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(72) Inventeurs/Inventors:
HORRES, ROLAND, DE;
HOFFMANN, MICHAEL, DE;
FAUST, VOLKER, DE;
HOFFMANN, ERIKA, DE;
DI BIASE, DONATO, DE

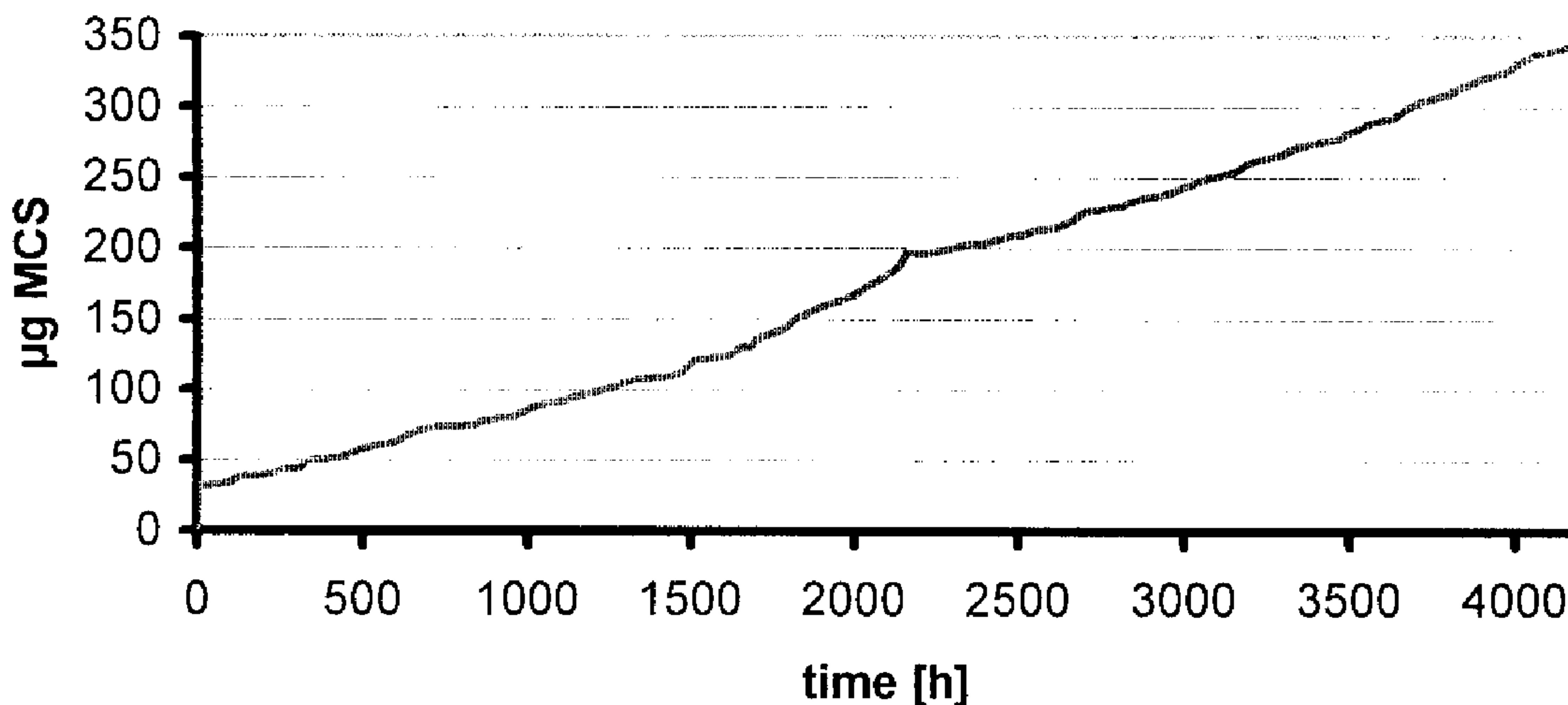
(73) Propriétaire/Owner:
HEMOTEQ AG, DE

(74) Agent: HICKS & ASSOCIATES

(54) Titre : REVETEMENT BIOCOMPATIBLE, BIOSTABLE DE SURFACES MEDICALES

(54) Title: BIOCOMPATIBLE, BIOSTABLE COATING OF MEDICAL SURFACES

Elution of MCS from polysulfone in a 3-layer-system with PVP



(57) Abrégé/Abstract:

The invention relates to medical products with at least one biocompatible, biostable polysulfone coating by means of which the elution kinetics of the at least one incorporated and/or deposited antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent can be controlled via the admixture of at least one hydrophilic polymer in a suitable amount and as well as a local separation of different active agents and active agent combinations, respectively, can be achieved by means of the layer system of biostable polymers, methods of manufacturing these medical products as well as their use in particular in the form of stents for the prevention of restenosis.

ABSTRACT

The invention relates to medical products with at least one biocompatible, biostable polysulfone coating by means of which the elution kinetics of the at least one incorporated and/or deposited antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent can be controlled via the admixture of at least one hydrophilic polymer in a suitable amount and as well as a local separation of different active agents and active agent combinations, respectively, can be achieved by means of the layer system of biostable polymers, methods of manufacturing these medical products as well as their use in particular in the form of stents for the prevention of restenosis.

BIOCOMPATIBLE, BIOSTABLE COATING OF MEDICAL SURFACES

FIELD OF THE INVENTION

The invention relates to medical surfaces with a biocompatible, biostable coating of polysulfones or/and polysulfone derivatives or copolymers, respectively, with polysulfone which contains at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent and/or is covered by agent, methods for the manufacture of these surfaces as well as their use in the form of long-term implants, in particular stents for the prevention of restenosis.

BACKGROUND OF THE INVENTION

In the last years, the implantation of stents in the balloon dilatation of occluded blood vessels has increased more and more. Although stents reduce the risk of a reoccurring vessel occlusion, they are until the present day not capable of completely preventing such restenoses.

An exact description of the term of restenosis cannot be found in the technical literature. The most frequently used morphologic definition of the restenosis is the one which defines the restenosis as a reduction of the vessel diameter to less than 50 % of the normal after successful PTCA (percutaneous transluminal coronary angioplasty). This is an empirically determined value whose hemodynamic relevance and relation to clinical pathology lacks of a stable scientific foundation. In practice, the clinical aggravation of a patient is often considered as a sign of a restenosis of the formerly treated vessel segment.

There are three different reasons for the restenosis caused by the stent:

a.) In the first time after the implantation, the stent surface is directly exposed to the blood and, due to the now present foreign surface, an acute thrombosis can occur, which again occludes the blood vessel.

b.) The implantation of the stent causes vessel injuries which, besides the above-mentioned thrombosis, also provoke inflammation reactions which play a decisive role for the recovery process during the first seven days. The herein occurring processes are among others related to the release of growth factors, wherewith an

increased proliferation of the smooth muscle cells is initiated, which rapidly leads to a reoccurring occlusion of the vessel due to uncontrolled growth.

c.) After few weeks, the stent starts to grow into the tissue of the blood vessel. That means that the stent is surrounded completely by smooth muscle cells and has no contact to the blood. This cicatrization can be too pronounced (neointima hyperplasia) and may lead to the fact that not only the stent surface is covered, but that the complete interior space of the stent is occluded.

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 however addresses as anti-coagulant only the first mentioned cause and moreover can only unfold its total effect in solution. This first problem can meanwhile be prevented almost totally by means of medical treatment by administration of anti-coagulants. It is intended to solve the second and third problem at the moment by locally inhibiting the growth of the smooth muscle cells at the stent. This is attempted e.g. with radioactive stents or with stents which contain pharmaceutically active agents.

Thus, US-A-5 891 108 discloses for example a hollow moulded stent, which can contain pharmaceutical active agents in its interior, which are released through a multitude of openings in the stent. EP-A-1 127 582 on the other hand describes a stent that shows ditches of 0.1 – 1 mm of depth and 7 – 15 mm of length on its surface which are suitable for the reception of an active agent. These active agent reservoirs release, comparable to the openings in the hollow stent, the pharmaceutically active agent contained therein punctually in a high concentration and over a relatively long period of time, which however leads to the fact that the smooth muscle cells are no longer, or only in a very delayed manner, capable of enclosing the stent. As a consequence, the stent is much longer exposed to the blood, which in turn leads to an increased number of vessel occlusions caused by thromboses (Liistro F., Colombo A., Late acute thrombosis after Paclitaxel eluting stent implantation. Heart (2001) 86, 262-4).

One approach for solving this problem is the phosphorylcholine coating of biocompatibles (WO 0101957), whereby phosphorylcholine, a component of the erythrocyte cell membrane, is destined to create a non-thrombogenic surface as a component of the deposited, non biodegradable polymer layer on the stent. Thereby the active agent is absorbed

by the phosphorylcholine layer containing polymer depending on the molecular weight or adsorbed on the surface.

Accordingly, an objective of the present invention is to provide a medical product with a hemocompatible surface as well as a manufacturing method for this medical product with the hemocompatible surface.

In particular, the hemocompatible surface of the medical product is designed to allow a continuous and controlled ingrowth of the medical product into the vessel wall.

This objective is solved by the technical teaching of the independent claims of the present invention. Further advantageous designs of the invention result from the dependent claims, the description, the figures, as well as the examples.

SUMMARY OF THE INVENTION

In accordance with the invention, there is provided a medical product, characterized in that its surface is coated at least partially with at least one biostable polysulfone layer.

In one embodiment, the medical product is characterized in that the polysulfone is selected from the group which comprises the following: polyethersulfone, substituted polyethersulfone, polyphenylsulfone, substituted polyphenylsulfone, polysulfone block copolymers, perfluorinated polysulfone block copolymers, semifluorinated polysulfone block copolymers, substituted polysulfone block copolymers and/or mixtures of the aforementioned polymers.

In another embodiment, the medical product is characterized in that the at least one biostable polysulfone layer contains at least one hydrophilic polymer.

In another embodiment the medical product is characterized in that the polysulfone containing the at least one hydrophilic polymer is present in a mixture ratio of 50% by weight : 50% by weight up to 99.999% by weight : 0.001% by weight.

In yet another embodiment, the medical product is characterized in that the hydrophilic polymer is selected from the group which comprises the following: polyvinylpyrrolidone, glycerine, polyethylene glycol, polypropylene glycol, polyvinyl alcohol, polyhydroxyethyl methacrylates, polyacrylamide, 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-ones), poly-para-dioxanones, polyanhydrides such as polymaleic acid anhydrides, fibrin, polycyanoacrylates, polycaprolactonedimethylacrylates, poly-b-maleic acid, polycaprolactone butylacrylates, multiblock polymers such as from oligocaprolactonedioles and oligodioxanonedioles, polyether ester multiblock polymers such as PEG and polybutylene terephthalate, 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, polyvinylalcohols, 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 copolymers thereof, 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, carboxymethyl sulphate, albumin, hyaluronic acid, chitosan and its derivatives, chondroitine sulphate, dextran, β -cyclodextrins, copolymers with PEG and polypropylene glycol, gum arabic, guar, gelatine, collagen, collagen-N-hydroxysuccinimide, lipids, phospholipids, modifications and copolymers and/or mixtures of the afore-mentioned substances.

In a further embodiment, the medical product is characterized in that the hydrophilic polymer is selected from the group which comprises: polyvinylpyrrolidone polyethylene glycol, polypropylene glycol and/or glycerin.

In yet a further embodiment, the medical product is characterized in that the pore size of the polysulfone coating is determined by the mixture ratio of polysulfone with the at least one hydrophilic polymer.

In a further embodiment, the medical product is characterized in that under and/or on the at least one biostable polysulfone layer with or without the at least one hydrophilic

polymer, at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent is present.

In a further still embodiment, the medical product is characterized in that the biostable layer is bound adhesively or covalently on the surface of the medical product.

In yet another embodiment, the medical product is characterized in that the coating of the surface of the medical product consists of one, two, three or more layers.

In a further embodiment, the medical product is characterized in that under and/or on the at least one biostable polysulfone layer with or without the at least one hydrophilic polymer at least one layer of completely desulphated and N-reacetylated heparin, desulphated and N-reacetylated heparin, N-carboxymethylated and/or partially N-acetylated chitosan and/or of mixtures of these substances is present.

In a further still embodiment, the invention is characterized in that in multiple layer systems the at least two biostable layers differ or do not differ in the proportion of hydrophilic polymer.

In yet another embodiment, the medical product is characterized in that in multiple layer systems the at least one polysulfone layer with or/and without admixture of at least one hydrophilic polymer covers the biostable polysulfone layer at least partially with at least one layer of at least one biodegradable polymer.

In a further still embodiment, the invention is characterized in that the at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent is selected from the group which comprises: sirolimus (rapamycin), everolimus, somatostatin, tacrolimus, roxithromycin, dunaimycin, ascomycin, bafilomycin, erythromycin, midecamycin, josamycin, concanamycin, clarithromycin, troleandomycin, folimycin, cerivastatin, simvastatin, lovastatin, fluvastatin, rosuvastatin, atorvastatin, pravastatin, pitavastatin, vinblastine, vincristine, vindesine, vinorelbine, etoposide, teniposide, nimustine, carmustine, lomustine, cyclophosphamide, C-type natriuretic peptide (CNP), 4-hydroxycyclophosphamide, estramustine, melphalan, ifosfamide, trofosfamide, chlorambucil, bendamustine, dacarbazine, busulfan, procarbazine, treosulfan, temozolomide, thiotepa, daunorubicin, doxorubicin, aclarubicin, epirubicin, mitoxantrone, idarubicin, bleomycin, mitomycin, dactinomycin, methotrexate, fludarabine, fludarabine-5'-dihydrogenphosphate,

cladribine, mercaptopurine, thioguanine, cytarabine, fluorouracil, gemcitabine, capecitabine, docetaxel, carboplatin, cisplatin, cryptophycine, anginex, oxaliplatin, amsacrine, irinotecan, topotecan, hydroxycarbamide, miltefosine, pentostatin, aldesleukin, tretinoin, asparaginase, pegaspargase, anastrozole, exemestane, letrozole, formestane, aminoglutethimide, adriamycin, azithromycin, spiramycin, cepharantin, smc proliferation inhibitor-2w, epothilone A and B, mitoxantrone, azathioprine, mycophenolatmofetil, c-myc-antisense, b-myc-antisense, betulinic acid, camptothecin, lapachol, β -lapachone, podophyllotoxin, betulin, podophyllic acid 2-ethylhydrazide, molgramostim (rhuGM-CSF), peginterferon α -2b, lenograstim (r-HuG-CSF), filgrastim, macrogol, anginex, Na-Uretic peptides, dacarbazine, basiliximab, daclizumab, selectin (cytokine antagonist), chryptophycines, CETP inhibitor, cadherines, cytokinin inhibitors, COX-2 inhibitor, AE-941 (Neovastat®) NFkB, angiopeptin, ciprofloxacin, camptothecin, fluroblastin, monoclonal antibodies, which inhibit the muscle cell proliferation, bFGF antagonists, probucol, prostaglandins, Ac-YVAD-CMK, 1,11-dimethoxycanthin-6-one, 1-hydroxy-11-methoxycanthin-6-one, scopoletin, colchicine, NO donors such as pentaerythritol tetranitrate and syndnoeimines, S-nitrosoderivatives, tamoxifen, staurosporine, β -estradiol, α -estradiol, estriol, estrone, ethinylestradiol, fosfestrol, medroxyprogesterone, estradiol cypionates, estradiol benzoates, tranilast, kamebakaurin and other terpenoids, which are applied in the therapy of cancer, verapamil, tyrosine kinase inhibitors (tyrphostines), cyclosporine A, paclitaxel and its derivatives such as 6- α -hydroxy-paclitaxel, baccatin, taxotere and others, synthetically produced as well as macrocyclic oligomers obtained from native sources of carbon suboxide (MCS) and its derivatives, mofebutazone, acetaminophen, diclofenac, lonazolac, dapsone, o-carbamoylphenoxyacetic acid, lidocaine, ketoprofen, mefenamic acid, piroxicam, meloxicam, chloroquine phosphate, penicillamine, hydroxychloroquine, auranofin, sodium aurothiomalate, oxaceprol, celecoxib, β -sitosterin, ademetionine, myrtecaine, polidocanol, nonivamide, levomenthol, benzocaine, aescin, ellipticine, D-24851 (Calbiochem), colcemid, cytochalasin A-E, indanocine, nocodazole, S 100 protein, bacitracin, vitronectin receptor antagonists, azelastine, guanidyl cyclase stimulator, tissue inhibitor of metal proteinase-1 and -2, free nucleic acids, nucleic acids incorporated into virus transmitters, DNA and RNA fragments, plasminogen activator inhibitor-1, plasminogen activator inhibitor-2, antisense oligonucleotides, VEGF inhibitors,

IGF-1, active agents from the group of antibiotics such as cefadroxil, cefazolin, cefaclor, cefotaxim, tobramycin, gentamycin, penicillins such as dicloxacillin, oxacillin, sulfonamides, metronidazol, antithrombotics such as argatroban, aspirin, abciximab, synthetic antithrombin, bivalirudin, coumadin, enoxaparin, desulphated and N-reacetylated heparin (hemoparin®), tissue plasminogen activator, GpIIb/IIIa platelet membrane receptor, factor X_a inhibitor antibody, heparin, hirudin, r-hirudin, PPACK, protamin, prourokinase, streptokinase, warfarin, urokinase, vasodilators such as dipyramidole, triazolopyrimidine (trapidil®), nitroprussides, PDGF antagonists such as triazolopyrimidine and seramin, ACE inhibitors such as captopril, cilazapril, lisinopril, enalapril, losartan, thioprotease inhibitors, prostacyclin, vapiprost, interferon α , β and γ , histamine antagonists, serotonin blockers, apoptosis inhibitors, apoptosis regulators such as p65 NF-kB or Bcl-xL antisense oligonucleotides, halofuginone, nifedipine, tocopherol, tranilast, molsidomine, tea polyphenols, epicatechin gallate, epigallocatechin gallate, Boswellic acids and its derivatives, leflunomide, anakinra, etanercept, sulfasalazine, etoposide, dicloxacillin, tetracycline, triamcinolone, mutamycin, procainamid, retinoic acid, quinidine, disopyrimide, flecainide, propafenone, sotalol, amidorone, natural and synthetically produced steroids such as bryophyllin A, inotodiol, maquiroside A, ghalakinoside, mansonine, strebloside, hydrocortisone, betamethasone, dexamethasone, non-steroidal substances (NSAIDS) such as fenoprofen, ibuprofen, indomethacin, naproxen, phenylbutazone and other antiviral agents such as acyclovir, ganciclovir and zidovudine, antimycotics such as clotrimazole, flucytosine, griseofulvin, ketoconazole, miconazole, nystatin, terbinafine, antiprozoal agents such as chloroquine, mefloquine, quinine, moreover natural terpenoids such as hippocaesculin, barringtogenol-C21-angelate, 14-dehydroagrostistachin, agroskerin, agrostistachin, 17-hydroxyagrostistachin, ovatodiolids, 4,7-oxycycloanisomelic acid, baccharinoids B1, B2, B3 and B7, tubeimoside, bruceanol A, B and C, bruceantinoside C, yadanziosides N and P, isodeoxyelephantopin, tomenphantopin A and B, coronarin A, B, C and D, ursolic acid, hyptatic acid A, zeorin, iso-iridogermanal, maytenfoliol, effusantin A, excisanin A and B, longikaurin B, sculponeatin C, kamebaunin, leukamenin A and B, 13,18-dehydro-6- α -seneciolyloxychaparrin, taxamairin A and B, regenilol, triptolide, furthermore cymarin, apocymarin, aristolochic acid, anopterin, hydroxyanopterin, anemonin, protoanemonin,

berberine, cheliburin chloride, cictoxin, sinococuline, bombrestatin A and B, cudraiso flavone A, curcumin, dihydronitidine, nitidine chloride, 12- β -hydroxypregnadiene-4,16-diene-3,20-dione, bilobol, ginkgol, ginkgolic acid, helenalin, indicine, indicine-N-oxide, lasiocarpine, inotodiol, glycoside 1a, podophyllotoxin, justicidin A and B, larreatin, malloterin, mallotochromanol, isobutyrylmallotochromanol, maquiroside A, marchantin A, maytansine, lycoridicin, margetine, pancratistatin, liriodenine, bisparthenolidine, oxoushinsunine, aristolactam-AII, bisparthenolidine, periplocoside A, bisparthenolidine, periplocoside A, ghalakinoside, ursolic acid, deoxypsorospermin, psychorubin, ricin A, sanguinarine, manwu wheat acid, methylsorbifolin, sphatheliachromen, stizophyllin, mansonine, strebloside, akagerine, dihydrousambarensine, hydroxyusambarine, strychnopentamine, strychnophylline, usambarine, usambarensine, berberine, liriodenine, oxoushinsunine, daphnoretin, lariciresinol, methoxylariciresinol, syringaresinol, umbelliferon, afromoson, acetylvismione B, desacetylvismione A, vismione A and B.

In yet another embodiment, the invention is characterized in that the at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent is selected from the group which comprises the following: paclitaxel and its derivatives, β -estradiol, simvastatin, PI-88 (Progen Ind.), macrocyclic carbon suboxides (MCS) and their derivatives, trapidil[®], N-(pyridine-4-yl)-[1-4-(4-chlorobenzyl)-indol-3-yl]-glyoxylamide (D-24851), activated protein C (aPC), Ac-YVAD-CMK, Anginex (β -Pep25), Neovastat[®], Cryptophycin 52, tacrolimus.

In a further still embodiment, the invention is characterized in that the at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent is contained in a pharmaceutically active concentration of 0.001 – 20 mg per cm² of surface.

In yet another embodiment, the invention is characterized in that in multiple layer systems, the at least two layers with or/and without admixture of at least one hydrophilic polymer contain at least one active agent in the same or in a different concentration of active agent which is covalently or/and adhesively bound.

In a further still embodiment, the invention is characterized in that in multiple layer systems, the last layer is a pure active agent layer is bound covalently or/and adhesively.

In yet another embodiment, the medical product is characterized in that the at least one biostable polysulfone layer which contains at least one active agent or/and is covered with at least one active agent is covered at least partially with a biodegradable polymer layer which contains covalently and/or adhesively either no active agent or at least one active agent in the same or a different concentration.

In another aspect of the invention, a method of biocompatible coating of medical products is provided, the method characterized by the following steps:

- a. Providing a stent, and
 - b. depositing at least one biostable polysulfone layer with or without at least one hydrophilic polymer, and
 - c. depositing and/or incorporating at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent onto and/or into the biostable layer,
- or
- b'. depositing at least one biostable polysulfone layer with or without the at least one hydrophilic polymer together with at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent.

In another embodiment of the method, the method comprises step b' and the further step:

- c'. depositing at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent onto the biostable polymer layer.

In a further embodiment of the method the method comprises the further step:

- d. depositing at least one second biostable polysulfone layer with or without a content of hydrophilic polymers which is equal or different to the first layer without or with incorporating or/and depositing at least one active agent in the same or a different concentration.

In yet another embodiment of the method, the method comprises the further step

d. depositing at least one further layer of at least one biodegradable polymer without or with incorporating or/and depositing at least one active agent in the same or a different concentration.

In further embodiments of the method, the method is characterized in that onto and/or under the at least one biostable polysulfone layer is deposited at least one layer of completely desulphated and N-reacetylated heparin, N-carboxymethylated and/or partially N-acetylated chitosan and/or mixtures of these substances.

In further still embodiments, the invention provides medical products which can be obtained according to the methods.

In further embodiments, the medical products are characterized in that the at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent is released in a controlled manner through the surface coating.

In yet further embodiments, the medical products are characterized in that the respective antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent is contained in a pharmaceutically active concentration of 0.001 – 10 mg per cm² of surface of the medical product and per layer which carries the active agent.

In yet another embodiment, the medical product is characterized in that the medical product is a stent.

DESCRIPTION OF THE FIGURES

Figure 1: Elution diagram of macrocyclic carbon suboxide (MCS) in a triple layer system with polysulfone as base coating, the active agent as medium layer and a polysulfone coating which covers completely the medium active agent layer with a proportion of 0.04% of polyvinylpyrrolidone.

Figure 2: Elution diagram of paclitaxel from a polysulfone matrix with an amount of 9.1% of polyvinylpyrrolidone.

Figure 3: Elution diagram of simvastatin from pure polysulfone matrix without proportion of hydrophilic polymer.

Figure 4: Elution diagram of β -estradiol with a proportion of 15% by weight of the pure polysulfone matrix without proportion of hydrophilic polymer.

Figure 5: Elution diagram of trapidil[®] from a polysulfone matrix with an amount of 4.5% of polyvinylpyrrolidone.

Figure 6: Elution diagram of trapidil[®] with an amount of 50% of the pure polysulfone matrix.

Figure 7: Photomicrography of the vessel segments after 4 weeks of implantation in the pig.

Figure A shows an enlarged section of a matrix stent

Figure B shows a cross-section of the vessel segment with the stent which is coated with polysulfone and loaded with MCS in higher concentration.

DETAILED DESCRIPTION

The present invention relates to medical products the surface/s of which is/are at least partially coated with at least one biostable polysulfone layer.

It was surprisingly found that the coating of medical surfaces being in permanent contact with blood, with polysulfone, polyethersulfone and/or polyphenylsulfone and its derivatives represents an extremely suitable biocompatible substrate for active agents. By admixing of hydrophilic biocompatible polymers or by the use of polysulfones with ambivalent properties, i.e. with lipophilic and hydrophilic moieties, the pore size of the polysulfone matrix can be varied such that hereby a plurality of possibilities can be made possible in respect of the used active agents, the applicable amount, as well as the desired release rate. Especially the elution kinetics of the at least one active agent can be regulated via the pore size in the biostable layer. The pore size in turn is determined by the type and amount of the used hydrophilic polymer, or respectively the amount of lipophilic and lipophobic groups in the polysulfone or polysulfone mixture. Besides the impact of the added hydrophilic polymer, the addition of small amounts of water (or also ethyl acetate) in the coating solution has impact on the future properties of the coated implant which is loaded with the active agent. The setting of the load distribution, of the release properties (as a function of the time and the eluted amount of active agent) and the spraying properties of the coating solution are decisively affected by the defined addition of water (or also ethyl acetate or other additives described below) into the spraying solution.

