyl alcohols, derivatives of polyvinyl alcohols, glycolated polyesters,

polyphosphoesters, polyethylene oxide propylene oxide, polyethylene oxide, hyaluronic acid, copolymers with PEG and polypropylene glycol, lipids, phospholipids, polyacrylic acid, polyacrylates, carboxymethyl chitosane, vanillin, farnesol, sorbitol, gelatine, derivatives of gelatine, fatty acid partial glycerides with a monocontent of 50 to 95% by weight, cellulose, derivatives of cellulose, hydroxypropyl cellulose, ethyl cellulose, starch, derivatives of starch, dextrines, dextranes, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, dimethyl-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, steroles, cholesterol, bile acids, cholic acid, lithocholic acid, N-alkyl lactames, N-dodecyl caprolactam, N-decyl caprolactam, N-octyl caprolactam, N-dodecyl valerolactam, N-decyl valerolactam, N-octyl valerolactam, polyoxyethylene sorbitan monolaurates, polyoxyethylene sorbitan monopalmitates, polyoxyethylene sorbitan monostearate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, polyoxyethylene oleyl ether, polyoxyethylene oleyl ether, bis-[alpha-methyl-(4-methyl-benzyl)]-phenyl-polyglycol ether, bis-[alpha-methyl-(4-n-dodecyl)]-phenyl-polyglycol ether, bis-(4-methyl-benzyl)-phenyl-polyglycol ether, bis-(4-n-dodecyl-benzyl)-phenyl-polyglycol ether, tris-[alpha-methyl-(4-methyl-benzyl)]-phenyl-polyglycol ether, nonylphenolic polyglycol ether and nonylphenolic diglycol ether.

[0042] Preferred are devices, wherein the at least one carrier is selected from the group comprising or consisting of: poly(N-vinyl) pyrrolidone, derivatives of polyvinyl alcohols, glycolated polyesters, polyacrylic acid, polyacrylates, sorbitol, gelatin, starch, derivatives of starch, cholic acid, lithocholic acid and polycarbonate urethanes.

[0043] In particular preferred are medical devices, wherein the at least one carrier is selected from the group comprising or consisting of dexpanthenol, hyaluronic acid, vanillin, carboxymethyl chitosane or polyethylene glycol.

[0044] Oils, fats or waxes are not preferred or are not used for the manufacture of an inventive coating in form of a stably spreadable solution. If polymers are used for the manufacture of the inventive coating, low-molecular polymers are preferred with a polymerization degree of n (=number of the monomer units), preferably below 100 (n<100), further preferred below 80 (n<80), even further preferred below 60 (n<60), even further preferred below 50 (n<50), even further preferred below 40 (n<40), even more preferred below 30 (n<30) and particular preferred below 20 (n<20). If polyethelene glycol is used, an average molecular mass of 1.000 to 10.000 g/mol is preferred. This paragraph is valid for all herein disclosed embodiments and not only for the aforementioned one.

[0045] A further embodiment concerns the use of a crystallization inhibitor as adjuvant in the coating of the inventive medical devices. The orderly aggregation of the drug molecules to a subnucleus and the crystallization or recrystallization is prevented by a crystallization inhibitor due to specific interactions with the active substance molecules.

[0046] Furthermore, the viscosity of the coating can be increased by addition of an adjuvant, if the distribution of the adjuvant in the carrier lowers the mobility of the active substance in the system. The present embodiments are therefore also directed to medical devices, wherein the surface of the device is coated completely or partially with a stably spreadable solution containing at least one molecular-disperse distributed active substance, at least one carrier and at least one adjuvant. It is preferred, if a maximum of 15 percent by weight, further preferred a maximum of 10 percent by weight, even further preferred a maximum of 5 percent by weight or especially preferred a maximum of 1 percent by weight of the adjuvant is contained in the inventive coating. The herein made details to the percentages by weight of the adjuvant are made with reference to the total weight of the composition for coating of the inventive devices or in other words to the total weight of the inventive coating. The adjuvants are preferably able to significantly reduce the molecular mobility of the drug molecules in the stably spreadable solution or to prevent the orderly aggregation of drug molecules to a crystal by interaction with the active substance. In case solvent residues are contained in the coating, these solvent residues make less than 5 percent by weight with reference to the total weight of the inventive coating.

[0047] The embodiments concern amongst others medical devices, in particular stents as well as catheter balloons with or without stent, wherein the surface of the device is coated completely or partially or at least partly with a stably spreadable solution containing at least one active substance and one carrier and the stably spreadable solution on the surface of the device can contain in addition optionally an adjuvant.

[0048] The embodiments concern amongst others medical devices, wherein the adjuvant is preferably a crystallization inhibitor selected from the group comprising or consisting of: sugar alcohols such as: glucose, mannitol, isomalt (palatinitol), lactitiol and maltitol, phenols amd biphenoles, urea, oleic acid, fatty acids, lecithin, soja lecithin, alkyl glycosides, glycerine, poly(N-vinyl) pyrrolidone, N-dodecyl pyrrolidone, N-decyl pyrrolidone, N-octyl pyrrolidone, sorbitan tristearate, sucrose esters and polyglycerine ester of fatty acids, carbamide acid esters, highly disperse silicon oxide, x-ray contrast agents.

[0049] Further preferred adjuvants are thickeners, gelling agents or binders. Thickeners are used to lower the molecular mobility. There are also higher molecular crystallization inhibitors that can be classified as adjuvants for increasing viscosity. Hence, in the following it is only referred to adjuvants in general. Thickeners can be able to bind water. As a result viscosity is increased or they can also be used to preserve the high viscosity especially during storage by binding e.g. condensed water.

[0050] Most thickeners are linear or branched macro molecules (e.g. polysaccharides or proteins) able to interact with each other through intermolecular interactions such as hydrogen bonds, hydrophobic interactions or ion relations. Preferably, thickeners are plant gums. Plant gums are polysaccharides of natural origin able to increase the viscosity of a solution even at low concentrations drastically. The food industry uses them as thickeners, gelling agents and stabilizers.

