

MEDICAL PRODUCTS COMPRISING A HAEMOCOMPATIBLE COATING, PRODUCTION AND USE THEREOF

Description

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The invention concerns the utilisation of polysaccharides containing the sugar building block N-acylglucosamine for the preparation of hemocompatible surfaces of medical devices, methods for the hemocompatible coating of surfaces with said polysaccharides as well as medical devices with these hemocompatible surfaces.

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In the human body the blood gets only in cases of injuries in contact with surfaces other than the inside of natural blood vessels. Consequently the blood coagulation system gets always activated to reduce the bleeding and to prevent a life-threatening loss of blood, if blood gets in contact with foreign surfaces. Due to the fact that an implant also represents a foreign surface, all patients, who receive an implant, which is in permanent contact with blood, are treated for the duration of the blood contact with drugs, so called anticoagulants, that suppress the blood coagulation, so that considerable side effects have to be taken in account.

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20 Whilst the usage of vessel supports, so-called stents, the described risk of thrombosis also occurs as one of the risk factors in blood bearing vessels. In cases of vessel strictures and sealings due to e.g. arteriosclerotic changes especially of the coronary arteries the stent is used for the expansion of the vessel walls. It fixes lime fragments in the vessels and improves the flow properties of the blood inside the vessel as it smoothens the surface of the interior space of the vessel. Additionally a stent leads to a resistance against elastic restoring forces of the expanded vessel part. The utilised material is mostly medicinal stainless steel.

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The stent thrombosis occurs in less than one percent of the cases already in the cardio catheter laboratory as early thrombosis or in two to five percent of the cases during the hospital recreation. In about five percent of the cases vessel injuries due to the intervention are caused because of the arterial lock and the possibility of causing pseudo-aneurysms by the expansion of vessels exists, too. Additionally the continuous application of heparin as anticoagulant increases the risk of bleeding.

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35 An additional and very often occurring complication is restenosis, the resealing of the vessel. Although stents minimise the risk of a renewed sealing of the vessel

they are until now not totally capable of hindering the restenosis. The rate of resealing (restenosis) after implantation of a stent is with up to 30 % one of the main reasons of a repeated hospital visit for the patients.

- 5 An exact conceptual description of the restenosis does not exist in the professional literature. The mostly used morphologic definition of the restenosis is that after a successful PTA (percutaneous transluminal angioplasty) the restenosis is defined as a reduction of the vessel diameter to less than 50 % of the normal one. This is an empirically defined value of which the hemodynamic relevance and
10 its relation to clinical symptomatics lacks of a massive scientific basis. In praxis the clinical aggravation of the patient is often viewed as a sign for a restenosis of the formerly treated vessel part.

- The vessel injuries caused during the implantation of the stents arise inflammation
15 reactions, which play an important role for the healing process during the first seven days. The herein concurrent processes are among others connected with the release of growth factors, which initiate an increased proliferation of the smooth muscle cells and lead with this to a rapid restenosis, a renewed sealing of the vessel because of uncontrolled growth. Even after a couple of weeks, when
20 the stent is grown into the tissue of the blood vessel and totally surrounded by smooth muscle cells, cicatrizations can be too distinctive (neointima hyperplasia) and lead to not only a coverage of the stent surface but to the sealing of the total interior space of the stent.

- 25 It was tried vainly to solve the problem of restenosis by the coating of the stents with heparin (J. Whörle et al., European Heart Journal (2001) 22, 1808-1816). Heparin addresses as anticoagulant only the first mentioned cause and is moreover able to unfold its total effect only in solution. This first problem is meanwhile almost totally avoidable medicamentously by application of
30 anticoagulants. The further problem is intended to be solved now by inhibiting the growth of the smooth muscle cells locally on the stent. This is carried out by e.g.. radioactive stents or stents, which contain pharmaceutical active agents.

- Consequently there is a demand on non-thrombogeneous, hemocompatible
35 materials, which are not detected as foreign surface and in case of blood contact does not activate the coagulation system and lead to the coagulation of the blood, with which an important factor for the restenosis stimulating processes is eliminated. Support is supposed to be guaranteed by addition of active agents

which shall suppress the inflammation reactions or which shall control the healing process accompanying cell division.

5 The undertakings are enormous on this area of producing a stent which can reduce the restenosis in this manner or eliminate totally. Herein different possibilities of realisation are examined in numerous studies. The most common construction type consists of a stent, which is coated with a suitable matrix, usually a biostable polymer. The matrix includes an antiproliferative or antiphlogistic agent, which is released in temporally controlled steps and shall suppress the
10 inflammation reactions and the excessive cell division.

US-A-5 891 108 reveals for example a hollow moulded stent, which can contain pharmaceutical active agents in its interior, that can be released throughout a various number of outlets in the stent. Whereas EP-A-1 127 582 describes a stent
15 that shows on its surface ditches of 0.1 – 1 mm depth and 7 – 15 mm length, which are suitable for the implementation of an active agent. These active agent reservoirs release, similarly to the outlets in the hollow stent, the contained pharmaceutical active agent in a punctually high concentration and over a relatively long period of time, which leads to the fact, that the smooth muscle cells
20 are not anymore or only very delayed capable of enclosing the stent. As a consequence the stent is much longer exposed to the blood, what leads again to increased vessel sealings by thrombosis (Liistro F., Colombo A., Late acute thrombosis after paclitaxel eluting stent implantation. Heart (2001) 86 262-4).

25 One approach to this problem is represented by the phosphorylcholine coating of Biocompatibles (WO 0101957), as here phosphorylcholine, a component of the erythrocytic cell membrane, shall create a non thrombogeneous surface as ingredient of the coated non biodegradable polymer layer on the stent. Dependent of its molecular weight the active agent is absorbed by the polymer containing
30 phosphorylcholine layer or adsorbed on the surface.

Disclosed herein are hemocompatibly coated medical devices as well as methods of hemocompatible coating and the use of hemocompatibly coated medical devices, especially stents, to prevent or reduce
35 undesired reactions as for example restenosis.

Disclosed further are stents which permit a continuous controlled ingrowth of the stent – on the one side by suppression of

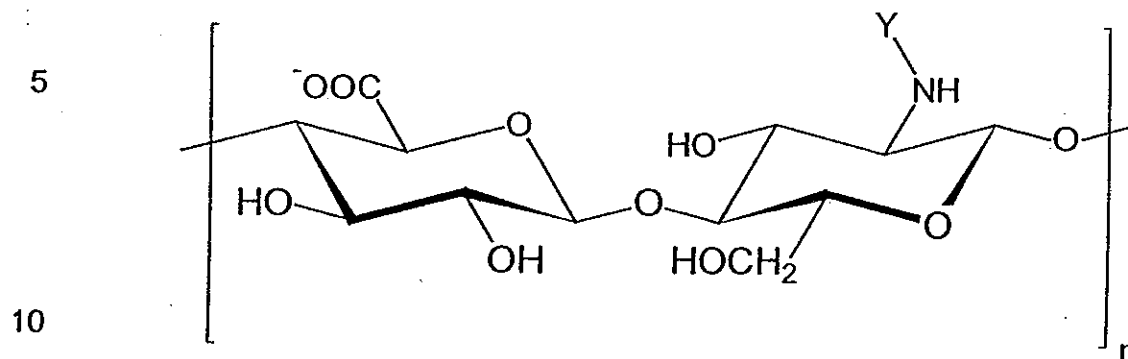
the cellular reactions in the primal days and weeks after implantation by the support of the selected agents and agent combinations and on the other side by providing an athrombogeneous resp. inert resp. biocompatible surface, which guarantees that with the decrease of the agent's influence no reactions to the existing foreign surface take place which also can lead to complications in a long term.

The intentions of creating a nearly perfect simulation of the native athrombogeneous conditions of that part of a blood vessel that is allocated on the blood side are enormous. EP-B-0 333 730 describes a process to produce hemocompatible substrates by recess, adhesion and/or modification and anchorage of non thrombogeneous endothelic cell surface polysaccharide (HS I). The immobilisation of this specific endothelic cell surface proteoheparane sulphate HS I on biological or artificial surfaces effects that suchlike coated surfaces get blood compatible and suitable for the permanent blood contact. A disadvantage whereas is, that this process for the preparation of HS I premises the cultivation of endothelic cells, so that the economical suitability of this process is strongly limited, because the cultivation of endothelic cells is time taking and greater amounts of cultivated endothelic cells are only obtainable with immense expenditure.

Disclosed are medical devices that show properties of a surface coating of determined polysaccharides and paclitaxel. Instead of or together with paclitaxel determined other antiphlogistic as well as anti-inflammatory drugs resp. agent combinations of simvastatine, 2-methylthiazolidine-2,4-dicarboxylic acid and the correspondent sodium salt), macrocyclic suboxide (MCS) and its derivatives, tyrphostines, D24851, thymosin a-1, interleucine-1 β inhibitors, activated protein C (aPC), MSH, fumaric acid and fumaric acid ester, PETN (pentaerythritol tetranitrate), PI88, dermicidin, baccatin and its derivatives, docetaxel and further derivatives of paclitaxel, tacrolimus, pimecrolimus, trapidil, a- and β -estradiol, sirolimus, colchicin, and melanocyte-stimulating hormone (α -MSH) can be used. Methods for the production of these hemocompatible surfaces are described herein. Preferred embodiments can be found in the dependent claims, the examples as well as the figures.

