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(54) Titre : IMPLANTS AVEC FK506
 (54) Title: IMPLANTS WITH FK506

(57) **Abrégé/Abstract:**

The invention relates to implants, in particular, for intracavernous or intravascular application, preferably for the treatment or prophylaxis of coronary or peripheral vascular constriction or occlusion, in particular constriction and stenoses or restenoses, preferably for the prophylaxis of restenoses, comprising FK506 in a chemically covalently or non-covalently bonded or physically fixed form, a method for production and use thereof.

Abstract

The invention relates to implants, in particular intracavernous or intravascular, preferably for the treatment or prophylaxis of coronary or peripheral vascular constrictions or vascular occlusions, in particular of constrictions and stenoses or restenoses, preferably for the prophylaxis of restenosis, which comprise FK506 in chemically covalently bound or non-covalently bound or physically immobilized form, processes for the production thereof and to the use thereof.

Implants with FK506

The invention relates to implants, in particular intracavernous or intravascular, preferably for the treatment or prophylaxis of coronary or peripheral vascular occlusions or vascular constrictions, in particular of constrictions and stenoses or restenoses, preferably for the prophylaxis of restenosis, which comprise FK506 in chemically covalently bound or non-covalently bound or physically immobilized form, processes for the production thereof and to the use thereof.

The formation of arteriosclerotic lesions in arterial blood vessels is the underlying disease for a large range of clinical symptoms which extend from angina pectoris via intermittent claudication to myocardial infarction and ischemic stroke; all based on atheromer formation and/or stenotic lesions. The term stenotic lesions refers to the local reduction of the vascular lumen to less than 60-70% of its normal diameter, which in turn leads to a marked reduction in the supply of oxygen and nutrients to the particular tissue. Although pharmacotherapy (statins, ACE inhibitors, gpIIa/IIIb blockers and plasminogen activators) have shown good therapeutic results especially in the area of cardiovascular diseases in recent decades, surgical interventions (bypass operations, etc.) are still necessary for many patients who have developed a complete ischemic state. These operations are moreover relatively complicated and costly and involve the risk of serious complications.

Minimally invasive surgical methods have been developed in order to prevent the development of ischemic heart diseases. The invention of percutaneous transluminal coronary angioplasty (PCTA) in the late 1970s was a great breakthrough in cardiology. PTCA involves the use of inflatable balloons which are advanced as far as the

stenotic lesion in the coronary arteries. These balloons are then inflated at the particular target positions and achieve dilatation of the stenotic region. A similar procedure can also be used for
5 dilatation of carotid or peripheral arteries.

Despite this, it was found relatively soon that a recurrent stenosis developed in a relatively large proportion of PTCA patients at the sites which had been
10 dilated with the balloon catheter. It was discovered in this connection that this so-called restenosis arises through reorganization of the vascular architecture of the tissue layers. The introduction of tubular vascular metal implants, so-called stents, in the transluminal
15 treatment of stenosis improved the situation. It has been demonstrated in clinical studies (Serruys et al., N. Engl. J. Med. 331 (1994) 489-495) that the use of stents at the balloon-dilated sites was able to reduce the occurrence of restenosis from about 45% to about
20 30%. Although this is to be regarded as a significant improvement in the prevention of residual restenosis, there is still a distinct stimulus for therapeutic improvements.

25 It was discovered in detailed studies of the pathophysiology of restenosis in the stent that this differs from PTCA-induced restenosis. Inflammatory reactions, hyperproliferation and in-migration of smooth muscle cells (SMCs) are important factors in
30 neointima formation which lead to restenosis in the stent. It has been found in the animal model of restenosis and even in human tissue that the hyperproliferation of the SMCs is associated with infiltration of macrophages and T cells into the tissue
35 around the reinforcements of the stent (Grewe et al., J. Am. Coll. Cardiol. 35 (2000) 157-63). In analogy to other clinical indications where inflammatory reactions and hyperproliferation of cells are involved and which can be controlled by medical treatment, attempts have

also been made to treat restenosis by pharmacotherapy. Selected active agents have been given either orally or intravenously or brought to the site of action through perforated catheters. Unfortunately, to date none of these active agents has been able to reduce restenosis significantly (Gruberg et al., Exp. Opin. Invest. Active agents 9 (2000) 2555-2578).

Direct delivery of pharmacologically active agents from active agent-coated stents is the method of choice here. Animal experiments and initial results of clinical trials with active agent-coated stents give the impression that delayed release of immunosuppressive or antiproliferative active agents can reduce the risk of restenosis. Paclitaxel, a cytostatic active agent, and rapamycin, an immunosuppressive and cytostatic active agent, have been tested in animal experiments. Both compounds inhibit neointima formation (Herdeg et al., Semin Intervent Cardiol 3 (1998) 197-199; Hunter et al., Adv. Active agent. Delivery Rev. 26 (1997) 199-207; Burke et al., J. Cardiovasc Pharmacol., 33 (1999) 829-835; Gallo et al., Circulation 99 (1999) 2164-2170). Nevertheless, an abolition of the effect was observed after 6 months of implantation of coated stents in pigs with paclitaxel (Heldman, International Local Active agent Delivery Meeting and Cardiovascular Course on Radiation, Geneva, Jan 25-27, 2001). Rapamycin showed good efficacy with complete abolition of restenosis in initial clinical applications (Sousa et al., Circulation 103 (2001) 192-195). On the other hand, this appears to go hand in hand with delayed healing of the vessel wall injured by balloon angioplasty and stent implantation.

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Speaking generally, a balance between healing of the arterial vessel wall after angioplasty and stent placement on the one hand and controlling neointima formation is very important. In order to achieve this

balance, active agents which selectively interfere with specific mechanisms leading to neointima formation should be used.

- 5 It was therefore an object of the invention to provide implants with favorable properties for the treatment and prophylaxis of restenosis.

10 The invention therefore relates to an implant comprising FK506 in chemically covalently bound or noncovalently bound or physically immobilized form, and optionally, at least one other active agent.

15 In this connection, it applies to every active agent mentioned for the purposes of this invention, including the active agent FK506, that the term active agent also describes direct derivatives of the active agent, and the active agent also in all types of salts, enantiomers, racemates, bases or free acids of the
20 active agent, and mixtures thereof.

It is preferred for the implant to be an intracavernous, preferably an intravascular, implant.

25 In this connection, intracavernous means inside a cavity, in particular inside a hollow organ or hollow organs such as blood vessels, gullets, ureters, bile ducts etc.

30 Intravascular means, in particular, the use in a blood vessel.

35 It is also preferred for the implant to be suitable for the treatment or prophylaxis of coronary or peripheral vascular constrictions or occlusions, in particular of constrictions or stenoses or restenoses, preferably for the prophylaxis of restenosis.

Particularly preferred therefore is an intracavernous, preferably intravascular, implant for the treatment or prophylaxis of coronary or peripheral vascular constrictions or occlusions, in particular of constrictions or stenoses or restenoses, preferably for the prophylaxis of restenosis, comprising FK506 in chemically covalently bound or noncovalently bound or physically immobilized form, and, optionally, at least one other active agent.

10

The macrolide antibiotic FK506 (tacrolimus, [3S-[3R*[E(1S*, 3S*, 4S*)], 4S*, 5R*, -8S*, 9E, 12R*, 14R*, 15S*, 16R*, 18S*, 19S*, 26aR*]]-5,6,8,11,12, 13, 14, 15, 16, 17, 18, 19, 24, 25, 25, 26, 26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7-20,21(4H,23H)-tetrone; Merck index No. 9000) is an active agent developed for transplantation medicine. FK506 inhibits the release of interleukin-2 (IL-2) and interferon- γ (IFN- γ) from T cells and thus blocks rejection of the implant (graft) (Wiederrecht et al., Ann. NY Acad Sci. 696 (1993) 9-19). FK506 has also been investigated in SMC cultures with a view to inhibition of the proliferation of smooth muscle cells (Mohacsi et al., J. Heart Lung Transplant. 16 (1997) 484-492; Marx et al., Circulation Res., 76 (1995) 412-417) and migration thereof (Poon et al., J. Clin. Invest. 98 (1996) 2777-2283). In general, FK506 has been assessed by various researchers as unsuitable, because of its low potency, for the prevention of restenosis (Mohacsi et al. (1997); Poon et al. (1996); Marx et al., 1995; Dell, Curr Med Chem 5 (1998) 179-94). Mohacsi et al. found a half-maximal inhibition of SMC proliferation between 100 nM and 1 μ M, while Marx et al. observed no effect at all at concentrations up to 123 nM. In contrast thereto, rapamycin is active in inhibiting the proliferation of SMC cultures in the nanomolar concentration range.

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Based on this prior art, it did not appear at all promising to use specifically FK506 for inhibiting restenosis (Mohacsi et al. (1997); Poon et al. (1996)).

5 However, contrary to the opinion of skilled workers, it has surprisingly emerged that the use in particular of FK506 as part of a stent but also of other implants is very effective in the treatment and prophylaxis of restenosis. Local administration of FK506 in particular

10 is favorable for preventing restenosis, and the effect is very balanced since it also allows good re-endothelialization of the injured vessel wall.