It was also found to be advantageous that the use of nitrogen as carrier gas for the spray coating leads to a load of the polymer layer containing the active agent with nitrogen which remains in the layer and provides here for the intactness of the active agent due to its capacity as protective gas. Therewith, the shelf life of the active agent is assured permanently in a form which remains effective in an unaltered way.

The modification of the polysulfone framework by polymer analogous reactions such as the preparation of new polysulfone copolymers (e.g. as polysulfone block copolymers or in statistical distribution) has impact on the physical behavior of the resulting polymers, whereby the properties of the polymer can be controlled, and are applicable either in combination with the non-modified polymers or individually as new hemocompatible coating material. Thus, a

polyethersulfone containing carboxylic groups can be prepared via the reaction of polysulfone copolymers with 4,4'-bis(hydroxyphenyl)pentanoic acid (BPA), which leads to a clear hydrophilicity of the polymer. The properties of the hydrophilic polysulfone can also be used as hydrophilic polymer additive to the non-modified polysulfone, as already mentioned above. Via the setting of the modification grade, the hydrophilicity grade is influenced, so that a polymer molecule results, in which every chain contains non-modified and modified regions and thus combines hydrophobic and hydrophilic properties in itself, which impart to the polymer also an altered spatial arrangement of the chain segments, the so-called secondary structure. Therefore, it is preferred to use a polysulfone for the coating, which has hydrophilic regions as well as hydrophobic regions. Suchlike polysulfones can be prepared by providing a polysulfone with hydrophilic side chains or functional groups after the polymerization via polymer analogous reactions, provided the polymer itself is hydrophobic, or inversely by providing a hydrophilic polysulfone with hydrophobic side chains or functional groups. In this preferred embodiment, the hydrophilic and hydrophobic properties are combined within one polymer molecule, generally with a statistic distribution, as the polymer analogous reactions proceed with a statistic distribution. Further, such systems of hydrophilic polysulfone with hydrophobic polysulfone can be prepared via statistic polymerization of at least one hydrophilic monomer and at least one hydrophobic monomer. Therefrom, structures result which are similar to the afore-mentioned embodiment of the subsequent modification via polymer analogous reactions. A third embodiment consists in the block copolymerization of at least one hydrophilic sulfone block polymer with at least one hydrophobic sulfone block polymer to a polysulfone which respectively disposes of the hydrophilic and hydrophobic properties in the individual blocks. Another variant consists in converting at least one hydrophilic monomer in an alternating copolymerization with at least one hydrophobic monomer. Hereby, the hydrophilic and hydrophobic properties in the obtained polysulfone are alternately distributed in the polymer chain. Further, a mixture of at least one hydrophilic polysulfone with at least one hydrophobic polysulfone can be applied in the coating according to the invention. Herein, the hydrophilic and hydrophobic properties are not combined in one polymer molecule but can be found again in the coating and result in the same effects as in the aforementioned embodiments.

For the preparation of the polysulfones, all polymerization reactions known to one skilled in the art are suitable, such as radical, anionic, cationic or thermal polymerization. Examples for the aforementioned polysulfones as well as possibilities for the preparation thereof will be described below.

Furthermore, there is the possibility of derivatizing introduced functional groups, for example the carboxylic group (Macrom. Chem. Phys. 1994, 195, 1709). Thus, the hydrophobicity of the active agent can easily be increased beyond the hydrophobic properties of the used polymer e.g. via introduction of fluorinated compounds (Coll. Polym. Sci. 2001, 279, 727). Via the introduction of functional groups, graft copolymers can be prepared, wherein the side chains now consist of other structure units than the main chain. For this purpose, biocompatible, biostable and biodegradable polymers can be used.

The functional groups can also be used for a bonding which is unstable to hydrolysis of active agents. Hence, the active agent is released in a form which is also controlled via the hydrolysis and depending on the type of bonding (thioester bonding, ester bonding). Herein, the advantage is the possibility to control the elution of the active agent in such a manner that the release curve takes another trajectory and that adaptations to many different courses of disease with diverse requirements concerning the active agent concentration depending on the time can be achieved with the implant. A variation consists in the covalent bonding of desulphated and N-reacetylated heparin and/or N-carboxymethylated and/or partially N-acetylated chitosan to the polymer chain, whereby the hemocompatibility of the polymer is improved by means of the athrombogeneous compound.

Due to the possibility of the construction of at least two layers of the polymer which is variable concerning its composition, as well as in the variation of the additives, a differentiation depending on the layer with regard to the applied active agents as well as with regard to the concentration can be proceeded. This adaptability distinguishes the polysulfone matrix as a universally applicable, biostable coating material for the prevention of the restenosis.

For the setting of the pore size and thus, of the active agent amount in the polysulfone matrix, not only hydrophilic polymers, but also minerals and even water can be used as additives. The pore size controls on the one hand the release kinetics of the at least one

antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent as well as the amount of active agent in determined embodiments, which can be incorporated or respectively deposited in a polysulfone coating, since the pores in the polysulfone can serve as an active agent reservoir.

For the creation of pores in the polysulfone matrix in the application of these additives, different strategies can, or respectively, must be pursued.

In principle, the creation of pores is carried out in such a way that the additives are deposited together with the matrix-building polysulfone on the medical product which is to be coated according to a suitable method. Herein, polysulfone homogenous compartments of the additive, which can be controlled in their dimension, are formed depending on the differences in the hydrophilicity of the applied additives as well as of the matrix-building polysulfone. The number of these homogenous compartments per volume unit of the polysulfone matrix can be controlled via the amount added by percentage of the additive.

As additives can be used in detail amino acids, polyamino acids, hydrophilic polymers, saccharides, oligosaccharides, polysaccharides, oligopeptides, polyvinylpyrrolidone, polyethylenimine, glycerin, polyethers, glycol, minerals and water.

In the case of the amino acids, the genetically coded acidic amino acids asparaginic acid, glutaminic acid; the neutral amino acids alanine, asparagine, cysteine, glutamine, glycine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine; and the basic amino acids arginine, histidine, lysine; as well as the genetically non-coded amino acids ornithine and taurine are preferred. In particular preferred are the representatives of the L-series of these amino acids. Further, the representatives of the D-series of these amino acids as well as D,L-mixtures of one amino acid as well as D,L-mixtures of more amino acids are preferred.

In the case of the polyamino acids, the amino acids poly-L-asparaginic acid, poly-L-glutaminic acid, poly-L-alanine, poly-L-asparagine, poly-L-cysteine, poly-L-glutamine, poly-L-glycine, poly-L-isoleucine, poly-L-leucine, poly-L-methionine, poly-L-phenylalanine, poly-L-proline, poly-L-serine, poly-L-threonine, poly-L-tryptophan, poly-L-tyrosine, poly-L-valine, poly-L-arginine, poly-L-histidine, poly-L-lysine as well as poly-ornithine and poly-aurine are preferred. Further also representatives of the D-series of these polyamino acids as

well as D,L-mixtures of one polyamino acid as well as D,L-mixtures of several polyamino acids are suitable.

In the case of the hydrophilic polymers, globular molecules such as organic nanoparticles, star polymers, dendrimers and/or high-branched polymers are preferred.

In the case of the minerals, carbonates, chlorates, phosphates and sulphates of the cations sodium, calcium, potassium and/or magnesium are preferred.

For the creation of the pore structure, these compartments are subsequently removed from the polysulfone matrix. What remains is the three-dimensional structure with the predetermined grade of porosity, which can be then "filled" with the active agent.

In the following, three preferred systems for the creation of the pore structure are briefly described on the basis of the additive classes of polymer, mineral and water.

System 1: Polymer

As polymeric additives are used e.g. special high-branched polyesters with thermo-unstable triazene groups in the main chain. The molecularly dispersed high-branched polymer is integrated into the polysulfone matrix. The subsequent thermal treatment of the system decomposes the high-branched pore creator into volatile products of decomposition under creation of a corresponding nanoporous polymer layer. Polysulfones distinguish themselves inter alia by their temperature stability and high dimension stability, whereby this strategy is applicable by all means. Moreover, this thermal treatment can be coupled with the step of sterilization, which results in an efficient method.

System 2: Mineral

As mineral additive, e.g. the physiologically harmless compound calcium carbonate is applied. The polysulfone matrix consists of double hydrophilic block copolymers. These double hydrophilic block copolymers comprise a hydrophilic block, which does not interact with the mineral additive, and a second polyelectrolyte block, which interacts strongly with the surfaces of the mineral additive. These block copolymers have growth modifying effects in the crystallization of calcium carbonate. The resulting mineral compartments have an approximately oval, bar-bell or spherical shape. Due to the excellent resistance of the polysulfones against aggressive chemicals as well as the hydrolysis stability, the mineral

additives can be completely removed in the acid bath. What remains is the desired nanoporous structure of the polysulfone matrix.

System 3: Water

As fluid additive, water comes into consideration as easiest solution in the case of the coating of the medical product with polar active agents. In the use of the spraying method, the polysulfone is present in an organic solvent such as e.g. chloroform. The chloroform solution saturated with polysulfone is only conditionally capable of the further reception of the active agent. Thus, the active agent dissolves principally in the aqueous phase, which, due to the phase separation, forms compartments after the deposition on the surface of the medical product. Subsequently, the water from these compartments can be removed completely from the system by means of e.g. the freeze drying. What remains are nanoporous structures loaded with the active agent. The active agent concentration of the pores can be increased in consecutive steps with active agent dissolved in water and preferably subsequent freeze drying. In the methods existing until the present day, the active agent was also dissolved together with the polysulfone in chloroform. The following increase of the concentration of the active agent was also effected from a chloroform solution. Since the chloroform can by no means be removed from the layer at 100 %, the chloroform concentrates more and more in the finished end product, which entails an unnecessary exposure of the patient. By the use of water as active agent substrate, chloroform is used only once for the deposition of the polysulfone matrix and the exposure is reduced to a minimum.

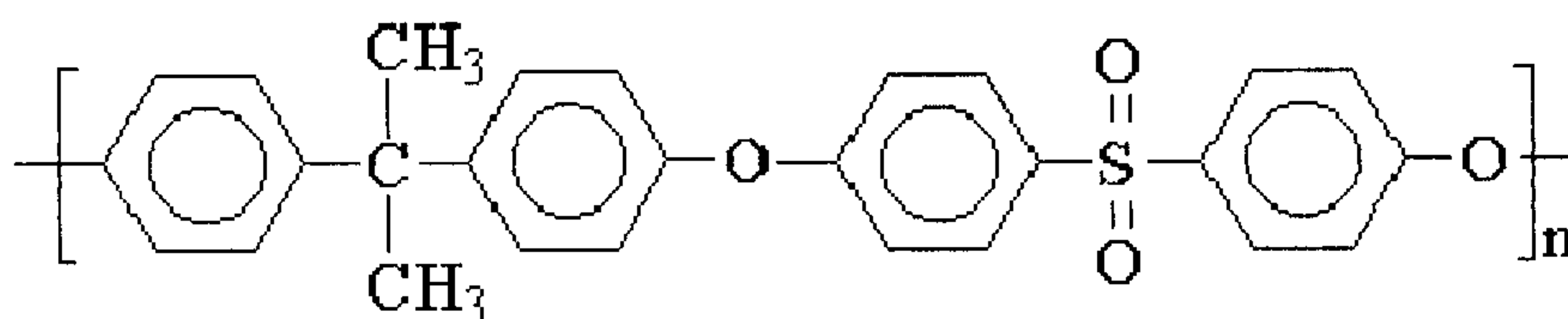
For the preparation of a spraying solution containing at least one polysulfone and at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent further preferably solvents are suitable, which evaporate easily, i.e. which are volatile, such as for example chloroform, dichloromethane, tetrahydrofuran, acetone, methanol, ethanol, isopropanol, diethyl ether and ethyl acetate and which moreover can be saturated with water or be prepared having a particular water content. Thereby, water contents from 1.6 – 15%, preferably 2.1 – 10%, more preferably 2.6 – 7.9% and especially preferably 3.3 – 6.8% are suitable. Further, it is preferred if organic solvent, water, polysulfone and active agent form a homogeneous solution.

Via the creation of copolymers, the hydrophilicity or, respectively, the hydrophobicity of the polysulfone can be also varied. Thus, it is for example possible to synthesize polysulfone copolymers by means of 4,4'-bis(hydroxyphenyl)-pentanoic acid (BPA), so that in this way, carboxylic side groups are introduced, which lower the hydrophobicity of the polysulfone matrix. Moreover, it is now possible to derivatize introduced functional groups, for example the carboxylic group (Macrom. Chem. Phys. 195 (1994), 1709; Coll. Polym. Sci. 279 (2001), 727).

Via the possibility of forming of at least two layers of the polymer, which is variable in its composition, as well as in the variation of the additives, additionally a layer-dependent differentiation in respect of the applied active agents as well as in respect of the concentration can be conducted. This adaptability distinguishes the polysulfone matrix as a universally applicable, biostable coating material for the prevention of restenosis.

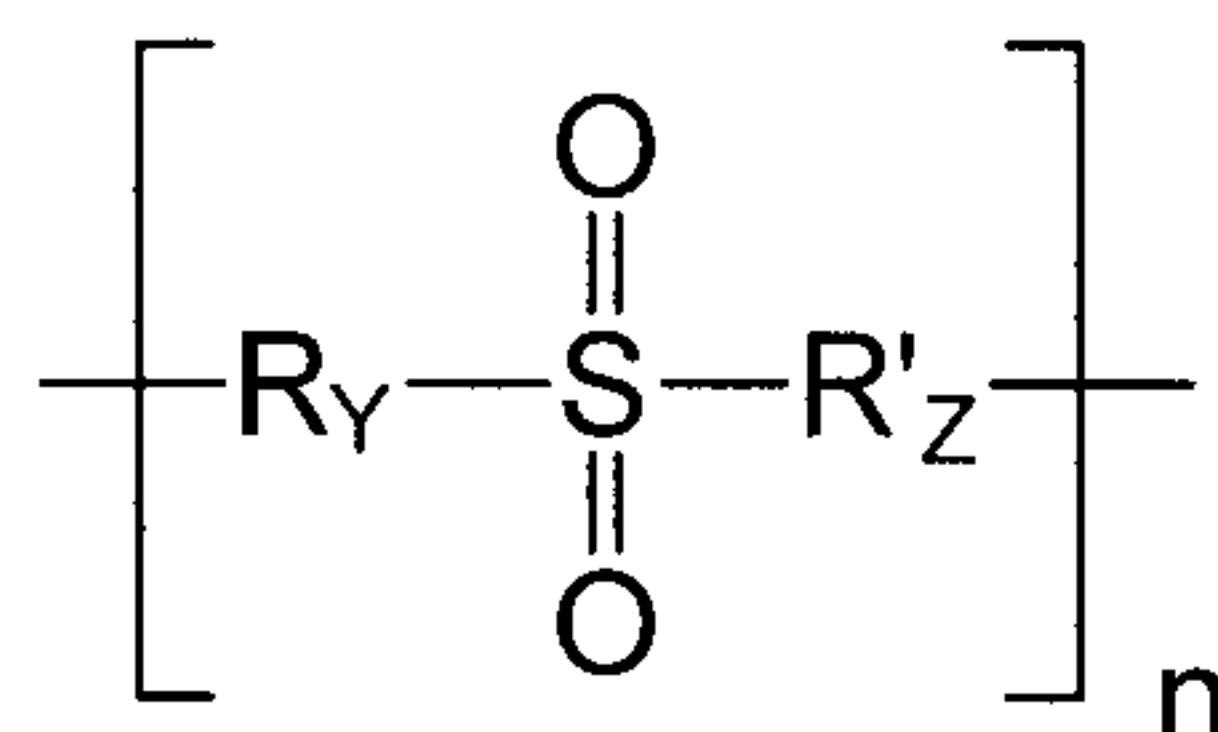
Further the use of thermoplastic polysulfones is preferred. Thermoplastic polysulfones can be deformed plastically (plastic) under the influence of heat (thermo). Generally, thermoplastic polysulfones consist of linear or less branched molecule chains. When heated, they can be extended by stretching. When further heated, they can be smelted completely and be rebuilt. In particular, it is preferred if these thermoplastic polysulfones have hydrophilic as well as hydrophobic properties. Such thermoplastic polysulfones having these ambivalent properties can be synthesized according to the above described methods via polymer analogous reactions, block copolymerizations or polymerization of hydrophilic with hydrophobic monomers. The thermoplastic polymers obtained in that way, or, respectively, the medical products coated therewith, distinguish by multiple sterilizability, resistance against hot steam and hydrolysis, high stability of dimension, resistance against aggressive chemicals as well as good thermal aging stability.

A preferred thermoplastic polysulfone is synthesized from bisphenol A and 4,4'-dichlorophenylsulfone via polycondensation reactions (see following formula (II)).



Poly[oxy-1,4-phenylene-sulfonyl-1,4-phenylene-oxy-(4,4'-isopropylidenediphenylene)]

The polysulfones which are applicable for the coating according to the invention have the following general structure according to formula (I):



wherein

n represents the grade of polymerization, which is in the range from n = 10 to n = 10,000, preferably in the range from n = 20 to n = 3,000, further preferably in the range from n = 40 to n = 1,000, further preferably in the range from n = 60 to n = 500, further preferably in the range from n = 80 to n = 250 and particularly preferable in the range from n = 100 to n = 200.

Further, it is preferred if n is in such a range that a weight average of the polymer of 60,000 – 120,000 g/mol, preferably 70,000 to 99,000 g/mol, further preferably 80,000 – 97,000 g/mol, still more preferably 84,000 – 95,000 g/mol, and particularly preferable 86,000 – 93,000 g/mol results.

Moreover, it is preferred if n is in such a range that the number average of the polymer in a range from 20,000 – 70,000 g/mol, preferably from 30,000 – 65,000 g/mol, further preferably 32,000 – 60,000, still more preferred 35,000 – 59,000, and particularly preferable from 45,000 – 58,000 g/mol results.

Y and z are integer numbers in the range from 1 to 10, and R and R' mean independently of each other an alkylene group having 1 to 12 carbon atoms, an aromatic group having 6 to 20 carbon atoms, a heteroaromatic group having 2 to 10 carbon atoms, a cycloalkylene group having 3 to 15 carbon atoms, an alkylenearylene group having 6 to 20 carbon atoms, an arylenalkylene group having 6 to 20 carbon atoms, an alkyleneoxy group having 1 to 12 carbon atoms, an arylenoxygroup having 6 to 20 carbon atoms, a heteroarylenoxy group having 6 to 20 carbon atoms, a cycloalkyleneoxy group having 3 to 15 carbon atoms, an alkylenearylenoxy group having 6 to 20 carbon atoms or an

arylenealkyleneoxy group having 6 to 20 carbon atoms. The foregoing groups can have further substituents, particularly those which are described below by "substituted" polysulfones.

Examples for the groups R and R' are $-R^1-$, $-R^2-$, $-R^3-$, $-R^4-$, $-R^5-$, $-R^6-$, $-R^1-R^2-$, $-R^3-R^4-$, $-R^5-R^6-$, $-R^1-R^2-R^3-$, $-R^4-R^5-R^6-$, $-R^1-R^2-R^3-R^4-$, $-R^1-R^2-R^3-R^4-R^5-$ as well as $-R^1-R^2-R^3-R^4-R^5-R^6-$;

wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 represent independently of each other the following groups:

$-CH_2-$, $-C_2H_4-$, $-CH(OH)-$, $-CH(SH)-$, $-CH(NH_2)-$, $-CH(OCH_3)-$, $-C(OCH_3)_2-$, $-CH(SCH_3)-$, $-C(SCH_3)_2-$, $-CH(NH(CH_3))-$, $-C(N(CH_3)_2)-$, $-CH(OC_2H_5)-$, $-C(OC_2H_5)_2-$, $-CHF-$, $-CHCl-$, $-CHBr-$, $-CF_2-$, $-CCl_2-$, $-CBr_2-$, $-CH(COOH)-$, $-CH(COOCH_3)-$, $-CH(COOC_2H_5)-$, $-CH(COCH_3)-$, $-CH(COC_2H_5)-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH(C_2H_5)-$, $-C(C_2H_5)_2-$, $-CH(CONH_2)-$, $-CH(CONH(CH_3))-$, $-CH(CON(CH_3)_2)-$,

$-C_3H_6-$, $-C_4H_8-$, $-C_5H_9-$, $-C_6H_{10}-$, cyclo- C_3H_4- , cyclo- C_3H_4- , cyclo- C_4H_6- , cyclo- C_5H_8- , $-OCH_2-$, $-OC_2H_4-$, $-OC_3H_6-$, $-OC_4H_8-$, $-OC_5H_9-$, $-OC_6H_{10}-$, $-CH_2O-$, $-C_2H_4O-$, $-C_3H_6O-$, $-C_4H_8O-$, $-C_5H_9O-$, $-C_6H_{10}O-$, $-NHCH_2-$, $-NHC_2H_4-$, $-NHC_3H_6-$, $-NHC_4H_8-$, $-NHC_5H_9-$, $-NHC_6H_{10}-$, $-CH_2NH-$, $-C_2H_4NH-$, $-C_3H_6NH-$, $-C_4H_8NH-$, $-C_5H_9NH-$, $-C_6H_{10}NH-$, $-SCH_2-$, $-SC_2H_4-$, $-SC_3H_6-$, $-SC_4H_8-$, $-SC_5H_9-$, $-SC_6H_{10}-$, $-CH_2S-$, $-C_2H_4S-$, $-C_3H_6S-$, $-C_4H_8S-$, $-C_5H_9S-$, $-C_6H_{10}S-$,

$-C_6H_4-$, $-C_6H_3(CH_3)-$, $-C_6H_3(C_2H_5)-$, $-C_6H_3(OH)-$, $-C_6H_3(NH_2)-$, $-C_6H_3(Cl)-$, $-C_6H_3(F)-$, $-C_6H_3(Br)-$, $-C_6H_3(OCH_3)-$, $-C_6H_3(SCH_3)-$, $-C_6H_3(COCH_3)-$, $-C_6H_3(COC_2H_5)-$, $-C_6H_3(COOH)-$, $-C_6H_3(COOCH_3)-$, $-C_6H_3(COOC_2H_5)-$, $-C_6H_3(NH(CH_3))-$, $-C_6H_3(N(CH_3)_2)-$, $-C_6H_3(CONH_2)-$, $-C_6H_3(CONH(CH_3))-$, $-C_6H_3(CON(CH_3)_2)-$,

$-OC_6H_4-$, $-OC_6H_3(CH_3)-$, $-OC_6H_3(C_2H_5)-$, $-OC_6H_3(OH)-$, $-OC_6H_3(NH_2)-$, $-OC_6H_3(Cl)-$, $-OC_6H_3(F)-$, $-OC_6H_3(Br)-$, $-OC_6H_3(OCH_3)-$, $-OC_6H_3(SCH_3)-$, $-OC_6H_3(COCH_3)-$, $-OC_6H_3(COC_2H_5)-$, $-OC_6H_3(COOH)-$, $-OC_6H_3(COOCH_3)-$,

Particularly preferred are polysulfones as well as their mixtures, wherein the groups $-R^1-$, $-R^2-$, $-R^3-$, $-R^1-R^2-$, $-R^1-R^2-R^3-$ represent independently of each other the following groups: $-C_6H_4O-$, $-C(CH_3)_2-$, $-C_6H_4-$, $-C_6H_4SO_2-$, $-SO_2C_6H_4-$, $-OC_6H_4-$, and $-C_6H_4O-C(CH_3)_2-C_6H_4-$.

R and R' can further represent independently of each other preferably a moiety which is bound to the sulfone group in the formulas (II) to (XV).