Disclosed further are medical devices the surface of which is at least partially covered with a hemocompatible layer, wherein the hemocompatible layer comprises at least one compound of the formula 1:

formula 1



wherein

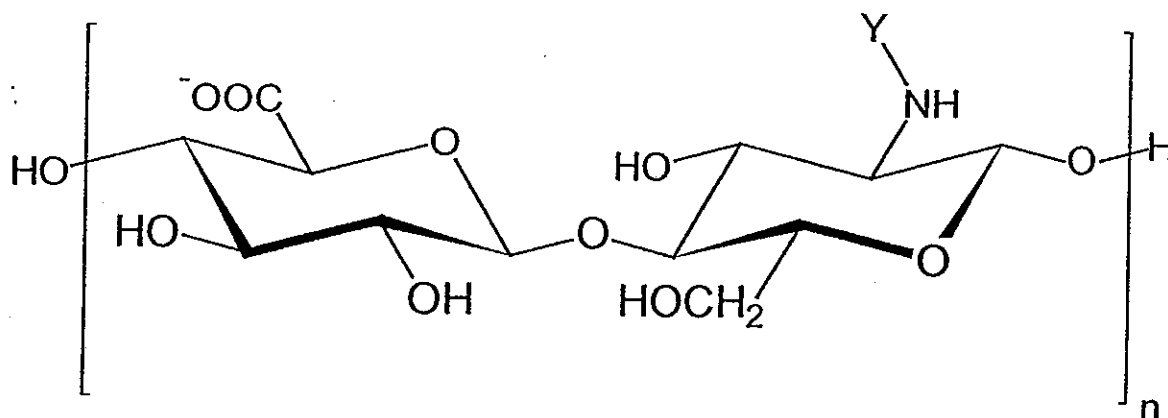
n is an integer between 4 and 1050 and

Y represents the residues $-\text{CHO}$, $-\text{COCH}_3$, $-\text{COC}_2\text{H}_5$, $-\text{COC}_3\text{H}_7$,
 15 $-\text{COC}_4\text{H}_9$, $-\text{COC}_5\text{H}_{11}$, $-\text{COCH}(\text{CH}_3)_2$, $-\text{COCH}_2\text{CH}(\text{CH}_3)_2$,
 $-\text{COCH}(\text{CH}_3)\text{C}_2\text{H}_5$, $-\text{COC}(\text{CH}_3)_3$, $-\text{CH}_2\text{COO}^-$, $-\text{C}_2\text{H}_4\text{COO}^-$, $-\text{C}_3\text{H}_6\text{COO}^-$,
 $-\text{C}_4\text{H}_8\text{COO}^-$.

It is also possible to use any salts of the compounds of formula 1. The
 20 hemocompatible layer can be added directly onto the surface of a preferably non
 hemocompatible medical device or deposited onto other biostable and/or
 biodegradable layers. Further on additional biostable and/or biodegradable and/or
 hemocompatible layers can be localised on the hemocompatible layer. In addition
 to this the active agent paclitaxel is present on, in and/or under the
 25 hemocompatible layer or the hemocompatible layers, respectively. The active
 agent (paclitaxel) can form herein an own active agent layer on or under the
 hemocompatible layer and/or can be incorporated in at least one of the biostable,
 biodegradable and/or hemocompatible layers. Preferably the compounds of the
 general formula 1 are used, wherein Y is one of the following groups: $-\text{CHO}$,
 30 $-\text{COCH}_3$, $-\text{COC}_2\text{H}_5$ or $-\text{COC}_3\text{H}_7$. Further on preferred are the groups $-\text{CHO}$,
 $-\text{COCH}_3$, $-\text{COC}_2\text{H}_5$ and especially preferred is the group $-\text{COCH}_3$.

Accordingly, a first aspect provides a medical device, wherein at least one part of the surface
 of the medical device is coated directly or via at least one interjacent biostable and/or
 biodegradable layer with a hemocompatible layer comprising at least one
 compound of the formula 1

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wherein

n represents an integer between 4 and 1050,

Y represents a residue $-\text{CHO}$, $-\text{COCH}_3$, $-\text{COC}_2\text{H}_5$, $-\text{COC}_3\text{H}_7$,
 $-\text{COC}_4\text{H}_9$, $-\text{COC}_5\text{H}_{11}$, $-\text{COCH}(\text{CH}_3)_2$, $-\text{COCH}_2\text{CH}(\text{CH}_3)_2$,
 $-\text{COCH}(\text{CH}_3)\text{C}_2\text{H}_5$, $-\text{COC}(\text{CH}_3)_3$, $-\text{CH}_2\text{COO}^-$, $-\text{C}_2\text{H}_4\text{COO}^-$, $-\text{C}_3\text{H}_6\text{COO}^-$,
 $-\text{C}_4\text{H}_8\text{COO}^-$,

as well as salts of these compounds,

and on, in and/or under the hemocompatible layer the active agent paclitaxel is present.

Accordingly, a second aspect provides a stent according to the medical device as defined above wherein the polymer is deposited in amounts between 0.01 mg to 3 mg / layer, preferred between 0.20 mg to 1 mg and especially preferred between 0.20 mg to 0.5 mg / layer.

Accordingly, a third aspect provides a method for the hemocompatible coating of biological and/or artificial surfaces of medical devices comprising the following steps: a) providing a surface of a medical device and b) deposition of at least one compound of the general formula 1 according to the first aspect as hemocompatible layer on this surface and/or b') deposition of a biostable and/or biodegradable layer on the surface of the medical device or the hemocompatible layer.

Accordingly, a fourth aspect provides a method as defined above comprising the further step c): c. deposition of paclitaxel in and/or on the hemocompatible layer or the biostable and/or biodegradable layer.

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Accordingly, a fifth aspect provides a method as defined above, comprising the further step d) or d'): d. deposition of at least one biodegradable layer and/or at least one biostable and/or biodegradable layer on the hemocompatible layer or the layer of paclitaxel respectively, or d') deposition of at least one compound of the general formula 1 according to claim 1 as hemocompatible layer on the biostable and/or biodegradable layer or the layer of paclitaxel.

Accordingly, a sixth aspect provides a method as defined above, comprising the further step e.):

e. deposition of paclitaxel in and/or on the at least one biodegradable and/or biostable layer or the hemocompatible layer.

Accordingly, a seventh aspect provides a medical device available by one method as defined above.

35 The compounds of the general formula 1 contain only a small amount of free amino groups. Because of the fact that with the ninhydrine reaction free amino groups could not be detected anymore, due to the sensitivity of this test it can be implied that less than 2%, preferred less than 1% and especially preferred less than 0.5% of all $-NH-Y$ groups are present as free amino groups, i.e. within this low percentage of the $-NH-Y$ groups Y represents hydrogen.

Because polysaccharides of the general formula 1 contain carboxylate groups and amino groups, the general formula covers alkali as well as alkaline earth metal salts of the corresponding polysaccharides. Alkali metal salts like the sodium salt, the potassium salt, the lithium salt or alkaline earth metal salts like the magnesium salt or the calcium salt can be mentioned. Further on with ammonia, primary, secondary, tertiary and quaternary amines, pyridine and pyridine derivatives ammonium salts, preferably alkylammonium salts and pyridinium salts can be formed. Among the bases, which form salts with the polysaccharides, are inorganic and organic bases as for example NaOH, KOH, LiOH, CaCO₃, Fe(OH)₃, NH₄OH, tetraalkylammonium hydroxide and similar compounds.

The polysaccharides according to formula 1 possess molecular weights from 2 kD to 15 kD, preferred from 4 kD to 13 kD, more preferred from 6 kD to 12 kD and especially preferred from 8 kD to 11 kD. The variable n is an integer in the range of 4 to 1050. Preferred n is an integer from 9 to 400, more preferred an integer from 14 to 260 and especially preferred an integer between 19 and 210.

The general formula 1 shows a disaccharide, which has to be viewed as the basic module for the used polysaccharides and that forms the polysaccharide by the n-fold (multiple) sequencing of the basic module. This basic module which is built of two sugar molecules shall not be interpreted in the manner, that the general formula 1 only includes polysaccharides with an even number of sugar molecules. The formula implements of course also polysaccharides with an odd number of sugar building units. The end groups of the polysaccharides are represented by hydroxyl groups.

Especially preferred are medical devices which contain immediately on the surface of the medical device a hemocompatible layer consisting of the compounds according to formula 1 and above it a layer of paclitaxel. The paclitaxel layer can diffuse partially into the hemocompatible layer or get taken up totally by the hemocompatible layer.

It is further preferred, if at least one biostable layer is present under the hemocompatible layer. In addition the hemocompatible layer can be coated totally and/or partially with at least one more, above lying biostable and/or biodegradable layer. Preferred is an external biodegradable or hemocompatible layer.

A further preferred embodiment contains a layer of paclitaxel under the hemocompatible layer or between the biostable and the hemocompatible layer, so that paclitaxel is released slowly through the hemocompatible layer. Paclitaxel can be bound covalently and/or adhesively in and/or on the hemocompatible layer and/or the biostable and/or the biodegradable layer, in which the adhesive bonding is preferred.

As biodegradable substances for the biodegradable layer(s) can be used: polyvalerolactones, poly- ϵ -decalactones, polylactonic acid, polyglycolic acid, polylactides, polyglycolides, copolymers of the polylactides and polyglycolides, poly- ϵ -caprolactone, polyhydroxybutanoic acid, polyhydroxybutyrates, polyhydroxyvalerates, polyhydroxybutyrate-co-valerates, poly(1,4-dioxane-2,3-diones), poly(1,3-dioxane-2-one), poly-para-dioxanones, polyanhydrides such as polymaleic anhydrides, polyhydroxymethacrylates, fibrin, polycyanoacrylates, polycaprolactonedimethylacrylates, poly-b-maleic acid, polycaprolactonebutylacrylates, multiblock polymers such as e.g. from oligocaprolactonedioles and oligodioxanonedioles, polyether ester multiblock polymers such as e.g. PEG and poly(butyleneterephthalates), polypivotolactones, polyglycolic acid trimethylcarbonates, polycaprolactone-glycolides, poly(g-ethylglutamate), poly(DTH-iminocarbonate), poly(DTE-co-DT-carbonate), poly(bisphenol-A-iminocarbonate), polyorthoesters, polyglycolic acid trimethylcarbonates, polytrimethylcarbonates, polyiminocarbonates, poly(N-vinyl)-pyrrolidone, polyvinylalcoholes, polyesteramides, glycolated polyesters, polyphosphoesters, polyphosphazenes, poly[p-carboxyphenoxy]propane], polyhydroxypentanoic acid, polyanhydrides, polyethyleneoxide-propyleneoxide, soft polyurethanes, polyurethanes with amino acid residues in the backbone, polyether esters such as polyethyleneoxide, polyalkeneoxalates, polyorthoesters as well as their copolymers, lipides, carrageenans, fibrinogen, starch, collagen, protein based polymers, polyamino acids, synthetic polyamino acids, zein, modified zein, polyhydroxyalkanoates, pectic acid, actinic acid, modified and non modified fibrin and casein, carboxymethylsulphate, albumin, moreover hyaluronic acid, chitosan and its derivatives, heparansulphates and its derivatives, heparins, chondroitinsulphate, dextran, b-cyclodextrins, copolymers with PEG and polypropyleneglycol, gummi arabicum, guar, gelatine, collagen, collagen-N-hydroxysuccinimide, lipids, phospholipids, modifications and copolymers and/or mixtures of the afore mentioned substances.