Without it being possible to assume this from the

15 onset, this might possibly be explained by the immunomodulatory activity of FK506, which is shown by a half-maximal inhibition of IL-2 release at concentrations around 0.1 nM (Kino et al., J. Antibiot. 40 (1987) 1256-1265) and an inhibitory effect on SMC

20 proliferation at concentrations around 300-500 nM. The use of FK506 is therefore favorable.

In this connection, stenosis means the occlusion or constriction of a vessel, and restenosis means the

25 recurrence of a stenosis.

In addition, in this connection, "comprising" also means inter alia for example a noncovalently bound coating.

30 In addition, in this connection, "peripheral" refers in particular to vessels or other hollow organs outside the heart and the coronary vessels.

35 "Chemically noncovalently" bound means in particular linkages through interactions such as hydrogen bonds, hydrophobic interactions, Van der Waals forces, etc.

Physically immobilized means, for example, the enclosing e.g. via a membrane in a hole, or steric entrapment through choice of the orifice sizes.

5 Implant means any type of artificial object which is introduced (even for only a limited time). These are, in particular, intracavernous, for example intravascular, implants. Examples are stents, grafts, stent grafts, graft connectors, guide wires, catheter
10 pumps or catheters.

Stent means for the purposes of this invention an elongate implant with a hollow interior and at least two orifices and usually a circular or elliptical, but
15 also any other, cross section (mostly made of metal, but, optionally, also of plastic materials or polymers) preferably with a perforated, lattice-like structure which is implanted into vessels, in particular blood vessels, in order to keep them open and functioning.

20 Graft means for the purposes of this invention an elongate implant with a hollow interior and with at least two orifices and usually circular or elliptical, but also any other, cross section and with at least one
25 closed polymer surface which is homogeneous or, optionally, woven from various strands and is impermeable for corpuscular constituents of blood and/or for water, which implant serves in general as vascular prosthesis and is usually employed for damaged
30 vessels or in place of vessels.

Stent graft means for the purposes of this invention the connection between stent and graft. Thus, a stent graft is basically a vascular prosthesis reinforced
35 with a stent (graft, see above), where the polymer layer is homogeneous or, optionally, woven from various strands and is impermeable for corpuscular constituents of blood and/or for water. In the narrower sense, this is a stent which has on at least 20% of the surface of

the implant a perforated (lattice-like), preferably metallic, outer layer and at least one closed polymer layer which is located inside or outside this outer layer, is homogeneous or, optionally, woven from
5 various strands, and is impermeable for corpuscular constituents of blood and/or for water, and, optionally (when the perforated layer is located outside), a further perforated (lattice-like), preferably metallic, inner layer which is located inside the polymer layer,
10 or a closed polymer layer which is located outside, and outside the perforated layer, is homogeneous or, optionally, woven from various strands, and is impermeable for corpuscular constituents of blood and/or for water.

15 Graft connector means for the purposes of this invention an implant which connects at least two hollow organs, vessels or grafts, consists of the materials defined for grafts or stent grafts and/or has the
20 structure defined for the latter, and correspondingly, has at least two, preferably three or four, orifices, in particular shows an asymmetric "T" shape.

Catheter means for the purposes of this invention a
25 tubular instrument for introduction into hollow organs. In the narrower, preferred sense, they are guide, angiography or balloon catheters.

Catheter pump means for the purposes of this invention
30 a catheter provided on its tip with a propeller able to assist the pumping of the myocardium.

It is a further preferred embodiment of the implant of the invention for the implant to have at least one
35 closed or perforated layer or surface which consists of a metal or a metal alloy and is homogeneous or formed from various strands.

Metal or metal alloy means for the purposes of this invention in particular steel or steel alloys or else nickel or nickel alloys, with the term metal also including from the outset metal alloys.

5

Perforated structures mean, in particular, lattice-like or woven or plaited ones.

10 It is a further preferred embodiment of the implant of the invention for the implant to have at least one closed or perforated layer or surface which consists of a polymer and is homogeneous or formed from various strands.

15 In a preferred embodiment, the implant has at least one polymer layer which covers completely or partly a closed or perforated layer or surface which consists of a metal or a metal alloy and is homogeneous or formed from various strands, preferably an optionally lattice-
20 like structure consisting of a metal or a metal alloy.

In a particularly preferred embodiment, the implant has at least one closed or perforated layer or surface which consists of a metal or a metal alloy and is
25 homogeneous or formed from various strands, and at least one closed or perforated layer or surface which consists of a polymer and is homogeneous or formed from various strands.

30 It is moreover particularly preferred with this implant for the layer or surface consisting of a metal or a metal alloy to be an optionally lattice-like structure consisting of a metal or a metal alloy, and/or for the layer or surface consisting of a polymer to be
35 homogeneously closed or woven and/or to be water- and/or corpuscle-impermeable, and/or for the sequence of layers and surfaces to be from the outside to the inside metal-polymer, polymer-metal, metal-polymer-metal or polymer-metal-polymer, and/or for either the

layer or surface consisting of a polymer to be nonchemically (covalently or noncovalently) connected to a layer or surface consisting of a metal or a metal alloy, or for the layer or surface consisting of a polymer to be connected by means of an adhesive to the layer or surface consisting of a metal or a metal alloy.

It is further preferred for the polymer used in the implants to be selected from Dacron; polytetrafluoroethylene (PTFE/Teflon), expandable or non-expandable; or polyurethane; preferably from polytetrafluoroethylene (PTFE), expandable or non-expandable; or polyurethane; in particular from PTFE.

It is also a preferred embodiment of the invention for the implant to be a stent, a stent graft, a graft, a graft connector, a guide wire, a catheter or a catheter pump, preferably a stent, a stent graft, a graft or a graft connector, in particular a stent or a stent graft.

It is particularly preferred for the implant of the invention to be coated with FK506.

Local administration of FK506 is achieved by direct delivery from the active agent-loaded surface of the coronary or peripheral stent. An active agent-loaded surface of a stent can be achieved by using various technological approaches. Each of these approaches can be carried out in such a way that the active agent is released from the surface either in a short (hours) or an extended period (days). The kinetics of release can be adapted by carrying out specific modifications on the surface, e.g. hydrophobic or hydrophilic side chains of a polymeric carrier or a ceramic surface. These surfaces may also in turn be modified on the surface, e.g. by Si groups on an aluminum oxide layer.

The kinetics of release can be adapted by employing specific polymers, block polymers, polymer blends, graft polymers alone or in a layer structure. The kinetics of release are controlled particularly suitably by using nanocapsules and/or liposomes and the polymer combinations described above. Nanocapsules mean in general the coating of micellar systems or colloidal solids to give ultrafine particles with a solid coating. The coated particles, whose size is in the nanometer range, form colloidal solutions. Nanoencapsulated active agents can thus be employed with prolonged activity. Liposomes are generally formed from phospholipids by dispersion in aqueous media and are of interest in this connection because hydrophilic active agents can be incorporated into the aqueous internal volume and into the aqueous intermediate layers and hydrophobic active agents into the lipid layers. If nanocapsules and/or liposomes differing in composition are used, the latter can be loaded with different active agents and thus a combination of active agents can be released in a targeted manner.

Ceramic coating

An aluminum oxide coating (patent applications DE 19855421, DE 19910188, WO 00/25841) with a porous surface can be loaded with FK506 in amounts between 10 μ g and 10 mg either by immersing, spraying on or a comparable technique. The dose of active agent depends on the type of target vessel and the condition of the patient and is chosen so that proliferation, migration and T-cell response are adequately inhibited without impeding the healing process. FK506 can be used as aqueous or organic solution, for example in DMSO, DMF and ethanol. After the spraying or immersing (optionally under weak vacuum), the treated stent is dried and the procedure is repeated 2-10 times. Another possibility for application consists of direct delivery of the active agent solution onto the stent strands

with the aid of a micropipette or of a robotic pipettor. After the last drying step, the stent can be rinsed in water or isotonic saline at room temperature for one minute and then redried. The active agent content can be analyzed by standard methods (HPLC, LC-MS) after the active agent has been dissolved out with a suitable solvent. Kinetics of release can be measured using a standard release-measuring apparatus. The ceramic approach can be combined with a polymeric (optionally biodegradable) coating.

It is moreover possible to employ every type of metal oxide coatings analogously, in particular, for example, iridium oxide as described in US patent 6,245,104 B1. Accordingly, every mention of aluminum oxide hereinafter is to be understood to mean other metal oxides such as, for example, iridium oxide are to be understood as included too.

20 **PTFE membrane: stent graft**

An approach comparable to the one described above is used in this case. FK506 is deposited in the recesses in the porous PTFE membrane.

25

General polymeric coating

Various polymers are suitable for active agent loading: methacrylate polymers, polyurethane coatings, PTFE coatings, hydrogel coatings. The active agent can either be applied to the final surface (see above) or is added directly to the polymerization solution. This technical approach corresponds in the other details to those already described above.