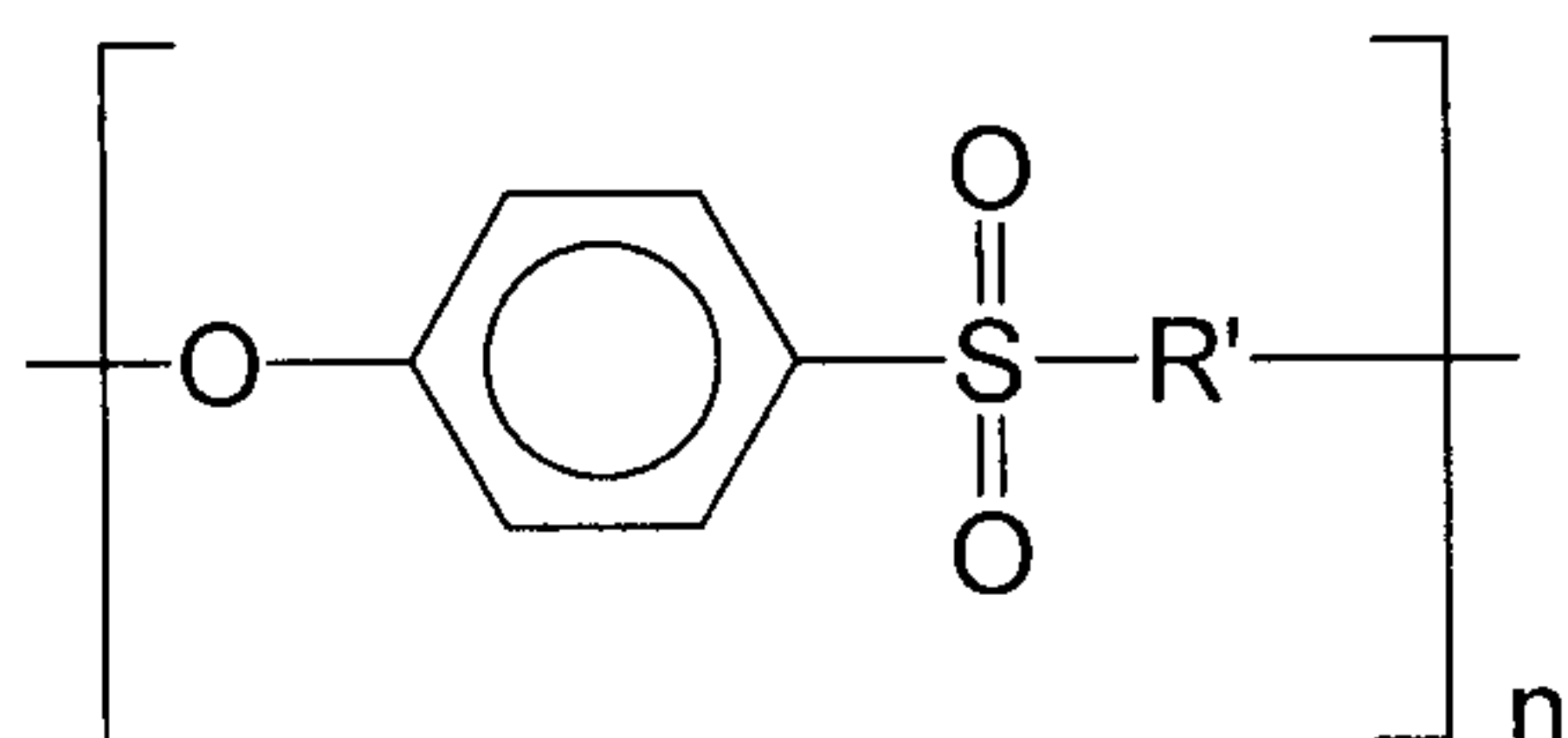
According to the invention, the polysulfone or the polysulfones, respectively, for the biostable layer or the biostable layers are selected from the group which comprises: polyethersulfone, substituted polyethersulfone, polyphenylsulfone, substituted polyphenylsulfone, polysulfone block copolymers, perfluorinated polysulfone block copolymers, semifluorinated polysulfone block copolymers, substituted polysulfone block copolymers and/or mixtures of the foregoing polymers.

The term "substituted" polysulfones is to be understood as polysulfones which possess functional groups. Especially the methylene units can have one or two substituents and the phenylene units one, two, three, or four substituents. Examples for these substituents (also referred to as: X, X', X'', X''') are:

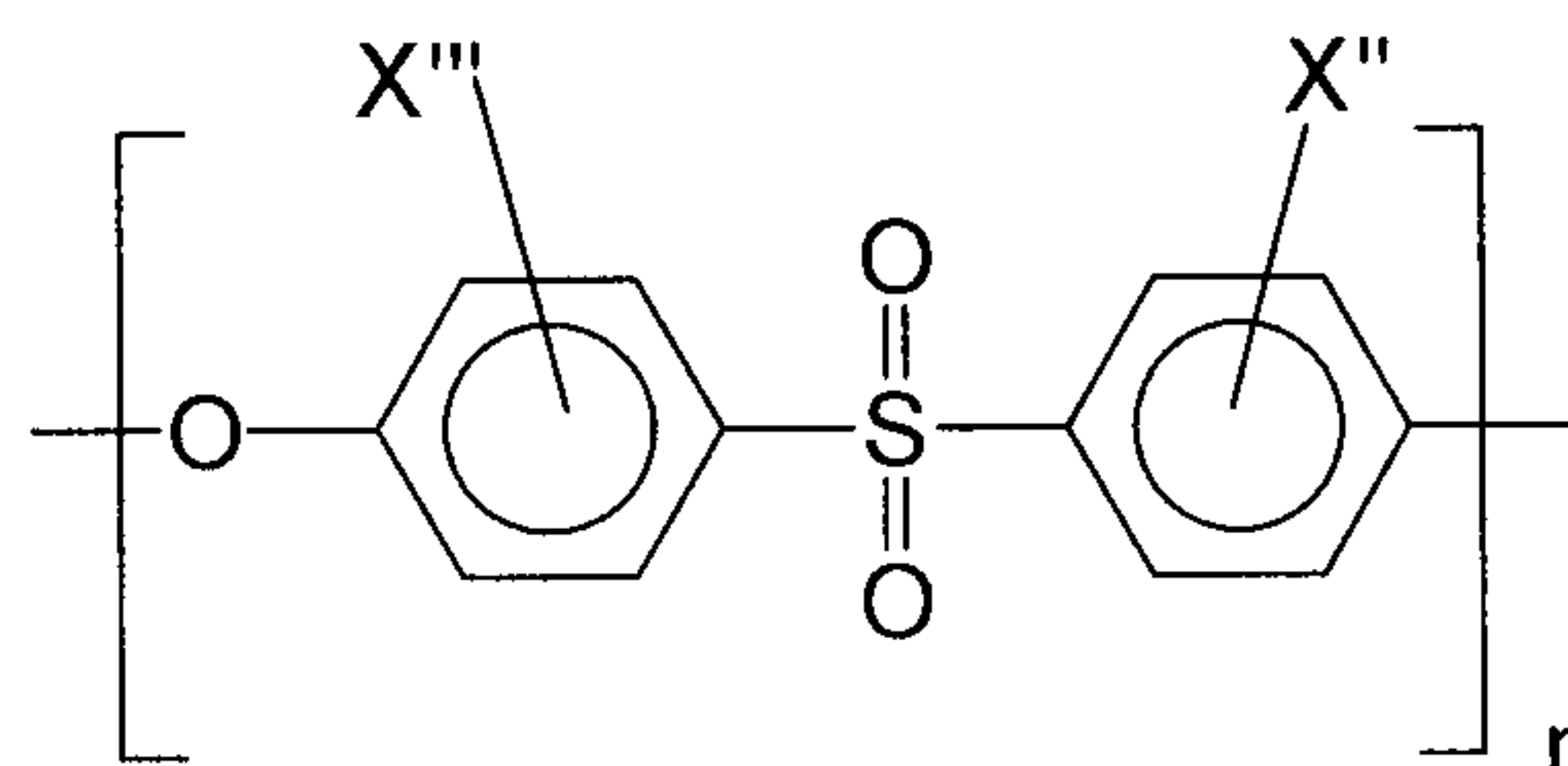
$-OH$, $-OCH_3$, $-OC_2H_5$, $-SH$, $-SCH_3$, $-SC_2H_5$, $-NO_2$, $-F$, $-Cl$, $-Br$, $-I$, $-N_3$, $-CN$, $-OCN$, $-NCO$, $-SCN$, $-NCS$, $-CHO$, $-COCH_3$, $-COC_2H_5$, $-COOH$, $-COCN$, $-COOCH_3$, $-COOC_2H_5$, $-CONH_2$, $-CONHCH_3$, $-CONHC_2H_5$, $-CON(CH_3)_2$, $-CON(C_2H_5)_2$, $-NH_2$, $-NHCH_3$, $-NHC_2H_5$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, $-SOCH_3$, $-SOC_2H_5$, $-SO_2CH_3$, $-SO_2C_2H_5$, $-SO_3H$, $-SO_3CH_3$, $-SO_3C_2H_5$, $-OCF_3$, $-O-COOCH_3$, $-O-COOC_2H_5$, $-NH-CO-NH_2$, $-NH-CS-NH_2$, $-NH-C(=NH)-NH_2$, $-O-CO-NH_2$, $-NH-CO-OCH_3$, $-NH-CO-OC_2H_5$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, $-CH_2Br$, $-CHBr_2$, $-CBr_3$, $-CH_2I$, $-CHI_2$, $-CI_3$, $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-CH(CH_3)_2$, $-C_4H_9$, $-CH_2-CH(CH_3)_2$, $-CH_2-COOH$, $-CH(CH_3)-C_2H_5$, $-C(CH_3)_3$, $-H$. Further preferred substituents or functional groups are $-CH_2-X$ and $-C_2H_4-X$.

The following general structural formulas represent preferred repeating units for polysulfones. Preferably, the polymers only consist of these repeating units. It is however also

possible that in one polymer other repeating units or blocks are present besides the shown repeating units. Preferred are:

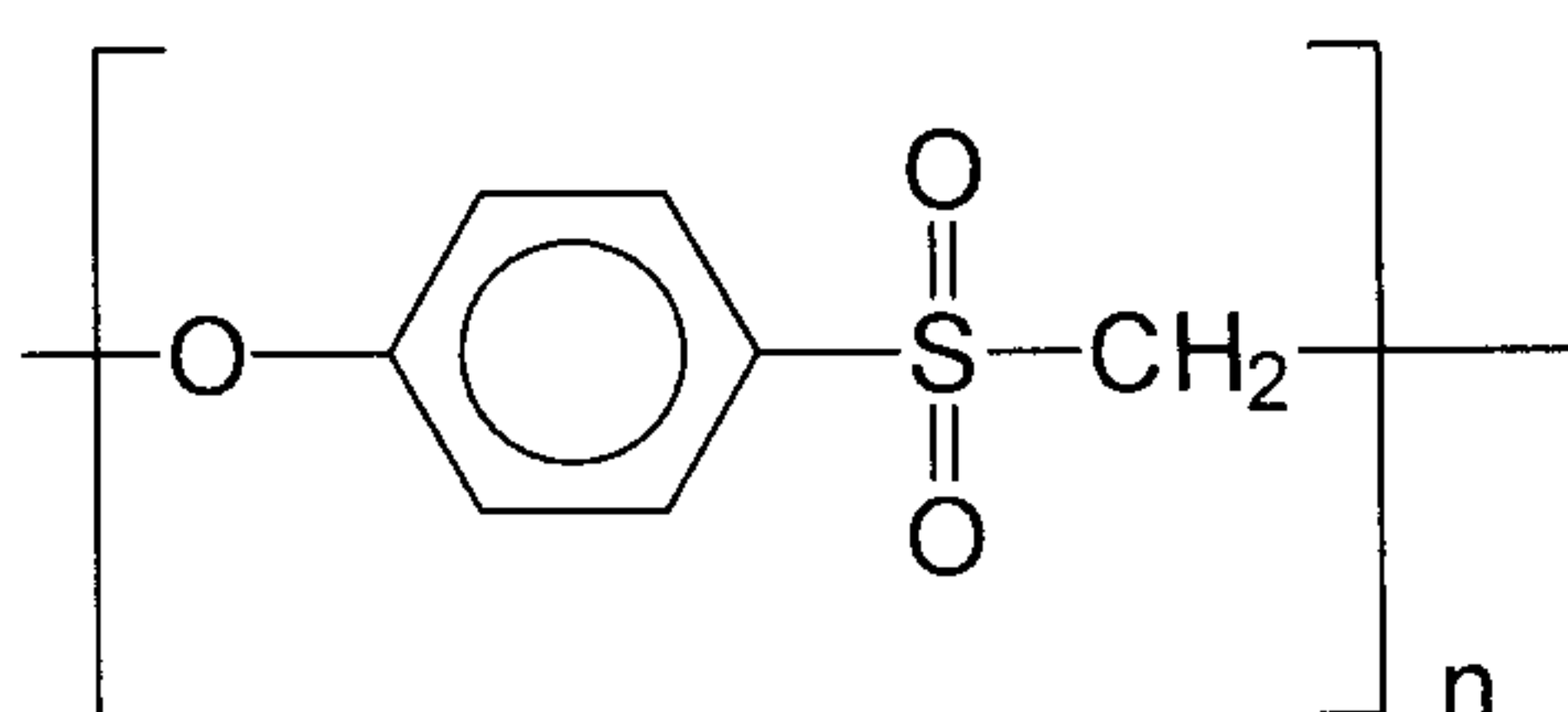


formula (III)

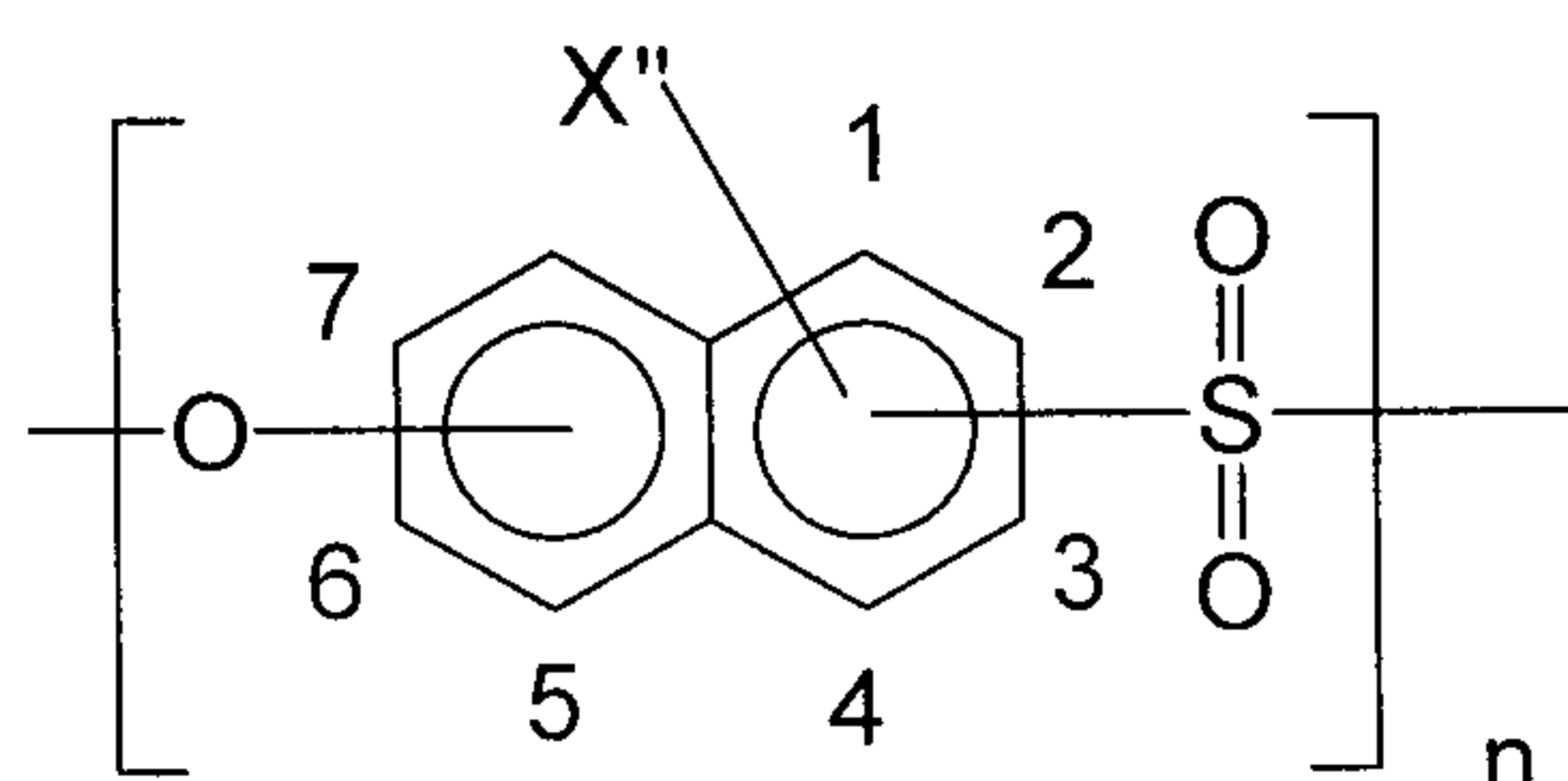


formula (IV)

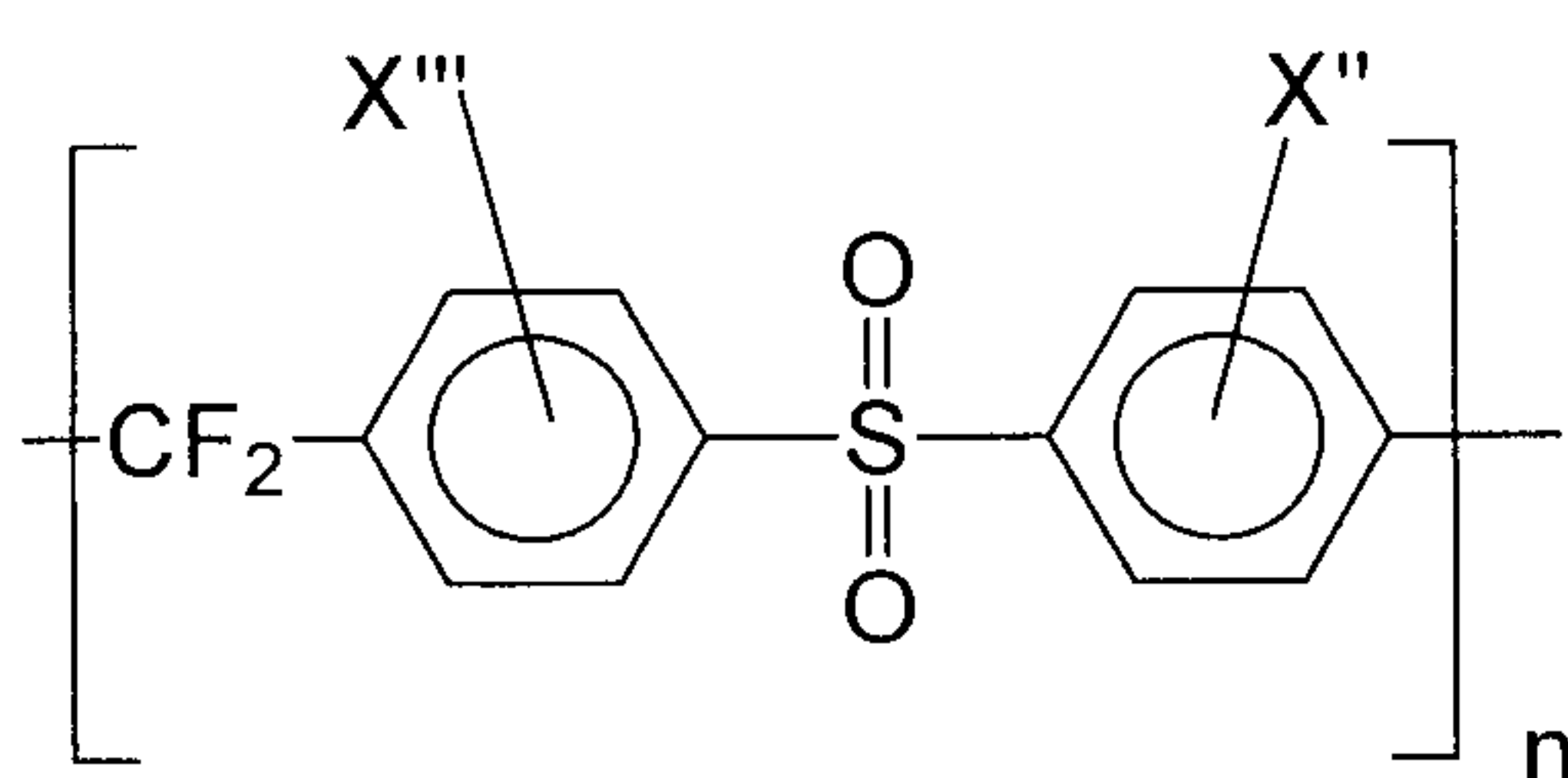
X, X', n and R' have independently of each other the above mentioned meaning.



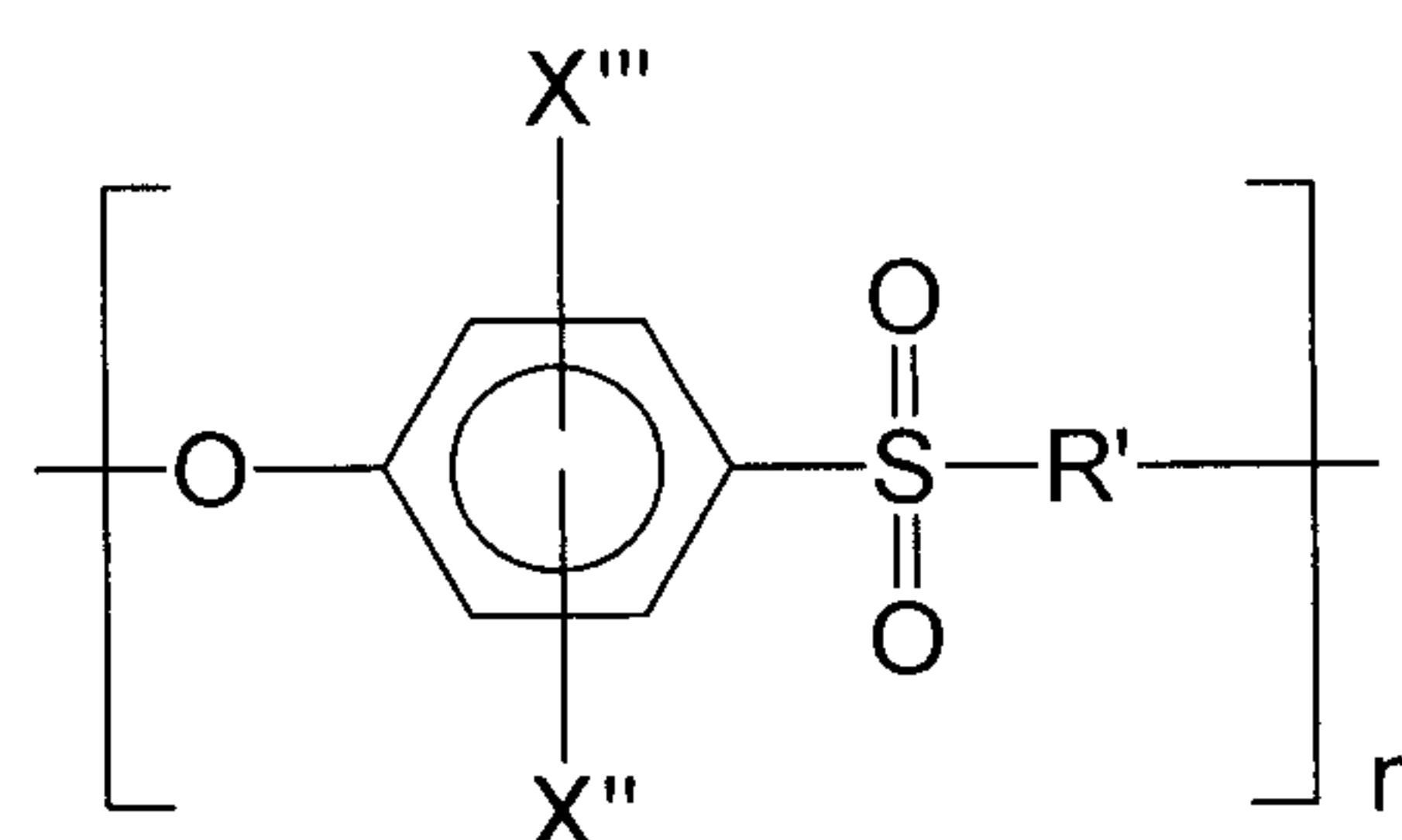
formula (V)



formula (VI)

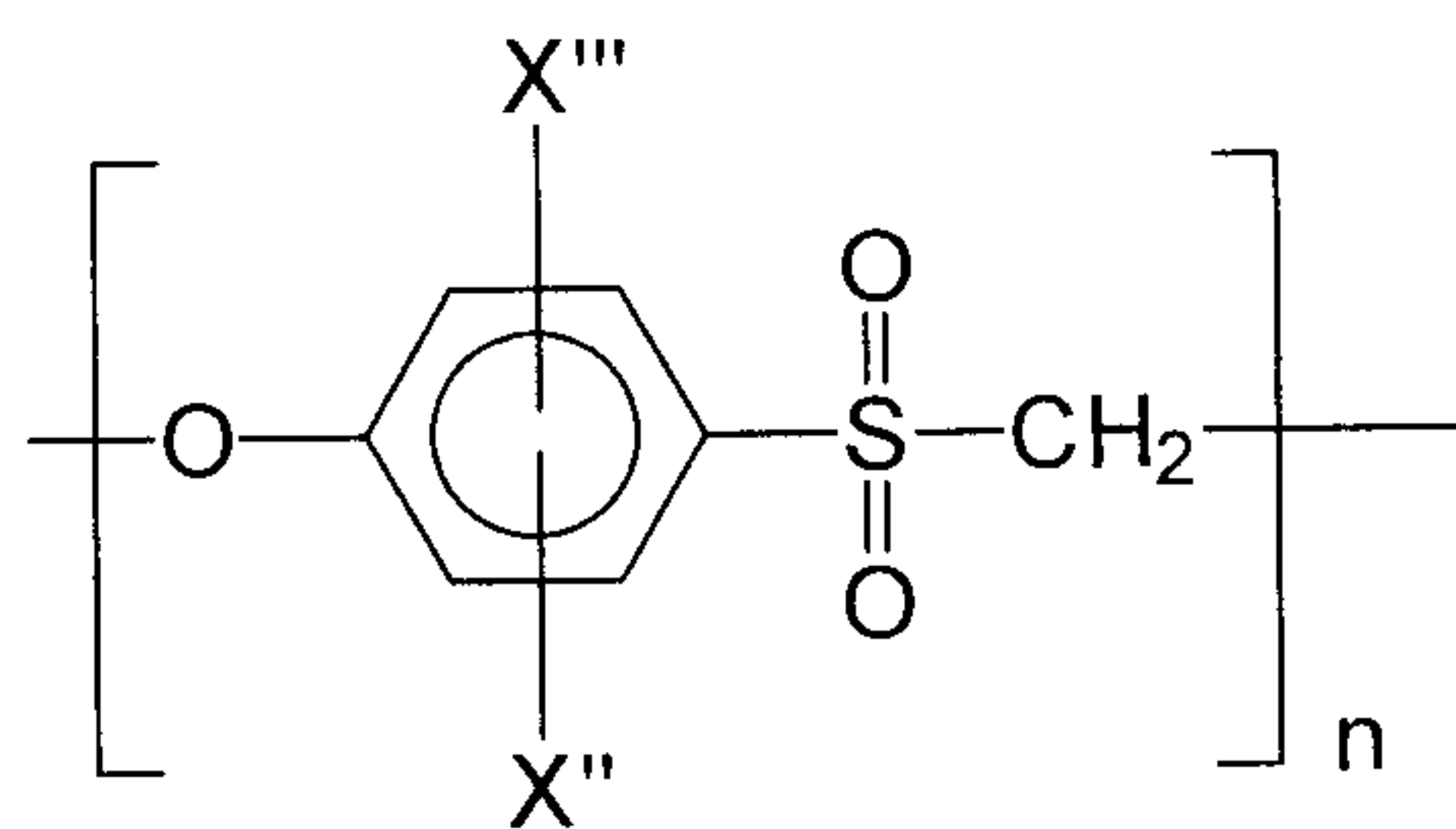


formula (VII)