As biostable substances for the biostable layer(s) can be used: polyacrylic acid and polyacrylates as polymethylmethacrylate, polybutylmethacrylate, polyacrylamide, polyacrylonitriles, polyamides, polyetheramides, polyethylenamine, polyimides, polycarbonates, polycarbourethanes, polyvinylketones, polyvinylhalogenides, polyvinylidenhalogenides, polyvinylethers, polyisobutylenes, polyvinylaromates, polyvinylesters, polyvinylpyrrolidones, polyoxymethylenes, polytetramethyleneoxide, polyethylene, polypropylene, polytetrafluoroethylene, polyurethanes, polyetherurethanes, silicone-polyetherurethanes, silicone-polyurethanes, silicone-polycarbonate-urethanes, polyolefine elastomeres, polyisobutylenes, EPDM gums, fluorosilicones, carboxymethylchitosanes, polyaryletheretherketones, polyetheretherketones, polyethylenterephthalate, polyvalerates, carboxymethylcellulose, cellulose, rayon, rayontriacetates, cellulosenitrates, celluloseacetates, hydroxyethylcellulose, cellulosebutyrates, celluloseacetatebutyrates, ethylvinylacetate copolymers, polysulphones, epoxy resins, ABS resins, EPDM gums, silicones as polysiloxanes, polydimethylsiloxanes, polyvinylhalogenes and copolymers, celluloseethers, cellulosetriacetates, chitosanes and copolymers and/or mixtures of these substances.

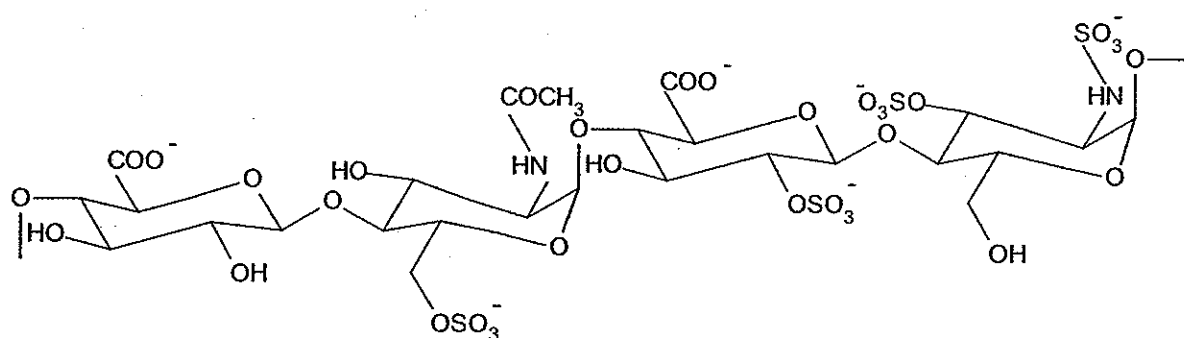
It is possible to furnish any medical devices with the herein disclosed hemocompatible surfaces, especially those, which shall be suitable for the short- or the longterm contact with blood or blood products. Such medical devices are for example prostheses, organs, vessels, aortas, heart valves, tubes, organ spareparts, implants, fibers, hollow fibers, stents, hollow needles, syringes, membranes, tinned goods, blood containers, titrimetric plates, pacemakers, adsorbing media, chromatography media, chromatography columns, dialyzers, connexion parts, sensors, valves, centrifugal chambers, recuperators, endoscopes, filters, pump chambers. The present invention is especially related to stents.

The polysaccharides of formula 1 can be formed from heparin and/or heparansulphates. These materials are in structurally view quite similar compounds. Heparansulphates occur ubiquitously on cell surfaces of mammals. In dependence from the cell type they differ strongly in molecular weight, degree of acetylation and degree of sulphation. Heparansulphate from liver shows for example an acetylation coefficient of about 50%, whereas the heparansulphate of the glycocalix from endothelial cells can exhibit an acetylation coefficient from about 90% and higher. Heparin shows only a quite low degree of acetylation from

about up to 5%. The sulphation coefficient of the heparansulphate from liver and of heparin is ~ 2 per disaccharide unit, in case of heparansulphate from endothelial cells close to 0 and in heparansulphates from other cell types between 0 and 2 per disaccharide unit.

The compounds of the general formula 1 are characterized by an amount of sulphate groups per disaccharide unit of less than 0.05. Further on the amount of free amino groups in these compounds is less than 1% based on all -NH-Y groups.

The following image shows a tetrasaccharide unit of a heparin or a heparansulphate with random orientation of the sulphate groups and with a sulphation coefficient of 2 per disaccharide unit as it is typical for heparin:



All heparansulphates have with heparin a common sequence in biosynthesis. First of all the core protein with the xylose-containing bonding region is formed. It consists of the xylose and two galactose residues connected to it. To the last of the two galactose units a glucuronic acid and a galactosamine is connected alternately until the adequate chain length is reached. Finally, a several step enzymatic modification of this common polysaccharide precursor of all heparansulphates and of heparin follows by means of sulphotransferases and epimerases which generate by their varying completeness of transformation the broad spectra of different heparansulphates up to heparin.

Heparin is alternately build of D-glucosamine and D-glucuronic acid resp. L-iduronic acid, in which the amount of L-iduronic acid is up to 75%. D-glucosamine and D-glucuronic acid are connected in a β -1,4-glycosidic resp. L-iduronic acid in an α -1,4-glycosidic bonding to the disaccharide, that forms the heparin subunits. These subunits are again connected to each other in a β -1,4-glycosidic way and

lead to heparin. The position of the sulphonyl groups is variable. In average one tetrasaccharide unit contains 4 to 5 sulphuric acid groups. Heparansulphate, also named as heparitinsulphate, contains with exception of the heparansulphate from liver less N- and O-bound sulphonyl groups as heparin but in exchange more N-
5 acetyl groups. The amount of L-iduronic acid compared to heparin is also lower.

As it is evident from figure 1 the compounds of the general formula (cf. figure 1b as example) are structurally similar to the natural heparansulphate of endothelial cells, but avoid the initially mentioned disadvantages by the use of endothelial cell
10 heparan sulphates.

For the antithrombotic activity a special pentasaccharide unit is made responsible, which can be found in commercial heparin preparations in about every 3rd molecule. Heparin preparations of different antithrombotic activity can be
15 produced by special separation techniques. In highly active, for example by antithrombin-III-affinitychromatography obtained preparations („High-affinity“-heparin) this active sequence is found in every heparin molecule, while in „No-affinity“-preparations no characteristical pentasaccharide sequences and thus no active inhibition of coagulation can be detected. Via interaction with this
20 pentasaccharide the activity of antithrombin III, an inhibitor of the coagulation key factor thrombin, is essentially exponentiated (bonding affinity increase up to the factor 2×10^3) [Stiekema J.C.J.; *Clin Nephrology* 26, Suppl. Nr 1, S3-S8, (1986)].

The amino groups of the heparin are mostly N-sulphated or N-acetylated. The
25 most important O-sulphation positions are the C2 in the iduronic acid as well as the C6 and the C3 in the glucosamine. For the activity of the pentasaccharide onto the plasmatic coagulation basically the sulphate group on C6 is made responsible, in smaller proportion also the other functional groups.

30 Surfaces of medicinal implants coated with heparin or heparansulphates are and remain only conditionally hemocompatible by the coating. The heparin or heparansulphate which is added onto the artificial surface loses partially in a drastic measure its antithrombotic activity which is related to a restricted interaction due to steric hindrance of the mentioned pentasaccharide units with
35 antithrombin III. Because of the immobilisation of these polyanionic substances a strong adsorption of plasma protein on the heparinated surface is observed in all cases what eliminates on the one hand the coagulation suppressing effect of heparin resp. of heparansulphates and initialises on the other hand specific

coagulation processes by adherent and hereby tertiary structure changing plasma proteins (e.g. albumin, fibrinogen, thrombin) and hereon adherent platelets.

Thus a correlation exists on the one hand between the limited interaction of the pentasaccharide units with antithrombin III by immobilisation on the other hand depositions of plasma proteins on the heparin- resp. heparansulphate layer on the medicinal implant take place, which leads to the loss(es) of the antithrombotic properties of the coating and which can even turn into the opposite, because the plasma protein adsorption, that occurs during a couple of seconds leads to the loss of the anticoagulational surface and the adhesive plasma proteins change their tertiary structure, whereby the antithrombogenicity of the surface turns vice versa and a thrombogenic surface arises. Surprisingly it could be detected, that the compounds of the general formula 1, despite of the structural differences to the heparin resp. heparansulphate, still show the hemocompatible properties of heparin and additionally after the immobilisation of the compounds no noteworthy depositions of plasma proteins, which represent an initial step in the activation of the coagulation cascade, could be observed. The hemocompatible properties of the compounds according to invention still remain also after their immobilisation on artificial surfaces.

Further on it is supposed that the sulphate groups of the heparin resp. the heparansulphates are necessary for the interaction with antithrombin III and impart thereby the heparin resp. the heparansulphate the anticoagulatory effect. The inventive compounds are not actively coagulation suppressive, i.e. anticoagulative, due to an almost complete desulphation the sulphate groups of the compounds are removed up to a low amount of below 0.2 sulphate groups per disaccharide unit.

The compounds of the general formula 1 can be generated from heparin or heparansulphates by first substantially complete desulphation of the polysaccharide and subsequently substantially complete N-acylation. The term "substantially completely desulphated" refers to a desulphation degree of above 90%, preferred above 95% und especially preferred above 98%. The desulphation coefficient can be determined according to the so-called ninhydrin test which indicates free amino groups. The desulphation takes place in the way as with DMMB (dimethylmethylen blue) no colour reaction is obtained. This colour test is suitable for the indication of sulphated polysaccharides but its detection limit is not known in technical literature. The desulphation can be carried out for example by

pyrolysis of the pyridinium salt in a solvent mixture. Especially a mixture of DMSO, 1,4-dioxane and methanol has proven of value.

Heparansulphates as well as heparin were desulphated via total hydrolysis and subsequently reacylated. Thereafter the number of sulphate groups per disaccharide unit (S/D) was determined by ^{13}C -NMR. The following table 1 shows these results on the example of heparin and desulphated, reacylated heparin (Ac-heparin).