35

Various polymers and combinations of the latter in the form of polymer blends, systems with a layer structure, block copolymers, graft copolymers can be used. Suitable polymers are: acrylates and methacrylates,

silicones such as, for example, polydimethylsiloxane, polymethylenemalonic esters, polyethers, polyesters, bioabsorbable polymers, polymers from vinylic monomers such as, for example, polyvinylpyrrolidone and vinyl
5 ethers, poly-cis-1,4-butadiene, poly-cis-1,4-isoprene, poly-trans-1,4-isoprene, and vulcanized products, polyurethanes, polyureas, polyamides, polyimides, polysulfones, and biopolymers such as, for example, cellulose and derivatives thereof and proteins and
10 fibrin glues. Particularly interesting properties are shown by hydrogels which display, because of their high water uptake, very good hemocompatibility as outermost layer (top coat). It is possible in this case to employ hydrogels such as, for example, polyacrylamide,
15 polyacrylic acid, polymers with oxygen as heteroatom in the main chain such as, for example, polyethylene oxide, polypropylene oxide, polytetrahydrofuran. The active agent can either be applied to the final surface or be administered embedded in nanocapsules and/or
20 liposomes. The active agent may, however, also be present directly in the polymerization solution or in the polymer solution. It is possible with some polymer/active agent systems for the active agent to be immobilized by swelling.

25

Mechanical approach

The mechanical approach is based on recesses introduced into the stent struts by means of a laser. These
30 recesses can then be filled with FK506. The mechanical (recess) approach can be combined with a polymeric, optionally, biodegradable coating which is itself loaded with active agent. After an initial release from the polymeric coating, active agent can be released
35 long-term from the active agent-filled recesses. This technical approach corresponds in the other details to those already described above.

Accordingly, it is another preferred embodiment of the implant of the invention for the implant to have a ceramic coating, in particular of aluminum oxide, to which FK506 is bound.

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It is another preferred embodiment of the implant of the invention for the implant to have a polymeric coating, in particular of methacrylate polymers, polyurethane, PTFE, hydrogel or hydrogel/polyurethane blend, in particular PTFE, to which FK506 is bound or in which FK506 has been dissolved before application of the coating.

It is another preferred embodiment of the implant of the invention for the metal of the implant to have recesses introduced by means of a laser, which are filled with FK506. It is particularly favorable in this case for the metal provided with FK506-filled recesses or at least the recesses to be coated with a biodegradable polymeric material, in which case FK506 is optionally bound to the polymeric coating, or FK506 has been dissolved in the polymeric material before polymerization of the coating.

25 In another very favorable embodiment of the implant of the invention, the implant can be produced by a process in which

a) an implant having at least one closed or perforated layer or surface which consists of a metal or a metal alloy and is homogeneous or formed from various strands, as claimed in any of claims 4, 6 or 7 to 10, which implant is coated with a ceramic coating, in particular of aluminum oxide, is employed

35

or

b) an implant having at least one closed or perforated layer or surface which consists of a polymer and is homogeneous or formed from

various strands, as claimed in any of claims 5 to 10, is employed,

or

5 c) an implant as claimed in any of claims 1 to 10, which is coated with a coating which is polymerized or polymerizing on the surface, in particular of methacrylate polymers, polyurethane, PTFE, hydrogel or hydrogel/polyurethane blend, is employed

10 or

d) an implant as claimed in any of claims 4, 6 or 7 to 10 having at least one closed or perforated layer or surface which consists of a metal or a metal alloy and is homogeneous or formed from various strands, and into which recesses have been introduced by means of a laser, which are filled with FK506, and then the implant is coated with a biodegradable coating which is polymerized or polymerizing on the surface, is employed,

15

e) then the implant according to a), b), c) or d) is brought into contact with an FK506 solution in aqueous or organic solvent, for example by sprinkling, spraying or immersing, optionally under vacuum,

25

f) then, optionally, the implant is dried, preferably until the solvent from step e) is removed,

30

g) then, optionally, step e), optionally followed by step f), is repeated, preferably several times, in particular 1 to 5 times, and,

h) optionally, subsequently the implant is rinsed one or more times with water or isotonic saline, and,

35

i) optionally, is subsequently dried.

It is preferred in this connection during the production of this implant of the invention which can be produced in this way for FK506 to be dissolved in

step e) in alcohol, preferably in ethanol, in particular in a concentration of 0.5-5 g/l in FK506 in ethanol and/or for the implant in step e) to be brought into contact with an FK506 solution in aqueous or
5 organic solvent by immersing under vacuum preferably overnight, and/or for steps f) and/or g) not to be carried out and/or for the implant in step h) to be washed several times with saline and/or for the implant in step i) to be dried overnight.

10

In an alternative particularly preferred embodiment of the invention, it is preferred in the production of this implant of the invention which can be produced as described above for the implant in step e) to be
15 introduced, preferably sterilely, into a preferably sterile vessel with a closure which can be perforated and which closes after completion of a perforation, for example into an injection vial, for FK506 solution, to be preferably sterilely introduced into the vessel, for
20 the latter to be closed with the closure which can be perforated and which closes after completion of a perforation, for a thin, preferably sterile, air-pervious ventilation tube, for example a cannula, to be pushed perforatingly through the closure, a vacuum to
25 be applied and, preferably, the FK506 solution to be agitated, and finally, preferably after about 12 h have elapsed, for the thin, preferably sterile, air-pervious ventilation tube to be removed and/or for FK506 in
30 step e) to be dissolved in alcohol, preferably in ethanol, in particular in a concentration of 3.3 mg of FK506 in 1 ml of ethanol and/or that the implant remains until used in the preferably sterile closed glass vessel from step e) and/or steps f) to i) are omitted.

35

In another very favorable embodiment of the implant of the invention, the implant can be produced by a process in which FK506 has been dissolved in the polymerization material before the formation of at least one closed or

perforated layer or surface consisting of a polymer, or of a polymeric coating of the implant.

It is further particularly preferred for FK506 to be released after implantation of the implant of the invention. It is moreover particularly favorable for the release to be delayed. In this connection it is a particularly preferred embodiment of the invention for FK506 to be released from the implant over a period of 24 h, preferably 48 h, in particular more than 96 h, after implantation. It is also favorable in particular for the FK506

- a) to be released within <48 h or
- b) over at least 48 h, preferably over at least 7 days, in particular over at least 2 and up to 21 days, from the implant after implantation, or that
- c) the implant shows both release patterns a) and b).

20

The latter variant in particular can be achieved by using two different types of coating, binding or physical immobilization. The laser recesses with FK506 which are sealed with FK506-loaded biodegradable membranes are one example. Rapid release from the membrane is followed by long-term release from the recesses.

It is a further preferred embodiment of the invention for at least one other active agent to be present in the implant, preferably a pharmaceutically active agent, in particular another active agent selected from the following active agents and derivatives thereof

(Group 1:) molsidomine, linsidomine, sodium nitroprusside, nitroglycerin or general NO donors; stimulators of soluble guanylate cyclase (sGC), for example BAY 41-2272 (5-(cyclopropyl-2-[1-fluorobenzyl])-1H-pyrazolo[3,4-n]pyridin-3-yl)-

- 18 -

- pyrimidin-4-ylamine); hydralazine, verapamil, diltiazem, nifedipine, nimodipine or other Ca²⁺ channel blockers; captopril, enalapril, lisinopril, quinapril or other inhibitors of angiotensin converting enzymes (angiotensin converting enzyme inhibitors); losartan, candesartan, irbesartan, valsartan or other antagonists of the angiotensin II receptor;
- 5
- (Group 2:) dexamethasone, betamethasone, prednisone or other corticosteroids; 17-beta-estradiol; cyclosporin; mycophenolic acid; VEGF, VEGF receptor activators; tranilast; meloxicam, celebrex, viox or other COX-2 antagonists; indomethacin, diclofenac, ibuprofen, naproxen or other COX-1 inhibitors; inhibitors of plasminogen activator 1 (plasminogen activator inhibitors-1) or serpins; thrombin inhibitors, for example hirudin, hirulog, agratroban, PPACK or interleukin-10;
- 10
- 15
- 20
- (Group 3:) rapamycin, SDZ RAD (40-O-(2-hydroxyethyl)rapamycin or other rapamycin derivatives; PDGF antagonists; paclitaxel or 7-hexanoyl-taxol; cisplatin; vinblastine; mitoxantrone; combretastatin A4; topotecan; methotrexate; flavopiridol; actinomycin D; Rheopro/abciximab or probucol.
- 25
- 30
- 35
- It is moreover particularly preferred for the other active agent to be selected from group 1 and to be released from the implant within the first 24 - 72 h after implantation and/or, if the other active agent is selected from group 2, for the latter to be released from the implant within the first 48 h - 21 days after implantation and/or, if the other active agent is selected from group 3, for the latter to be released from the implant within 14 days to 3 months after implantation.

The invention further relates to a process for producing an implant of the invention, in which FK506 has been dissolved in the polymerization material before the formation of at least one closed or perforated layer or surface consisting of a polymer, or of a polymeric coating of the implant.