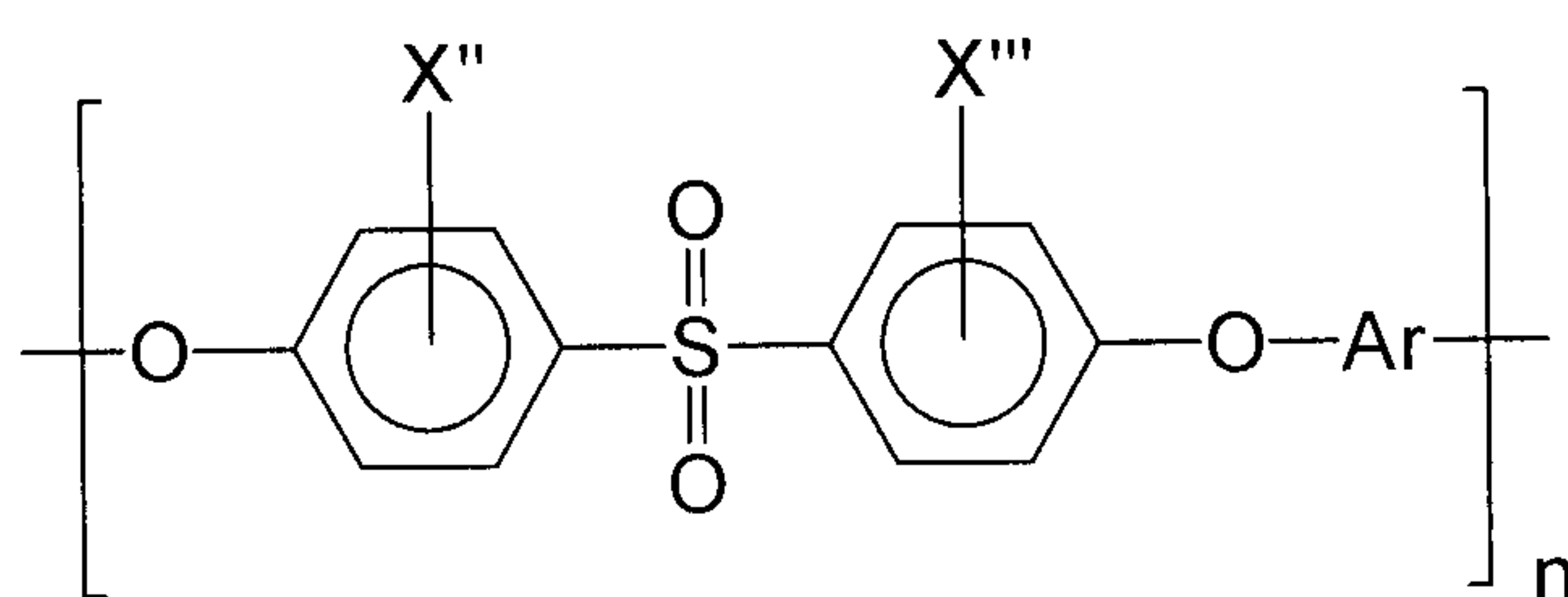
formula (VIII)

X, X', n and R' have independently of each other the above mentioned meaning.

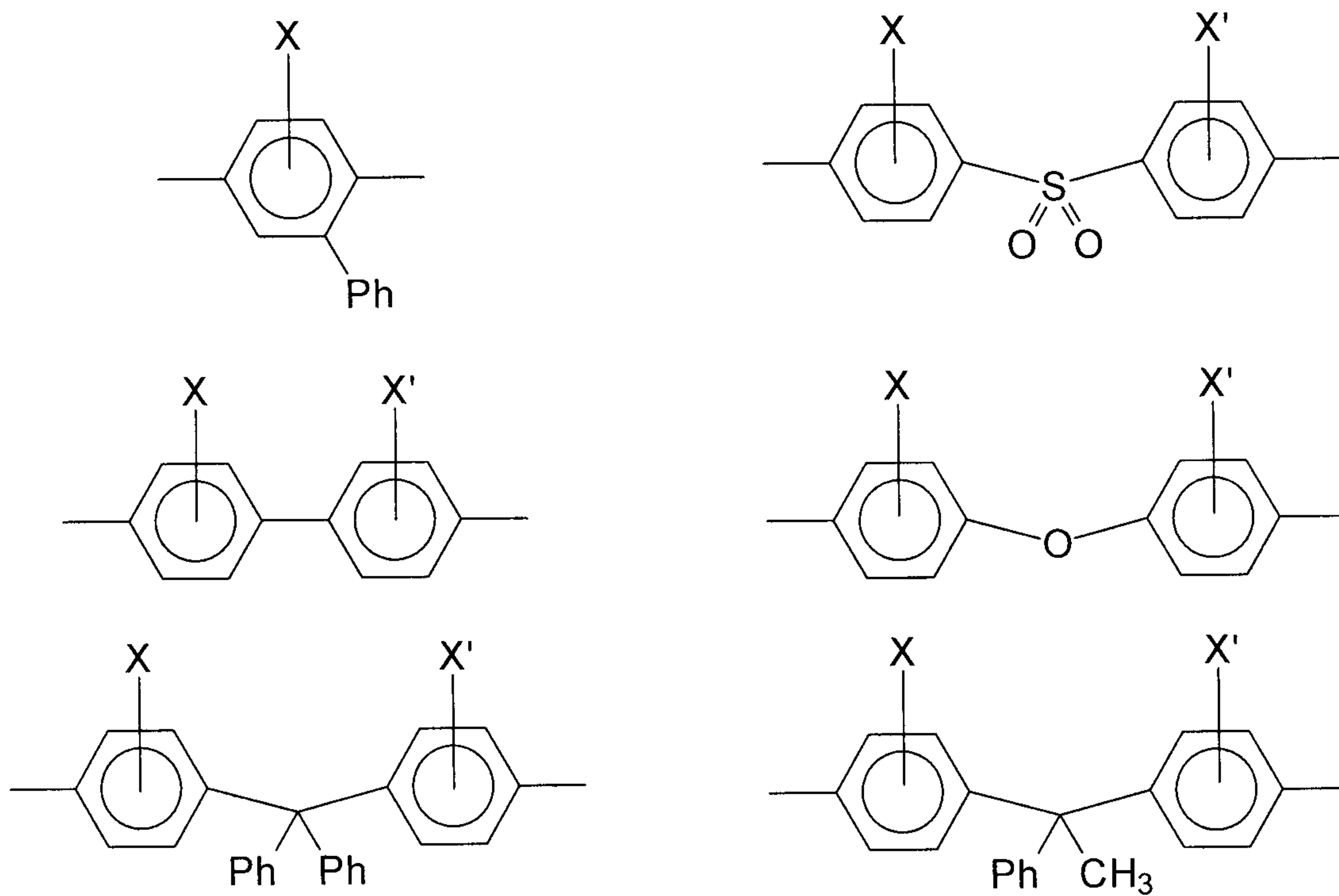


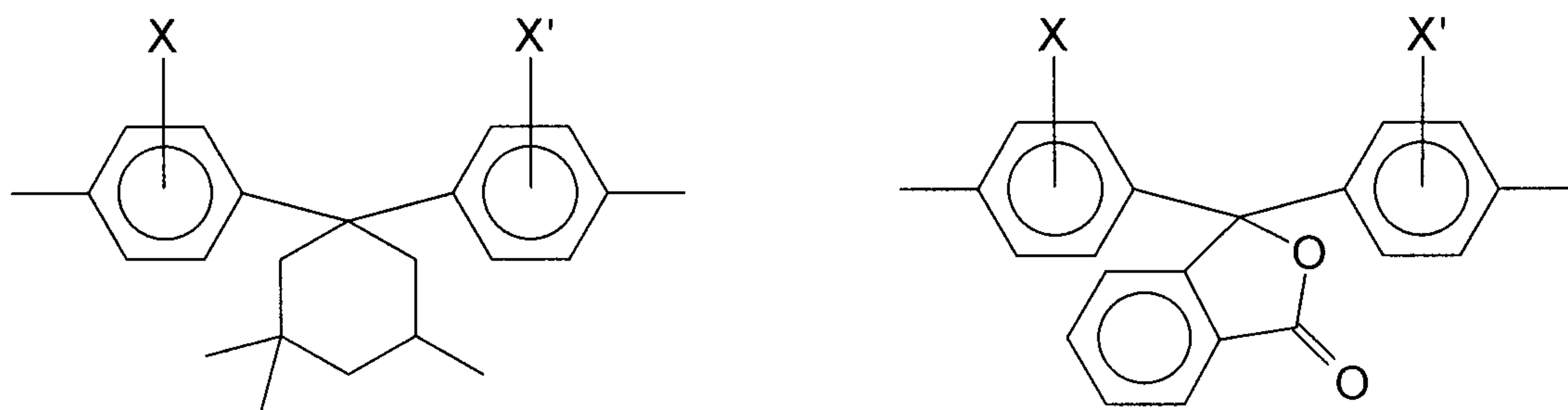
formula (IX)

Further, polysulfones of the following general formula (X) are preferred:



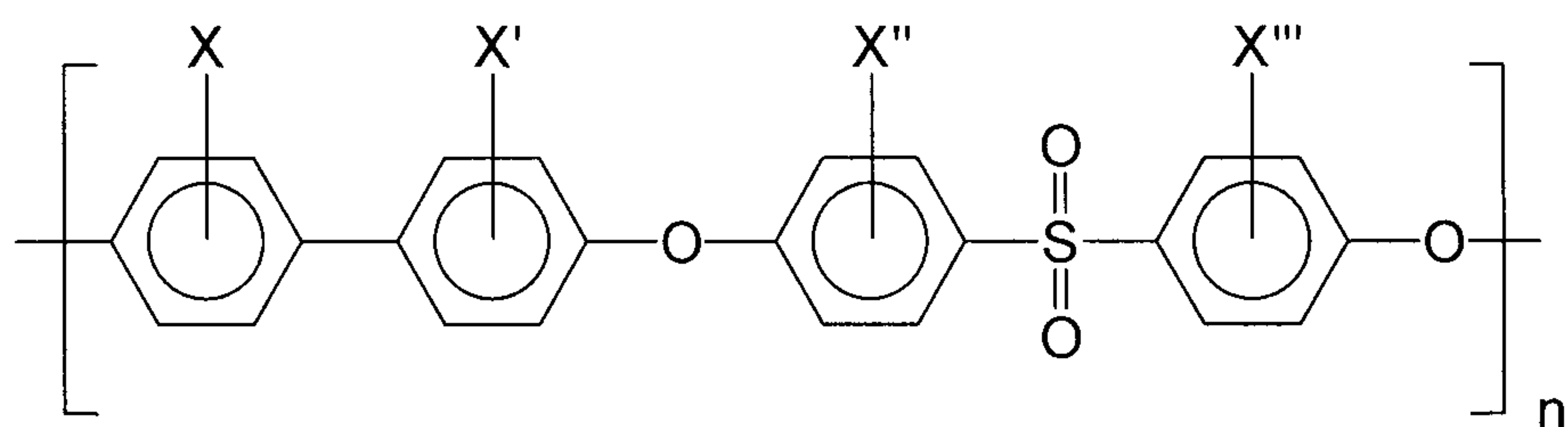
wherein Ar represents:



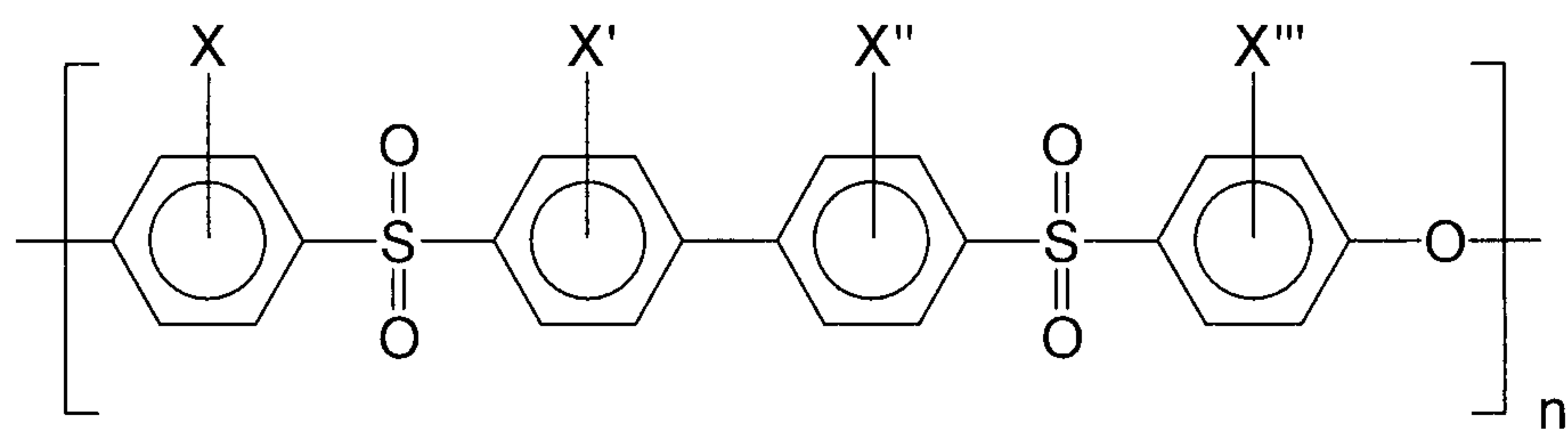


X, X' and n have independently of each other the above mentioned meaning.

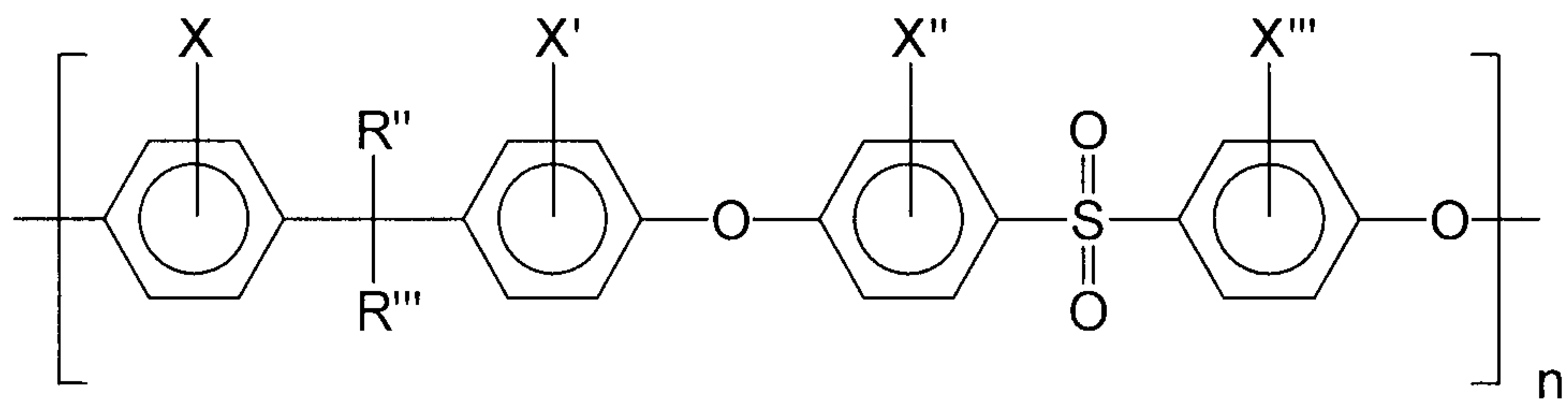
Furthermore, the following repeating units are preferred:



formula (XI)



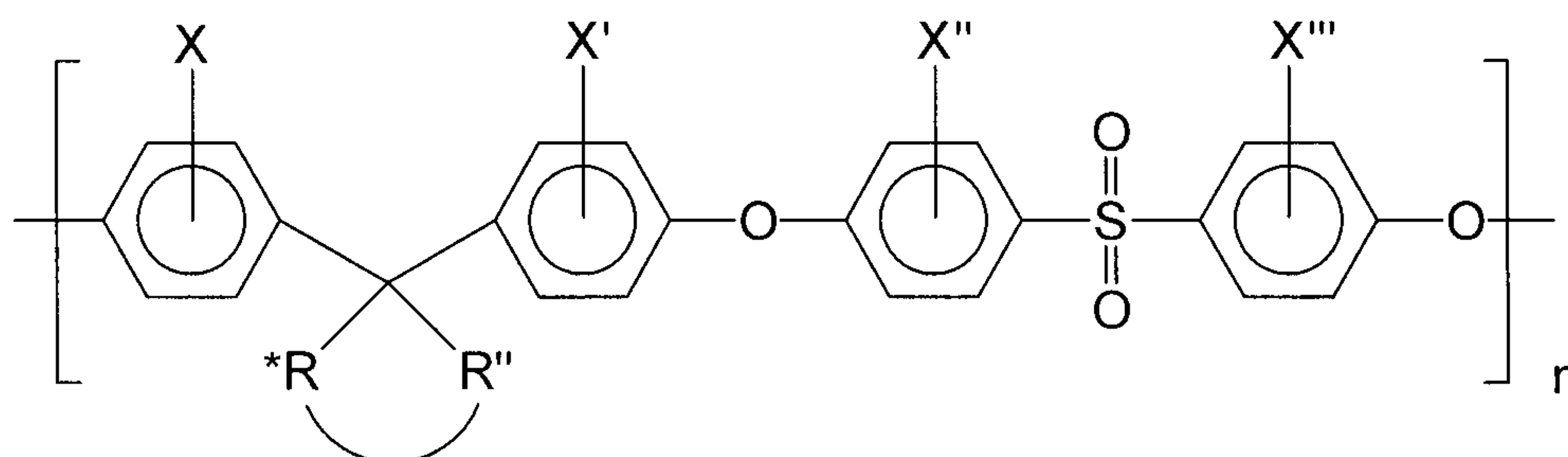
formula (XII)



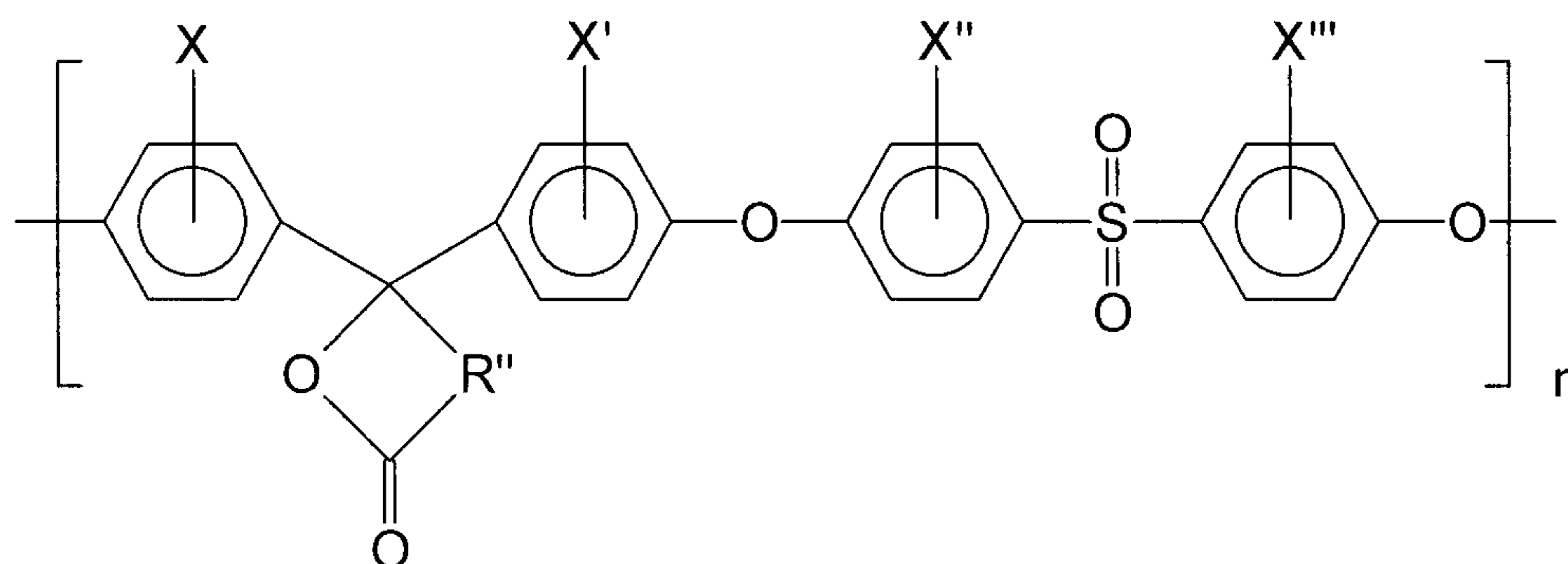
formula (XIII)

X, X', X'', X''' and n have independently of each other the above mentioned meaning. R'' and R''' can represent independently of each other a substituent, as it is defined for X or X', or can represent independently of each other a group $-R^1-H$ or $-R^2-H$.

Another preferred repeating unit has a cyclic substituent between two aromatic rings such as for example formula (XIV) or (XV):



formula (XIV)

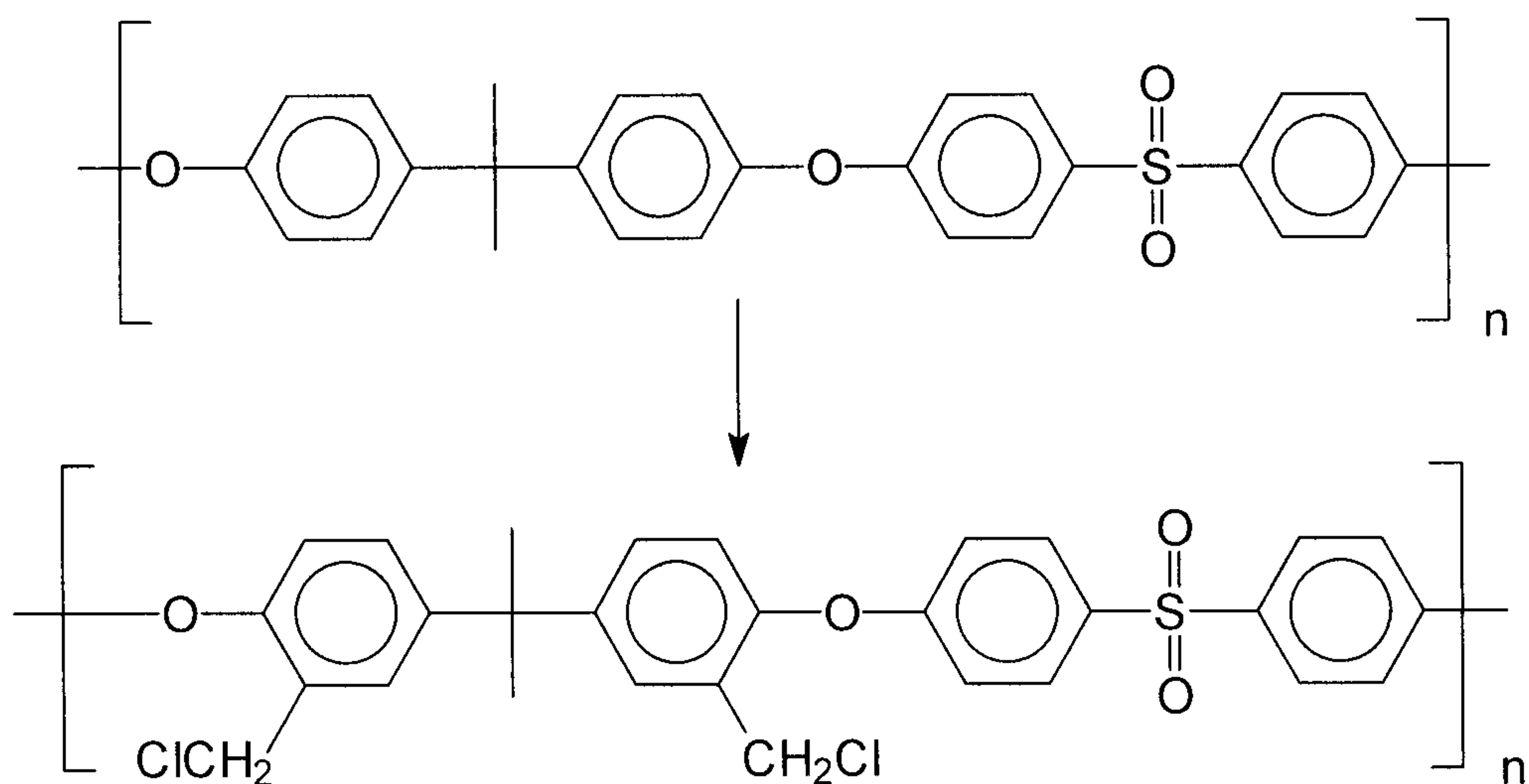


formula (XV)

R'' preferably represents $-CH_2-$, $-OCH_2-$, $-CH_2O-$, $-O-$, $-C_2H_4-$, $-C_3H_6-$, $-CH(OH)-$. The group $-*R-R''-$ preferably represents a cyclic ester, amide, carbonate, urea or urethane such as for example: $-O-CO-O-$, $-O-CO-O-CH_2-$, $-O-CO-O-C_2H_4-$, $-CH_2-O-CO-O-CH_2-$, $-C_2H_4-$, $-C_3H_6-$, $-C_4H_8-$, $-C_5H_{10}-$, $-C_6H_{12}-$, $-O-CO-NH-$, $-NH-CO-NH-$, $-O-CO-NH-CH_2-$, $-O-CO-NH-C_2H_4-$, $-NH-CO-NH-CH_2-$, $-NH-CO-NH-C_2H_4-$, $-NH-CO-O-CH_2-$, $-NH-CO-O-C_2H_4-$, $-CH_2-O-CO-NH-CH_2-$, $-C_2H_4-SO_2-$, $-C_3H_6-SO_2-$, $-C_4H_8-SO_2-$, $-C_2H_4-SO_2-CH_2-$, $-C_2H_4-SO_2-C_2H_4-$, $-C_2H_4-O-$, $-C_3H_6-O-$, $-C_4H_8-O-$, $-C_2H_4-O-CH_2-$, $-C_2H_4-O-C_2H_4-$, $-C_2H_4-CO-$,

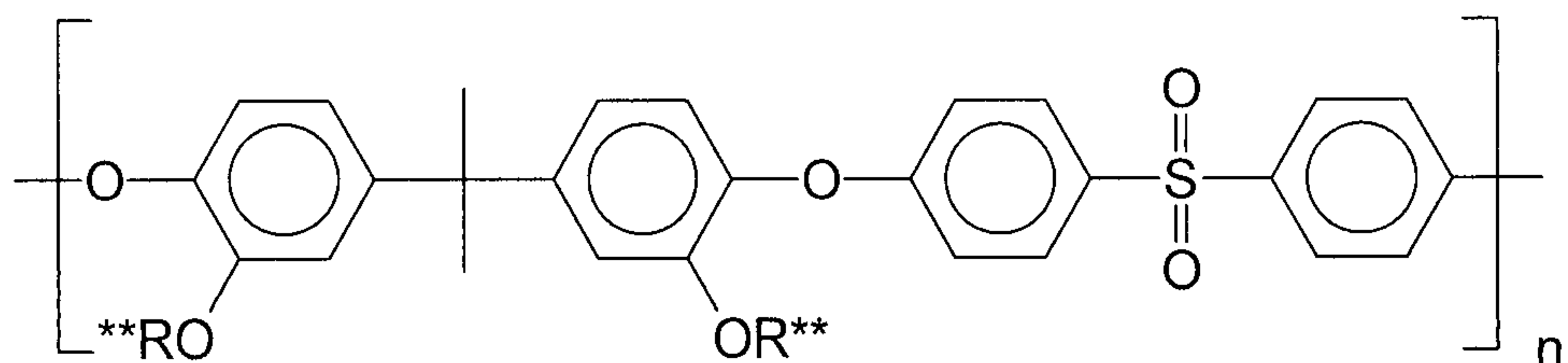
$-\text{C}_3\text{H}_6-\text{CO}-$, $-\text{C}_4\text{H}_8-\text{CO}-$, $-\text{C}_2\text{H}_4-\text{CO}-\text{CH}_2-$, $-\text{C}_2\text{H}_4-\text{CO}-\text{C}_2\text{H}_4-$, $-\text{O}-\text{CO}-\text{CH}_2-$, $-\text{O}-\text{CO}-\text{C}_2\text{H}_4-$, $-\text{O}-\text{CO}-\text{C}_2\text{H}_2-$, $-\text{CH}_2-\text{O}-\text{CO}-\text{CH}_2-$, or cyclic esters, which contain an aromatic ring.