Tab. 1: Distribution of functional groups per disaccharide unit on the example of heparin and Ac-heparin as determined by ^{13}C -NMR-measurements.

	2-S	6-S	3-S	NS	N-Ac	NH ₂	S/D
Heparin	0.63	0.88	0.05	0.90	0.08	0.02	2.47
Ac-heparin	0.03	0	0	0	1.00	-	0.03

2-S, 3-S, 6-S: sulphate groups in position 2, 3, 6 respectively

NS: sulphate groups on the amino groups

N-Ac: acetyl groups on the amino groups

NH₂: free amino groups

S/D: sulphate groups per disaccharide unit

A sulphate content of about 0.03 sulphate groups / disaccharide unit (S/D) in case of Ac-heparin in comparison with about 2.5 sulphate groups / disaccharide unit in case of heparin was reproducibly obtained.

As described above the difference in the sulphate contents of heparin resp. heparansulphates has a considerable influence on the activity adverse to antithrombin III and the coagulatory effects of these compounds. These compounds have a content of sulphate groups per disaccharide unit of less than 0.2, preferred less than 0.07, more preferred less than 0.05 and especially preferred less than 0.03 sulphate groups per disaccharide unit.

By the removal of the sulphate groups of heparin, to which the active coagulation suppressive working mechanism is accredited to, one receives for a surface refinement suitable hemocompatible, coagulation inert oligo- resp. polysaccharide which on the one hand has no active role in the coagulation process and which on the other hand is not detected by the coagulation system as foreign surface. Accordingly this coating imitates successfully the nature given highest standard of

hemocompatibility and passivity against the coagulation active components of the blood. The examples 3 and 4 clarify, that surfaces, which are coated with the compounds according to invention, especially are coated covalently, result in a passivative, athrombogeneous and hemocompatible coating. This is definitely proven by the example of Ac-heparins.

Substantially completely N-acylated refers to a degree of N-acylation of above 94%, preferred above 97% and especially preferred above 98%. The acylation runs in such a way completely that with the ninhydrin reaction for detection of free amino groups no colour reaction is obtained anymore. As acylation agents are preferably used carboxylic acid chlorides, -bromides or -anhydrides. Acetic anhydride, propionic anhydride, butyric anhydride, acetic acid chloride, propionic acid chloride or butyric acid chloride are for example suitable for the synthesis of the compounds according to invention. Especially suitable are carboxylic anhydrides as acylation agents.

As solvent especially for carboxylic acid anhydrides deionised water is used, especially together with a cosolvent which is added in an amount from 10 to 30 volume percent. As cosolvents are suitable methanol, ethanol, DMSO, DMF, acetone, dioxane, THF, ethyl acetate and other polar solvents. In case of the use of carboxylic acid halogenides preferably polar water free solvents such as DMSO or DMF are used.

The compounds of the general formula can comprise in the half of the sugar molecules a carboxylate group and in the other half a N-acyl group.

Disclosed herein is the use of the compounds with the general formula 1 as well as salts of these compounds for the coating, especially a hemocompatible coating of natural and/or artificial surfaces. Under "hemocompatible" the characteristic of the compounds according to invention is meant, not to interact with the compounds of the blood coagulation system or the platelets and so not to initiate the blood coagulation cascade.

In addition disclosed herein are polysaccharides for the hemocompatible coating of surfaces. Preferred are polysaccharides in the range of the above mentioned molecular weight limits. The used polysaccharides are characterised in that they contain the sugar building unit N-acylglucosamine in a great amount. This means that 40 to 60 % of the sugar building units are N-acylglucosamine and

substantially the remaining sugar building units bear each a carboxyl group. The polysaccharides consist generally in more than 95%, preferred in more than 98%, of only two sugar building units, whereas one sugar building unit bears a carboxyl group and the other one a N-acyl group.

5

One sugar building unit of the polysaccharides is N-acylglucosamine preferred N-acetylglucosamine and in case of the other one it is the uronic acids glucuronic acid and iduronic acid. Preferred are polysaccharides, which conspire substantially the sugar glucosamine, whereas substantially the half of the sugar building units bears a N-acyl group, preferred a N-acetyl group, and the other half of the glucosamine building units bears one carboxyl group which is bond directly by the amino group or by one or more methylenyl groups. In the case of these carboxylic acid groups bound to the amino group it is concerned to be preferred the carboxymethyl- or carboxyethyl groups. Furthermore, polysaccharides are preferred which substantially conspire in one half of N-acylglucosamine, preferred of N-acetylglucosamine and substantially conspire in the other half of the uronic acids glucuronic acid and iduronic acid. Especially preferred are the polysaccharides, that show a substantially alternating sequence of N-acylglucosamine and one of the both uronic acids.

20

Surprisingly it was shown, that for the applications according to invention especially desulphated and substantially N-acylated heparin is especially suitable. Especially N-acetylated heparin is suitable for the hemocompatible coating.

25 The term „substantially“ shall make clear, that statistical variations are to be taken into account. One substantially alternating sequence of the sugar building units implies, that generally no two equal sugar building units are bound to each other but does not exclude totally such a defect connection. In accordance “substantially the half” means almost 50% but allows small variations, because especially in the case of biosynthetically synthesised macromolecules the ideal case is never reached and some variations are always to be taken into account, because enzymes do not work perfectly and in catalysis always some error rate has to be anticipated. Whereas in case of natural heparin a strongly alternating sequence of N-acetylglucosamine and the uronic acid units is existing.

35

Furthermore, methods for hemocompatible coating of surfaces are disclosed which are especially destined for the direct blood contact. In case of these

methods a natural and/or artificial surface is provided and the above described polysaccharides are immobilised on this surface.

5 The immobilisation of the polysaccharides on these surfaces can be achieved via hydrophobic interactions, van der Waals forces, electrostatic interactions, hydrogen bonds, ionic interactions, cross-linking of the polysaccharides and/or by covalent bonding onto the surface. Preferred is the covalent linkage of the polysaccharides (side-on bonding), more preferred the covalent single-point linkage (side-on bonding) and especially preferred the covalent end-point linkage
10 (end-on bonding).

In the following the coating methods are described.

Biological and/or artificial surfaces of medical devices can be provided with a hemocompatible coating by means of the following method:

- 15 a) providing a surface of a medical device and
b) deposition of at least one compound of the general formula 1 according to claim 1 as hemocompatible layer onto this surface and/or
b') deposition of a biostable and/or biodegradable layer onto the surface of the medical device or the hemocompatible layer.

20 „Deposition“ shall refer to at least partial coating of a surface with the adequate compounds, wherein the compounds are positioned and/or immobilised or anyhow anchored on and/or in the subjacent surface.

25 Under “substantially the remaining sugar building units” is to be understood that 93% of the remaining sugar building units, preferred 96% and especially preferred 98% of the remaining 60% - 40% of the sugar building units bear a carboxyl group.

30 An uncoated and/or non hemocompatible surface is preferably provided. “Non hemocompatible” surfaces shall refer to such surfaces that can activate the blood coagulatory system, thus are more or less thrombogeneous.

An alternative embodiment comprises the steps:

- 35 a) providing surface of a medical device and
b) deposition of at least one inventive polysaccharide according to formula 1,
b') deposition of a biostable layer onto the surface of the medical device

and

- d') deposition of a further hemocompatible layer of at least one inventive polysaccharide according to formula 1.

5 The last-mentioned embodiment makes sure, even in the case of e.g. mechanical damage of the polymeric layer and therewith also of the exterior hemocompatible layer, that the surface coating does not lose its characteristic of being blood compatible.

10 Under "biological or artificial" surface is the combination of an artificial medical device with an artificial part to be understood, .e.g. pork heart with an artificial heart valve.

The single layers are deposited preferably by dipping or spraying methods,
15 whereas one can deposit also paclitaxel at the same time with the deposition of one layer onto the medical device surface, which is then implemented in the respective layer covalently and/or adhesively bound. In this way it is possible at the same time with the deposition of a hemocompatible layer onto the medical device to deposit the active agent paclitaxel. The substances for the biostable or
20 biodegradable layers were itemised already above.

Onto this first biostable and/or biodegradable or hemocompatible layer it is then possible in an additional non compulsory step c) to deposit an agent layer of paclitaxel. In a preferred embodiment paclitaxel is bound covalently on the
25 subjacent layer. Also paclitaxel is preferably deposited by dipping or spraying methods on and/or in the hemocompatible layer or the biostable layer.

After the step b) or the step c) an additional step d) can follow which implements the deposition of at least one biodegradable layer and/or at least one biostable
30 layer onto the hemocompatible layer resp. the layer of paclitaxel.

According to the alternative embodiments after step b') or step c) a step d') can follow which implements the deposition of at least one compound of the general formula 1 as hemocompatible layer onto the biostable and/or biodegradable layer
35 resp. the layer of paclitaxel. Preferably after step b') the step d') follows.

After step d) resp. d') the deposition of paclitaxel can take place into and/or onto the at least one biodegradable and/or biostable layer or the hemocompatible layer.

The single layers as well as paclitaxel are preferably deposited and/or implemented by dipping or spraying methods onto and/or into the subjacent layer.

5 According to a preferred embodiment the biostable layer is deposited on the surface of the medical device and completely or incompletely covered with a hemocompatible layer which (preferably covalently) is bound to the biostable layer.

10 Preferably the hemocompatible layer comprises heparin of native origin of regioselectively synthesised derivatives of different sulphation coefficients (sulphation degrees) and acylation coefficients (acylation degrees) in the molecular weight range of the pentasaccharide, which is responsible for the antithrombotic activity, up to the standard molecular weight of the purchasable heparin of 13 kD, heparansulphate and its derivatives, oligo- and polysaccharides
15 of the erythrocytic glycocalix, desulphated and N-reacetylated heparin, N-carboxymethylated and/or partially N-acetylated chitosan as well as mixtures of these substances.

20 Disclosed are also medical devices which are hemocompatibly coated according to one of the herein mentioned methods. In the case of the medical devices it is preferably a matter of stents.

25 The conventional stents, which can be coated according to the methods disclosed, consist of stainless steel, nitinol or other metals and alloys or of synthetic polymers.