The invention further relates to a process for producing an implant of the invention with the following steps:

a) an implant having at least one closed or perforated layer or surface which consists of a metal or a metal alloy and is homogeneous or formed from various strands, as claimed in any of claims 4, 6 or 7 to 10, which implant is coated with a ceramic coating, in particular of aluminum oxide,

or

b) an implant having at least one closed or perforated layer or surface which consists of a polymer and is homogeneous or formed from various strands, as claimed in any of claims 5 to 10,

or

c) an implant as claimed in any of claims 1 to 10, which is coated with a coating which is polymerized or polymerizing on the surface, in particular of methacrylate polymers, polyurethane, PTFE, hydrogel or hydrogel/polyurethane blend,

or

d) an implant as claimed in any of claims 4, 6 or 7 to 10 having at least one closed or perforated layer or surface which consists of a metal or a metal alloy and is homogeneous or formed from various strands, and into which recesses have been introduced by means of a laser, which are filled with FK506, and then

- 20 -

the implant is coated with a biodegradable coating which is polymerized or polymerizing on the surface, is employed,

5 e) then the implant according to a), b), c) or d) is brought into contact with an FK506 solution in aqueous or organic solvent, for example by sprinkling, spraying or immersing, optionally under vacuum,

10 f) then, optionally, the implant is dried, preferably until the solvent from step e) is removed,

g) then, optionally, step e), optionally followed by step f), is repeated, preferably several times, in particular 1 to 5 times, and,

15 h) optionally, subsequently the implant is rinsed one or more times with water or isotonic saline, and,

i) optionally, is subsequently dried.

20 This process is particularly preferred when in step e) FK506 is dissolved in alcohol, preferably in ethanol, in particular in a concentration of 0.5-5 g/l FK506 in ethanol and/or that in step e) the implant is brought into contact with an FK506 solution in aqueous or
25 organic solvent by dipping under vacuum preferably overnight, and/or that steps f) and/or g) are not carried out, and/or that in step h) the implant is washed several times with saline, and/or that in step
30 i) the implant is dried overnight.

A particularly preferred alternative of the process of the invention is when the implant in step e) is introduced, preferably sterilely, into a preferably sterile vessel with a closure which can be perforated
35 and which closes after completion of a perforation, for example into an injection vial, FK506 solution, is preferably sterilely introduced into the vessel, for the latter to be closed with the closure which can be perforated and which closes after completion of a

perforation, a thin, preferably sterile, air-pervious ventilation tube, for example a cannula, is pushed perforatingly through the closure, a vacuum is applied and, preferably, the FK506 solution is agitated, and finally, preferably after about 12 h have elapsed, the thin, preferably sterile, air-pervious ventilation tube is removed and/or that in step e) FK506 is dissolved in alcohol, preferably in ethanol, in particular in a concentration of 3.3 mg of FK506 in 1 ml of ethanol and/or the implant that remains until used in the sterile closed glass vessel from step e) and/or steps f) to i) are omitted.

This alternative of the process is particularly favorable, previously entirely undisclosed and extremely advantageous both in the costs and in the time and steps for production, especially since the implant results immediately and is already in a sterile packaging. It is also generally applicable and, of course, not confined to FK506 but functions with a large number of active agents. However, there is a deficiency in particular of such favorable and simple processes, so that this is a problem.

The application therefore further relates separately to a process, which is specified generally below, for the production of implants coated with active agents, with the following steps:

- a) the implant is introduced, preferably sterilely, into a preferably sterile vessel with a closure which can be perforated and closes after completion of a perforation, for example an injection vial,
- b) preferably sterile active agent solution, preferably in an organic solvent with a low vapor pressure, in particular in alcohol such as ethanol or methanol, is introduced into the vessel,

- 22 -

- c) the vessel is closed with the closure which can be perforated and closes after completion of a perforation,
- d) a thin, preferably sterile, air-pervious ventilation tube, for example a cannula, is pushed perforatingly through the closure,
- e) optionally a vacuum is applied, whereby the active agent solution is preferably agitated,
- f) finally, preferably after about 12 h have elapsed, the thin, preferably sterile, air-pervious ventilation tube is removed and,
- g) optionally, the implant is left until used in the preferably sterile closed glass vessel from step a).

15

It is moreover favorable for this general process if the implant from step a) has at least one metallic perforated or closed surface or layer, has a ceramic coating, has a polymeric coating and/or has at least one polymeric, perforated or closed surface or layer.

20

The general process is likewise preferred for an implant which is a stent, stent graft, graft, graft connector, polymeric surface stent or catheter.

25

The general process is further preferred if the active agent is selected from pharmaceutically active agents such as, for example, immunosuppressants or antibiotics, is preferably selected from the following active agents and derivatives thereof

30

(Group 1:) molsidomine, linsidomine, sodium nitroprusside, nitroglycerin or general NO donors; stimulators of soluble guanylate cyclase (sGC), for example BAY 41-2272 (5-(cyclopropyl-2-[1-fluorobenzyl]-1H-pyrazolo[3,4-n]pyridin-3-yl]pyrimidin-4-ylamine); hydralazine, verapamil, diltiazem, nifedipine, nimodipine or other Ca^{2+} channel

35

blockers; captopril, enalapril, lisinopril, quinapril or other inhibitors of angiotensin converting enzymes (angiotensin converting enzyme inhibitors); losartan, candesartan, irbesartan, valsartan or other antagonists of the angiotensin II receptor;

(Group 2:) dexamethasone, betamethasone, prednisone or corticosteroids; 17-beta-estradiol; cyclosporin; mycophenolic acid; VEGF, VEGF receptor activators; tranilast; meloxicam, celebrex, viox or other COX-2 antagonists; indomethacin, diclofenac, ibuprofen, naproxen or other COX-1 inhibitors; inhibitors of plasminogen activator-1 (plasminogen activator inhibitors-1) or serpins; thrombin inhibitors, for example hirudin, hirulog, agratroban, PPACK; interleukin-10;

(Group 3:) sirolimus, rapamycin, SDZ RAD (40-O-(2-hydroxyethyl)rapamycin or other rapamycin derivatives; PDGF antagonists; paclitaxel or 7-hexanoyl-taxol; cisplatin; vinblastine; mitoxantrone; combretastatin A4; topotecan; methotrexate; flavopiridol;

actinomycin D; Rheopro/abciximab or probucol,

in particular is selected from

(Group 1:) molsidomine, linsidomine, sodium nitroprusside, nitroglycerin or general NO donors; stimulators of soluble guanylate cyclase (sGC), for example BAY 41-2272 (5-(cyclopropyl-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-n]pyridin-3-yl]pyrimidin-4-ylamine); captopril, enalapril, lisinopril, quinapril or other inhibitors of angiotensin

converting enzymes (angiotensin converting enzyme inhibitors); losartan, candesartan, irbesartan, valsartan or other antagonists of the angiotensin II receptor;

5

(Group 2:) dexamethasone, betamethasone, prednisone or corticosteroids; FK506 (tacrolimus); VEGF, VEGF receptor activators; inhibitors of plasminogen activator 1 (plasminogen activator inhibitors-1) or serpins;

10

(Group 3:) sirolimus, rapamycin, SDZ RAD (40-O-(2-hydroxyethyl)rapamycin or other rapamycin derivatives; PDGF-antagonists; paclitaxel or 7-hexanoyl-taxol; mitoxantrone; combretastatin A4; flavopiridol.

15

The invention further relates to the use of an implant
20 of the invention for the treatment or prophylaxis of coronary or peripheral vascular constrictions or occlusions, in particular of constrictions or stenoses or restenoses, preferably for the prophylaxis of restenosis.

25

The application further relates, importantly, to the use of FK506, called FK506 use hereinafter, for coating or for producing an implant for the treatment or prophylaxis of coronary or peripheral vascular
30 constrictions or occlusions, in particular of constrictions or stenoses or restenoses, preferably for the prophylaxis of restenosis.

35

It is preferred for the FK506 use if the implant is a stent, a stent graft, a graft, a graft connector, a guide wire, a catheter or a catheter pump, preferably a stent, a stent graft, a graft or a graft connector, in particular a stent or a stent graft or a polymeric surface stent.

It is further favorable for the FK506 uses if the FK506 is bound or attached to the implant in such a way that it is released, preferably in a delayed manner, from the implant after implantation.

5

The application further relates, separately, to the use of FK506 for the treatment or prophylaxis of coronary or peripheral vascular constrictions or occlusions, in particular of constrictions or stenoses or restenoses, preferably for the prophylaxis of restenosis. As stated above, FK506 has particularly favorable properties in this connection, as has been found within the scope of this application.

15 Within the scope of the invention, a stent having a polymer layer or consisting of polymers or a graft or a stent graft, has proved particularly suitable for FK506. Implants of this type, referred to comprehensively as polymeric surface stents within the scope of this invention, have not previously been used with active agent coating. However, they are outstandingly suitable precisely for this purpose, as proved by the investigations done within the scope of this application, because they are easy to load with active agent and then deliver the active agent again uniformly and efficiently. This property is not, however, confined to FK506, so that the application further relates, separately, to a polymeric surface stent comprising, in chemically covalently bound or noncovalently bound or physically immobilized form, at least one physiologically and/or pharmaceutically active active agent. For the purposes of this invention, a polymeric surface stent means an intravascular implant for the purposes of the invention which has a polymeric surface. In the wider sense, polymeric surface stents thus include grafts and stent grafts, graft connectors, stents coated with polymers or consisting of polymers, in the narrower sense stents

coated with polymers or consisting of polymers, and stent grafts.