In the following, polymer analogous reactions will be described, which are known to one skilled in the art and serve for the modification of the polysulfones.



formula (IIA)

Chloromethylene groups as moieties X and X' can be introduced by use of formaldehyde, ClSiMe_3 and a catalyst such as SnCl_4 , which then can be further substituted. Via these reactions, for example hydroxyl groups, amino groups, carboxylate groups, ether or alkyl groups can be introduced by a nucleophilic substitution, which are bound to the aromatic ring via a methylene group. A reaction with alcoholates, such as for example a phenolate, benzylate, methanolate, ethanolate, propanolate or isopropanolate results in a polymer in which a substitution occurred at over 75 % of the chloromethylene groups. The following polysulfone with lipophilic side groups is obtained:

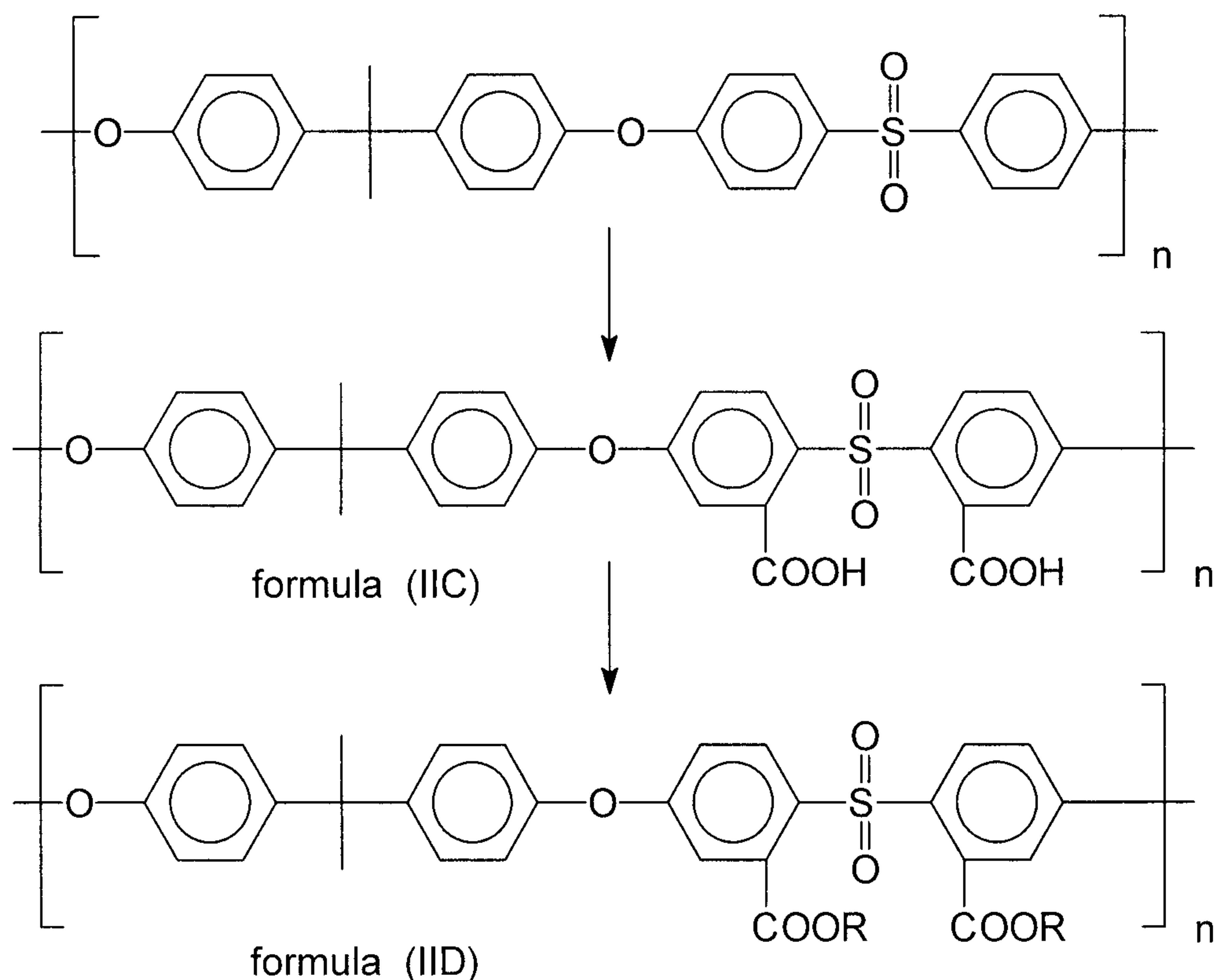


formula (IIB)

wherein

R** for example represents an alkyl moiety or aryl moiety.

The moieties X'' and X''' can be introduced, as far as not yet present in the monomers, at the polymer by following reaction:



Besides an ester group, diverse other substituents can be introduced, by at first proceeding a single or double deprotonation by means of a strong base, e.g. n-BuLi or tert-BuLi, and by subsequently adding an electrophile. In the above exemplary case, carbon dioxide was added for the introduction of the ester group and the obtained carbonic acid group was esterified in another step.

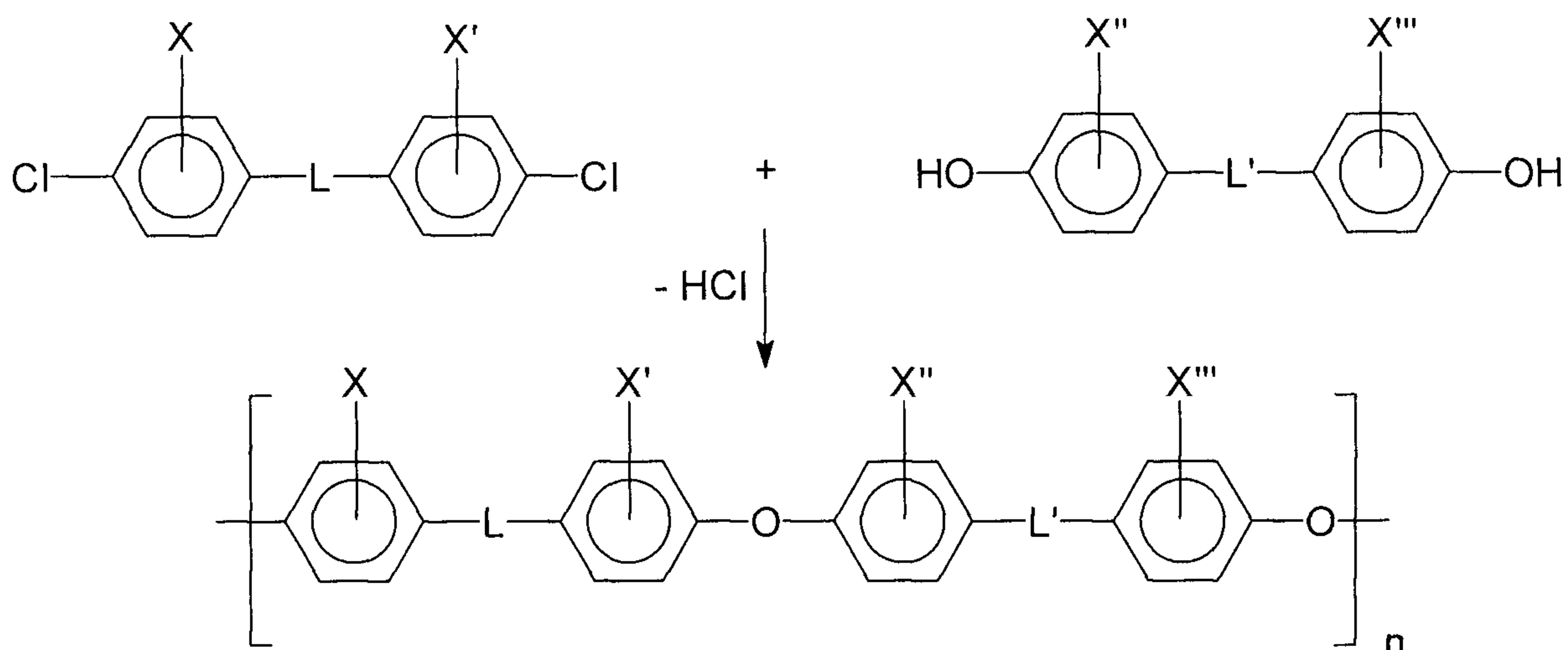
A combination according to the invention of a polysulfone with lipophilic moieties and a polysulfone with lipophobic moieties is achieved for example by the use of polysulfone according to formula (IIB) together with polysulfone according to formula (IIC). The amount ratios of both polysulfones to each other can range from 98% : 2% to 2% : 98%. Preferred

ratios are 10% to 90%, 15% to 85%, 22% to 78% and 27% to 73%, 36% to 64%, 43% to 57% and 50% to 50%. These percentage values are to be applied for any combination of hydrophilic and hydrophobic polysulfones and are not limited to the above-mentioned mixture.

An example of a polysulfone with hydrophilic and hydrophobic moieties in one molecule can be obtained for example by esterifying only incompletely the polysulfone according to formula (IIC) and thus, hydrophilic carboxylate groups and hydrophobic ester groups are present in one molecule. The mole ratio (number) of carboxylate groups to ester groups can be 5% : 95% to 95% : 5%. These percentage values are to be applied for any combination of hydrophilic and hydrophobic groups and are not limited to the aforementioned ones.

It is supposed that by means of this combination according to the invention of hydrophilic groups or, respectively, polymers with hydrophobic groups or, respectively, polymers, amorphous polymer layers are built on the medical product. It is very important that the polymer layers made of polysulfone are not crystalline or principally crystalline, as crystallinity leads to rigid layers, which begin breaking and detach. Flexible polysulfone coatings serving as a barrier layer can be achieved only with amorphous or principally amorphous polysulfone layers.

Of course it is also possible to apply monomers which are already substituted correspondingly for obtaining the desired substitution pattern after the polymerization being effected. The corresponding polymers then result by the known way according to the following reaction scheme:



wherein

L and L' represent for example the following groups independently of each other:

$-\text{SO}_2-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{C}(\text{Ph})_2-$ or $-\text{O}-$. L and L' can thus have the meanings of the corresponding groups in the formulas (I) to (XV). Such nucleophilic substitution reactions are known to the one skilled in the art, which are illustrated exemplarily by the above scheme.

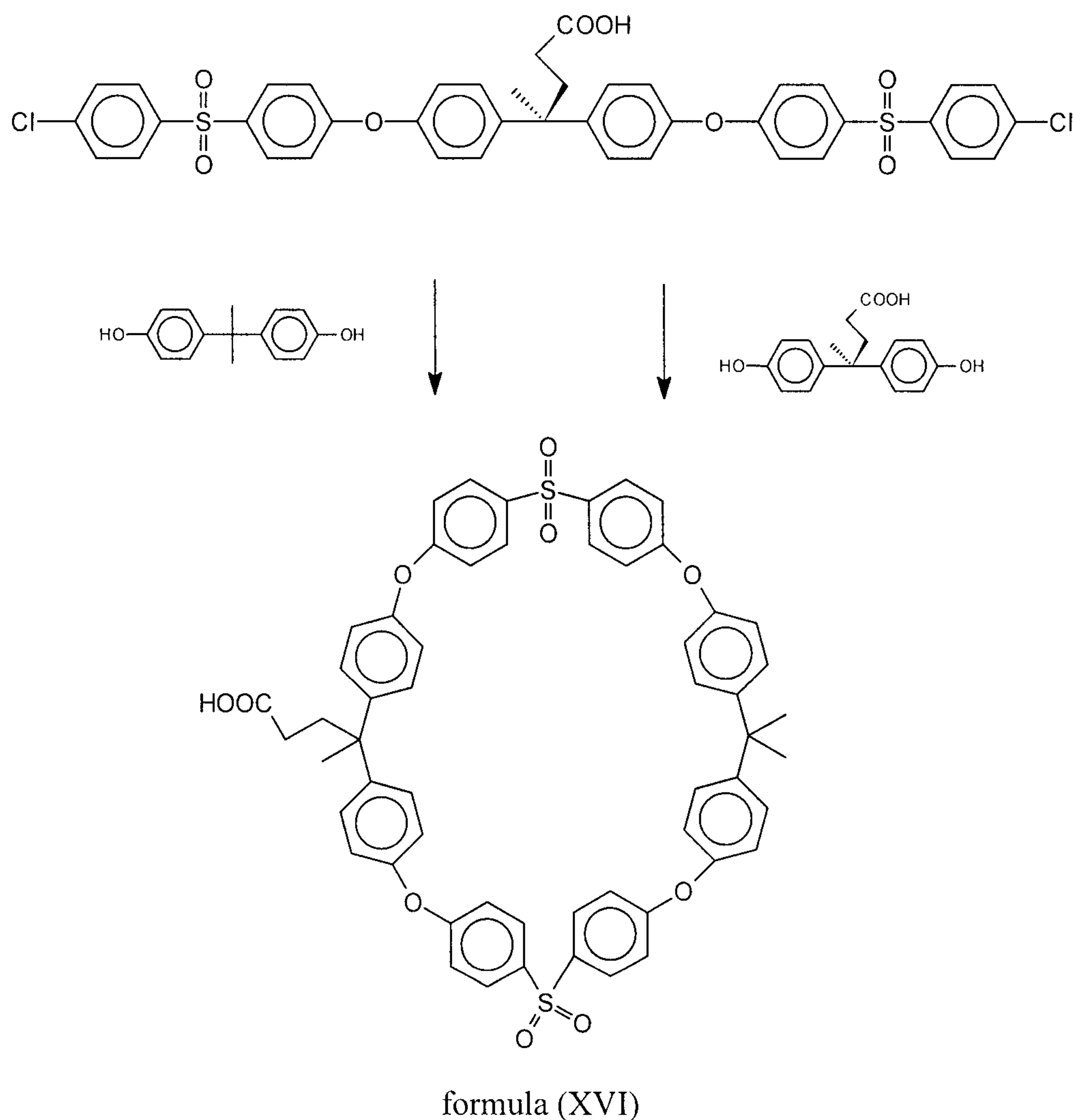
As already mentioned, it is especially preferred if the polymers possess hydrophilic and hydrophobic properties, on the one hand within one polymer and on the other hand by use of at least one hydrophilic polymer in combination with at least one hydrophobic polymer. Thus, it is preferred if for example X and X' have hydrophilic substituents and X'' and X''' have hydrophobic substituents, or vice versa.

As hydrophilic substituents can be applied: $-\text{OH}$, $-\text{CHO}$, $-\text{COOH}$, $-\text{COO}^-$, $-\text{CONH}_2$, $-\text{NH}_2$, $-\text{N}^+(\text{CH}_3)_4$, $-\text{NHCH}_3$, $-\text{SO}_3\text{H}$, $-\text{SO}_3^-$, $-\text{NH}-\text{CO}-\text{NH}_2$, $-\text{NH}-\text{CS}-\text{NH}_2$, $-\text{NH}-\text{C}(=\text{NH})-\text{NH}_2$, $-\text{O}-\text{CO}-\text{NH}_2$ and particularly protonated amino groups.

As hydrophobic substituents can be applied: $-\text{H}$, $-\text{OCH}_3$, $-\text{OC}_2\text{H}_5$, $-\text{SCH}_3$, $-\text{SC}_2\text{H}_5$, $-\text{NO}_2$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{N}_3$, $-\text{CN}$, $-\text{OCN}$, $-\text{NCO}$, $-\text{SCN}$, $-\text{NCS}$, $-\text{COCH}_3$, $-\text{COC}_2\text{H}_5$, $-\text{COCN}$, $-\text{COOCH}_3$, $-\text{COOC}_2\text{H}_5$, $-\text{CONHC}_2\text{H}_5$, $-\text{CON}(\text{CH}_3)_2$, $-\text{CON}(\text{C}_2\text{H}_5)_2$, $-\text{NHC}_2\text{H}_5$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{C}_2\text{H}_5)_2$, $-\text{SOCH}_3$, $-\text{SOC}_2\text{H}_5$, $-\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{C}_2\text{H}_5$, $-\text{SO}_3\text{CH}_3$, $-\text{SO}_3\text{C}_2\text{H}_5$, $-\text{OCF}_3$, $-\text{O}-\text{COOCH}_3$, $-\text{O}-\text{COOC}_2\text{H}_5$, $-\text{NH}-\text{CO}-\text{OCH}_3$, $-\text{NH}-\text{CO}-\text{OC}_2\text{H}_5$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CH}_2\text{Cl}$, $-\text{CHCl}_2$, $-\text{CCl}_3$, $-\text{CH}_2\text{Br}$, $-\text{CHBr}_2$, $-\text{CBr}_3$, $-\text{CH}_2\text{I}$, $-\text{CHI}_2$, $-\text{CI}_3$, $-\text{CH}_3$, $-$

C_2H_5 , $-\text{C}_3\text{H}_7$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}_4\text{H}_9$, $-\text{CH}_2-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2-\text{COOH}$,
 $-\text{CH}(\text{CH}_3)-\text{C}_2\text{H}_5$, $-\text{C}(\text{CH}_3)_3$.

Moreover, cyclic polysulfones are preferred, which possess for example a structure as it is shown in formula (XVI):



The carboxyethylene group is not essential for the above exemplary reaction. Instead of the carboxyethylene and the methyl substituents, any other substituents or also hydrogen can be present.

Polysulfones are characterized by their high resistance against aggressive chemicals, they are stable to hydrolysis and heat and possess very good mechanical and tribological (no

surface abrasion) properties. As further particular properties as material for the application in the living organism, the high dimension stability and the multiple sterilizability can be stressed. Polysulfones are used already for a long time as medical polymers. The main use concentrates on hollow fibres e.g. in blood dialyzers where the polysulfone fibres of the Fresenius company are leading on the global market due to their good hemocompatibility and membrane-forming properties. Thereby, the problem of dialysis consists primarily in the necessity that during the hemodialysis, an anticoagulant, generally heparin, has to be administered, the adverse effects of which multiply after a couple of years. During a five-hour treatment, about 75 liters of blood – this is equivalent to approximately 15-times the blood amount which the patient possess – flow through the dialyzer. Thus, it is clear that the membrane has to correspond to very high hemocompatibility requirements.

Another large field is the use of polysulfone capillaries in ophthalmology and in form of flat membranes in various medical technologic auxiliary means.

It is preferred if at least one hydrophilic polymer is added to the polysulfone used for the biostable layer. Thereby, the ratio of polysulfone to hydrophilic polymer can be 50% by weight to 50% by weight up to 99.999% by weight to 0.001% by weight in the respective polysulfone layer.

As hydrophilic polymers are suitable polyvinylpyrrolidone, glycerin, polyethylene glycol, polypropylene glycol, polyvinyl alcohol, polyhydroxyethyl methacrylates, polyacrylamide, polyvalerolactones, poly- ϵ -decalactones, polylactic 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-ones), poly-para-dioxanones, polyanhydrides such as polymaleic anhydrides, fibrin, polycyanoacrylates, polycaprolactonedimethylacrylates, poly-b-maleic acid, polycaprolactone butylacrylates, multiblock polymers such as e.g. from oligocaprolactonedioles and oligodioxanonedioles, polyether ester multiblock polymers such as PEG and polybutylene terephthalate, 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 trimethyl-carbonates,

polytrimethylcarbonates, polyiminocarbonates, poly(N-vinyl)-pyrrolidone, polyvinylalcohols, 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 copolymers thereof, 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, carboxymethyl sulphate, albumin, hyaluronic acid, chitosan and its derivatives, chondroitine sulphate, dextran, b-cyclodextrins, copolymers with PEG and polypropylene glycol, gum arabic, guar, gelatin, collagen, collagen-N-hydroxysuccinimide, lipids, phospholipids, modifications and copolymers and/or mixtures of the afore-mentioned substances, polyvinylpyrrolidone, polyethylene glycol and glycerin are preferably used.

For example, for increasing the viscosity in the production of the polysulfone solution, polyvinylpyrrolidone (PVP) is added, which is soluble in the precipitation agent during the manufacture of the hollow fibres and is thus removed again. The completed porous hollow fibre still contains at an average an amount of 1 – 2% PVP. The addition of polyvinylpyrrolidone is not only conducive to the viscosity during the production, i.e. increases viscosity, but also a factor which co-determines the pore size of the polysulfone and thus decisive for the permeability properties of the end product, because of this one is dependent of the pore size and the particle size. Thus, the pore size, and thus the permeability, of the produced polysulfone can be regulated via the amount and the molecular weight of the admixed polyvinylpyrrolidone.

The biocompatible and good mechanical properties of polysulfone and the possibility of regulation of the pore size by the addition of polyvinylpyrrolidone and/or another hydrophilic polymer and/or water (ethyl acetate) makes of this polymer the ideal substrate for all pharmaceuticals, which can be applied for the targeted local application, such as for example in cardiology for the prevention of reoccurring occlusion of blood vessels.

Simultaneously the enclosed nitrogen provides for the shelf life of the active agent. The preferred amount of the added polymer is in the range from 0-50% by weight, further

preferred are 1-20% by weight, particularly preferred are 2-10% by weight. The added amount complies substantially with the desired elution velocity of the applied active agent.

The medical products according to the invention possess a surface which can be made of any material. This surface is preferably not hemocompatible. Further this surface is preferably not coated, especially not with polymers and/or organic macromolecules.

The biostable polysulfone layer can be bound adhesively or covalently as well as partially adhesively and partially covalently to this surface. Preferred is the covalent bonding. The polysulfone layer covers the surface of the medical product at least partially, preferably however completely. If the medical product is a stent, at least the surface exposed to the blood is coated with the polysulfone

Preferably at least one layer containing at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent can be deposited and/or incorporated on this first biostable polysulfone layer and/or into this first polysulfone layer. The at least one layer containing at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent can completely consist of one or more active agents or can be another biostable polysulfone layer, in which the active agent or the active agents are located, or can be a hemocompatible layer, in which the active agent or the active agents are located. Whereas hydrophobic active agents can be deposited in and/or on and/or under a biostable layer, hydrophilic active agents are preferably deposited on and/or under a biostable layer.

Thus, the medical products according to the invention can have surfaces, which are coated with one, two, three or more layers wherein one, two or three layers and particularly two layers are preferred.

The antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent(s) can be bound to the respective layer adhesively or covalently or partially adhesively and partially covalently, wherein the adhesive bonding is preferred.