[0051] Therefore, embodiments are also directed to medical devices, wherein the adjuvant is preferably a thickener selected from the group comprising or consisting of: agar, alginic acid, alginate, chicle, dammar, althaea extract, gellan gum (E 418), guar gum (E 412), gum Arabic (E 414), gum from plantago, gum from spruce juice, locust bean gum (E 410), karaya (E 416), konjac flour (E 425), mastix, pectin, tara gum (E 417), tragacanth (E 413), xanthan (E 415), carrageenan, cellulose, cellulose ether, gelatin, sago and starch.

[0052] It is a prerequisite for an adjuvant that the corresponding adjuvant dissolves in the carrier to interact with the dissolved drug molecules on a molecular level.

[0053] The stably spreadable solution can be prepared by melt-embedding, co-precipitation, evaporation of a solvent or

condensing of a solution or a combination of these methods. The preparation of stably spreadable solutions by melt-embedding consists of a mixture of carrier, active substance and eventually adjuvants in molten state. This mixture has preferably either a melting point below the body temperature and also below the storage temperature or remains in the region of an undercooled melt.

[0054] Preferably, a solution of an active substance and a carrier, eventually in combination with an adjuvant in a volatile solvent is applied for the coating. While the solvent evaporates, an extremely high viscous, homogenous solution of the carrier, eventually an adjuvant and the active substance remains, containing the active substance in molecular-disperse form without any crystals or particles of the active substance. The mixture of carrier and active substance thereby form a stably spreadable solution.

[0055] Since a crystallization of the active substance shall be prevented, solvents with a high vapour pressure are preferred, i.e. solvents that are gaseous at low temperatures (e.g. 50° C.) or are highly volatile at room temperature. The boiling range of the solvent lies preferably between 0 and 150° C. and further preferred between 10° C. and 100° C. and particular preferred between 20° C. and 50° C. Suitable organic solvents are acetonitrile, dimethylsulfoxide, ethers such as dioxane, tetrahydrofurane (THF), light petroleum, diethyl ether, methyl-tert.-butyl ether (MTDC), ketones such as acetone, butanone or pentanone, alcohols such as methanol, ethanol, propanol, isopropanol, carboxylic acids such as formic acid, acetic acid, propionic acid, amides such as dimethylformamide (DMF) or dimethylacetamide, aromatic solvents such as toluene, benzene, xylene, pure hydrocarbon solvents such as pentane, hexane, cyclohexane, halogenated solvents such as chloroforme, methylene chloride, carbon tetrachloride, as well as carboxylic acid esters such as acetic acid ethyl ester.

[0056] Suitable methods for rapid undercooling of a melt are melt-solidification, spray-solidification and hot-spin-melting. A general prerequisite for the preparation of stably spreadable solutions by melt-solidification is the miscibility of the carrier, active substance and adjuvants in the molten state. The molecular-disperse distribution, which is necessary for the development of a stably spreadable solution, can only be achieved by dissolving the active substance in the molten carrier. An active substance is immiscible, if it is not miscible with the melt of a carrier in a concentration of ≧1%. The execution of such melting experiments is well within the competence of the skilled artisan and even any chemical lab technician.

[0057] It has been found that the set task can be particularly good solved by coating methods of the following type. The method for coating a catheter balloon comprises the following steps:

[0058] a) Providing an uncoated medical device, and

[0059] b) providing a coating solution containing at least one anti-restenotic active substance and a carrier in at least one solvent, and

[0060] c) applying the coating solution of at least one active substance and carrier by spraying, dipping, spreading, brushing, pipetting, chemical vapor deposition or squirting and

[0061] d) evaporating the solvent or drying at elevated temperature and/or under reduced pressure.

[0062] Embodiments also include coated medical devices obtainable according to above method.

[0063] The surface can be provided with an additional hemocompatible layer as base coat by applying semisynthetic heparin derivatives, such as desulfated reacetylated heparin or chitosane derivatives such as N-carboxy methylated, partially N-acetylated chitosane through covalent immobilization.

[0064] After introduction or implantation of the inventive medical device into the body, the coating is pressed against the surrounding tissue, adheres there due to its high viscosity and releases the active substance in molecular-disperse, dissolved and/or in micro crystalline form to the tissue. In the latter case, the formation of microcrystals is triggered by contact with the aqueous system blood or the aqueous system extracellular liquid, because there are no crystals in the coating.

[0065] In the following methods for characterization of stably spreadable solutions are disclosed. In particular the distinctions to suspensions such as pastes are described.

[0066] A macroscopic examination already allows distinction between a solution and a suspension. Suspensions appear milky and cloudy, because similar to an emulsion, an inclusion of droplets of the lower concentrated phase occurs in the carrier. A crystalline active substance in a carrier shows macroscopic clouding of the transparent carrier. The only exception is, when the refraction indices of the active substance phase and the phase of the carrier are not different. Hence, the occurrence of clouding or a milky appearance is either a sign for a (re)crystallization of the active substance or for a suspension. Thus, stably spreadable solutions appear preferably clear or transparent. This does not exclude that they are colored or also glass colored but nonetheless clear or transparent. For a better quality control, it can be advantageous, to introduce a small amount of a coloring agent into the coating.

[0067] Temperature dependent changes in a sample can be observed by thermal analyzing methods. These are especially phase transitions of first and second order. Phase transitions of first order are phase transitions that are associated with an absorption or emission of latent heat. Plotting enthalpy H against the temperature then shows a step at the transformation temperature. Phase transitions of second order proceed without absorption or emission of latent heat. The enthalpy shows here a kink at the transformation temperature and the heat capacity shows a step when plotted against the temperature.