The stents as disclosed are coated with an according to the general formula 1 preferred covalently bound hemocompatible layer. A second layer covers this first hemocompatible layer completely or also incompletely. This
30 second layer conspires preferably paclitaxel. The hemocompatible coating of a stent provides on the one hand the necessary blood compatibility and reduces so the risk of thrombosis and also the containment of inflammation reactions due to the intrusion and the absence of a non-endogenous surface, and paclitaxel, which is preferred to be distributed homogeneously over the total surface of the stent
35 provides that the covering of the stent surface with cells, especially smooth muscle and endothelial cells, takes place in a controlled way, so that the interplay of thrombosis reactions and inflammation reactions, the release of growth factors,

proliferation and migration of cells during the recovery process provides the generation of a novel "repaired" cell layer, which is referred to as neointima.

5 Thus, the use of paclitaxel, covalently or/and adhesively bound to the subjacent layer or/and covalently or/and adhesively implemented in at least one layer, ensures, that this active agent is set free continuously and in small doses, so that the population of the stent surface by cells is not inhibited, however an excessive population and the ingrowth of cells into the vessel lumen is prevented. This combination of both effects awards the ability to the stent according to invention, 10 to grow rapidly into the vessel wall and reduces both the risk of restenosis and the risk of thrombosis. The release of paclitaxel spans about a period from 1 to 12 months, preferably 1 to 3 months after implantation.

15 Paclitaxel is preferred contained in a pharmaceutical active concentration from 0.001-10 mg per cm² stent surface, preferred 0.01 – 5 mg and especially preferred 0.1 – 1.0 mg per cm² stent surface. Additional active agents can be contained in similar concentration in the same or in the hemocompatible layer.

20 The applied amounts of polymer are per layer between 0.01 mg to 3 mg, preferred 0.20 mg to 1 mg and especially preferred between 0.2 mg to 0.5 mg. Suchlike coated stents release the active agent paclitaxel controlled and continuously and hence are excellently suitable for the prevention and reduction of restenosis.

25 These stents with a hemocompatible coating are generated, as one provides stents and deposits preferred covalently one hemocompatible layer according to the general formula, which masks the surface of the implantate permanently after the release of the active agent and so after the decay of the active agent influence.

30 The preferred embodiment of the stents according to invention shows a coating, which consists of at least two layers. Thereby named as second layer is that layer, which is deposited on the first layer. According to the two-layer design the first layer conspires the hemocompatible layer, which is substantially completely covered by a second layer, which consists of paclitaxel, that is covalently and/or 35 adhesively bound to the first layer.

The paclitaxel layer is dissolved slowly, so that the active agent is released according to the velocity of the solution process. The first hemocompatible layer

guarantees the necessary blood compatibility of the stent in the degree as the active agent is removed. By the release of the active agent the adhesion of cells is strongly reduced only for a certain period of time and an aimed controlled adhesion is enabled, where the external layer had been already widely degraded. Finally the hemocompatible layer remains as athrombogeneous surface and masks the foreign surface in such a way, that no life-threatening reaction can occur anymore.

Suchlike stents can be generated by a method of the hemocompatible coating of stents, to which the following principle underlies:

- a. providing of a stent
- b. deposition of a preferred covalently bound hemocompatible layer
- c. substantially complete covering of the hemocompatible layer by a dipping or spraying method with the antiproliferative active agent paclitaxel.

The stents as disclosed solve both the problem of acute thrombosis and the problem of neointima hyperplasia after a stent implantation. In addition the stents are especially well suited, because of their coating for the continuous release of one or more antiproliferative, immuno-suppressive active agents. Due to this capability of the aimed continuous active agent release in a required amount the inventively coated stents prevent the danger of restenosis almost completely.

The natural and/or artificial surfaces which had been coated according to the above described method with a hemocompatible layer of aforesaid polysaccharides, are suitable especially as implants resp. organ replacement parts, that are in direct contact with the blood circuit and blood, preferably in the form of stents in combination with an antiproliferative active agent, preferably paclitaxel, for the prevention of restenosis.

The coated medical devices are suited especially but not only for the direct and permanent blood contact, but show surprisingly also the characteristic to reduce or even to prevent the adhesion of proteins onto suchlike coated surfaces. The adhesion of plasma proteins on foreign surfaces which come in contact with blood is an essential and initial step for the further events concerning the recognition and the implementing action of the blood system.

This is for example important in the in vitro diagnostics from body fluids. Thus the deposition of the inventive coating prevents or at least reduces for example the

unspecific adhesion of proteins on micro-titer plates or other support mediums which are used for diagnostic detection methods, that disturb the generally sensitive test reactions and can lead to a falsification of the analysis result.

- 5 By use of the coating disclosed on adsorption media or chromatography media the unspecific adhesion of proteins is also prevented or reduced, whereby better separations can be achieved and products of greater purity can be generated.

10 Description of figures

Figure 1 shows a tetrasaccharide unit of a heparin or heparansulphate with statistic distribution of the sulphate groups and a sulphation coefficient of 2 per disaccharide unit as it is typical for heparin (figure 1a). For comparison of the structural similarities figure 1b shows an example of a compound according to the general formula in the description.

Figure 2 shows the influence of an into a PVC-tube expanded, surface modified stainless steel coronary stent on the platelet loss (PLT-loss). An uncoated stainless steel coronary stent was measured as reference. As zero value the level of the platelet loss in case of the PVC-tube without stainless steel coronary stent was set. Thereby SH1 is a with heparin covalently coated stent, SH2 is a with chondroitinsulphate coated stent; SH3 is a stent coated with polysaccharides gained from the erythrocytic glycocalix and SH4 is a with Ac-heparin covalently coated stainless steel coronary stent.

Figure 3 shows a schematic presentation of the restenosis rate of with completely desulphated and N-reacetylated heparin (Ac-heparin) covalently coated stents and with oligo- and polysaccharides of the erythrocytic glycocalix (polysacch. of erythro. glycoc.) coated stents in comparison to the uncoated stent and with polyacrylic acid (PAS) coated stents after 4 weeks of implantation time in pork.

Figure 4 quantitative coronary angiography:
Images of the cross sections through the stent containing vessel-segment of one with Ac-heparin coated stent (a.) and as comparison

of one uncoated (unco. or bare) stent (b.). After four weeks in the animal experiment (pork) a clear difference in the thicknesses of the formed neointimas can be observed.

5 Figure 5 elution plot of paclitaxel from the stent (without support medium).

Examples

10 Example 1

Synthesis of desulphated reacylated heparin:

100 ml amberlite IR-122 cation exchange resin were added into a column of 2 cm diameter, with 400 ml 3M HCl in the H^+ -form converted and rinsed with distilled water, until the eluate was free of chloride and pH neutral. 1 g sodium-heparin was dissolved in 10 ml water, added onto the cation exchange column and eluted with 400 ml of water. The eluate was added dropwise into a receiver with 0.7 g pyridine and afterwards titrated with pyridine to pH 6 and freeze-dried.

0.9 g heparin-pyridinium-salt were added in a round flask with a reflux condenser with 90 ml of a 6/3/1 mixture of DMSO/1,4-dioxan/methanol (v/v/v) and heated for 24 hours to 90°C. Then 823 mg pyridinium chloride were added and heated additional 70 hours to 90°C. Afterwards it was diluted with 100 ml of water and titrated with dilute sodium hydroxide to pH 9. The desulphated heparin was dialyzed contra water and freeze-dried.

100 mg of the desulphated heparin were solved in 10 ml of water, cooled to 0°C and added with 1.5 ml methanol under stirring. To this solution were added 4 ml dowex 1x4 anion exchange resin in the OH^- -form and afterwards 150 µl of acetic anhydride and stirred for 2 hours at 4°C. Then the resin was removed by filtration and the solution was dialyzed contra water and freeze-dried.

Example 2

Synthesis of desulphated N-propionylated heparin:

100 ml amberlite IR-122 cation exchange resin were added into a column of 2 cm diameter, with 400 ml 3M HCl in the H^+ -form converted and rinsed with distilled water, until the eluate was free of chloride and pH neutral. 1 g sodium-heparin was

dissolved in 10 ml water, added onto the cation exchange column and eluted with 400 ml of water. The eluate was added dropwise into a receiver with 0.7 g pyridine and afterwards titrated with pyridine to pH 6 and freeze-dried.

- 5 0.9 g heparin-pyridinium-salt were added in a round flask with a reflux condenser with 90 ml of a 6/3/1 mixture of DMSO/1,4-dioxan/methanol (v/v/v) and heated for 24 hours to 90°C. Then 823 mg pyridiniumchloride were added and heated additional 70 hours to 90°C. Afterwards it was diluted with 100 ml of water and titrated with dilute sodium hydroxide to pH 9. The desulphated heparin was
10 dialyzed contra water and freeze-dried.

- 100 mg of the desulphated heparin were solved in 10 ml of water, cooled to 0°C and added with 1.5 ml methanol under stirring. To this solution were added 4 ml
15 dowex 1x4 anion exchange resin in the OH⁻-form and afterwards 192 µl of propionic anhydride and stirred for 2 hours at 4°C. Then the resin was removed by filtration and the solution was dialyzed contra water and freeze-dried.

Example 3

- 20 Hemocompatibility measurements of compounds according to the general formula 1 by ISO 10933-4 (in vitro measurements):

- For the measurement of the hemocompatibility of the compounds according to formula 1 cellulose membranes, silicon tubes and stainless steel stents were
25 covalently coated with a compound according to formula 1 and tested contra heparin as well as contra the corresponding, in the single tests utilised uncoated material surfaces.

- 3.1. Cellulose membranes (cuprophane) coated with desulphated, reacylated
30 heparin (Ac-heparin)

- For the examination of the coagulatory physiologic interactions between citrated whole blood and the Ac-heparin- resp. heparin-coated cuprophane membranes the open perfusion system of the Sakariassen-modified Baumgartner-chamber is
35 used [Sakariassen K.S. et al.; *J. Lab. Clin. Med.* 102 : 522-535 (1983)]. The chamber is composed of four building parts plus conical nipples and threaded joints and is manufactured of polymethylmethacrylate and allows the parallel investigation of two modified membranes, so that in every run a statistic coverage

is included. The construction of this chamber permits quasi-laminar perfusion conditions.

5 After 5 minutes of perfusion at 37°C the membranes are extracted and after
fixation of the adherent platelets the platelet occupancy is measured. The
respective results are set into relation to the highly thrombogeneous
subendothelial matrix as negative standard with a 100% platelet occupancy. The
adhesion of the platelets takes place secondary before the formation of the
10 plasma protein layer on the foreign material. The plasma protein fibrinogen acts
as cofactor of the platelet aggregation. The such induced activation of the
platelets results in the bonding of several coagulation associated plasma proteins,
as e.g. vitronectin, fibronectin and von Willebrand-factor on the platelet surface.
By their influence finally the irreversible aggregation of the platelets occurs.