It is preferred for the polymeric surface stent when the active agent is selected from pharmaceutically active agents such as, for example, immunosuppressants or antibiotics, is preferably selected from the following active agents and derivatives thereof

10 (Group 1:) molsidomine, linsidomine, sodium nitroprusside, nitroglycerin or general NO donors; stimulators of soluble guanylate cyclase (sGC), for example BAY 41-2272
15 (5-(cyclopropyl-2-[1-fluorobenzyl)-1H-pyrazolo[3,4-n]pyridin-3-yl]pyrimidin-4-ylamine); hydralazine, verapamil, diltiazem, nifedipine, nimodipine or other Ca²⁺ channel blockers; captopril, enalapril, lisinopril, quinapril or other inhibitors of angiotensin converting enzymes (angiotensin converting enzyme inhibitors); losartan, candesartan,
20 irbesartan, valsartan or other antagonists of the angiotensin II receptor;

25 (Group 2:) dexamethasone, betamethasone, prednisone or corticosteroids; FK 506 (tacrolimus) 17-beta-estradiol; cyclosporin; mycophenolic acid; VEGF, VEGF receptor activators; tranilast; meloxicam, celebrex,
30 vioxx or other COX-2 antagonists; indomethacin, diclofenac, ibuprofen, naproxen or other COX-1 inhibitors; inhibitors of plasminogen activator-1 (plasminogen activator inhibitors-1) or serpins; thrombin inhibitors, for example
35 hirudin, hirulog, agratroban, PPACK; interleukin-10;

(Group 3:) sirolimus, rapamycin, SDZ RAD (40-O-(2-hydroxyethyl)rapamycin or other rapamycin

derivatives; PDGF antagonists; paclitaxel or 7-hexanoyl-taxol; cisplatin; vinblastine; mitoxantrone; combretastatin A4; topotecan; methotrexate; flavopiridol;

5

actinomycin D; Rheopro/abciximab or probucol,

in particular is selected from

10 (Group 1:) molsidomine, linsidomine, sodium nitroprusside, nitroglycerin or general NO donors; stimulators of soluble guanylate cyclase (sGC), for example BAY 41-2272 (5-(cyclopropyl-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-n]pyridin-3-yl]pyrimidin-4-ylamine); captopril, enalapril, lisinopril, quinapril or other inhibitors of angiotensin converting enzymes (angiotensin converting enzyme inhibitors); losartan, candesartan, irbesartan, valsartan or other antagonists of the angiotensin II receptor;

25 (Group 2:) dexamethasone, betamethasone, prednisone or corticosteroids; FK506 (tacrolimus); VEGF, VEGF receptor activators; inhibitors of plasminogen activator 1 (plasminogen activator inhibitors-1) or serpins;

30 (Group 3:) sirolimus, rapamycin, SDZ RAD (40-O-(2-hydroxyethyl)rapamycin or other rapamycin derivatives; PDGF-antagonists; paclitaxel or 7-hexanoyl-taxol; mitoxantrone; combretastatin A4; flavopiridol;

35

and/or that the polymeric surface stent comprises at least two, preferably 2 or 3, physiologically and/or pharmaceutically active agents selected

from one of groups 1 to 3, preferably a maximum of one active agent from one group.

5 It applies to a further preferred embodiment of this polymeric surface stent that, when the other active agent is selected from aforementioned group 1, this active agent is released from the implant within the first 24-72 h after implantation, and/or, if the other active agent is selected from aforementioned group 2,
10 this active agent is released from the implant within the first 48 h-21 days after implantation, and/or, if the other active agent is selected from aforementioned group 3, this active agent is released from the implant within 14 days to 3 months after implantation.

15 It applies generally to polymeric surface stents of the invention that all embodiments, production processes and uses described above of the implants specifically comprising FK506 are also preferred for the polymeric surface stent of the invention, and thus this invention,
20 relates thereto as long as the embodiments are still polymeric surface stents.

25 The invention further relates also to the treatment with or by an implant of the invention or a polymeric surface stent of a human or animal requiring this treatment.

30 The invention is further explained by examples in the following section, without restricting it thereto.

Examples and figures:

Figures:

35

Figure 1 shows the release of FK506 from a coronary stent graft in which the surface, which consists of PTFE, has been loaded with FK506.

Figure 2 shows the release of candesartan and quinapril from a stent graft in which the surface, which consists of PTFE, has been coated with candesartan and quinapril.

5

Figure 3 shows the release of candesartan and quinapril from a polyurethane-coated stent in which this coating has been supplemented with candesartan and quinapril.

10 Figure 4 shows the release of candesartan and quinapril from a stent coated with polyurethane/hydrogel blend, in which this coating has been supplemented with candesartan and quinapril.

15 Figure 5 shows the release of FK506 in the blood after implantation of correspondingly coated stents in rabbits.

20 Figure 6 shows the area of the intima on implanted stents with and without corresponding coating with FK506.

25 Figure 7 shows the inflammatory reaction to implantation of stents with and without corresponding coating with FK506.

Examples:

Example 1:

30 **Loading of interesting compounds onto stent grafts**

All values are stated in μg .

Table 1

Active agent/ type of stent	FK 506 (tacrolimus)	Vin- blastine	Pac- litaxel (Taxol)	Cis- platin	Mitoxan- trone
A	1382	4	128	15*	116
	1671	125	155	14*	142
	1625	238	148	14*	113
	Average	1559	146	144	14
B	18				
	16				
	21				
	Average	18			
C	194				
	165				
	Average	180			

* measured by AAS

5 A: Experiments with dissolved solids in which stent grafts with a PTFE polymer layer were immersed in the solution.

10 B: Experiments with i.v. solutions in which stent grafts with a PTFE polymer layer were immersed in the solution.

15 C: Experiments with i.v. solutions in which polyurethane-coated stents were immersed in the solution.

Example 2:

Release patterns of stent grafts of the invention produced in various ways, as well as general polymeric surface stents:

20

All values are stated in μg .

To analyze the active agent release, a stent was incubated at 37°C in 10 ml of PBS buffer (stabilized with Na azide) at 37°C. After defined periods of time had elapsed, 2 × 1 ml of the solution were removed and analyzed. These 2 ml were replaced by fresh PBS buffer (stabilized with Na azide).

The tables indicate the total released content of active agent in the solution. This means that the amount of active agent in the buffer volume removed for the analysis was added onto the amount removed the next time.

Table 2:

Vin- blastine	after 1 h	after 3 h	after 8 h	after 24 h	after 96 h after 72 h
Active agent/ type					
A	73 and 75 Average: 74	108 and 114 Average: 109	121 and 126 Average: 124	106 and 120 Average: 113	132 and 140 (96 h) Average: 136
	37 and 41 Average: 39	48 and 51 Average: 50	47 and 58 Average: 42	57 and 62 Average: 60	56 and 57 (72 h) Average: 57
	80 and 86 Average: 83	99 and 104 Average: 102	108 and 117 Average: 113	117 and 127 Average: 122	113 and 121 (72 h) Average: 117

15 A: Experiments with dissolved solids in which stent grafts with a PTFE polymer layer were immersed in the solution.

Table 3:

FK 506 (tacrolimus)	after 1 h	after 3 h	after 8 h	after 24 h	after 96 h	after 192 h
Active agent/ type						
A 1st stent	14 and 13 Average :14	62 and 62 Average :62	92 and 99 Average: 95	148 and 145 Average: 147	145 and 151 Average: 148	195 and 198 Average: 196
	after 1 h	after 3 h	after 8 h	after 24 h	after 96 h	
A 2nd stent	34 and 26 Average: 30	56 and 57 Average: 57	82 and 78 Average: 80	108 and 109 Average: 109	159 and 164 Average: 161	
	after 1 h	after 3 h	after 8 h	after 24 h	after 96 h	
A 3rd stent	12 and 9 Average: 11	47 and 43 Average: 45	101 and 93 Average: 95	154 and 155 Average: 154	184 and 190 Average: 187	

A: Experiments with dissolved solids in which stent grafts with a PTFE polymer layer were immersed in the solution.

Table 4:

FK 506 (tacrolimus)	after 1 h	after 3 h	after 8 h	after 24 h	after 96 h	
Active agent/ type						
C 1st stent	19 and 20 Average: 20	25 and 26 Average: 26	33 and 33 Average: 33	41 and 39 Average: 40	43 and 38 Average: 41	
	after 1 h	after 3 h	after 8 h	after 24 h	after 96 h	after 264 h
C 2nd stent	20 and 27 Average: 24	21 and 24 Average: 22	26 and 30 Average: 28	34 and 31 Average: 32	37 and 35 Average: 36	85
	after 367 h					
	88 and 94 Average: 91					

C: Experiments with i.v. solutions in which polyurethane-coated stents were immersed in the solution.

Table 5

Paclit- axel	after 1 h	after 3 h	after 8 h	after 24 h	after 96 h	after 192 h
Active agent/ type						
A	0.14 and 0.23 Average: 0.19	0.46 and 0.53 Average: 0.50	1.42 and 1.25 Average: 1.34	1.65 and 1.42 Average: 1.54	1.42 and 1.93 Average: 1.68	2.22 and 2.24 Average: 2.23
	0.42 and 0.52 Average: 0.47	0.90 and 0.90 Average: 0.90	1.16 and 1.21 Average: 1.19	2.44 and 2.40 Average: 2.42	2.79 and 2.78 Average: 2.79	
	0.20 and 0.16 Average: 0.18	0.51 and 0.95 Average: 0.73	0.89 and 0.94 Average: 0.92	2.26 and 2.27 Average: 2.27	2.82 and 2.82 Average: 2.82	

A: Experiments with dissolved solids in which stent grafts with a PTFE polymer layer were immersed in the solution.