[0068] A distinction between a solid solution, an undercooled melt, or a highly viscose solution, can be made by differential scanning calorimetry (DSC). By means of DSC a predication about the miscibility of substances can also be taken. In a heterogeneous mixture, phase transitions of both pure substances can be observed, wherein in homogenous mixtures only phase transitions of the mixture can be observed.

[0069] In heat flux DSC, sample and reference are located on a thermoconductive disc with a good thermal conductivity, under which temperature sensors are affixed. The difference between the heat flows of sample and reference are measured. If sample and reference are equal, the heat flow difference is zero. A difference in the heat flow arises, if one sample changes during the measurement, e.g. by phase transformation, melting, or evaporation.

[0070] Melting processes are characterized by a positive heat flow and crystallization processes by a negative heat flow. The transition of an amorphous substance from glass-like state to the region of undercooled melt is characterized by

a sudden increase of heat capacity, however, without the occurrence of an additional heat transfer. Therefore, during a DSC, an elevated differential heat flow to the sample can be measured, after the glass transition temperature Tg is exceeded. The characterization of the coatings can also be done by means of release studies, i.e. the way of distribution of an active substance in the carrier can be determined.

[0071] The medical device is therefore placed in a release-medium (adapted to the corresponding, the implant surrounding liquid, such as a physiological saline solution or blood) so that the coating can dissolve or rather release the active substance. During the dissolution process or the mixing process of a stably spreadable solution, the active substance, dissolved in the carrier substance, has a higher thermodynamic solubility due to the omission of the melting enthalpy. Thereby, the dissolution rate and solubility are increased maximal. In particular, if the carrier dissolves quickly, occurrence of a temporary oversaturation of active substance in the release-medium is possible. From the extent of oversaturation and the rate of release of active substance in the release-medium, conclusions about the bioavailability can be made.

[0072] The present embodiments are directed preferably to cathether balloons with or without a stent, wherein the surface of the catheter balloon as well as the surface of the stent is coated completely or partially with a stably spreadable solution containing at least one active substance. It is preferred, if the active substance is anti-restenotic and water insoluble or rather poorly water soluble. In particular preferred are substances with already proven anti-restenotic efficacy on stents, as the taxanes such as paclitaxel, docetaxel as well as the limus-compounds such as rapamycin (sirolimus), biolimus A9, zotarolimus, everolimus, myolimus, novolimus, pimecrolimus, tacrolimus, ridaforolimus and temsirolimus. However, the choice of active substances is not restricted to these two groups. In principal, any given active substance, able to hinder the development of restenosis, can be used, such as antiproliferative, antiangiogenic or antimigrative substances.

[0073] Common catheter balloons, bifurcation balloons and folding balloons or special balloons such as the slit balloon or the scoring balloon can be used as catheter balloons.

[0074] Preferably a solution of an active substance and a carrier, eventually in combination with an adjuvant in a volatile solvent is applied for coating. While the solvent evaporates, an extremely high viscous, homogenous solution of the carrier, eventually an adjuvant and the active substance remains, containing the active substance in molecular-disperse form without any crystals or particles of the active substance. The carrier and the at least one active substance thereby form a stably spreadable solution.

[0075] During balloon dilatation the coating is pressed against the vessel wall, adheres there due to its high viscosity and releases the active substance in molecular-disperse, dissolved and/or in micro crystalline form to the vessel wall. In the latter case, the formation of micro crystals is triggered by contact with the aqueous system blood, after the coating in form of a stably spreadable solution is transferred to the vessel wall, because the inventive coating contains no active substance crystals or active substance particles.

[0076] It is preferred, if the whole balloon surface is coated evenly with a stably spreadable solution containing the active substance, this includes the areas under the folds as well as the surfaces not covered by the folds of the catheter balloon. Further it is preferred, if the at least one active substance is evenly distributed on the balloon surface. In the case of valvuloplasty balloon, a coating of the middle third of the balloon is preferred as only this area of the balloon comes into contact with the heart valve. The distal and ventral end of the catheter ballon remains preferably uncoated, in order to save active substance and to minimize the active substance exposure to the patient.

[0077] Preferably, the inventive coated catheter balloons are used without a stent, however, use with a biostable or biodegradable stent is also possible. This stent can either be uncoated or can be coated together with the catheter balloon or can already be coated before attachment, i.e. before crimping the stent on the catheter balloon either with the same or with another active substance as well as either with the same or with another carrier.

[0078] The complete surface of the catheter balloon or only the folds of the balloon as well as the surface of the stent can be coated completely or partially with a stably spreadable solution containing at least one anti-restenotic active substance and one carrier. Of course, the stent can also be provided with another coating of choice. Also the release kinetic of the anti-restenotic active substance on the stent can be different from the release kinetic of the active substance on the catheter balloon. Therefore, the inventive expandable system also provides a combination of catheter balloon with a stent. Moreover, the stent can also be provided only with a hemocompatible coating, with or without an active substance. The catheter balloon with a crimped stent can be coated simultaneously or the catheter balloon and the stent can be coated separately and afterwards the coated stent is crimped on the coated catheter balloon.

[0079] The term "coating" shall not only comprise a coating of the surface of the catheter balloon but also a filling or coating of folds, cavities, pores, microneedles or other fillable spaces on or between or in the balloon material.

[0080] The inventive coating is characterized by the absence of solids or solid particles. Therefore, it can be necessary to add as much crystallization inhibitor to the active substance, so that after evaporation or removal of the solvent of the coating solution the active substance does not crystallize or solid active substance particles are not formed in the carrier.

[0081] The term "crystallization inhibitor", as used herein, describes a substance that prevents or decreases the formation of crystals after addition to an active substance in a stably spreadable solution.

[0082] Carriers (T_{OW}) are termed as "hydrophil" if the partition coefficient between n-octanol and water is $T_{OW}<6.30$ ($\log T_{OW}<0.80$), preferably $T_{OW}<1.80$ ($\log T_{OW}<0.26$), more preferred $T_{OW}<0.63$ ($\log T_{OW}<-0.20$) and further preferred $T_{OW}<0.40$ ($\log T_{OW}<-0.40$).