In case the surface coating has more biostable polysulfone layers and/or hemocompatible layers and/or active agent layers, each of these layers can consist of different polysulfones with different hydrophilic polymers and different amounts of hydrophilic polymers as well as different hemocompatible compounds or different active agents.

Further, it is preferred if the medical product has a surface which comprises a hemocompatible layer, which is deposited and/or incorporated on or in the lowest first biostable polysulfone layer. This hemocompatible layer can also form a second or third layer, which lies directly or indirectly on the lowest biostable layer and/or on or under an active agent layer or a second biostable polysulfone layer. Moreover, it is preferred if the hemocompatible layer forms the lowest layer and if on this layer can be found an active agent layer, covered in turn by a biostable polysulfone layer, or if a biostable polysulfone layer with an active agent or an active agent combination is deposited on the lowest hemocompatible layer.

This hemocompatible layer consists preferably of completely desulphated and N-reacetylated heparin, desulphated and N-reacetylated heparin, N-carboxymethylated, partially N-acetylated chitosan and/or mixtures of these substances. The hemocompatible layer can comprise besides the aforementioned substances other hemocompatible organic substances, but consists preferably only of the aforementioned substances.

Concerning the medical products according to the invention, it is preferred if a sole hemocompatible layer is present. Further preferred is if this sole hemocompatible layer forms the external or the lowest layer.

Further it is preferred that a layer completely covers the subjacent surface or the subjacent layer, wherein however a partial covering is possible as well.

Further it is particularly preferred if the medical product according to the invention is a stent. This stent can be formed of any material and material mixtures. Preferred are metals and plastics such as for example medical stainless steel, titanium, chromium, vanadium, tungsten, molybdenum, gold and nitinol. The stent is preferably uncoated and/or not or only conditionally hemocompatible. Particularly, the stent does not have a coating made of organic material. Medical wires can be excluded as medical products.

These stents according to the invention are preferably provided with at least one biocompatible layer of biostable polysulfone covering the stent completely or incompletely with or without a defined proportion of a hydrophilic polymer and with at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent.

Thereby, the active agent can be present in the matrix and/or cover the matrix as second layer. In this context, the second layer is referred to as the layer deposited on the first layer, etc.

Another preferred embodiment of the stents according to the invention has a coating, which consists of at least two polysulfone layers. According to this dual layer design, the first layer consists of a layer which is covered substantially completely by another biostable layer of the same or different pore size. One or both layers contain at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent. As well, active agent combinations are used which mutually support and/or complement each other in the effect which is executed by them.

Starting from this dual layer design, there is the possibility to incorporate different active agents separately from each other in the layer which is respectively suitable for the corresponding active agent, so that for example a hydrophobic active agent is located in the layer which is more hydrophilic and has another elution kinetics as another hydrophobic active agent, which is located in the more hydrophobic polymer layer or vice versa. This offers a broad field of possibilities to establish a distinct reasonable sequence in the availability of the active agents as well as to control the elution time and concentration.

Another preferred embodiment of the stents according to the invention has a coating which consists of at least three layers. According to this triple layer design, the first layer consists of a layer, which is covered substantially completely or incompletely by another second layer of pure active agent or active agent combinations, which in turn is covered by a third biostable polysulfone layer of same or different pore size. The polysulfone layers contain either no active agent or one or both represent matrices for at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent. Also used are active agent combinations, which mutually support and/or complement each other in their effect.

This embodiment is particularly suitable for the use of hydrophilic active agents or active agent combinations in the form of a pure active agent layer. The superjacent biostable polymer layer with a defined content of hydrophilic polymer serves for the controlled elution of the active agent. Active agent combinations with at least one hydrophilic active agent result in different elution kinetics.

As top coating can also be used the hydrophilic polymer, which can be admixed to the polysulfone, which is subjacent as well.

The biocompatible coating of a stent provides for the necessary hemocompatibility and the active agent (or active agent combination), which is equally distributed over the total surface of the stent, results in the fact that the ongrowth of the stent surface with cells, in particular smooth muscle cells and endothelial cells, proceeds in a controlled manner. Thus, no rapid ongrowth and overgrowth with cells on the stent surface occurs, which could lead to restenosis; however the ongrowth with cells on the stent surface is not completely prevented via a high drug concentration, which entails the danger of a thrombosis.

Thus, the use of polysulfone assures that the active agent or the active agent combination, bound adhesively on the subjacent layer and/or incorporated adhesively in the layer, is released continuously and in small dosages, so that the ongrowth of the stent surface with cells is not prevented, but an overgrowth. This combination of both effects confers to the stent according to the invention the ability of rapidly growing into the vessel wall and reduces the risk of a restenosis, as well as the risk of a thrombosis. The release of the active agent or of the active agents extends over a period of time from 1 to 24 months, preferably over 1 to 12 months after implantation, in particular preferably 1 to 3 months after implantation.

The release of the active agent can be adapted via the regulation of the pore size with the addition of the polyvinylpyrrolidone or a similar hydrophilic polymer in such a way that the individual characteristics of the active agent, the elution rate as well as its pharmacological kinetics and, in the case of more than one active agent, also the elution sequence can fulfil the required demands.

As active agents are used antiproliferative substances, antiphlogistic as well as antithrombotic agents. As antiproliferative active agents, preferably cytostatics, macrolide antibiotics and/or statins are used. Applicable antiproliferative active agents are sirolimus (rapamycin), everolimus, pimecrolimus, somatostatin, tacrolimus, roxithromycin, dunnamycin, ascomycin, bafilomycin, erythromycin, midecamycin, josamycin, concanamycin, clarithromycin, troleandomycin, folimycin, cerivastatin, simvastatin, lovastatin, fluvastatin, rosuvastatin, atorvastatin, pravastatin, pitavastatin, vinblastine, vincristine, vindesine, vinorelbine, etoposide, teniposide, nimustine, carmustine, lomustine, cyclophosphamide, 4-

hydroxycyclophosphamide, estramustine, melphalan, betulinic acid, camptothecin, lapachol, β -lapachone, podophyllotoxin, betulin, trofosfamide, podophyllic acid 2-ethylhydrazide, ifosfamide, chlorambucil, bendamustine, dacarbazine, busulfan, procarbazine, treosulfan, temozolomide, thiotepa, daunorubicin, doxorubicin, aclarubicin, epirubicin, mitoxantrone, idarubicin, bleomycin, mitomycin, dactinomycin, methotrexate, fludarabine, fludarabine-5'-dihydrogenphosphate, mofebutazone, acetaminophen, diclofenac, lonazolac, dapsone, o-carbamoylphenoxyacetic acid, lidocaine, ketoprofen, mefenamic acid, piroxicam, meloxicam, chloroquine phosphate, penicillamine, hydroxychloroquine, auranofin, sodium aurothiomalate, oxaceprol, celecoxib, β -sitosterin, ademetionine, myrtecaine, polidocanol, nonivamide, levomenthol, benzocaine, aescin, cladribine, mercaptopurine, thioguanine, cytarabine, fluorouracil, gemcitabine, capecitabine, docetaxel, carboplatin, cisplatin, oxaliplatin, amsacrine, irinotecan, topotecan, hydroxycarbamide, miltefosine, pentostatin, aldesleukin, tretinoin, asparaginase, pegaspargase, anastrozole, exemestane, letrozole, formestane, aminoglutethimide, adriamycin, azithromycin, spiramycin, cepharantin, smc proliferation inhibitor-2w, epothilone A and B, mitoxantrone, azathioprine, mycophenolatmofetil, c-myc-antisense, b-myc-antisense selectin (cytokine antagonist) CETP inhibitor, cadherines, cytokinin inhibitors, COX-2 inhibitor, NFkB, angiopeptin, ciprofloxacin, camptothecin, fluroblastin, monoclonal antibodies, which inhibit the muscle cell proliferation, bFGF antagonists, probucol, prostaglandins, folic acid and derivatives, vitamins of the B-row, vitamin D derivatives such as calcipotriol and tacalcitol, thymosine α -1, fumaric acid and its derivatives such as dimethylfumarate, IL-1 β inhibitor, colchicine, NO donors such as pentaerythritol tetranitrate and syndnoeimines, S-nitrosoderivatives, tamoxifen, staurosporine, β -estradiol, α -estradiol, estrone, estriol, ethinylestradiol, fosfestrol, medroxyprogesterone, estradiol cypionates, estradiol benzoates, tranilast, kamebakaurin and other terpenoids which are applied in the therapy of cancer, verapamil, tyrosine kinase inhibitors (tyrphostines), cyclosporine A, paclitaxel and its derivatives (6- α -hydroxy-paclitaxel, baccatin, taxotere, and other), synthetically produced macrocyclic oligomers of carbon suboxide (MCS) and its derivatives as well as those obtained from native sources, molgramostim (rhuGM-CSF), peginterferon α -2b, lenograstim (r-HuG-CSF), filgrastim, macrogol, dacarbazine, basiliximab, daclizumab, ellipticine, D-24851 (Calbiochem),

colcemid, cytochalasin A-E, indanocine, nocodazole, S 100 protein, PI-88, melanocyte stimulating hormone (α -MSH), bacitracin, vitronectin receptor antagonists, azelastine, guanidyl cyclase stimulator, tissue inhibitor of metal proteinase-1 and -2, free nucleic acids, nucleic acids incorporated into virus transmitters, DNA and RNA fragments, plasminogen activator inhibitor-1, plasminogen activator inhibitor-2, antisense oligonucleotides, VEGF inhibitors, called IGF-1. From the group of antibiotics furthermore cefadroxil, cefazolin, cefaclor, cefotaxim, tobramycin, gentamycin are applied. Positive impact on the postoperative phase have as well penicillins such as dicloxacillin, oxacillin, sulfonamides, metronidazol, antithrombotics such as argatroban, aspirin, abciximab, synthetic antithrombin, bivalirudin, coumadin, enoxaparin, hemoparin[®] (desulphated and N-reacetylated heparin), tissue plasminogen activator, GpIIb/IIIa platelet membrane receptor, factor X_a inhibitor, activated protein C, antibodies, heparin, hirudin, r-hirudin, PPACK, protamine, prourokinase, streptokinase, warfarin, urokinase, vasodilators such as dipyridole, triazolopyrimidine (trapidil[®]), nitroprussides, PDGF antagonists such as triazolopyrimidine and seramin, ACE inhibitors such as captopril, cilazapril, lisinopril, enalapril, losartan, thioprotease inhibitors, caspase inhibitors, Ac-YVAD-CMK, apoptosis inhibitors, apoptosis regulators such as p65 NF- κ B and Bcl-xL antisense oligonucleotides and prostacyclin, vapiprost, α , β and γ interferon, histamine antagonists, serotonin blockers, halofuginone, nifedipine, tocopherol, tranilast, molsidomine, tea polyphenols, epicatechin gallate, epigallocatechin gallate, Boswellic acids and their derivatives, leflunomide, anakinra, etanercept, sulfasalazine, etoposide, dicloxacillin, tetracycline, triamcinolone, mutamycin, procainamid, retinoic acid, quinidine, disopyramide, flecainide, propafenone, sotalol, amidorone. Further active agents are steroids (hydrocortisone, betamethasone, dexamethasone), non-steroidal substances (NSAIDS) such as fenoprofen, ibuprofen, indomethacin, naproxen, phenylbutazone and others. Antiviral agents such as acyclovir, ganciclovir and zidovudine are also applyable. Different antimycotics are used in this field. Examples are clotrimazole, flucytosine, griseofulvin, ketoconazole, miconazole, nystatin, terbinafine. Antiprotozoal agents such as chloroquine, mefloquine, quinine are active agents of equal efficiency, furthermore natural terpenoids such as hippocaesculin, barringtonol-C21-angelate, 14-dehydroagrostistachin, agroskerin, agrostistachin, 17-hydroxyagrostistachin, ovatodiols, 4,7-oxycycloanisomelic acid,

baccharinoids B1, B2, B3, tubeimoside, bruceanol A, B and C, bruceantinoside C, yadanziosides N and P, isodeoxyelephantopin, tomenphantopin A and B, coronarin A, B, C and D, ursolic acid, hyptatic acid A, zeorin, iso-iridogermanal, maytenfoliol, effusantin A, excisanin A and B, longikaurin B, sculponeatin C, kamebaunin, leukamenin A and B, 13,18-dehydro-6- α -seneciolyloxychaparrin, 1,11-dimethoxycanthin-6-one, 1-hydroxy-11-methoxycanthin-6-one, scopoletin, taxamairin A and B, regenilol, triptolide, furthermore cymarín, apocymarín, aristolochic acid, anopterin, hydroxyanopterin, anemonin, protoanemonin, berberine, cheliburin chloride, cictoxin, sinococuline, bombrestatin A and B, cudraiso flavone A, curcumin, dihydronitidine, nitidine chloride, 12- β -hydroxypregnadiene-4,16-diene-3,20-dione, bilobol, ginkgol, ginkgolic acid, helenalin, indicine, indicine-N-oxide, lasiocarpine, inotodiol, glycoside 1a, podophyllotoxin, justicidin A and B, larreatin, malloterin, mallotochromanol, isobutyrylmallotochromanol, maquiroside A, marchantin A, maytansine, lycoridicin, margetine, pancratistatin, liriodenine, oxoushinsunine, aristolactam-AII, bisparthenolidine, periplocoside A, ghalakinoside, ursolic acid, deoxypsorospermin, psychorubin, ricin A, sanguinarine, manwu wheat acid, methylsorbifolin, sphatheliachromen, stizophyllin, mansonine, strebloside, akagerine, dihydrousambarensine, hydroxyusambarine, strychnopentamine, strychnophylline, usambarine, usambarensine, berberine, liriodenine, oxoushinsunine, daphnoretin, lariciresinol, methoxylariciresinol, syringaresinol, umbelliferon, afromoson, acetylvismione B, desacetylvismione A, vismione A and B, further natural terpenoids such as hippocaesculin, 14-dehydroagrostistachin, c-type natriuretic peptide (CNP) agroskerin, agrostistachin, 17-hydroxyagrostistachin, ovatodiolids, 4,7-oxycycloanisomelic acid, yadanziosides N and P, isodeoxyelephantopin, tomenphantopin A and B, coronarin A, B, C and D, ursolic acid, hyptatic acid A, zeorin, iso-iridogermanal, maytenfoliol, effusantin A, excisanin A and B, longikaurin B, sculponeatin.

The active agents are used separately or combined in the same or a different concentration. Especially preferred are active agents which have, besides their antiproliferative effect, also immunosuppressive properties. Among such active agents count erythromycin, midecamycin, tacrolimus, sirolimus, paclitaxel and its derivatives and josamycin as well as triazolopyrimidines (trapidil®), D-24851, α - and β -estradiol,

macrocyclic carbon suboxide (MCS) and its derivatives, PI-88, sodium salt of 2-methylthiazolidine-1,4-dicarboxylic acid and derivatives, and sirolimus.

Furthermore preferred is a combination of several antiproliferatively acting substances or of antiproliferative active agents with immunosuppressive active agents.

Especially preferred, the active agents are selected from the group comprising paclitaxel and its derivatives, β -estradiol, simvastatin, PI-88 (sulphated oligosaccharide; Progen Ind.), macrocyclic carbon suboxides (MCS) and their derivatives, trapidil[®], N-(pyridine-4-yl)-[1-4-(4-chlorobenzyl)-indol-3-yl]-glyoxylamide (D-24851), and tacrolimus.

The active agent is preferably contained in a pharmaceutical active concentration from 0.001 – 20 mg per cm² of stent surface, further preferred 0.005 – 15 and especially preferred 0.01 – 10 mg per cm² of stent surface. Other active agents can be contained in a similar concentration in the same or in other layers. As well preferred is an embodiment, which contains two different active agents in the same layer or in different layers. Further preferred is an embodiment, which possesses a pure active agent layer as supreme layer.

The amounts of polymer deposited per medical product and especially per stent per layer are preferably in the range between 0.01 mg/ cm² to 3 mg/ cm² of surface, further preferred 0.20 mg to 1 mg and especially preferred 0.2 mg to 0.5 mg/ cm² of surface.

Moreover, embodiments are preferred which contain an active agent in two layers. This can be two different active agents as well. If the same active agent is contained in two layers, it is preferred, that the two layers have a different active agent concentration. Further it is preferred, when the lower layer has a smaller active agent concentration than the upper layer.

The stents according to the invention can be manufactured by a method for the biocompatible coating of stents whose basis is the following principle:

- a. Providing a stent, and
- b. depositing at least one biostable polysulfone layer with or without at least one hydrophilic polymer, and
- c. depositing and/or incorporating at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent onto and/or into the biostable layer, or

b'.depositing at least one biostable polysulfone layer with or without the at least one hydrophilic polymer together with at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent.

After the step b', preferably also the step c' can follow:

c'.depositing at least one antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent onto the biostable polymer layer.

After the steps a, b and c or the steps a, b' or the steps a, b' and c', still another step d can follow:

d. depositing of at least one second biostable polysulfone layer.

This second biostable polysulfone layer can consist on the one hand of a polysulfone other than the first subjacent layer and can contain on the other hand a different amount of the same or of another hydrophilic polymer. Preferred is if this second biostable polysulfone layer contains at least one active agent. In particular preferred are embodiments with a biostable polysulfone layer with or without hydrophilic polymer as external layer.

The antiproliferative, antiinflammatory, antiphlogistic and/or antithrombotic active agent is preferably selected from the group listed above.

Further, embodiments are preferred which have a hemocompatible layer. This hemocompatible layer consists of the above-mentioned hemocompatible substances, especially of completely desulphated and N-reacetylated heparin, desulphated and N-reacetylated heparin, N-carboxymethylated, partially N-acetylated chitosan and/or of mixtures of these substances and is indirectly or directly deposited on the lower biostable layer. This hemocompatible layer can be located between two other layers as well as form the supreme layer. Embodiments with two hemocompatible layers are also possible, wherein however only one hemocompatible layer is preferred. The hemocompatible layer can be bound adhesively as well as covalently or partially adhesively and partially covalently to the subjacent layer.

The respective layers are deposited preferably via the dipping or spraying method. Furthermore, the individual layers are preferably not deposited onto the subjacent layer until it is dry.

Preferred is a method, which consists of the two steps a) and b').

The coating principle offers a broad range of variation in respect of the requirements concerning the active agent and also the properties of the applied polysulfone, so that different variants of coating result, which can be also combined with each other.

The possibility of influencing the properties of the polysulfone via the amount and the molecular weight of the added hydrophilic polymer such as PVP, represents in respect of the applied active agents a broad field of adaptability of the components to a dovetailed system.

Further layers of polysulfone without addition of PVP and/or with equal or different PVP content with and without active agents are possible. In the same manner, a layer, which is preferably bound covalently directly to the surface, of completely N-deacetylated and reacetylated heparin, desulphated and N-reacetylated heparin, N-carboxymethylated and/or partially N-acetylated chitosan and/or of mixtures of these substances can be deposited, whose athrombogeneous properties can provide the masking of the subjacent foreign surface in case of lesion of the superjacent biostable layer or layers surface, as it occurs for example preliminarily to or also during the implantation by mechanical destruction of the coating. This inert layer can be applied, if necessary, optionally covalently or adhesively between two layers as well and/or as top layer.

Variant A:

- a.) Providing an uncoated stent,
- b.) depositing one biostable polysulfone layer with or without hydrophilic polymer,
- c.) depositing an active agent or active agent combination in and/or on the polysulfone layer via dipping or spraying method,
- d.) substantially complete and/or incomplete coating of the biostable polysulfone layer containing the active agent with at least another biostable polysulfone layer corresponding to the first layer or differing from this first layer in its content of hydrophilic polymer and thus, in the pore size
- e.) depositing the same or another active agent or active agent combination in and/or on the external biostable layer, so that different active agents and/or active agent combinations can be deposited on the stent in a targeted manner separately of each other by means of both layers, as well as in case of different

pore size of the polymer a different loading with active agent can be realized as well as a different elution velocity of the same and/or another active agent is possible.

In particular, the term "depositing" in step c) and/or step e) means "diffusion" of the active agent into the respective layer.

Preferred are medical products with two biostable polysulfone layers, which can contain different hydrophilic polymers in different concentrations.

The deposition of all provided polymer layers can be executed before diffusion of the active agent into these layers, when the same active agent or active agent combination shall be contained in both layers.

Additionally, another layer of a suitable polysulfone or even of the pure hydrophilic polymer can be deposited as diffusion barrier and top coating.

Variant B

- a.) Providing an uncoated stent,
- b.) depositing one biostable polysulfone layer with or without hydrophilic polymer,
- c.) substantially complete and/or incomplete coating of the biostable polysulfone layer with at least one antiproliferative, antiphlogistic and/or antithrombotic active agent and/or active agent combination via spraying method,
- d.) substantially complete and/or incomplete coating of the active agent layer with at least another biostable polysulfone layer, which corresponds to the first layer or differs from this first layer in its content of hydrophilic polymer and thus, in pore size, with or without active agent and/or active agent combination, and/or
- d'.) substantially complete and/or incomplete coating of the active agent layer with a hydrophilic polymer as top coating with or without active agent and/or active agent combination.

By means of these variants, it is possible to adapt the coating material to the active agents and also the temporally released amount of active agent to the requirements at the corresponding segment.

In multi layer systems, the layer which has been newly deposited substantially covers the subjacent layer completely. "Substantially" means by 50 – 100%, preferably 70 – 100%, further preferred 80 – 100%, further preferably 90 – 100% and especially preferred up to over 96% and in particular further preferably up to over 98%.

Object of the invention are as well the medical products which can be manufactured according to the aforementioned methods and particularly stents.

The stents according to the invention solve both the problem of acute thrombosis as well as the problem of neointima hyperplasia after a stent implantation. Moreover, the stents according to the invention whether as single layer or as multi layer system, are particularly suitable for the continuous release of one or more antiproliferative, antiinflammatory, antiphlogistic, antithrombotic and/or immunosuppressive active agents due to their coating. Due to this ability of continuously releasing the active agent in a targeted way in a required amount, the coated stents according to the invention almost completely prevent the danger of restenosis.

The prevention or reduction of restenosis takes place on the one hand by suppression of the cellular reactions during the first days and weeks after implantation by means of the selected active agents and active agent combinations and on the other hand by provision of a biocompatible surface, so that with the decrease of the influence of the active agent no reactions start on the present foreign surface, which would as well lead to a reoccurring occlusion of the blood vessel in the long term.

Examples

Example 1

Coating of stents with polyethersulfone

Spray solution:

a. PS solution:

176 mg of PS (polyethersulfone, Udel®, available from Solvay) are weighed in and filled up to 20 g with chloroform.

→ 0.88 % PS

Stent	spray solution	before coating	after coating	mass coating
	2.0 ml	0.01754 g	0.01826 g	0.72 mg
	2.0 ml	0.01814 g	0.01889 g	0.75 mg
	2.0 ml	0.01751 g	0.01832 g	0.81 mg
	2.0 ml	0.01742 g	0.01816 g	0.74 mg
	2.0 ml	0.01734 g	0.01814 g	0.80 mg
	2.0 ml	0.01736 g	0.01815 g	0.80 mg

Example 2

Coating of stents with polyethersulfone (basis coating) and polyethersulfone with 0.04% of PVP or respectively 0.08% of PVP as top coating

Spray solutions:

a. Polysulfone solution:

17.6 mg of PS are weighed in and filled up to 2 g with chloroform.

→ 0.88 % of PS

b. Polysulfone / PVP solution:

25.2 mg of PS and 1.2 mg of PVP are weighed in and filled up to 3 g with chloroform.

→ 0.84 % of PS, 0.04 % of PVP

b'. Polysulfone / PVP solution:

24 mg of PS and 2.4 mg of PVP are weighed in and filled up to 3 g with chloroform.

→ 0.80 % of PS, 0.08 % of PVP

Spray coating:

The stents which have been weighed in are spray-coated with the spray solutions in the indicated order with a.) 0.5 ml and b.) 0.85 ml. Thereby, after each spraying process, a

time period of at least 6 hours passes until the next layer is deposited. After drying at room temperature overnight in the clean room, it is weighed again.

Stent	before coating	after coating	mass coating
1b	0.02058 g	0.02132 g	0.75 mg
1b'	0.01968 g	0.02022 g	0.54 mg
2b'	0.01968 g	0.02034 g	0.66 mg

Example 3

Manufacture of stents with MCS and polyethersulfone in the 3-layer-system according to variant B

Spray solutions:

- a) Polyethersulfone solution: (1st layer: base coating, basis coating):
70.4 mg of PS are weighed in and filled up to 8 g with chloroform.
→ 0.88 % of PS
- b) MCS solution (2nd layer: middle coating):
39.6 mg of MCS are weighed in and filled up to 18 g with 20% ethanol in water.
→ 0.22 % of MCS
- c) Polyethersulfone / PVP solution (3rd layer: top coating):
100.8 mg of PS and 4.8 mg of polyvinylpyrrolidone are weighed in and filled up to 12 g with chloroform.
→ 0.84 % of PS, 0.04 % of PVP

Spray coating:

Non-expanded stainless steel stents are weighed and spray-coated after their cleaning. The stents are sprayed with the corresponding amount of the respective spray solution with a) 0.5 ml; b.) 1.5 ml and c.) 0.85 ml in the indicated order. Thereby, after each layer a time period of at least 6 hours passes until the next layer is sprayed. After drying at room

temperature overnight it is weighed again. The average value of the active agent content on the stents is $153 \pm 9 \mu\text{g}$.