Table 6:

Cisplatin	after 1 h	after 3 h	after 8 h	after 24 h
Active agent/ type				
A	11.7 and 11.9 Average: 11.8	15.4 and 15.4 Average: 15.4	16.3 and 16.5 Average: 16.4	16.1 and 15.9 Average: 16.0
	5.7 and 5.4 Average: 5.5	7.8 and 7.7 Average: 7.8	9.9 and 9.8 Average: 9.8	10.9 and 11.1 Average: 11.0
	10.0 and 10.0 Average: 10.0	11.4 and 11.8 Average: 11.6	12.2 and 12.3 Average: 12.2	12.4 and 12.2 Average: 12.3

A: Experiments with dissolved solids in which stent grafts with a PTFE polymer layer were immersed in the solution.

5

Table 7:

Mitoxantrone	after 1 h	after 3 h	after 8 h	after 24 h
Active agent/ type				
A	57 and 86 Average: 71	55 and 52 Average: 54	49 and 47 Average: 48	42 and 49 Average: 45
	70 and 74 Average: 72	80 and 83 Average: 81	80 and 82 Average: 81	72 and 75 Average: 74
	29 and 27 Average: 28	25 and 27 Average: 26	23 and 21 Average: 22	24 and 29 Average: 27

A: Experiments with dissolved solids in which stent grafts with a PTFE polymer layer were immersed in the solution.

10

Example 3:**Production process (1) for FK506-coated implants:**

- 5 • 10 mg of FK506 are dissolved in 3 ml of ethanol
- Uncoated stainless steel stents are immersed in the solution at room temperature under vacuum overnight
- 10 • Wash three times with saline for 1 minute
- Drying overnight.

Example 4:**Production processes (2) for FK506-coated stent grafts:**

- 15 • The dosage of FK506 may vary according to the stent length and diameter and according to the use in the body. A dosage of 10-200 μg of FK506 per cm of stent length was used in this case.
- 20 • FK506 is dissolved (appropriate for the desired dosage) in ethanol in a small glass vessel, and the solution is examined visually for crystals.
- 25 • The unpretreated stent grafts ("JOSTENT Coronary Stent Graft") consisting of a sandwich construction of two stainless steel stents with a PTFE membrane are mounted on holders
- 30 • A pipette is used to pipette the appropriate amount of FK506 solution (5 to 30 μl) onto the mounted stent graft.
- 35 • This step can be repeated as desired in order to apply larger amounts of FK506 to the implant, normally once or twice. In the present case, the procedure was repeated once.

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- After the stent graft is completely loaded, it is cautiously pushed off the holder.
- After brief drying in air (about 5 min), optionally with input of heat, the stents can be packaged.
- All stents are examined under a lens for medicament flocculation and optionally discarded.

10 **Example 5:**

Production process (3) for FK506-coated stent which have a ceramic coating:

- 50 mg of FK506 are dissolved in 10 ml of ethanol in a glass vessel. All further concentrations are prepared from this stock solution, as required, by dilution (dilutions between 1:1 and 1:20).
- The solution is examined visually for crystals.
- The unloaded stents coated with an aluminum oxide layer (as disclosed in PCT application WO 00/25841, see also example 7 on ceramic coating) are mounted on holders.
- A hypodermic syringe is used to apply the FK506 solution (5 to 50 μ l) dropwise to the stent. This should entail the solution being distributed over the complete stent.
- The loaded stent is cautiously removed from the holder.
- After brief drying in air (about 5 min), optionally with input of heat, the stents can be packaged.
- All stents are examined under a lens for medicament flocculation and optionally discarded.

Example 6:

Novel alternative production process (4) (applicable inter alia to FK506 but also to other active agents), in particular for producing sterile stents, stent grafts or/and polymeric surface stents:

- 5 • Small injection vials which are not much larger than the stent are used.
- 10 • Sterile coronary stent grafts (CSGs) are placed sterilely in the sterile injection vial.
- 0.5 ml of sterile-filtered FK506 solution (3.3 mg/ml in ethanol) are added to the vials.
- 15 • The vials are closed with rubber stoppers.
- The middle of the rubber stopper is pierced with a sterile injection cannula with sterile filter.
- 20 • The vials are placed horizontally on a roller apparatus under vacuum in a desiccator.
- The vials are rolled under vacuum overnight.
- 25 • The injection needle is removed.
- No rinsing is carried out.
- The sterile CSGs are ready for use.

30

Example 7:

A selection of possible active agents for an active agent-releasing stent, in particular with a plurality of layers, for example polymeric surface stents or stent grafts etc.

35

The loading methods are described as technical approaches below.

The listed active agents also include derivatives and all types of salts, enantiomers, racemates, bases or free acids.

- 5 Of particular interest here are stents, stent grafts and polymeric surface stents which comprise and correspondingly release at least one, two or three of the active agents listed below.
- 10 The listed active agents are classified into groups 1-3 according to their preferred release profile or the release time period.

15 It is moreover preferred for the stents, stent grafts and polymeric surface stents to comprise active agents from different groups.

Table 8

Phase I - Vasodilation (group 1)		
Active agents which are released in particular during the first 24-72 h after placing of the stent.		
Active agent		
molsidomine, linsidomine, sodium nitroprusside, nitroglycerin, NO donors in general		
stimulators of soluble guanylate cyclase such as BAY 41-2272 (5-(cyclopropyl-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-n]pyridin-3-yl]pyrimidin-4-ylamine		
hydralazine		
verapamil, diltiazem, nifedipine, nimodipines and other Ca ²⁺ channel blockers		
captopril, enalapril, lisinopril, quinapril and other inhibitors of angiotensin converting enzymes		
losartan, candesartan, irbesartan, valsartan and other angiotensin II receptor antagonists		

Table 9

Phase II - Inhibition of inflammation, immunosuppression, promotion of cell growth of endothelial cells, inhibition of cell migration (group 2)		
Active agents which are released in particular during the first 2-21 days after placing of the stent.		
Active agent		
dexamethasone, betamethasone, prednisone and other corticosteroids		
17-beta-estradiol		
FK506 (tacrolimus)		
cyclosporin		
mycophenolic acid		
VEGF, VEGF receptor activators		
tranilast		
meloxicam, celebrex, vioxx and other COX-2 antagonists		
indomethacin, diclofenac, ibuprofen, naproxen and other COX-1 inhibitors		
plasminogen activator inhibitor 1 and other serpins		
thrombin inhibitors such as hirudin, hirulog, agratroban, PPACK etc.		
interleukin-10		

Table 10

Phase III - Inhibition of cellular proliferation (group 3)		
Active agents which are released in particular within the first 14 days to 3 months after placing of the stent		
Active agent		
sirolimus, SDZ RAD (40-O-(2-hydroxyethyl)-rapamycin and other rapamycin derivatives		
PDGF antagonists		
paclitaxel		
cisplatin		
vinblastine		
mitoxantrones		
combretastatin A4		
topotecan		
methotrexate		
flavopiridol		

Local administration of the active agent is achieved by direct delivery from the active agent-loaded surface of a coronary or peripheral stent. An active agent-loaded surface of a stent can be achieved by using various technological approaches. Each of these approaches can be carried out in such a way that the active agent is released from the surface either in a short (hours) or an extended period (days). The kinetics of release can be adapted by carrying out specific modifications on the surface, e.g. hydrophobic or hydrophilic side chains of a polymeric carrier or a ceramic surface.

15 • Ceramic coating

An aluminum oxide coating (patent applications DE 19855421, DE 19910188, WO 00/25841) with a porous surface can be loaded with active agent (for example FK506 in amounts between 10 µg and 10 mg) either by immersing, spraying on or a comparable technique. The dose of active agent depends on the

type of target vessel and the condition of the patient and is chosen so that proliferation, migration and T-cell response are adequately inhibited without impeding the healing process. The active agent can be used as aqueous or organic solution, for example in DMSO, DMF and ethanol. After the spraying or immersing (under weak vacuum), the treated stent is dried and the procedure is repeated 1 to 5 times. After the last drying step, the stent is rinsed in water or isotonic saline at room temperature for 1 min and then dried again. The active agent content can be analyzed by standard methods (HPLC, LC-MS) after the active agent has been dissolved out with a suitable solvent. Kinetics of release can be measured using a standard release-measuring apparatus.

- PTFE membrane: stent graft

An approach comparable to the one described above is used in this case. The active agent is deposited in the recesses in the porous PTFE membrane.

- General polymeric coating

Various polymers are suitable for loading with active agents:

methacrylate polymers, polyurethane coatings, PTFE coatings, hydrogel coatings. The active agent can either be applied to the final surface (see above) or is added directly to the polymerization solution. This technical approach corresponds in the other details to those already described above.

- Mechanical approach

The mechanical approach is based on recesses introduced into the stent struts by means of a cutting laser. These recesses can then be filled with active agent. The mechanical (recess) approach can be combined with a thin biodegradable coating

which is itself loaded with active agent. After an initial release from the biodegradable coating, active agent can be released long-term from the active agent-filled recesses. This technical approach corresponds in the other details to those already described above.