[0083] Anti-restenotic active substances are termed as "hydrophobic" or "lipophilic" if the partition coefficient between n-butanol and water is $\geqq 0.5$, preferably $\geqq 0.7$, more preferred $\geqq 0.9$ and in particular preferred $\geqq 1.1$.

[0084] Surprisingly, stably spreadable solutions are in particular suitable for a coating containing active substances and preferably hydrophobic, anti-restenotic active substances and impart the following properties for successful local application:

[0085] 1) The contact time of the catheter balloon is sufficient for transfer of a suitable quantity of a therapeutic active substance into and on the vessel wall,

[0086] 2) during contact, in the course of balloon dilatation, sufficient active substance containing coating material adheres to the vessel wall, to achieve the desired therapeutic effect, and

[0087] 3) the active substance containing coating provided on the catheter ballon, has a higher affinity to the vessel wall than to the balloon surface, so that an optimal transfer of the active substance to the target site is ensured.

[0088] 4) The coating is not brittle, but very thick and therefore does not tear open during dilatation, hence, no fragments occur, which could find their way into the blood circulation.

[0089] 5) The viscosity of the coating ensures that the coating is sufficiently stable to adhere safely to the catheter balloon during introduction of the catheter all the way to the application site.

[0090] 6) There is no release of particles during dilatation.

[0091] 7) There is no release of active substance particles and transfer to the vessel wall during dilatation.

[0092] 8) The active substance is transferred in molecular form, i.e. as single molecules to the vessel segment to be treated and not as colloides, crystals or amorphous particles, whereby the highest efficacy can be achieved and the quantity of active substance used can be minimized.

[0093] 9) The high viscosity of the coating and the higher affinity of the coating to the vessel wall than to the balloon surface, results in a prolonged active substance release, when compared to the actual contact time of the vessel wall with the balloon catheter.

[0094] 10) The coating adhered to the vessel wall, dissolves, due to its high viscosity, evenly with no residues and without the risk of releasing free solid particles into the blood circulation.

[0095] Therefore it has been found that a coating method of the following art solves the task at hand particularly well.

[0096] The method for coating a catheter balloon comprises the following steps:

[0097] a) Providing an uncoated catheter balloon with or without a stent, and

[0098] b) Providing a coating solution containing at least one anti-restenotic active substance and a carrier in at least one solvent, and

[0099] c) Applying the coating solution of at least one active substance and the carrier and at least one solvent by spraying, dipping, spreading, brushing, pipetting, chemical vapor deposition or squirting on the uncoated catheter ballon and

[0100] d) Evaporating the solvent or drying at elevated temperature and/or under reduced pressure.

[0101] Preferably, dilatable catheter balloons are coated by this method. In step c) of the above method for coating or loading a catheter balloon, the coating solution is applied to all surfaces to be coated. This includes the surface of the catheter balloon as well as the surface of the catheter balloon and the stent. The catheter balloon can also be coated only partially.

[0102] The catheter balloon can be coated in its folded or comprimated (deflated) state as well as in its dilated or expanded (inflated) state, whereby after applying the coating the balloon is then refolded. Moreover, the catheter balloon can be coated without a stent and also with a stent crimped thereon, i.e. a crimped stent, so that the abluminal surface of the stent and also the balloon surface, in particular between the stent struts is coated with the stably spreadable, viscous solution containing at least one anti-restenotic active substance and at least one carrier. An uncoated stent or an already coated stent can be used with the catheter balloon. The stent surface can be provided with an additional hemocompatible layer as basic coating, by application of semisynthetic heparin derivatives through covalent immobilization, such as desulfated reacetylated heparin or chitosane derivatives such as N-carboxy methylated and partially N-acetylated chitosane on the stent surface.

[0103] After coating the catheter balloon with the solution of at least one anti-restenotic active substance, a suitable carrier and preferably an adjuvant, a coating of a stably spreadable solution containing an anti-restenotic active substance in a carrier, optionally with an adjuvant is obtained after evaporating or removing the solvent at elevated temperature and/or under reduced pressure. The anti-restenotic active substance is thereby molecular-disperse distributed in the solidified or highly viscous carrier. In this way, usability of hydrophobic active substances is extended to hydrophil systems without changes to the structure of the active substance.

[0104] The coating can also be dried actively by heating or by applying a vacuum or in a gas flow. Use of temperatures between 50° C. and 100° C. is preferred.

[0105] With reference to a catheter balloon and/or a stent, preferred are all anti-restenotic effective hydrophobic substances such as paclitaxel, docetaxel, rapamycin (sirolimus), biolimus A9, zotarolimus, everolimus, myolimus, novolimus, pimecrolimus, tacrolimus, ridaforolimus, temsirolimus, cyclosporines, vitamin K, propofol, and diazepam. Particularly preferred are taxanes and rapamycin and its derivatives (limus-compounds).

[0106] In general, the term taxane is used in the application as generic term for paclitaxel, paclitaxel derivatives and paclitaxel analogs. The term limus-compounds stand for sirolimus (rapamycin) and its derivatives and analogs.

[0107] The term derivative denotes a derived substance of similar structure to a corresponding basic structure. Derivatives are substances, which molecules have in place of an H-atom or a functional group another atom or another functional group, whereby one or more atoms/functional groups are removed and/or added and/or exchanged.

[0108] Particularly preferred is a catheter balloon, wherein the at least one taxane is preferably paclitaxel or the at least one limus-compound is rapamycin. The active substances paclitaxel or rapamycin are thereby provided in combination with a suitable carrier in the coating of the catheter balloon.