Stent	before coating	after coating	mass coating	mass MCS
	0.01829 g	0.01894 g	0.65 mg	141 μg
	0.01753 g	0.01826 g	0.73 mg	159 μg
	0.01772 g	0.01836 g	0.64 mg	139 μg
	0.01719 g	0.01790 g	0.71 mg	154 μg
	0.01833 g	0.01903 g	0.70 mg	152 μg
	0.01774 g	0.01836 g	0.62 mg	135 μg
	0.01729 g	0.01802 g	0.73 mg	159 μg

Example 4

Determination of the elution kinetics of MCS from polyethersulfone with 4.5 % of PVP

Into each one of snap-on cap glasses, one stent is given, mixed with 2 ml of PBS buffer, closed with parafilm and incubated for defined times in the drying closet at 37°C. After the chosen time period has passed, the supernatant is depipetted and its UV absorption at 207 nm is measured. The respective stent is again mixed with 2 ml of PBS and incubated again at 37°C. This operation is repeated several times.

Example 5

Coating of stents polysulfone matrix which is loaded with simvastatin

Spray solutions:

a. PS / simvastatin solution:

26.4 mg of PS and 8.8 mg of simvastatin are weighed in and filled up to 4 g with chloroform.

→ 0.66 % of PS, 0.22 % of simvastatin

b. PS / simvastatin / PVP solution:

24.8 mg of PS, 8.8 mg of simvastatin und 1.6 mg of PVP are weighed in and filled up to 4 g with chloroform.

→ 0.62 % of PS, 0.22 % of Simvastatin, 0.04 % of PVP

Stent	spray solution	before coating	after coating	mass coating	mass simvastatin
	2.0 ml a)	0.02164 g	0.02171 g	1.08 mg	270 µg
	2.0 ml b)	0.02129 g	0.02253 g	1.24 mg	310 µg

Example 6

Coating of stents with polysulfone matrix which is loaded with simvastatin with high proportion of PVP

Spray solution:

a. PS / simvastatin / PVP solution:

23.2 mg of PS, 8.8 mg of simvastatin and 3.2 mg of PVP are weighed in and filled up to 4 g with chloroform.

→ 0.58 % of PS, 0.22 % of simvastatin, 0.08 % of PVP

tent	spray solution	before coating	after coating	mass coating	mass simvastatin
	2.0 ml a)	0.02164 g	0.02171 g	1.08 mg	270 µg
	2.0 ml a)	0.02129 g	0.02253 g	1.24 mg	310 µg

Example 7

Coating of stents with polysulfone matrix which is loaded with paclitaxel

Spray solutions:

a. PS / paclitaxel solution:

13.2 mg of PS and 4.4 mg of paclitaxel are weighed in and filled up to 2 g with chloroform.

→ 0.66 % of PS, 0.22 % of paclitaxel

b. PS / PVP / paclitaxel solution:

11.6 mg of PS, 1.6 mg of PVP and 4.4 mg of paclitaxel are weighed in and filled up to 2 g with chloroform.

→ 0.58 % of PS, 0.08 % of PVP, 0.22 % of paclitaxel

Stent	spray solution	before coating	after coating	Mass coating	mass paclitaxel
	1.0 ml a)	0.01725 g	0.01770 g	0.45 mg	113 µg
	1.0 ml b)	0.01735 g	0.01790 g	0.55 mg	138 µg

Example 8

Coating of stents with 17- β -estradiol in polysulfone matrix

Spray solutions:

a. PS / 25 % 17- β -estradiol solution:

46.2 mg of PS and 15.4 mg of 17- β -estradiol are weighed in and filled up to 7 g with chloroform.

→ 0.66 % of PS, 0.22 % of 17- β -estradiol

b. PS / 20 % 17- β -estradiol solution:

28.2 mg of PS and 7 mg of 17- β -estradiol are weighed in and filled up to 4 g with chloroform.

→ 0.704 % of PS, 0.176 % of 17- β -estradiol

c. PS / 15 % 17- β -estradiol solution:

29.9 mg of PS and 5.3 mg of 17- β -estradiol are weighed in and filled up to 4 g with chloroform.

→ 0.748 % of PS, 0.132 % of 17- β -estradiol

Stent	spray solution	before coating	after coating	mass coating	mass 17- β -estradiol

	2.2 ml a)	0.02052 g	0.02166 g	1.14 mg	285 µg
	2.2 ml a)	0.02065 g	0.02189 g	1.24 mg	310 µg
	2.2 ml b)	0.02080 g	0.02206 g	1.27 mg	254 µg
	2.2 ml c)	0.02064 g	0.02213 g	1.49 mg	224 µg

Example 9

Coating of stents with a polysulfone matrix which contains triazolopyrimidine (trapidil[®])

Spray solution:

PS / trapidil[®] solution:

19.8 mg of PS and 6.6 mg of trapidil[®] are weighed in and filled up to 3 g with chloroform.

→ 0.66 % PS, 0.22 % trapidil[®]

Stent	spray solution	before coating	after coating	mass coating	mass trapidil [®]
1	1.7 ml	0.01742 g	0.01855 g	1.13 mg	283 µg

Example 10

In vivo examination of stents with polyethersulfone as matrix with and without macrocyclic suboxide

Into the coronary arteries of 13 domestic pigs of different sex with a weight of 20-25 kg were implanted stents coated with polyethersulfone. Three groups of stents were distinguished. One group contained a high dosage of paclitaxel, the second contained a low dosage of paclitaxel and the last group was the pure matrix stent without active agent additive. After four weeks, the stents were removed and analyzed for inflammation reactions (peri-strut) and formation of neointima.

Histomorphometric evaluation after 4 weeks of implantation time				
Coating	number of stents	thickness of intima [mm]	stenosis [%]	grade of injury
Matrix / high concentration of active agent	6	0.14±0.06	19±9	0.32±0.19
Matrix / low concentration of active agent	6	0.23±0.07	32±10	0.46±0.29
Matrix without active agent	4	0.17±0.06	23±8	0.15±0.12

All analyzed stents independently of the coating showed only minimal inflammations around the stent struts and on the adventitia. The higher average thickness of intima of the stents with the low load of active agent could be ascribed to the stronger overexpansion of the vessel during the implantation. The pure matrix stent shows no noticeable problems in the vessel reactions which are to be ascribed to the polymer, which argues in favor of its hemocompatibility and suitability as active agent substrate.

Example 11

In vivo examinations of stents with polyethersulfone as matrix with and without paclitaxel

By analogy to the previous example 10, stents which had been coated with polyethersulfone were compared to stents which had been coated with polyethersulfone and loaded with paclitaxel:

Histomorphometric evaluation after 4 weeks of implantation time				
Coating	amount of stents	thickness of intima [mm]	stenosis [%]	grade of injury
Matrix / active	6	0.21±0.10	26±12	0.23±0.20

agent				
Matrix	4	0.14±0.06	18±8	0.10±0.07

The results of this study as well show the profit of the polysulfone coating.

Example 12

Preparation of the polysulfone according to formula (IIA).

The polysulfone (IIA) was prepared according to the instruction of E. Avram et al. J. Macromol Sci. Pure Appl. Chem., 1997, A34, 1701.

3 mole equivalents of benzyl alcohol are dissolved in toluene and deprotonated with sodium. 1 mole equivalent of the polysulfone (IIA) is added and subsequently, the reaction mixture is heated to boiling temperature. The reaction product is obtained in a yield of 22%.

Example 13

Preparation of the polysulfone according to formula (IIC).

The polysulfone (IIC) was prepared according to the instruction of M. D. Guiver et al., Brit. Polym. L. 1990, 23, 29.

1 g of the obtained polysulfone (IIC) was esterified by using ortho ethyl acetate, whereas toluene was applied as solvent and the volatile reaction products were removed from the reaction equilibrium via distillation. 40% of the carboxylate groups were converted into ethyl ester groups.

According to example 7, this polymer was deposited together with paclitaxel onto a stent.

The stent shows good hemocompatibility and an amorphous polysulfone coating, which was suitable for the controlled release of the paclitaxel.

Example 14

1 g of the polysulfone prepared according to example 12 is admixed with 200 mg of the polysulfone according to formula (IIC) and deposited according to example 7 together with the active agent paclitaxel on a stent.

The coated stent has a good hemocompatibility and an amorphous polysulfone coating, which was suitable for the controlled release of the paclitaxel.

Example 15

Introduction of chlorosulfone groups on polysulfone.

2.4 g of polysulfone is dissolved in 700 ml of chloroform and cooled to $-20\text{ }^{\circ}\text{C}$. Subsequently, 23.3 ml of chlorosulfonic acid are slowly added dropwise. As the reaction is highly exothermic, the reaction vessel is cooled in the ice bath. After addition of the chlorosulfonic acid, the solution is heated up to room temperature under stirring. After 30 minutes the polymer is precipitated in ethanol and subsequently rinsed with deionized water. For completely removing the chlorosulfonic acid, it is extracted again for 10 minutes in deionized water.

Example 16

S-alkoxy-de-chlorination.

10 g of ethanol are dissolved in 100 ml of water and admixed with 2-3 drops of methyl red in acetone. This solution is given on 5 g of fine grained chlorosulfonated polysulfone.

The solution is admixed drop wise with 5N KOH until the change of color from yellow to red occurs. Subsequently, the vessel is closed and well shaken. Caustic potash solution is added and it is shaken until the change of color does no longer occur. The formed polysulfone ester is sucked off, washed with water and recrystallized for purification.

Example 17

S-alkoxy-de-chlorination.

10 g of dry ethanol are admixed with 60 ml of pyridine. This solution is added under ice cooling to 40 g of fine pulverized chlorosulfonated polysulfone. Subsequently, it is stirred under exclusion of moisture overnight at room temperature. Subsequently, the suspension is poured into ice water and acidified carefully with concentrated hydrochloric acid. The washing is carried out with aqueous hydrogen carbonate solution. After filtration, the esterified polysulfone can be recrystallized.

Example 18

Coating with a mixture of polysulfone and polysulfone according to formula (IIC).

24 mg of PS and 2.4 mg of polysulfone according to formula (IIC) are weighed in and filled up to 3 g with chloroform.

→ 0.80 % PS, 0.08 % PVP

A stent is coated according to example 7 with this mixture by the spraying method.

Claims

1. A medical product, characterized in that its surface is coated at least partially with at least one biostable polysulfone layer, wherein the at least one biostable polysulfone layer comprises pores.
2. The medical product according to claim 1, characterized in that the polysulfone is selected from the group which comprises the following: polyethersulfone, substituted polyethersulfone, polyphenylsulfone, substituted polyphenylsulfone, polysulfone block copolymers, perfluorinated polysulfone block copolymers, semifluorinated polysulfone block copolymers, substituted polysulfone block copolymers and mixtures of the aforementioned polymers.
3. The medical product according to claim 1 or 2, characterized in that the at least one biostable polysulfone layer further contains at least one hydrophilic polymer.
4. The medical product according to claim 3, characterized in that the polysulfone containing the at least one hydrophilic polymer is present in a mixture ratio of polysulfone to hydrophilic polymer of 50% by weight : 50% by weight up to 99.999% by weight : 0.001% by weight.
5. The medical product according to claim 3 or 4, characterized in that the hydrophilic polymer is selected from the group which comprises the following: polyvinylpyrrolidone, glycerine, polyethylene glycol, polypropylene glycol, polyvinyl alcohol, polyhydroxyethyl methacrylates, polyacrylamide, 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-ones), poly-para-dioxanones, polyanhydrides, fibrin, polycyanoacrylates, polycaprolactonedimethylacrylates, poly-b-maleic acid, polycaprolactone butylacrylates, multiblock polymers, multiblock polymers polyether ester multiblock polymers, 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 trimethylcarbonates, polytrimethylcarbonates, polyiminocarbonates, poly(N-vinyl)-pyrrolidone, polyvinylalcohols, polyesteramides, glycolated polyesters, polyphosphoesters, polyphosphazenes, poly[p-carboxyphenoxy)propane], polyhydroxypentanoic acid, polyethyleneoxide-propyleneoxide, polyurethanes with amino acid residues in the backbone, polyether esters, polyethyleneoxide, polyalkeneoxalates, polyorthoesters as well as copolymers thereof, 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, carboxymethyl sulphate, albumin, hyaluronic acid, chitosan and its derivatives, chondroitine sulphate, dextran, b-cyclodextrins, copolymers with PEG and polypropylene glycol, gum arabic, guar, gelatine, collagen, collagen-N-hydroxysuccinimide, phospholipids, modifications and copolymers and mixtures of the aforementioned substances.

6. The medical product according to claim 5, characterized in that the hydrophilic polymer is selected from the group which comprises: polyvinylpyrrolidone polyethylene glycol, polypropylene glycol and glycerin.
7. The medical product according to claim 3, characterized in that the pores of the polysulfone coating have a size which is determined by the mixture ratio of polysulfone with the at least one hydrophilic polymer.
8. The medical product according to any one of claims 3 to 7, characterized in that in, under and/or on the at least one biostable polysulfone layer with or without the at least one hydrophilic polymer, at least one antiproliferative, anti-inflammatory, antiphlogistic and/or antithrombotic active agent is present.
9. The medical product according to any one of claims 1 to 8, characterized in that the biostable layer is bound adhesively or covalently on the surface of the medical product.
10. The medical product according to any one of claims 1, 2, 7 or 9, characterized in that the coating of the surface of the medical product consists of one, two, three or more layers.
11. The medical product according to any one of claims 3-6 or 8, characterized in that the coating of the surface of the medical product consists of one, two, three or more layers.
12. The medical product according to any one of claims 3 to 11, characterized in that under and/or on the at least one biostable polysulfone layer with or without the at least one hydrophilic polymer at least one layer of desulphated and N-reacetylated heparin, N-carboxymethylated and/or partially N-acetylated chitosan and/or of mixtures of these substances is present.
13. The medical product according to claim 11, characterized in that in multiple layer systems the at least two biostable layers differ or do not differ in the proportion of hydrophilic polymer.

14. The medical product according to any one of claims 8 to 13, characterized in that the at least one antiproliferative, anti-inflammatory, antiphlogistic and/or antithrombotic active agent is selected from the group which comprises: sirolimus, everolimus, somatostatin, tacrolimus, roxithromycin, dunaimycin, ascomycin, bafilomycin, erythromycin, midecamycin, josamycin, concanamycin, clarithromycin, troleandomycin, folimycin, cerivastatin, simvastatin, lovastatin, fluvastatin, rosuvastatin, atorvastatin, pravastatin, pitavastatin, vinblastine, vincristine, vindesine, vinorelbine, etoposide, teniposide, nimustine, carmustine, lomustine, cyclophosphamide, C-type natriuretic peptide, 4-hydroxycyclophosphamide, estramustine, melphalan, ifosfamide, trofosfamide, chlorambucil, bendamustine, dacarbazine, busulfan, procarbazine, treosulfan, temozolomide, thiotepe, daunorubicin, doxorubicin, aclarubicin, epirubicin, mitoxantrone, idarubicin, bleomycin, mitomycin, dactinomycin, methotrexate, fludarabine, fludarabine-5'-dihydrogenphosphate, cladribine, mercaptopurine, thioguanine, cytarabine, fluorouracil, gemcitabine, capecitabine, docetaxel, carboplatin, cisplatin, cryptophycine, anginex, oxaliplatin, amsacrine, irinotecan, topotecan, hydroxycarbamide, miltefosine, pentostatin, aldesleukin, tretinoin, asparaginase, pegaspargase, anastrozole, exemestane, letrozole, formestane, aminoglutethimide, adriamycin, azithromycin, spiramycin, cepharantin, smc proliferation inhibitor-2w, epothilone A and B, mitoxantrone, azathioprine, mycophenolatmofetil, c-myc-antisense, b-myc-antisense, betulinic acid, camptothecin, lapachol, β -lapachone, podophyllotoxin, betulin, podophyllic acid 2-ethylhydrazide, molgramostim, peginterferon α -2b, lenograstim, filgrastim, macrogol, anginex, Na-Uretic peptides, dacarbazine, basiliximab, daclizumab, selectin, chryptophycines, CETP inhibitor, cadherines, cytokinin inhibitors, COX-2 inhibitor, AE-941, NFkB, angiopeptin, ciprofloxacin, camptothecin, fluroblastin, bFGF antagonists, probucol, prostaglandins, Ac-YVAD-CMK, 1,11-dimethoxycanthin-6-one, 1-hydroxy-11-methoxycanthin-6-one, scopoletin, colchicine, NO donors, S-nitrosoderivatives, tamoxifen, staurosporine, β -estradiol, α -estradiol, estriol, estrone, ethinylestradiol, fosfestrol, medroxyprogesterone, estradiol cypionates, estradiol benzoates, tranilast, kamebakaurin and other terpenoids, which are applied in the therapy of cancer, verapamil, tyrosine kinase inhibitors, cyclosporine A, paclitaxel 6- α -hydroxy-paclitaxel, baccatin, taxotere, synthetically produced as well as macrocyclic oligomers obtained from native sources of carbon suboxide and its derivatives, mofebutazone, acetaminophen, diclofenac, lonazolac, dapsone, o-carbamoylphenoxyacetic acid, lidocaine, ketoprofen, mefenamic acid, piroxicam, meloxicam, chloroquine phosphate, penicillamine, hydroxychloroquine, auranofin, sodium aurothiomalate, oxaceprol, celecoxib, β -sitosterin, ademetionine, myrtecaine, polidocanol, nonivamide, levomenthol, benzocaine, aescin, ellipticine, D-24851, colcemid, cytochalasin A-E, indanocine, nocodazole, S 100 protein, bacitracin, vitronectin receptor antagonists, azelastine, guanidyl cyclase stimulator, tissue inhibitor of metal proteinase-1 and -2, free nucleic acids, nucleic acids incorporated into virus transmitters, DNA and RNA fragments, plasminogen activator inhibitor-1, plasminogen

activator inhibitor-2, antisense oligonucleotides, VEGF inhibitors, IGF-1, active agents from the group of antibiotics, penicillins, sulfonamides, metronidazol, antithrombotics, tissue plasminogen activator, GpIIb/IIIa platelet membrane receptor, factor Xa inhibitor antibody, heparin, hirudin, r-hirudin, PPACK, protamin, prourokinase, streptokinase, warfarin, urokinase, vasodilators, PDGF antagonists, ACE inhibitors, losartan, thioprotease inhibitors, prostacyclin, vapirost, interferon α , β and γ , histamine antagonists, serotonin blockers, apoptosis inhibitors, apoptosis regulators, halofuginone, nifedipine, tocopherol, tranilast, molsidomine, tea polyphenols, epicatechin gallate, epigallocatechin gallate, Boswellic acids and its derivatives, leflunomide, anakinra, etanercept, sulfasalazine, etoposide, dicloxacillin, tetracycline, triamcinolone, mutamycin, procainamid, retinoic acid, quinidine, disopyrimide, flecainide, propafenone, sotalol, amidorone, natural and synthetically produced steroids, inotodiol, maquiroside A, ghalakinoside, mansonine, strebloside, hydrocortisone, betamethasone, dexamethasone, NSAIDS, antiviral agents, antimycotics, antiprozoal agents, and natural terpenoids.

15. The medical product according to claim 8, characterized in that the at least one antiproliferative, anti-inflammatory, antiphlogistic and/or antithrombotic active agent is selected from the group which comprises the following: paclitaxel and its derivatives, β -estradiol, simvastatin, PI-88, macrocyclic carbon suboxides and their derivatives, trapidil[®], N-(pyridine-4-yl)-[1-4-(4-chlorobenzyl)-indol-3-yl]-glyoxylamide, activated protein C, Ac-YVAD-CMK and tacrolimus.
16. The medical product according to any one of claims 8 to 15, characterized in that the at least one antiproliferative, anti-inflammatory, antiphlogistic and/or antithrombotic active agent is contained in a pharmaceutically active concentration of 0.001 – 20 mg per cm² of surface.
17. The medical product according to any one of claims 10 to 16, characterized in that in multiple layer systems, the at least two layers with or/and without admixture of at least one hydrophilic polymer contain at least one active agent in the same or in a different concentration of active agent which is covalently or/and adhesively bound to the respective layer.
18. The medical product according to any one of claims 10 to 17, characterized in that in multiple layer systems, the last layer is a pure active agent layer is bound covalently or/and adhesively to the respective layer.
19. A method of biocompatible coating of medical products, characterized by the following steps:
 - a. providing a medical product, and

- b. depositing at least one biostable polysulfone layer with or without at least one hydrophilic polymer, and
 - c. depositing and/or incorporating at least one antiproliferative, anti-inflammatory, antiphlogistic and/or antithrombotic active agent onto and/or into the biostable layer,
 - or
 - b'. depositing at least one biostable polysulfone layer with or without the at least one hydrophilic polymer together with at least one antiproliferative, anti-inflammatory, antiphlogistic and/or antithrombotic active agent.
20. The method according to claim 19, comprising the step b' and the further step:
- c'. depositing at least one antiproliferative, anti-inflammatory, antiphlogistic and/or antithrombotic active agent onto the biostable polymer layer.
21. The method according to claim 19 or 20, comprising the further step:
- d. depositing at least one second biostable polysulfone layer with or without a content of hydrophilic polymers which is equal or different to the first layer without or with incorporating or/and depositing at least one active agent in the same or a different concentration.
22. The method according to any one of claims 19 to 21, characterized in that onto and/or under the at least one biostable polysulfone layer is deposited at least one layer of completely desulphated and N-reacetylated heparin, N-carboxymethylated and/or partially N-acetylated chitosan and/or mixtures of these substances.
23. A medical product coated according to the method of any one of claims 19 to 22.
24. A medical product according to any one of claims 8 to 18 or 23, characterized in that the at least one antiproliferative, anti-inflammatory, antiphlogistic and/or antithrombotic active agent is released in a controlled manner through the surface coating.
25. A medical product according to any one of claims 8 to 18, 23 or 24, characterized in that the respective antiproliferative, anti-inflammatory, antiphlogistic and/or antithrombotic active agent is contained in a pharmaceutically active concentration of 0.001 – 10 mg per cm² of surface of the medical product and per layer which carries the active agent.
26. A medical product according to any one of claims 1 to 18 or 23 to 25, characterized in that the medical product is a stent.