15 The platelet occupancy presents because of the described interactions an
accepted quantum for the thrombogenicity of surfaces in case of the foreign surface
contact of blood. From this fact the consequence arises: the lower the platelet
occupancy is on the perfused surface the higher is the hemocompatibility of the
examined surface to be judged.

20 The results of the examined heparin-coated and Ac-heparin-coated membranes
show clearly the improvement of the hemocompatibility of the foreign surface
through the coating with Ac-heparin. Heparin-coated membranes show a 45 - 65%
platelet occupancy, whilst Ac-heparin-coated surfaces show values from 0 - 5%
(reference to subendothelial matrix with 100% platelet occupancy).

25 The adhesion of the platelets on the Ac-heparinated surface is extremely
aggravated due to the absent, for the activation of platelets essential plasma
proteins. Unlike to this the heparin-coated surface with the immediately incipient
plasma protein adsorption offers optimal preconditions for activation, deposition
30 and aggregation of platelets, and ultimately the blood reacts with the
corresponding defense mechanisms to the inserted foreign surface. Ac-heparin
fulfills by far superior than heparin the requirements to the hemocompatibility of
the foreign surface.

35 The interaction of plasma protein adsorption and platelet occupancy as direct
quantum for the thrombogenicity of a surface, in dependence of the to the blood
offered coating, is made clear especially well by this in-vitro test. Thus the
utilisation of covalently bound heparin as antithrombotic operant surface is only

strongly limited or not possible at all. The interactions of immobilised heparin with blood revert themselves here into the undesired opposite – the heparin-coated surface gets thrombogeneous.

5 Obviously the outstanding importance of heparin as an antithrombotic is not transferable to covalently immobilised heparin. In the systemic application in dissolved form it can fully unfold its properties. But if heparin is not covalently immobilised, its antithrombotic properties, if at all, is only short-lived. Different is the Ac-heparin („No-affinity“-heparin), that due to the desulphation and N-reacetylation in fact totally loses the active antithrombotic properties of the initial molecule, but acquires in return distinctive athrombogeneous properties, that are demonstrably founded in the passivity versus antithrombin III and the missing affinity towards coagulation initiating processes and remain after covalent bonding.

15 Thereby Ac-heparin and thus the compounds of the general formula 1 in total are optimally suitable for the camouflage of foreign surfaces in contact with the coagulation system.

20 3.2. Immobilisation on silicone

Through a 1 m long silicon tube with 3 mm inside diameter 100 ml of a mixture of ethanol/water 1/1 (v/v) was pumped in a circular motion for 30 minutes at 40°C. Then 2 ml 3-(triethoxysilyl)-propylamine were added and pumped in a circular motion for additional 15 hours at 40°C. Afterwards it was rinsed in each case for 2 hours with 100 ml ethanol/water and 100 ml water.

3 mg of the deacetylated and reacetylated heparin (Ac-heparin) were dissolved at 4°C in 30 ml 0.1 M MES-buffer pH 4.75 and mixed with 30 mg CME-CDI (*N*-cyclohexyl-*N'*-(2-morpholinoethyl)carbodiimidemethyl-*p*-toluenesulphonate).

30 This solution was pumped in a circular motion for 15 hours at 4°C through the tube. Afterwards it was rinsed with water, 4 M NaCl solution and water in each case for 2 hours.

35 3.3 Determination of the platelet number (EN30993-4)

In a 1 m long silicone tube with 3 mm inside diameter two 2 cm long formfitting glass tubes were placed. Then the tube was closed with a shrinkable tubing to a

circle and filled under exclusion of air via syringes with a 0.154 M NaCl solution. In doing so one syringe was used to fill in the solution and the other syringe was used to remove the air. The solution was exchanged under exclusion of air (bleb-free) with the two syringes against citrated whole blood of a healthy test person.

5 Then the recess holes of the syringes were closed by pushing the glass tubes over them and the tube was clamped taut into a dialysis pump. The blood was pumped for 10 minutes with a flow rate of 150 ml/min. The platelet content of the blood was measured before and after the perfusion with a coulter counter. For uncoated silicone tubes the platelet loss was of 10%. In contrast to it the loss was
10 in silicon tubes, which were coated according to example 5.2, in average at 0% (number of experiments: n=3).

Also in this dynamic test system it is shown, that the activation of platelets on an Ac-heparin coated surface is reduced. Simultaneously it can be recorded, that the
15 immobilisation of heparin executes a negative effect on the hemocompatibility of the utilised surface. Against it Ac-heparin shows, in accordance to its passive nature, no effects in contact with the platelets.

3.4 Whole blood experiments on 316 LVM stainless steel coronary stents

20

In line with the biocompatibility experiments 31 mm long 316 LVM stainless steel stents were covalently coated with Ac-heparin. In case of a total surface of 2 cm² and a occupancy coefficient of about 20 pm/cm² stent surface the charging of such a stent is about 0.35 µg Ac-heparin. As comparison: in case of thrombosis
25 prophylaxis the usual daily application rate of heparin is in contrast 20-30 mg and thus would correspond to the at least 60.000 times the value.

These experiments were carried out with the established hemodynamic Chandler loop-system [A. Henseler, B. Oedekoven, C. Andersson, K. Mottaghy;
30 *KARDIOTECHNIK* 3 (1999)]. Coated and uncoated stents were expanded and tested in PVC tubes (medical grade PVC) with 600 mm length and 4 mm inside diameter. The results of these experiments confirm the according to the silicone tubes discussed experiments. The initially to the stent attributed platelet loss in the perfusate of 50% is reduced by the refinement of the stent surface with Ac-heparin
35 by more than 80%.

The influence of in the tube expanded, surface modified coronary stents to the platelet loss is evaluated in further Chandler tests during a 45 minute whole blood

perfusion. For this primarily the stent-free PVC tube is analysed, the outcome of this is the zero value. The empty tube shows an average platelet loss of 27.4 % regarding to the donor blood at a standard aberration of solely 3.6 %. This base value underlied different surface modified stents are expanded in the PVC tubes and are analysed under analogous conditions on the by them caused platelet loss. It occurs also in this case, that the stent covered surface, which solely accounts for about 0.84% of the total test surface, causes a significant and reproducible effect on the platelet content. According to the empty tube (base value) the analysis of the polished, chemically not surface coated stent yields an additional average platelet loss of 22.7%. Therewith causes this compared to the PVC empty tube less than 1% measurable foreign surface an approximately comparable platelet loss. A direct result is that the medicinal stainless steel 316 LVM used as stent material induces an about 100 times stronger platelet damage compared to a medical grade PVC surface, although this test surface only accounts for 0.84% of the total surface.

The analysed surface coatings on the stainless steel coronary stents show to be able to reduce very clearly the enormous dimension of the stent induced platelet damage (see fig. 2). As most effective proved with 81.5% the Ac-heparin (SH4).

If the effects of the Ac-heparin-coated stents on the platelet loss are considered, then good congruent values result. The correlation of the platelet loss in the perfusate resp. the adhesion of the platelets to the offered surfaces show the reliability of the measurements.

3.4.1 Covalent hemocompatible coating of stents

Not expanded stents of medicinal stainless steel LVM 316 were degreased in the ultrasonic bath for 15 minutes with acetone and ethanol and dried at 100°C in the drying closet. Then they were dipped for 5 minutes into a 2% solution of 3-aminopropyltriethoxysilane in a mixture of ethanol/water (50/50 : (v/v)) and then dried for 5 minutes at 100°C. Afterwards the stents were washed with demineralised water over night.

3 mg desulphated and reacylated heparin were dissolved at 4°C in 30 ml 0.1 M MES-buffer (2-(N-morpholino)ethanesulphonic acid) pH 4.75 and mixed with 30 mg N-cyclohexyl-N'-(2-morpholinoethyl)carbodiimide-methyl-p-toluenesulphonate.

In this solution 10 stents were stirred for 15 hours at 4 °C. Then they were rinsed with water, 4 M NaCl solution and water in each case for 2 hours.

3.4.2 Determination of the glucosamine content of the coated stents by HPLC

Hydrolysis: the coated stents are given in small hydrolysis tubes and are abandoned with 3 ml 3 M HCl for exactly one minute at room temperature. The metal probes are removed and the tubes are incubated after sealing for 16 hours in the drying closet at 100 °C. Then they are allowed to cool down, evaporated three times until dryness and taken up in 1 ml de-gased and filtered water and measured contra an also hydrolysed standard in the HPLC:

stent	sample area	desulphat. + reacet. heparin [g/sample]	area [cm ²]	desulphat. + reacet. heparin [g/cm ²]	desulphat. + reacet. heparin [pmol/cm ²]
1	129.021	2.70647E-07	0.74	3.65739E-07	41.92
2	125.615	2.63502E-07	0.74	3.56084E-07	40.82
3	98.244	1.93072E-07	0.74	2.60908E-07	29.91
4	105.455	2.07243E-07	0.74	2.80058E-07	32.10
5	119.061	2.33982E-07	0.74	3.16192E-07	36.24
6	129.202	2.53911E-07	0.74	3.43124E-07	39.33
7	125.766	2.53957E-07	0.74	3.43185E-07	39.34

Example 4

In vivo examination of coated coronary stents (fig. 5)

4.1. In vivo examinations of coronary stents coated with Ac-heparin

Due to the data on hemocompatibility, which Ac-heparin yielded in the in-vitro experiments, the suitability of the Ac-heparin surface as athrombogeneous coating of metal stents was discussed in vivo (animal experiment).

The target of the experiments was primarily to evaluate the influence of the Ac-heparin coating on the stent induced vessel reaction. Besides the registration of possible thrombotic events the relevant parameters for restenotic processes like neointima area, vessel lumen and stenosis degree were recorded. For the

examinations 6 – 9 month old domestic pigs were used, one for the validation of stents for a long time established and approved animal model.

5 As expected in these experiments neither acute, subacute nor late acute thrombotic events were registered, what may be assessed as proof for the athrombogeneous properties of Ac-heparin.