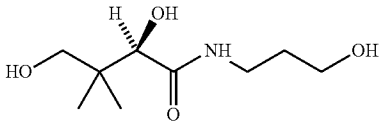
[0109] The active substance releasing coating on the catheter balloon and/or the stent can contain the following substances: polyether, polylactonic acid, polyethylene glycol (PEG), poly(N-vinyl) pyrrolidone, N-dodecyl pyrrolidone, N-decyl pyrrolidone, N-octyl pyrrolidone, polyvinyl alcohols, derivatives of polyvinyl alcohols, glycolated polyester, polyphosphoester, polyethylene oxide propylene oxide, polyethylene oxide, hyaluronic acid, copolymers with PEG and polypropylene glycol, lipids, phospholipids, polyacrylic acid, polyacrylates, carboxymethyl chitosane, lanolin, vanillin, sorbitol, gelatine, derivatives of gelatine, fatty acid partial glycerides with a monocontent of 50 to 95 w.-%, highly disperse silicion oxide, cellulose, derivatives of cellulose, hydroxypropyl cellulose, ethyl cellulose, starch, derivatives of starch, dextrines, dextranes, α-cyclodextrin, β-cyclodex-

trin, γ-cyclodextrin, dimethyl-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, steroles, cholesterol, bile acids, cholic acid, lithocholic acid, N-alkyl lactames, N-dodecyl caprolactam, N-decyl caprolactam, N-octyl caprolactam, N-dodecyl valerolactam, N-decyl valerolactam, N-octyl valerolactam, polyoxyethylene sorbitan monolaurates, polyoxyethylene sorbitan monopalmitates, polyoxyethylene sorbitan monostearate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, polyoxyethylene oleyl ether, polyoxyethylene oleyl ether, bis-[alpha-methyl-(4-methyl-benzyl)]-phenyl-polyglycol ether, bis-[alpha-methyl-(4-n-dodecyl)]-phenyl-polyglycol ether, bis-(4-methyl-benzyl)-phenyl-polyglycol ether, bis-(4-n-dodecyl-benzyl)-phenyl-polyglycol ether, tris-[alpha-methyl-(4-methyl-benzyl)]-phenyl-polyglycol ether, nonylphenolic polyglycol ether and nonylphenolic diglycol ether.

[0110] Particularly preferred as carrier are dexpanthenol, hyaluronic acid, carboxymethyl chitosane, vanillin and PEG and especially dexpanthenol.

[0111] Dexpanthenol is known under the trademark Bepanthen® and the synonyms panthothenol, D-panthenol or panthenol and the IUPAC name (+)-(R)-2,4-dihydroxy-N-(3-hydroxypropyl)-3,3-dimethyl butyramide.

[0112] The chemical structure is as follows:



[0113] Usually, an amount of 0.5 μg to 50 μg active substance is applied to the surface of the balloon per mm2 surface of the balloon catheter to be coated and preferably an amount of 1 μg to 20 μg active substance per mm2 surface of the balloon catheter to be coated. Per catheter balloon preferably 10 to 1000 μg active substance and particularly preferred 20 μg to 400 μg active substance are applied on the balloon.

[0114] Chloroform, ethanol, methanol, tetrahydrofuran, acetone, methyl acetate, ethyl acetate, methylene chloride or its mixtures, such as methanol/ethanol-mixtures or ethanol/water-mixtures can be used as solvent for the mixture of active substance and carrier. A suitable solvent dissolves the required amount of active substance and carrier and does not or only slightly damages the material of the catheter balloon. Particularly preferred are acetone, ethanol and ethyl acetate.

[0115] In one mL of the chosen solvent preferably 0.1 mg-600 mg, further preferred 1 mg to 500 mg and particularly preferred 10 mg-250 mg active substance are dissolved. Furthermore, in one mL of the chosen solvent preferably 0.1 mg-600 mg, more preferred 1 mg to 250 mg and particularly preferred 10 mg-250 mg carrier are dissolved.

[0116] Further preferred is a catheter balloon with a coating exhibiting a proportion of anti-restenotic active substance and carrier of 90 percent by weight anti-restenotic active substance to 10 percent by weight carrier to 10 percent by weight anti-restenotic active substance to 90 percent by weight carrier.

[0117] Moreover preferred is a catheter balloon with a coating exhibiting a molar ratio of active substance to carrier of 90% active substance to 10% carrier to 10% active substance to 90% carrier. Further preferred are mixtures of 1:5 to 5:1 and even more preferred of 1:2 to 2:1.

[0118] It is also possible to include a further adjuvant, e.g. as crystallization inhibitor in the active substance solution. Further suitable adjuvants are for example biologically acceptable organic substances that improve the coating properties and increase the uptake of active substances in the vessel such as amino acids, vitamins, benzoic acid benzyl ester, triethyl- and dimethyl phthalate, fatty acids esters such as isopropyl myristate and -palmitate, triacetin and the like. Mixtures of these different substances also proved to be suitable. For example the mixture of the polysaccharide carrageenan, lecithin and glycerine showed to be a suitable active substance carrier system. Also physiological acceptable salts can be used as adjuvants for incorporation of the active substance.

[0119] A further preferred embodiment comprises a coated catheter balloon with a crimped stent.

[0120] In this embodiment, the stent can be uncoated or have the same inventive coating as the catheter balloon.

[0121] The catheter balloon with or without a stent is coated completely or partially with a glass-like solid solution of anti-restenotic active substance in a carrier by spraying, brushing, squirting, dragging, rolling or pipetting method or electrospinning, wherein a further adjuvant such as a crystallization inhibitor can be added to the coating solution.

[0122] The catheter balloon can be coated partially or completely in the expanded or in the folded state or together with a stent crimped thereon. Moreover, the coating can be applied exclusively to the folds or exclusively outside of the folds.

[0123] The coating can be realized by spraying, dipping, brushing, squirting, dragging, thread dragging, rolling or pipetting method. The pipetting, dragging, rolling or squirting method is especially suitable for use on a folded catheter balloon or a catheter balloon with folds, because with these methods it is possible to apply substances directly in the folds or under the folds. Drying of the coated balloon catheters with or without a stent can be done by rotation-drying. The coating methods are described in detail in WO2008086794A.