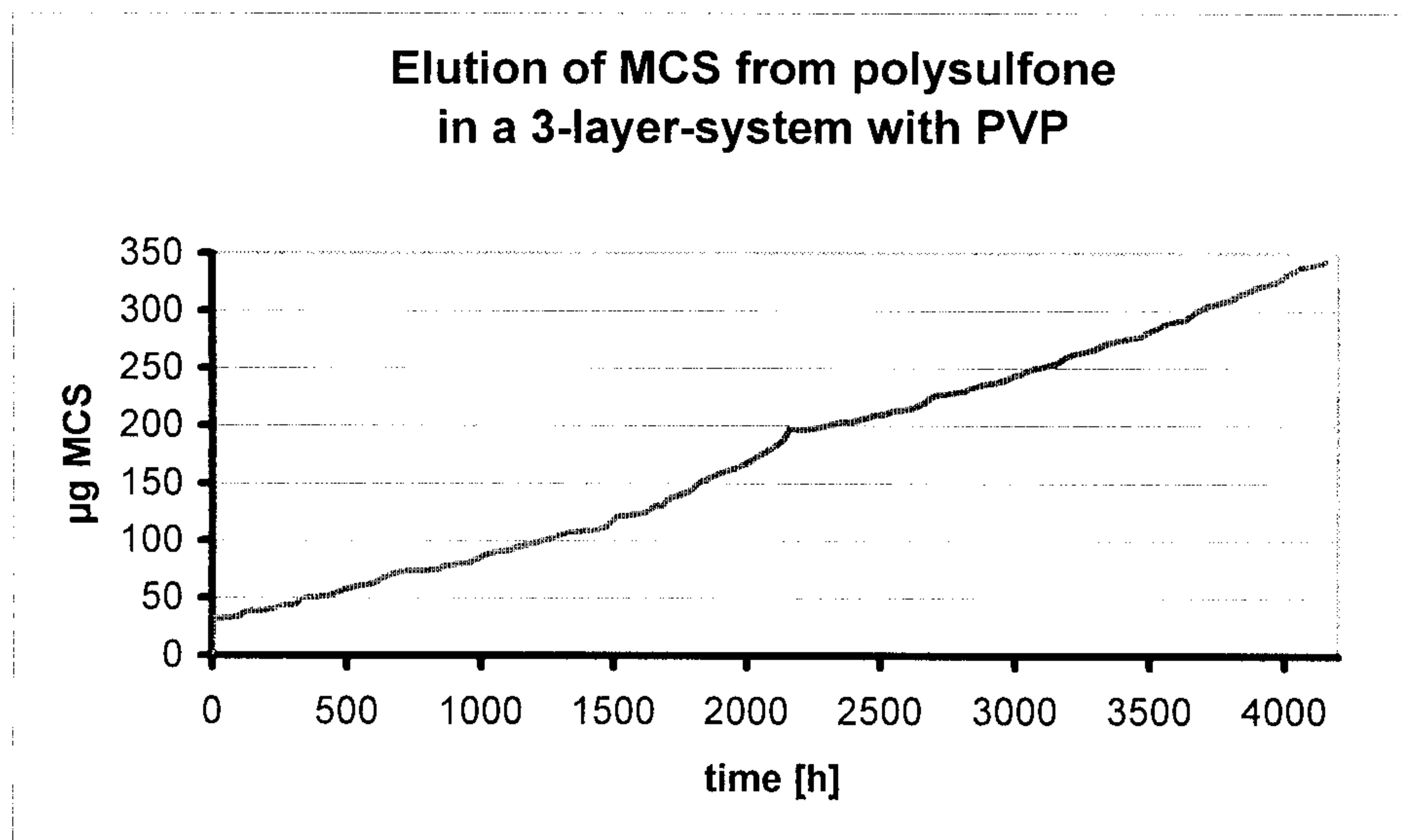


Fig. 1

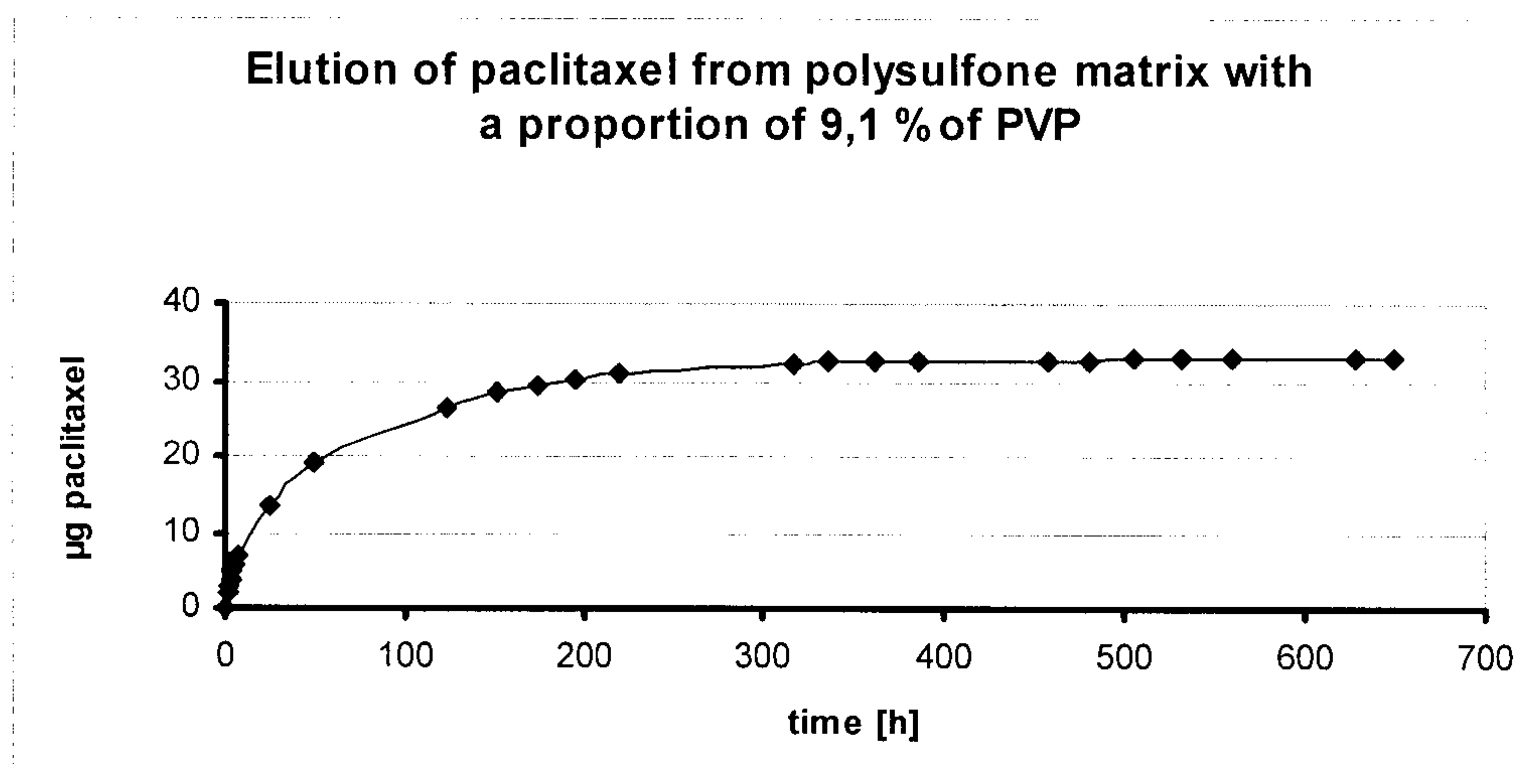
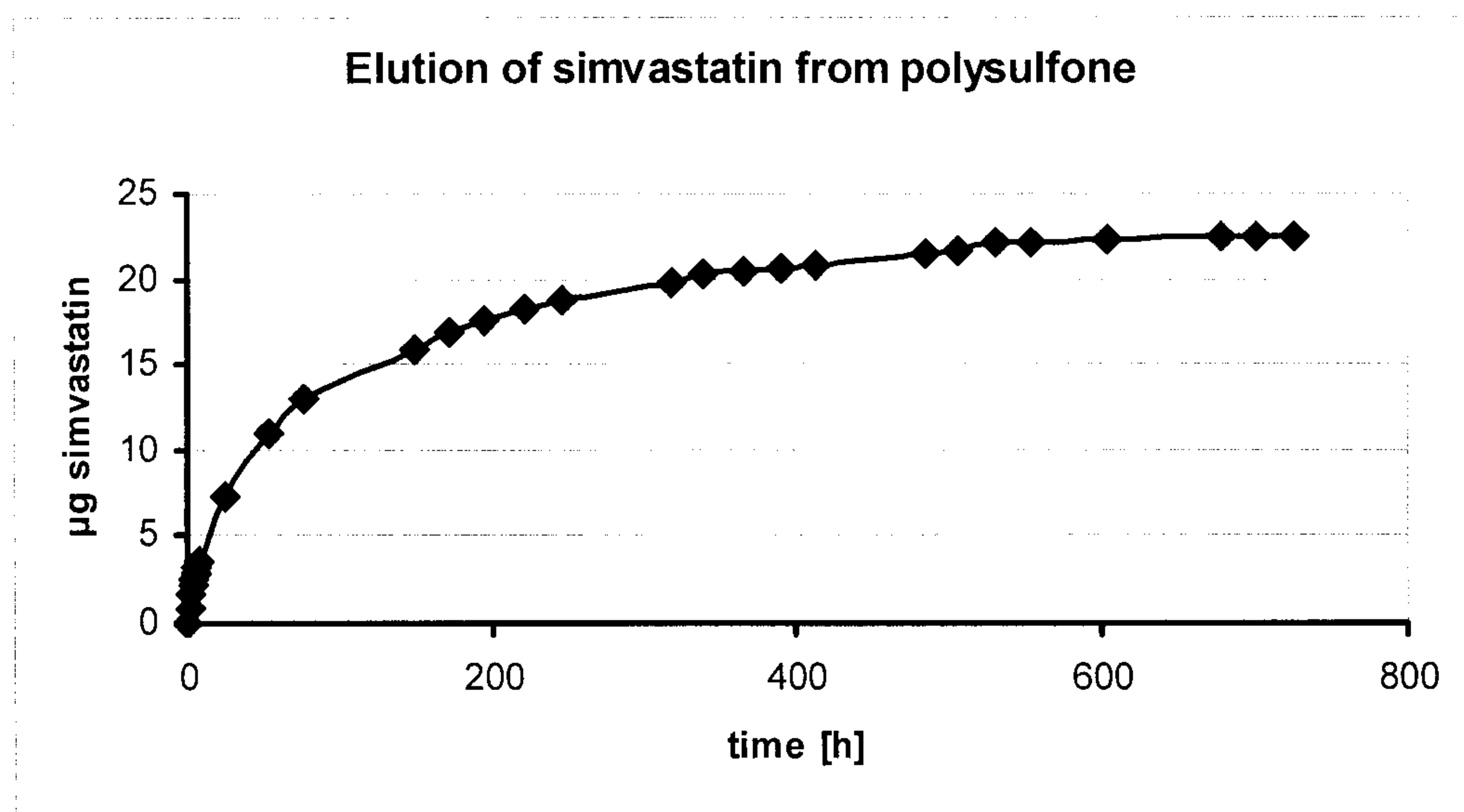
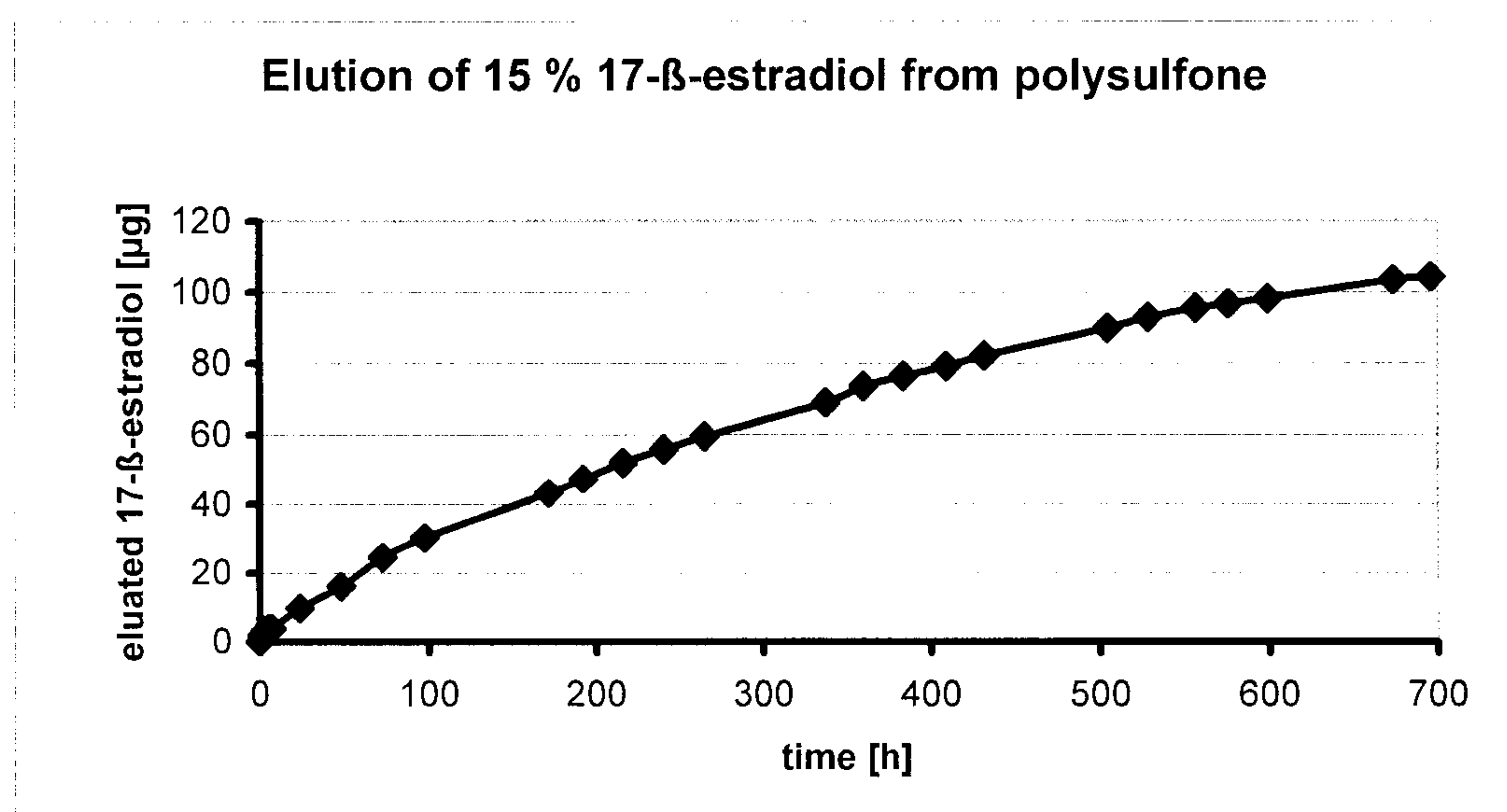


Fig. 2

**Fig. 3****Fig. 4**

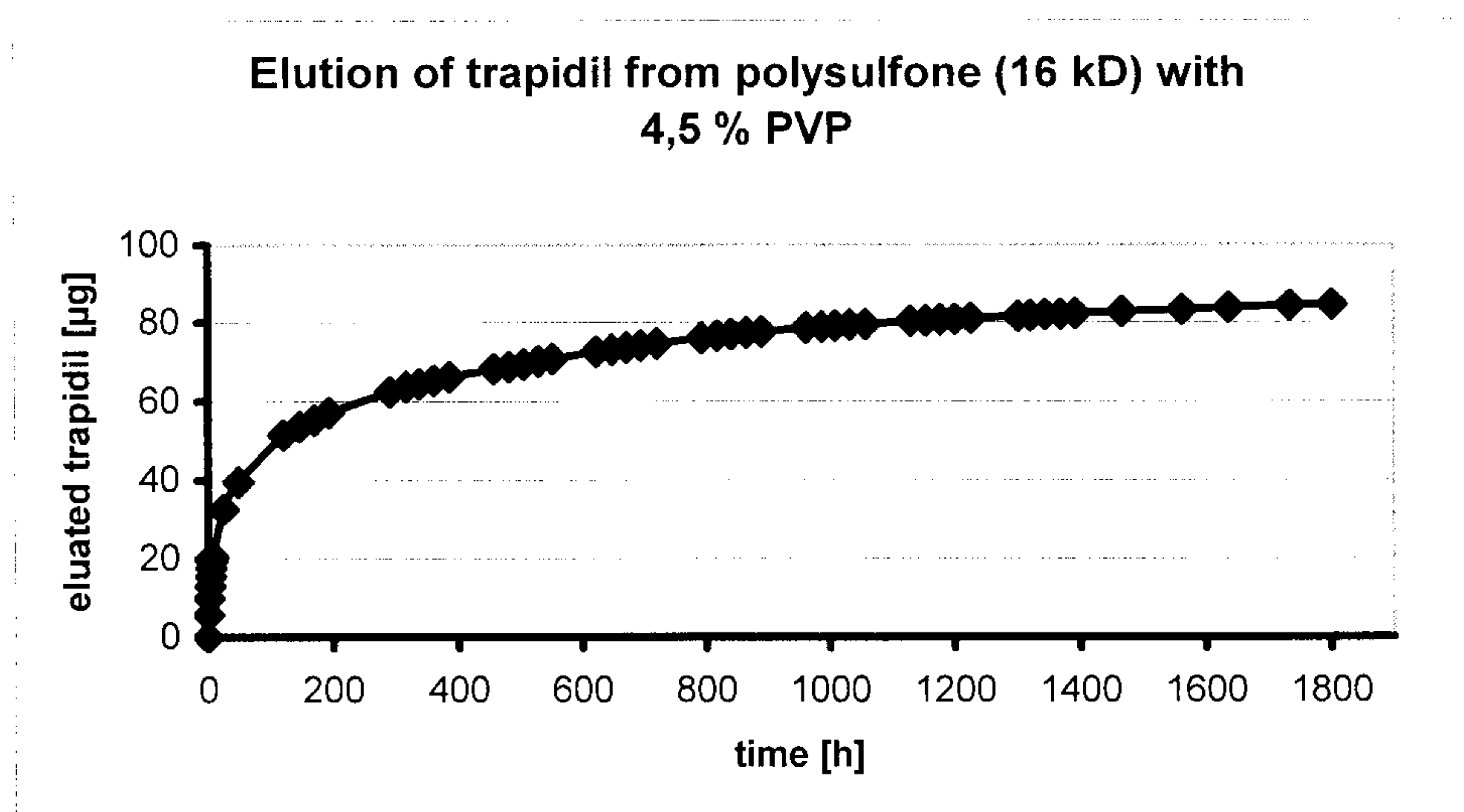
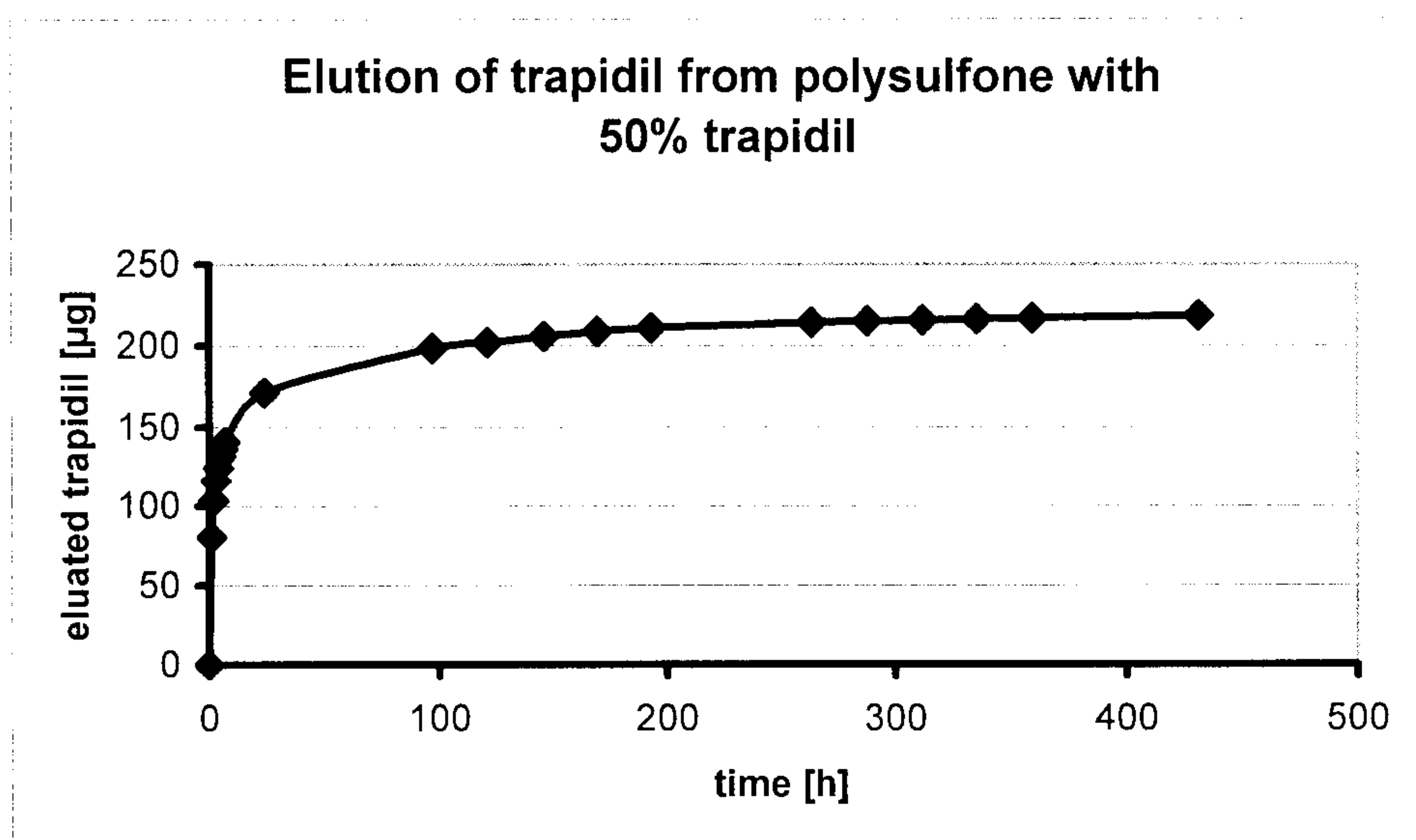
**Fig. 5****Fig. 6**

Fig. 7A

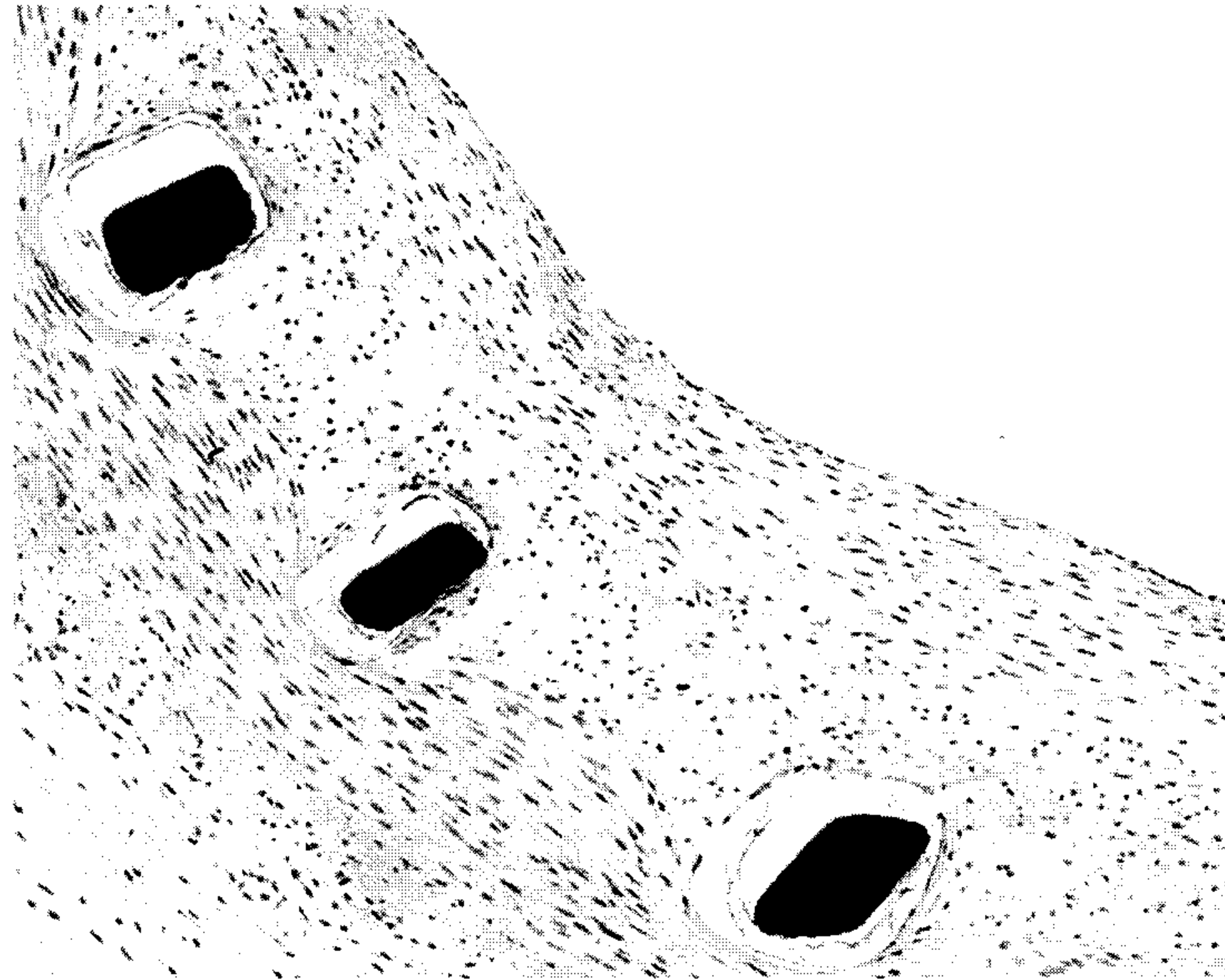
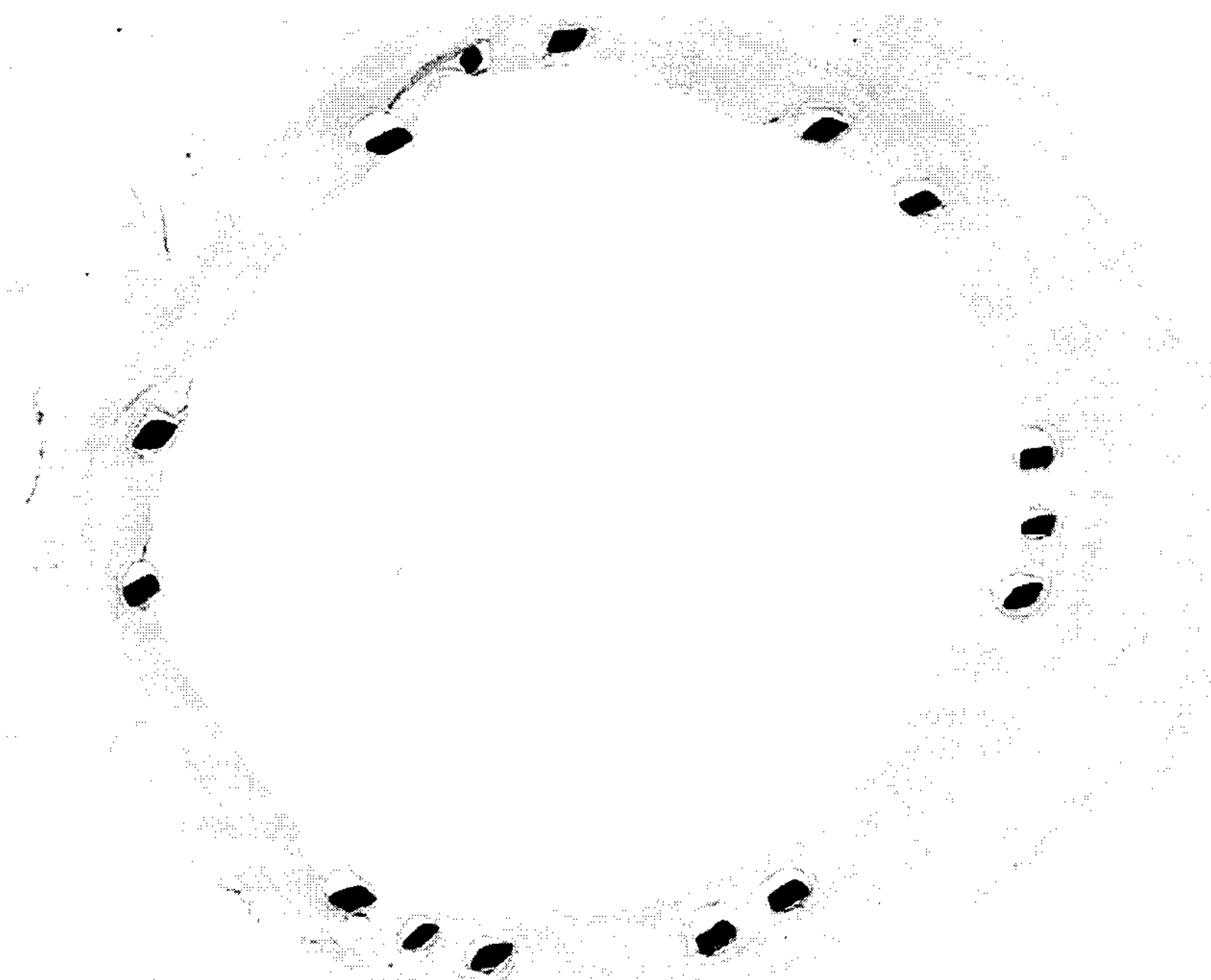


Fig. 7B



Elution of MCS from polysulfone in a 3-layer-system with PVP