Example 8:

Active agent release of candesartan and quinapril from (polymer-)coated implants:

- a) Stents were provided with a porous PTFE membrane. This membrane was then loaded with an active agent mixture of candesartan and quinapril (1 mg each). The two active agents are released simultaneously. The release was measured in PBS (phosphate buffered saline). Figure 2 shows the active agent release of candesartan and quinapril from the stent.
- b) Open-cell stainless steel stents were provided with a polyurethane coating. An active agent mixture of candesartan and quinapril (15% each based on the polyurethane content) was introduced into a 5% solution of the polyurethane in dimethylacetamide and applied to the stent by a spraying process. Figure 3 shows the corresponding active agent release.
- d) Open-cell stainless steel stents were provided with a polyurethane/hydrogel coating. An active agent mixture of candesartan and quinapril (15% each based on the polymer content) was introduced into a 5% solution of the polymer blend in dimethylacetamide and applied to the stent by a spraying process. Figure 4 shows the corresponding active agent release.

Example 9:**Animal study of the kinetics of release and mode of action of FK506**

5 Stainless steel coronary stents (JOSTENT Flex, 16 mm)
were coated with an aluminum oxide ceramic layer. This
coating served as carrier of FK506 (as described in
Example 5 and Example 7 under "Ceramic coating"). In
this case, the stents were loaded with a total of 60 μ g
10 of FK506. In an animal study in rabbits (n=7), these
FK506 coated stents and normal stents without coating
were implanted into the carotid artery of New Zealand
rabbits. The release of FK506 and the effect of FK506
on the growth of the intima and the formation of
15 macrophages and lymphocytes was investigated.

The release of FK506 were determined by HPLC
determination of the amount of FK506 in the blood of
the rabbits after 1 h, 8 h, 24 h and 48 h. Very good
20 kinetics of release of FK506 over time is clearly seen
in figure 5. The rabbits were sacrificed after 28 days,
and the implanted stents were examined. The area of
newly grown intima (neointima) within the stent was
quantified under the optical microscope. It is
25 unambiguously evident from figure 6 that the formation
of neointima is distinctly reduced in the ceramically
coated stents loaded with FK506 compared with normal
stents. There is a reduction of 53% on loading with
60 μ g of FK506. This reduction was moreover accompanied
30 by a detectable decrease in the foci of inflammation.
As is evident from figure 7, the formation of
macrophages and lymphocytes is distinctly reduced
compared with the normal stent.

35 The use of stents with a ceramic coating onto which
FK506 is applied thus leads to a distinct reduction in
neointima and in foci of inflammation after the
implantation.

Claims

1. An implant comprising FK506 in chemically covalently bound or noncovalently bound or physically immobilized form, and, optionally, at least one other active agent.
5
2. The implant as claimed in claim 1, characterized in that it is an intracavernous, preferably intravascular, implant.
10
3. The implant as claimed in either of claims 1 or 2, characterized in that the implant is suitable for the treatment or prophylaxis of coronary or peripheral vascular constrictions or occlusions, in particular of constrictions or stenoses or restenoses, preferably for the prophylaxis of restenosis.
15
4. The implant as claimed in any of claims 1 to 3, characterized in that the implant has at least one closed or perforated layer or surface which consists of a metal or a metal alloy and is homogeneous or formed from various strands.
20
25
5. The implant as claimed in any of claims 1 to 4, characterized in that the implant has at least one closed or perforated layer or surface which consists of a polymer and is homogeneous or formed from various strands.
30
6. The implant as claimed in claim 5, characterized in that at least one polymer layer covers completely or partly a closed or perforated layer or surface which consists of a metal or a metal alloy and is homogeneous or formed from various strands, preferably an optionally lattice-like structure consisting of a metal or a metal alloy.
35

7. The implant as claimed in claim 5, characterized in that the implant has at least one closed or perforated layer or surface which consists of a metal or a metal alloy and is homogeneous or formed from various strands, and at least one closed or perforated layer or surface which consists of a polymer and is homogeneous or formed from various strands.
8. The implant as claimed in claim 7, characterized in that the layer or surface consisting of a metal or a metal alloy is an optionally lattice-like structure consisting of a metal or a metal alloy, and/or the layer or surface consisting of a polymer is homogeneously closed or woven and/or is water- and/or corpuscle-impermeable, and/or the sequence of layers and surfaces is from the outside to the inside metal-polymer, polymer-metal, metal-polymer-metal or polymer-metal-polymer, and/or either the layer or surface consisting of a polymer is nonchemically (covalently or noncovalently) connected to a layer or surface consisting of a metal or a metal alloy, or the layer or surface consisting of a polymer is connected by means of an adhesive to the layer or surface consisting of a metal or a metal alloy.
9. The implant as claimed in any of claims 5 to 8, characterized in that the polymer is selected from Dacron; polytetrafluoroethylene (PTFE/Teflon), expandable or non-expandable; polyurethane; methacrylate polymers; hydrogel or hydrogel/polyurethane blend, preferably from polytetrafluoroethylene (PTFE), expandable or non-expandable; or polyurethane; in particular from PTFE.
10. The implant as claimed in any of claims 1 to 9, characterized in that the implant is a stent, a

stent graft, a graft, a graft connector, a guide wire, a catheter or a catheter pump, preferably a stent, a stent graft, a graft or a graft connector, in particular a stent or a stent graft.

5

11. The implant as claimed in any of claims 1 to 10, characterized in that the implant is coated with FK506.
- 10 12. The implant as claimed in any of claims 4, 6 or 7 to 10, characterized in that the implant has a ceramic coating, in particular of aluminum oxide or iridium oxide, to which FK506 is bound.
- 15 13. The implant as claimed in claim 12, characterized in that the ceramic coating is completely or partly covered by a polymeric, preferably biodegradable, coating to which, optionally, FK506 and/or another active agent is bound or in which
20 FK506 and/or another active agent has been dissolved before application of the coating.
14. The implant as claimed in any of claims 5 to 10 or
25 13, characterized in that the implant has a polymeric coating, in particular of methacrylate polymers, polyurethane, PTFE, hydrogel or hydrogel/polyurethane blend, in particular PTFE, to which FK506 is bound or in which FK506 has been dissolved before application of the coating.
- 30 15. The implant as claimed in any of claims 4, 6 or 7 to 10, characterized in that the metal of the implant has recesses which have been introduced by means of a laser and which are filled with FK506.
- 35 16. The implant as claimed in claim 15, characterized in that the metal provided with FK506-filled recesses or at least the recesses is/are coated with a biodegradable polymeric material, whereby,

optionally, FK506 being bound to the polymeric coating, or FK506 having been dissolved in the polymeric material before application of the coating.

5

17. The implant as claimed in any of claims 11 to 16, characterized in that FK506 is present in the form of loaded nanoparticles or liposomes.

10

18. The implant as claimed in any of claims 1 to 10 which can be produced by a process in which

15

a) an implant having at least one closed or perforated layer or surface which consists of a metal or a metal alloy and is homogeneous or formed from various strands, as claimed in any of claims 4, 6 or 7 to 10, which implant is coated with a ceramic coating, in particular of aluminum oxide, is employed

or

20

b) an implant having at least one closed or perforated layer or surface which consists of a polymer and is homogeneous or formed from various strands, as claimed in any of claims 5 to 10, is employed,

25

or

30

c) an implant as claimed in any of claims 1 to 10, which is coated with a coating which is polymerized or polymerizing on the surface, in particular of methacrylate polymers, polyurethane, PTFE, hydrogel or hydrogel/polyurethane blend, is employed

or

35

d) an implant as claimed in any of claims 4, 6 or 7 to 10 having at least one closed or perforated layer or surface which consists of a metal or a metal alloy and is homogeneous or formed from various strands, and into which recesses have been introduced by means of a laser, which are filled with FK506, and then

the implant is coated with a biodegradable coating which is polymerized or polymerizing on the surface, is employed,

5 e) then the implant according to a), b), c) or d) is brought into contact with an FK506 solution in aqueous or organic solvent, for example by sprinkling, spraying or immersing, optionally under vacuum,

10 f) then, optionally, the implant is dried, preferably until the solvent from step e) is removed,

g) then, optionally, step e), optionally followed by step f), is repeated, preferably several times, in particular 1 to 5 times, and,

15 h) optionally, subsequently the implant is rinsed one or more times with water or isotonic saline, and,

i) optionally, is subsequently dried.

20 19. The implant as claimed in claim 18, characterized in that in step e) FK506 is dissolved in alcohol, preferably in ethanol, in particular in a concentration of 0.5-5 g/l FK506 in ethanol and/or in step e) the implant is brought into contact
25 with an FK506 solution in aqueous or organic solvent by immersing under vacuum preferably overnight, and/or steps f) and/or g) are not carried out and/or in step h) the implant is washed several times with saline and/or in step i)
30 the implant is dried overnight.

20. The implant as claimed in claim 18, characterized in that in step e) the implant is introduced, preferably sterilely, into a preferably sterile
35 vessel with a closure which can be perforated and which closes after completion of a perforation, for example into an injection vial, FK506 solution, is preferably sterilely introduced into the vessel, the latter is closed with the closure

which can be perforated and which closes after completion of a perforation, a thin, preferably sterile, air-pervious ventilation tube, for example a cannula, is pushed perforatingly through the closure, a vacuum is applied and, preferably, the FK506 solution is agitated, and finally, preferably after about 12 h have elapsed, the thin, preferably sterile, air-pervious ventilation tube is removed and/or in that in step e) FK506 is dissolved in alcohol, preferably in ethanol, in particular in a concentration of 3.3 mg of FK506 in 1 ml of ethanol and/or in that the implant remains until used in the preferably sterile closed glass vessel from step e) and/or in that steps f) to i) are omitted.