Pipetting Method—Capillary Method

[0124] This method is described in detail in the patent application of the international patent application WO2008086794 p. 74, line 33 to p. 78, line 9.

Squirting Method or Syringe Method:

[0125] This method is described in detail in the patent application of the international patent application WO2008086794 p. 78, line 12 to p. 82, line 8.

Spraying Method or Fold Spray Method:

[0126] This method is described in detail in the patent application of the international patent application WO2008086794 p. 82, line 10 to p. 84, line 19.

Drag Method or Drop-Drag Method:

[0127] This method is described in detail in the patent application of the international patent application WO2008086794 p. 84, line 21 to p. 86, line 25.

Thread Drag Method:

[0128] This method is described in detail in the patent application of the international patent application WO2008086794 p. 86, line 27 to p. 88, line 3.

Ballpoint Method or Roll Method:

[0129] This method is described in detail in the patent application of the international patent application WO2008086794 p. 88, line 7 to p. 89, line 6.

Rotation-Drying:

[0130] This method is described in detail in the patent application of the international patent application WO2008086794 p. 89, line 8 to p. 91, line 8.

[0131] The term "active substance containing composition" or "coating solution" as used herein is to be understood as the mixture of at least one active substance, a carrier and a solvent or solvent mixture, thus, an actual solution of an active substance, a carrier and at least one further component selected from the solvents mentioned herein. An adjuvant can be added to the coating. This can be a crystallization inhibitor or a substance that further accelerates the dissolving of the coating during dilatation, fatty acid esters, amino acids, vitamins, salts and/or membrane-forming or membrane-disruptive substances. The term "solution" shall further clarify that a liquid mixture is concerned, which can have a rubber-like, gel-like, thick or paste-like (thickly viscous or highly viscous) consistency.

[0132] The coating solution is not necessarily a stably spreadable solution. These can be obtained by use of a coating solution, only after application and after removal of the solvent e.g. by drying.

[0133] With the melting method, stably spreadable solutions can mostly only be obtained by rapid cooling or shock-freezing of the melt of active substance and carrier. It is also possible to coat the balloon catheter by applying a melt of at least one anti-restenotic active substance and a carrier. In this case no further solvent is present.

[0134] Furthermore, the inventive coated catheter balloons without a crimped stent are in particular suitable for treatment of small vessels, preferably small blood vessels. Small vessels are those with a vessel diameter smaller than 2.5 mm, preferably smaller than 2.2 mm.

[0135] Moreover, the inventive coated catheter balloons without crimped stent are in particular suitable for treatment of periphery blood vessels, where the implantation of a stent is problematic.

[0136] The following examples show possible embodiments, but shall not limit the scope of protection to these concrete examples.

EXAMPLES

Example 1

Preparation of a Coating Solution of Paclitaxel (Ptx) and Dexpanthenol

[0137] Herefore 120 mg paclitaxel (Sigma-Aldrich Chemie GmbH, Germany) is dissolved in acetone. Likewise 30 mg dexpanthenol (Cal Roth GmbH, Germany) is dissolved in 500 µl ethanol. Afterwards both solutions are combined.

Example 2A

Preparation of a Coating Solution of Paclitaxel (Ptx) and PEG (1:2:2 w:w:w)

[0138] Herefore 100 mg paclitaxel and 200 mg PEG A and 200 mg PEG B are dissolved in 1000 µl acetone.

[0139] PEG A is PEG 400 (Sigma-Aldrich Chemie GmbH, Germany) and has a molecular mass between 380 and 420 and an average molecular mass M_n of 400.

[0140] PEG B is a polyethylene glycol (Sigma-Aldrich Chemie GmbH, Germany) with a molecular mass between 950 and 1050.

Example 2B

Preparation of a Coating Solution of Sirolimus and PEG (1:2:2 w:w:w)

[0141] Herefore 100 mg sirolimus (Merck4Biosciences, Germany) is dissolved in ethyl acetate and 200 mg PEG A and 200 mg PEG B are dissolved in 1000 µl absolute ethanol. Both solutions are combined.

Example 3

Complete Coating of a Folding Balloon with a Coating Solution of PEG/Paclitaxel According to Example 2A

[0142] The folding balloon is held in a horizontal position on a revolvable axis and sprayed with active substance containing solution. The solvent is evaporated afterwards in a drying chamber at 70° C. for 30 min.

[0143] Subsequently, if desired, a coated or uncoated (bare stent) stent can be crimped thereon. There is also the possibility to coat a hemocompatible coated stent with the coating of choice by pipetting method or spray method, while it is crimped on the already coated balloon catheter.

Example 4

Coating of a Folding Balloon with a Coating Solution of Paclitaxel/Dexpanthenol According to Example 1 in the Folds of the Balloon

[0144] The folding balloon is held in a horizontal position on a revolvable axis, such that the fold to be filled always comes to rest on the upper side. Each fold is then filled step by step with the viscous active substance containing solution of example 1 by filling each fold slowly from the beginning of the fold to the end of the fold with a Teflon cannula as extension to a needle tip and subsequent drying in a drying chamber at 70° C. for 30 min. The result is a folding balloon, wherein exclusively the folds are coated with a transparent, stably spreadable solution. This can be seen particularly well after dilatation. For a better quality control, a small amount of a couloring agent such as curcumin can be introduced.

[0145] Subsequently, if desired, a coated or uncoated (bare stent) stent can be crimped thereon. There is also the possibility to coat a hemocompatible coated stent with the coating of choice by pipetting method or spray method, while it is crimped on the already coated balloon catheter.

Example 5

Preparation of a Coating Solution of Paclitaxel and Vanilin

[0146] Herefore 100 mg paclitaxel is dissolved in 1000 µL acetone. Likewise 100 mg vanillin is dissolved in 500 µL ethanol. Afterwards both solutions are combined.