10 After four weeks the animals were dispatched (euthanized), the stented coronary artery segments extracted and histomorphometrically analysed. Indications to a possible acute or subchronic toxicity, allergisation reactions or ulterior irritations as consequence of the implantation of Ac-heparin coated stents are not observed during the complete experimental phase, especially in the histologic examination. During the stent implantation as well as the follow-up coronary-angiographic data sets were ascertained, which permit an interpretation with regard to the vessel
15 reaction to the stent implantation.

The difference between the uncoated control stent and the Ac-heparin coated stent is unambiguous. The generation of a distinct neointima layer is in case of the uncoated control stent very well observable. Already after four weeks the
20 proliferation promotional effect of the uncoated stent surface on the surrounding tissue occurs in such a degree, that ultimately the danger of the vessel occlusion in the stent area is given.

Contrary in case of the Ac-heparin coated stents a clearly thinner neointima layer is observed, which argues for a well modulated ingrowth of the stent under
25 maintenance of a wide, free vessel lumen.

The detailed histomorphometric and coronary angiographic data substantiate this conclusion, as it can be observed congruently, that via the Ac-heparin coating (SH4) the neointima hyperplasia („restenosis“) was repressed by about 17-20% in
30 comparison to the uncoated control stent. This result is unexpected and remarkably at the same time. Surely it is not demanded of an athrombogeneous surface to have an influence also on processes that lead to a neointima hyperplasia, i.e. to prevent restenoses, in addition to the preposition of hemocompatible characteristics.

35 On the one hand with a dense, permanent occupancy of the stent surface with Ac-heparin a direct cell contact to the metal surface is prevented. As in technical literature the emission of certain metal ions into the implant close tissue is

discussed as one probable reason of restenosis, an anti-restenoic potency could be founded by one of the coating caused prevention of a direct metal contact.

On the other hand such a positive side effect is plausible, because on a passive, athrombogenenous stent surface with the absence of a platelet aggregation also the proliferative effects of the thereby released growth factors are to be missed. Thus an important, starting from the lumen side, stimulus of the neointimal proliferation is omitted.

10 Example 5

Coating of the stents with taxol by the spraying method

The via example 1 and example 2 prepared not expanded stents are balanced and horizontally hung onto a thin metal bar ($d = 0.2 \text{ mm}$), which is stuck on the rotation axis of the rotation and feed equipment and rotates with 28 r/min. The stents are fixed in that way, that the inside of the stents does not touch the bar. At a feeding amplitude of 2.2 cm and a feeding velocity of 4 cm/s and a distance of 6 cm between stent and spray valve the stent is sprayed with the particular spray solution. After the drying (about 15 minutes) at room temperature and proximate in the fume hood over night it is balanced again.

Fabrication of the spray solution: 44 mg taxol are dissolved in 6g chloroform.

stent no.	before coating	after coating	coating mass
1	0.0194 g	0.0197 g	0.30 mg

25

Example 6

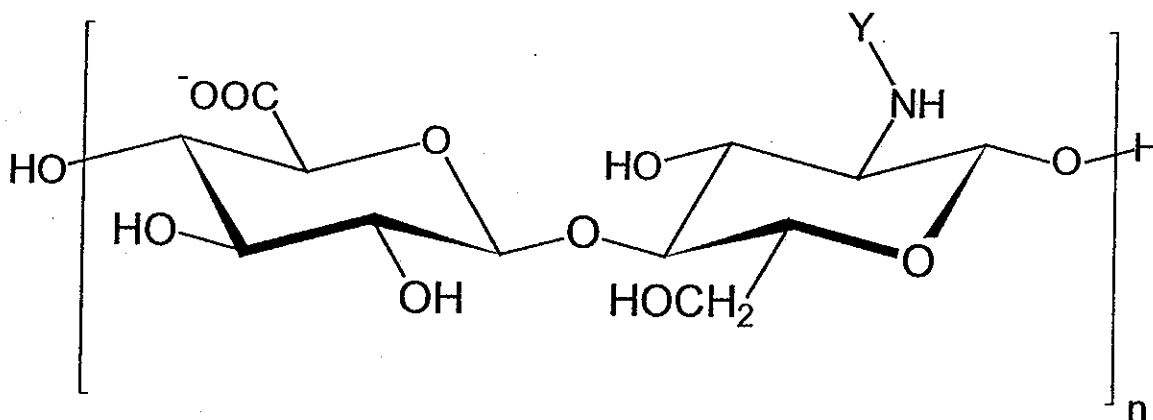
Determination of the elution behaviour in PBS-buffer

Per stent in a sufficient small flask 2 ml PBS-buffer is added, sealed with para-film and incubated in the drying closet at 37°C. After expiry of the chosen time intervals in each case the excess solution is depipetted and its UV absorption at 306 nm is measured.

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Claims

1. Medical device, wherein at least one part of the surface of the medical device is coated directly or via at least one interjacent biostable and/or biodegradable layer with a hemocompatible layer comprising at least one compound of the formula 1



wherein

n represents an integer between 4 and 1050,

Y represents a residue $-\text{CHO}$, $-\text{COCH}_3$, $-\text{COC}_2\text{H}_5$, $-\text{COC}_3\text{H}_7$, $-\text{COC}_4\text{H}_9$, $-\text{COC}_5\text{H}_{11}$, $-\text{COCH}(\text{CH}_3)_2$, $-\text{COCH}_2\text{CH}(\text{CH}_3)_2$, $-\text{COCH}(\text{CH}_3)\text{C}_2\text{H}_5$, $-\text{COC}(\text{CH}_3)_3$, $-\text{CH}_2\text{COO}^-$, $-\text{C}_2\text{H}_4\text{COO}^-$, $-\text{C}_3\text{H}_6\text{COO}^-$, $-\text{C}_4\text{H}_8\text{COO}^-$,

as well as salts of these compounds,

and on, in and/or under the hemocompatible layer the active agent paclitaxel is present.

2. Medical device according to claim 1, wherein Y represents the residue $-\text{CHO}$, $-\text{COCH}_3$, $-\text{COC}_2\text{H}_5$, $-\text{COC}_3\text{H}_7$, as well as salts of these compounds.
3. Medical device according to claim 2, wherein Y is $-\text{COCH}_3$.
4. Medical device according to one of the previous claims, wherein the hemocompatible layer is directly placed on the surface of the medical device and onto said hemocompatible layer paclitaxel as well as mixtures of these active agents are deposited.

5. Medical device according to one of the previous claims, wherein under the hemocompatible layer or between two hemocompatible layers at least one biostable and/or biodegradable layer is present.

5 6. Medical device according to one of the previous claims, wherein the hemocompatible layer is coated completely or/and incompletely with at least one additional, above lying biostable and/or biodegradable layer.

10 7. Medical device according to one of the previous claims, in which at least one active agent layer of paclitaxel is present between the biostable and the hemocompatible layer.

15 8. Medical device according to one of the previous claims, in which paclitaxel is bound covalently and/or adhesively in and/or on the hemocompatible layer and/or the biostable and/or the biodegradable layer.

20 9. Medical device according to one of the previous claims, characterised in, that as biodegradable substances for the biodegradable layer polyvalerolactones, poly- ϵ -decalactones, polylactonic acid, polyglycolic acid, polylactides, polyglycolides, copolymers of the polylactides and polyglycolides, poly- ϵ -caprolactone, polyhydroxybutanoic acid, polyhydroxybutyrates, polyhydroxyvalerates, polyhydroxybutyrate-co-valerates, poly(1,4-dioxane-2,3-diones), poly(1,3-dioxane-2-one), poly-para-dioxanones, polyanhydrides as polymaleic anhydrides, polyhydroxymethacrylates, fibrin, 25 polycyanoacrylates, polycaprolactonedimethylacrylates, poly-b-maleic acid, polycaprolactonebutyl-acrylates, multiblock polymers as e.g. from oligocaprolactonedioles and oligodioxanonedioles, polyetherester multiblock polymers as e.g. PEG and poly(butyleneterephthalates), polypivotolactones, polyglycolic acid trimethyl-carbonates, polycaprolactone-glycolides, poly(g-ethylglutamate), poly(DTH-iminocarbonate), poly(DTE-co-DT-carbonate), 30 poly(bisphenol-A-iminocarbonate), polyorthoesters, polyglycolic acid trimethyl-carbonates, polytrimethylcarbonates, polyiminocarbonates, poly(N-vinyl)-pyrrolidone, polyvinylalcoholes, polyesteramides, glycolated polyesters, polyphosphoesters, polyphosphazenes, poly[p-carboxyphenoxy]propane], 35 polyhydroxypentane acid, polyanhydrides, polyethyleneoxide-propyleneoxide, soft polyurethanes, polyurethanes with amino acid rests in the backbone, polyetheresters as polyethyleneoxide, polyalkeneoxalates, polyorthoesters as well as their copolymers, lipids, carrageenans, fibrinogen,

starch, collagen, protein based polymers, polyamino acids, synthetic polyamino acids, zein, modified zein, polyhydroxyalkanoates, pectic acid, actinic acid, modified and non modified fibrin and casein, carboxymethylsulphate, albumin, moreover hyaluronic acid, chitosane and its derivatives, heparansulphates and its derivatives, heparin, chondroitinsulphate, dextran, b-cyclodextrins, copolymers with PEG and polypropyleneglycol, gummi arabicum, guar, gelatine, collagen, collagen-N-Hydroxysuccinimide, lipids, phospholipids, modifications and copolymers and/or mixtures of afore mentioned substances are used.

10. Medical device according to one of the previous claims, characterised in, that as biostable substances for the biostable layer polyacrylic acid and polyacrylates as polymethylmethacrylate, polybutylmethacrylate, polyacrylamide, polyacrylonitriles, polyamides, polyetheramides, polyethylenamine, polyimides, polycarbonates, polycarbourethanes, polyvinylketones, polyvinylhalogenides, polyvinylidenhalogenides, polyvinylethers, polyisobutylenes, polyvinylaromates, polyvinylesters, polyvinylpyrrolidones, polyoxymethylenes, polytetramethyleneoxide, polyethylene, polypropylene, polytetrafluoroethylene, polyurethanes, polyetherurethanes, silicone-polyetherurethanes, silicone-polyurethanes, silicone-polycarbonate-urethanes, polyolefine elastomeres, polyisobutylenes, EPDM gums, fluorosilicones, carboxymethylchitosanes, polyaryletheretherketones, polyetheretherketones, polyethylenterephthalate, polyvalerates, carboxymethylcellulose, cellulose, rayon, rayontriacetates, cellulosenitrates, celluloseacetates, hydroxyethylcellulose, cellulosebutyrates, celluloseacetatebutyrates, ethylvinylacetate copolymers, polysulphones, epoxy resins, ABS resins, EPDM gums, silicones as polysiloxanes, polydimethylsiloxanes, polyvinylhalogenes and copolymers, celluloseethers, cellulosetriacetates, chitosanes and copolymers and/or mixtures of these substances are used.