Example 6

Complete Coating of a Stent with a Coating Solution of Vanillin/Paclitaxel

[0147] Initially the stent is crimped on a folding balloon. The folding balloon with stent is held in a horizontal position on a revolvable axis and sprayed with active substance containing solution. The solvent is evaporated afterwards in a drying chamber at 80° C. for 30 min.

Example 7

Preparation of a Coating Solution of Rapamycin, Glycerine and Carrageenan

[0148] Herefore 100 mg rapamycin is dissolved in 500 μL ethanol and 500 μL glycerine is added. Therein 5 mg carrageenans are added.

Example 8

Complete Coating of a Folding Balloon with a Coating Solution of Rapamycin, Glycerine and Carrageenan

[0149] The folding balloon is held in a horizontal position on a revolvable axis and is slightly delated and then brushed with the active substance containing solution. The solvent is evaporated afterwards in a drying chamber at 60° C. for 20 min. After that the balloon is again folded. Subsequently, if desired, a coated or uncoated stent can be crimped thereon.

Example 9

Preparation of a Coating Solution of Paclitaxel (Ptx), Carbopol®980 and Mastix

[0150] Herefore 100 mg paclitaxel is dissolved in 1000 μL ethanol. This solution is mixed with 8 mg of molten chiosmastix (Sigma-Aldrich Chemie GmbH, Germany) (heated to approximately 80° C.). Likewise 20 mg Carbopol is dissolved in 500 μl water. Afterwards both solutions are combined.

Example 10

Complete Coating of a Folding Balloon with a Coating Solution of Paclitaxel (Ptx), Carbopol®980 and Mastix

[0151] The folding balloon is held in a horizontal position on a revolvable axis and sprayed with the active substance containing solution according to example 9. The solvent is evaporated afterwards in a drying chamber at 70° C. for 30 min.

[0152] Subsequently, if desired, a coated or uncoated (bare stent) stent can be crimped thereon. There is also the possibility to coat a hemocompatible coated stent with the coating of choice by pipetting method or spray method, while it is crimped on the already coated balloon catheter.

Example 11

Preparation of a Coating Solution of Paclitaxel (Ptx), Dexpanthenol and Ricinoleic Acid

[0153] Herefore 120 mg paclitaxel is dissolved in 1000 μL acetone. Likewise 30 mg dexpanthenol is dissolved in 500 μL ethanol. Afterwards both solutions are combined and 10 mg ricinoleic acid is added.

Example 12

Coating of a Folding Balloon with a Coating Solution of Paclitaxel/Dexpanthenol and Ricinoleic Acid in the Folds of the Balloon

[0154] The folding balloon is held in a horizontal position on a revolvable axis, such that the fold to be filled always comes to rest on the upper side. Each fold is then filled step by step with the viscous active substance containing solution of example 11 by filling each fold slowly from the beginning of the fold to the end of the fold with a Teflon cannula as extension to a needle tip and subsequent drying in a drying chamber at 70° C. for 30 min.

[0155] Subsequently, if desired, a coated or uncoated (bare stent) stent can be crimped thereon. There is also the possibility to coat a hemocompatible coated stent with the coating of choice by pipetting method or spray method, while it is crimped on the already coated balloon catheter.

Example 13

Preparation of a Coating Solution of Paclitaxel (Ptx), Polyethylene Glycol and Resorcin

[0156] Herefore 120 mg paclitaxel is dissolved in 800 μL ethanol and 2 mg resorcin is added (Merck4Biosciences, Germany). Likewise 200 mg PEG B (see example 2) is dissolved in 1000 μL acetone. Afterwards both solutions are combined.

Example 14

Coating of a Balloon Catheter with a Coating Solution of Paclitaxel (Ptx), Polyethylene Glycol and Resorcin

[0157] The balloon catheter is pinned through an adapter to the drive shaft of a rotation motor and is fixated in such a way that it comes to rest in the horizontal plane without being bended. After applying a small under pressure to the balloon, the whole balloon surface is coated with the solution by painting the balloon with a set number of paintings. By means of the dosage needle and the welded drag-wire, a drop of the solution is dragged over the rotating balloon, until the solvent is evaporated so far that a stably spreadable solution is formed. Afterwards, the catheter is taken from the machine and dried at 60° C. and further rotation over night.

[0158] Subsequently, if desired, a coated or uncoated (bare stent) stent can be crimped thereon. There is also the possibility to coat a hemocompatible coated stent with the coating of choice by pipetting method or spray method, while it is crimped on the already coated balloon catheter.

Example 15

Preparation of a Coating Solution of Rapamycin, Dexpanthenol and Isomalt

[0159] Herefore 150 mg rapamycin (Merck4Biosciences, Germany) is dissolved in 1000 μl ethyle acetate. Likewise 60 mg dexpanthenol is dissolved in 500 μL ethanol. Afterwards both solutions are combined and 5 mg isomalt (Carl Roth GmbH, Germany) is added.

Example 16

Coating of a Stent with a Coating Solution of Rapamycin/Dexpanthenol and Isomalt in the Folds of a Balloon

[0160] After cleaning the stents, a first layer of the coating solution from example 15 is sprayed on the stent. After drying this layer at room temperature, a second layer of the coating solution from example 15 is sprayed on the stent and then the stent is dried in a drying chamber at 70° for 30 min.

[0161] Subsequently, if desired, a coated or uncoated (bare stent) stent can be crimped thereon. There is also the possibility to coat a hemocompatible coated stent with the coating of choice by pipetting method or spray method, while it is crimped on the already coated balloon catheter.

Example 17

Investigations on the Adhesive Properties of a Coating

[0162] Herefore a blood vessel is extracted from a pig and stored in physiological saline solution, which shall also perfuse through the vessel. Subsequently, the balloon catheter is expanded in the vessel and the amount of coating adhered to as well as remaining on the balloon catheter is determined. This test showed that all catheter balloons, which were manufactured according to the examples, only had small amounts (<15%) of the coating remaining on the balloon surface.