11. Medical device according to one of the previous claims, whereas instead of the active agent paclitaxel one of the following active agents is used: simvastatin, 2-methylthiazolidine-2,4-dicarboxylic acid and the correspondent sodium salt, macrocyclic suboxide (MCS), derivatives of MCS, activated protein C (aPC), PETN, trapidil, β -estradiol as well as mixtures of these active agents or mixtures of one of these active agents with paclitaxel.

12. Medical device according to one of the previous claims, characterised in, that the medical device comprises prostheses, organs, vessels, aortas, heart valves, tubes, organ spareparts, implants, fibers, hollow fibers, stents, hollow needles, syringes, membranes, tinned goods, blood containers, titrimetric plates, pacemakers, adsorbing media, chromatography media, chromatography columns, dialyzers, connexion parts, sensors, valves, centrifugal chambers, recuperators, endoscopes, filters, pump chambers.
13. Medical device according to claim 12, characterised in, that the medical device is a stent.
14. Stents according to claim 13, wherein the polymer is deposited in amounts between 0.01 mg to 3 mg / layer, preferred between 0.20 mg to 1 mg and especially preferred between 0.2 mg to 0.5 mg / layer.
15. Stent according to claim 13 or 14, characterised in, that the active agent is used in a pharmaceutically active concentration of 0.001 - 10 mg per cm² stent surface and per layer.
16. The stent according to one of the claims 13-15, characterised in, that the medical device comprises paclitaxel, simvastatin, 2-methylthiazolidine-2,4-dicarboxylic sodium salt, macrocyclic, suboxide (MCS), derivatives of MCS, activated protein C (aPC), PETN, trapidil and/or β -estradiol.
17. The medical devices according to one of the claims 1-16, characterised in, that the hemocompatibly coated surface of the medical device is a surface of micro-titer plates or other carrier media for detection processes.

18. The medical devices according to one of the claims 1 to 16, characterised in, that the hemocompatibly coated surface of the medical device is the surface of adsorber media or chromatography media.
19. Method for the hemocompatible coating of biological and/or artificial surfaces of medical devices comprising the following steps:
 - a) providing a surface of a medical device and
 - b) deposition of at least one compound of the general formula 1 according to claim 1 as hemocompatible layer on this surface and/or
 - b') deposition of a biostable and/or biodegradable layer on the surface of the medical device or the hemocompatible layer.
20. Method according to claim 19, wherein the hemocompatible layer or the biostable and/or biodegradable layer is coated via dipping or spraying method with at least one biodegradable and/or biostable layer which conspires paclitaxel covalently and/or adhesively bound.
21. Method according to claim 19 or 20 comprising the further step c):
 - c. deposition of paclitaxel in and/or on the hemocompatible layer or the biostable and/or biodegradable layer.
22. Method according to claim 21, wherein paclitaxel is implemented and/or deposited via dipping or spraying methods on and/or in the hemocompatible layer or the biostable and/or biodegradable layer and/or is bound via covalent and/or adhesive coupling to the hemocompatible layer or the biostable and/or biodegradable layer.
23. Method according to one of the claims 19-22, comprising the further step d) or d'):
 - d. deposition of at least one biodegradable layer and/or at least one biostable and/or biodegradable layer on the hemocompatible layer or the layer of paclitaxel respectively,
or
 - d') deposition of at least one compound of the general formula 1 according to claim 1 as hemocompatible layer on the biostable and/or biodegradable layer or the layer of paclitaxel.

24. Method according to one of the claims 19 - 23, comprising the further step e.):
e. deposition of paclitaxel in and/or on the at least one biodegradable and/or biostable layer or the hemocompatible layer.

25. Method according to claim 24, wherein paclitaxel is deposited and/or implemented via dipping or spraying methods on and/or in the at least one biodegradable and/or biostable layer or the hemocompatible layer and/or is bound via covalent and/or adhesive coupling to the at least one biodegradable and/or biostable layer or the hemocompatible layer.

26. Method according to one of the claims 19 - 25, wherein the biostable and/or biodegradable layer is covalently and/or adhesively bound on the surface of the medical device and the hemocompatible layer is covalently bound to the biostable and/or biodegradable layer and covers it completely or incompletely.

27. Method according to one of the claims 19 - 26, characterised in, that the hemocompatible layer comprises heparin of native origin of regioselectively synthesised derivatives of different sulphation coefficients and acylation coefficients in the molecular weight range of the pentasaccharide, which is responsible for the antithrombotic activity, up to the standard molecular weight of the purchasable heparin of 13 kD, heparansulphate and its derivatives, oligo- and polysaccharides of the erythrocytic glycocalix, desulphated and N-reacetylated heparin, N-carboxymethylated and/or partially N-acetylated chitosan as well as mixtures of these substances.

28. Method according to one of the claims 19 - 27, characterised in, that as biodegradable substances for the biodegradable layer polyvalerolactones, poly- ϵ -decalactones, polylactonic acid, polyglycolic acid, polylactides, polyglycolides, copolymers of the polylactides and polyglycolides, poly- ϵ -caprolactone, polyhydroxybutanoic acid, polyhydroxybutyrates, polyhydroxyvalerates, polyhydroxybutyrate-co-valerates, poly(1,4-dioxane-2,3-diones), poly(1,3-dioxane-2-one), poly-para-dioxanones, polyanhydrides as polymaleic anhydrides, polyhydroxymethacrylates, fibrin, polycyanoacrylates, polycaprolactonedimethylacrylates, poly-b-maleic acid, polycaprolactonebutyl-acrylates, multiblock polymers as e.g.. from oligocaprolactonedioles and oligodioxanonedioles, polyetherester multiblock

polymers as .e.g. PEG and poly(butylene terephthalates), polypivotolactones,
 polyglycolic acid trimethyl-carbonates, polycaprolactone-glycolides, poly(g-
 ethylglutamate), poly(DTH-iminocarbonate), poly(DTE-co-DT-carbonate),
 poly(bisphenol-A-iminocarbonate), polyorthoesters, polyglycolic acid
 5 trimethyl-carbonates, polytrimethylcarbonates, polyiminocarbonates, poly(N-
 vinyl)-pyrrolidone, polyvinylalcohols, polyesteramides, glycolated polyesters,
 polyphosphoesters, polyphosphazenes, poly[p-carboxyphenoxy]propane],
 polyhydroxypentane acid, polyanhydrides, polyethyleneoxide-
 propyleneoxide, soft polyurethanes, polyurethanes with amino acid rests in
 10 the backbone, polyetheresters as polyethyleneoxide, polyalkeneoxalates,
 polyorthoesters as well as their copolymers, lipides, carrageenanes,
 fibrinogen, starch, collagen, protein based polymers, polyamino acids,
 synthetic polyamino acids, zein, modified zein, polyhydroxyalkanoates, pectic
 acid, actinic acid, modified and non modified fibrin and casein,
 15 carboxymethylsulphate, albumin, moreover hyaluronic acid, chitosane and its
 derivatives, heparansulphates and its derivatives, heparin,
 chondroitinsulphate, dextran, β -cyclodextrins, copolymers with PEG and
 polypropyleneglycol, gummi arabicum, guar, gelatine, collagen, collagen-N-
 Hydroxysuccinimide, lipids, phospholipids, modifications and copolymers
 20 and/or mixtures of afore mentioned substances are used.

29. Method according to one of the claims 19 - 28, characterised in, that as
 biostable substances for the biostable layer polyacrylic acid and
 polyacrylates as polymethylmethacrylate, polybutylmethacrylate,
 25 polyacrylamide, polyacrylonitriles, polyamides, polyetheramides,
 polyethylenamine, polyimides, polycarbonates, polycarbourethanes,
 polyvinylketones, polyvinylhalogenides, polyvinylidenhalogenides,
 polyvinylethers, polyisobutylenes, polyvinylaromates, polyvinylesters,
 polyvinylpyrrolidones, polyoxymethylenes, polytetramethyleneoxide,
 30 polyethylene, polypropylene, polytetrafluoroethylene, polyurethanes,
 polyetherurethanes, silicone-polyetherurethanes, silicone-polyurethanes,
 silicone-polycarbonate-urethanes, polyolefine elastomers, polyisobutylenes,
 EPDM gums, fluorosilicones, carboxymethylchitosanes,
 polyaryletheretherketones, polyetheretherketones, polyethylterephthalate,
 35 polyvalerates, carboxymethylcellulose, cellulose, rayon, rayontriacetates,
 cellulosenitrates, celluloseacetates, hydroxyethylcellulose,
 cellulosebutyrates, celluloseacetatebutyrates, ethylvinylacetate copolymers,
 polysulphones, epoxy resins, ABS resins, EPDM gums, silicones as

polysiloxanes, polydimethylsiloxanes, polyvinylhalogenes and copolymers, celluloseethers, celluloseetriacetates, chitosanes and copolymers and/or mixtures of these substances are used.

30. Method according to one of the claims 19 - 29, characterised in, that the deposition of the polysaccharides of the formula 1 according to claim 1 is achieved via hydrophobic interactions, van der Waals forces, electrostatic interactions, hydrogen bonds, ionic interactions, cross-linking and/or covalent bonding.

10

31. Method according to one of the claims 19 - 30, wherein instead of the active agent paclitaxel one of the following active agents is used: simvastatin, 2-methylthiazolidine-2,4-dicarboxylic sodium salt, macrocyclic suboxide (MCS), derivatives of MCS, activated protein C (aPC), PETN, trapidil, β -estradiol as well as mixtures of these active agents or mixtures of one of these active agents with paclitaxel.

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32. Medical device available by one method according to one of the claims 19 - 31.

Abstract

- 5 The invention relates to the use of polysaccharides, that comprise the sugar building unit N-acylglucosamine, for the preparation of hemocompatible surfaces as well as methods for the hemocompatible coating of surfaces with these polysaccharides, which are classified to be the common biosynthetic precursor substances of heparin and heparansulphates. Described are medical devices
- 10 coated according to invention, especially stents, which comprise paclitaxel as antiproliferative active agent as well as the use of these stents for the prevention of restenosis.