Example 18

Covalent Hemocompatible Coating of Stents

[0163] Not-expanded, cleaned stents made of medical stainless steel LVM 316 were dipped for 5 minutes in a 2% solution of 3 aminopropyltriethoxysilane in a mixture of ethanol/water (50/50: (v/v)) and dried afterwards. Subsequently, the stents were washed over night with demineralized water.

[0164] 3 mg desulfated and reacetylated heparin is dissolved in 30 ml 0.1 M MES buffer (2 (N-morpholino) ethane sulfonic acid) pH 4.75 and mixed with 30 mg N-cyclohexyl-N' (2-morpholinoethyl) carbodiimide-methyl p toluenesulfonate. The stents were stirred in this solution at 4° C. over night. This was followed by extensive washing with water and 4M NaCl-solution.

[0165] Further modifications and alternative embodiments of various aspects of the invention will be apparent to those skilled in the art in view of this description. Accordingly, this description is to be construed as illustrative only and is for the purpose of teaching those skilled in the art the general manner of carrying out the invention. It is to be understood that the forms of the invention shown and described herein are to be taken as examples of embodiments. Elements and materials may be substituted for those illustrated and described herein, parts and processes may be reversed, and certain features of the invention may be utilized independently, all as would be apparent to one skilled in the art after having the benefit of this description of the invention. Changes may be made in the elements described herein without departing from the spirit and scope of the invention as described in the following claims.

1. Medical device, wherein the surface of the device is coated completely or partially with a stably spreadable solution containing at least one molecular-disperse distributed active substance and at least one carrier.

2. Medical device according to claim **1**, wherein the proportion of the at least one active substance and the at least one carrier ranges from 90% by weight of the active substance to 10% by weight of the carrier to 10% by weight of the active substance to 90% by weight of the carrier.

3. Medical device according to claim **1**, wherein the at least one carrier is selected from the group comprising or consisting of polyether, polylactonic acid, polyethylene glycol, poly (N-vinyl) pyrrolidone, N-dodecyl pyrrolidone, N-decyl pyrrolidone, N-octyl pyrrolidone, polyvinyl alcohols, derivatives of polyvinyl alcohols, glycolated polyester, polyphosphoester, polyethylene oxide propylene oxide, polyethylene oxide, hyaluronic acid, copolymers with PEG and polypropylene glycol, lipids, phospholipids, polyacrylic acid, polyacrylates, carboxymethyl chitosane, lanolin, vanillin, sorbitol, gelatine, derivatives of gelatine, fatty acid partial glycerides with a monocontent of 50 to 95 w.-%, highly disperse silicion oxide, cellulose, derivatives of cellulose, hydroxypropyl cellulose, ethyl cellulose, starch, derivatives of starch, dextrines, dextranes, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, dimethyl-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, steroles, cholesterol, bile acids, cholic acid, lithocholic acid, N-alkyl lactames, N-dodecyl caprolactam, N-decyl caprolactam, N-octyl caprolactam, N-dodecyl valerolactam, N-decyl valerolactam, N-octyl valerolactam, polyoxyethylene sorbitan monolaurates, polyoxyethylene sorbitan monopalmitates, polyoxyethylene sorbitan monostearate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, polyoxyethylene oleyl ether, polyoxyethylene oleyl ether, bis-[alpha-methyl-(4-methyl-benzyl)]-phenyl-polyglycol ether, bis-[alpha-methyl-(4-n-dodecyl)]-phenyl-polyglycol ether, bis-(4-methyl-benzyl)-phenyl-polyglycol ether, bis-(4-n-dodecyl-benzyl)-phenyl-polyglycol ether, tris-[alpha-methyl-(4-methyl-benzyl)]-phenyl-polyglycol ether, nonylphenolic polyglycol ether and nonylphenolic diglycol ether.

4. Medical device according to claim **3**, wherein the at least one carrier is dexpanthenol, hyaluronic acid, vanillin, carboxymethyl chitosan or PEG.

5. Medical device according to claim **1**, wherein the stably spreadable solution on the surface of the device further contains at least one adjuvant.

6. Medical device according to claim **5**, wherein the adjuvant is a crystallization inhibitor and/or thickener.

7. Medical device according to claim **5**, wherein the at least one adjuvant is selected from the group comprising or consisting of: agar, alginic acid, chicle, dammar, althaea extract, gellan gum (E 418), guar gum (E 412), gum Arabic (E 414), gum from plantago, gum from spruce juice, locust bean gum (E 410), karaya (E 416), konjac flour (E 425), mastix, pectin, tara gum (E 417), tragacanth (E 413), xanthan (E 415), carrageenan, cellulose, cellulose ether, gelatin, sago and starch.

8. Method for coating a catheter balloon comprising the following steps:

a) Providing an uncoated catheter balloon with or without a stent, and

b) providing a coating solution containing at least one anti-restenotic active substance and a carrier in at least one solvent, and

c) applying the coating solution of at least one active substance and the carrier by spraying, dipping, spreading, brushing, pipetting, chemical vapor deposition or squirting and

d) evaporating the solvent or drying at elevated temperature and/or under reduced pressure.

9. Coated catheter balloon with or without a stent obtainable by the method according to claim **8**.

10. Medical device according to claim **1**, wherein the medical device is a catheter balloon with or without a stent.

11. Catheter balloon according to claim **10**, wherein the at least one active substance is anti-restenotic and is selected from the group comprising or consisting of: paclitaxel, docetaxel, sirolimus, biolimus A9, zotarolimus, everolimus, myolimus, novolimus, pimecrolimus, tacrolimus, ridaforolimus, temsirolimus, cyclosporine, vitamin K, propofol and diazepam.

12. Catheter balloon according to claim **11**, wherein the at least one anti-restenotic active substance is paclitaxel.

13. Catheter balloon according to claim **11**, wherein the at least one anti-restenotic active substance is sirolimus.

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