21. The implant as claimed in any of claims 5 to 10 which can be produced by a process in which FK506 has been dissolved in the polymerization material before the formation of at least one closed or perforated layer or surface consisting of a polymer, or of a polymeric coating of the implant.
22. The implant as claimed in any of claims 1 to 21, characterized in that FK506 is released after implantation of the implant.
23. The implant as claimed in claim 22, characterized in that delayed release takes place.
24. The implant as claimed in claim 23, characterized in that FK506 is released from the implant over a period of 24 h, preferably 48 h, in particular more than 96 h, after implantation.
25. The implant as claimed in claim 23, characterized in that the FK506 e) is released within <48 h or

- f) over at least 48 h, preferably over at least 7 days, in particular over at least 2 and up to 21 days, from the implant after implantation, or in that
- 5 g) the implant shows both release patterns d) and e).
26. The implant as claimed in any of claims 1 to 25, characterized in that the implant comprises at least one other active agent, preferably a pharmaceutically active agent, in particular another active agent selected from the following active agents and derivatives thereof
- 10
- 15 (Group 1:) molsidomine, linsidomine, sodium nitroprusside, nitroglycerin or general NO donors; stimulators of soluble guanylate cyclase (sGC), for example BAY 41-2272 (5-(cyclopropyl-2-[1-fluorobenzyl)-1H-pyrazolo[3,4-n]pyridin-3-yl]pyrimidin-4-ylamine); hydralazine, verapamil, diltiazem, nifedipine, nimodipine or other Ca²⁺ channel blockers; captopril, enalapril, lisinopril, quinapril or other inhibitors of angiotensin converting enzymes (angiotensin converting enzyme inhibitors); losartan, candesartan, irbesartan, valsartan or other antagonists of the angiotensin II receptor;
- 20
- 25
- 30 (Group 2:) dexamethasone, betamethasone, prednisone or other corticosteroids; 17-beta-estradiol; cyclosporin; mycophenolic acid; VEGF, VEGF receptor activators; tranilast; meloxicam, celebrex, vioxx or other COX-2 antagonists; indomethacin, diclofenac, ibuprofen, naproxen or other COX-1 inhibitors; inhibitors of plasminogen activator 1 (plasminogen activator inhibitors-1) or serpins; thrombin inhibitors, for example
- 35

hirudin, hirulog, agratroban, PPACK;
interleukin-10;

(Group 3:) sirolimus, rapamycin, SDZ RAD (40-O-
5 (2-hydroxyethyl)rapamycin or other rapamycin
derivatives; PDGF antagonists; paclitaxel or
7-hexanoyl-taxol; cisplatin; vinblastine;
mitoxantrone; combretastatin A4; topotecan;
methotrexate; flavopiridol;

10

actinomycin D; Rheopro/abciximab or probucol.

27. The implant as claimed in claim 26, characterized
in that if the other active agent is selected from
15 group 1 this active agent is released from the
implant within the first 24 - 72 h after
implantation and/or, if the other active agent is
selected from group 2, the latter is released from
the implant within the first 48 h - 21 days after
20 implantation and/or, if the other active agent is
selected from group 3, the latter is released from
the implant within 14 days to 3 months after
implantation.

25 28. A process for producing an implant as claimed in
any of claims 1 to 25 with the following steps:

a) an implant having at least one closed or
perforated layer or surface which consists of a
metal or a metal alloy and is homogeneous or
30 formed from various strands, as claimed in any
of claims 4, 6 or 7 to 10, which implant is
coated with a ceramic coating, in particular of
aluminum oxide or irridium oxide,

or

35 b) an implant having at least one closed or
perforated layer or surface which consists of a
polymer and is homogeneous or formed from
various strands, as claimed in any of claims 5
to 10,

or

5 c) an implant as claimed in any of claims 1 to 10,
which is coated with a coating which is
polymerized or polymerizing on the surface, in
particular of methacrylate polymers,
polyurethane, PTFE, hydrogel or
hydrogel/polyurethane blend,

or

10 d) an implant as claimed in any of claims 4, 6 or
7 to 10 having at least one closed or
perforated layer or surface which consists of a
metal or a metal alloy and is homogeneous or
formed from various strands, and into which
15 recesses have been introduced by means of a
laser, which are filled with FK506, and then
the implant is coated with a preferably
biodegradable coating which is polymerized or
polymerizing on the surface, is employed,

20 e) then the implant according to a), b), c) or d)
is brought into contact with an FK506 solution
in aqueous or organic solvent, for example by
sprinkling, spraying or immersing, optionally
under vacuum,

25 f) then, optionally, the implant is dried,
preferably until the solvent from step e) is
evaporated,

g) then, optionally, step e), optionally followed
by step f), is repeated, preferably several
times, in particular 1 to 5 times, and,

30 h) optionally, subsequently the implant is rinsed
one or more times with water or isotonic
saline, and,

i) optionally, is subsequently dried.

35 29. The process as claimed in claim 29, characterized
in that in step e) FK506 is dissolved in alcohol,
preferably in ethanol, in particular in a
concentration of 0.5-5 g/l FK506 in ethanol and/or
in that in step e) the implant is brought into

contact with an FK506 solution in aqueous or organic solvent by immersing under vacuum preferably overnight, and/or in that steps f) and/or g) are not carried out, and/or in that in step h) the implant is washed several times with saline, and/or in that in step i) the implant is dried overnight.

30. The process as claimed in claim 28, characterized in that in step e) the implant is introduced, preferably sterilely, into a preferably sterile vessel with a closure which can be perforated and which closes after completion of a perforation, for example into an injection vial, FK506 solution, is preferably sterilely introduced into the vessel, the latter is closed with the closure which can be perforated and which closes after completion of a perforation, a thin, preferably sterilely, air-pervious ventilation tube, for example a cannula, is pushed perforatingly through the closure, a vacuum is applied and, preferably, the FK506 solution is agitated, and finally, preferably after about 12 h have elapsed, the thin, preferably sterile, air-pervious ventilation tube is removed and/or in step e) FK506 is dissolved in alcohol, preferably in ethanol, in particular in a concentration of 3.3 mg of FK506 in 1 ml of ethanol and/or in that the implant remains until used in the preferably sterile closed glass vessel from step e) and/or in that steps f) to i) are omitted.

31. The process for producing implants as claimed in any of claims 5 to 10, in which FK506 has been dissolved in the polymerization material before the formation of at least one closed or perforated layer or surface consisting of a polymer, or of a polymeric coating of the implant.

32. A process for producing implants coated with active agents, with the following steps:

- 5 a) the implant is introduced, preferably sterile, into a preferably sterile vessel with a closure which can be perforated and closes after completion of a perforation, for example an injection vial,
- 10 b) preferably sterile solution of the active agent, preferably in an organic solvent with a low vapor pressure, in particular in alcohol such as ethanol or methanol, is introduced into the vessel,
- 15 c) the vessel is closed with the closure which can be perforated and closes after completion of a perforation,
- d) a thin, preferably sterile, air-pervious ventilation tube, for example a cannula, is pushed perforatingly through the closure,
- 20 e) optionally a vacuum is applied, whereby the active agent solution is preferably agitated,
- f) finally, preferably after about 12 h have elapsed, the thin, preferably sterile, air-pervious ventilation tube is removed and,
- 25 g) optionally, the implant is left until used in the preferably sterile closed glass vessel from step a).

33. The process as claimed in claim 32, characterized in that the implant from step a) has at least one metallic perforated or closed surface or layer, has a ceramic coating, has a polymeric coating and/or has at least one polymeric, perforated or closed surface or layer.

35

34. The process as claimed in either of claims 32 or 33, characterized in that the implant is a stent, stent graft, graft, graft connector, polymeric surface stent or catheter.

35. The process as claimed in any of claims 32 to 34, characterized in that the active agent is selected from pharmaceutical active agents such as, for example, immunosuppressants or antibiotics, is preferably selected from the following active agents and derivatives thereof
- 5
- 10 (Group 1:) molsidomine, linsidomine, sodium nitroprusside, nitroglycerin or general NO donors; stimulators of soluble guanylate cyclase (sGC), for example BAY 41-2272 (5-(cyclopropyl-2-[1-fluorobenzyl]-1H-pyrazolo[3,4-n]pyridin-3-yl]pyrimidin-4-ylamine); hydralazine, verapamil, diltiazem,
- 15 nifedipine, nimodipine or other Ca^{2+} channel blockers; captopril, enalapril, lisinopril, quinapril or other inhibitors of angiotensin converting enzymes (angiotensin converting enzyme inhibitors-1); losartan, candesartan,
- 20 irbesartan, valsartan or other antagonists of the angiotensin II receptor;
- (Group 2:) dexamethasone, betamethasone, prednisone or corticosteroids; 17-beta-estradiol; cyclosporin; mycophenolic acid;
- 25 VEGF, VEGF receptor activators; tranilast; meloxicam, celebrex, vioxx or other COX-2 antagonists; indomethacin, diclofenac, ibuprofen, naproxen or other COX-1 inhibitors;
- 30 inhibitors of plasminogen activator-1 (plasminogen activator inhibitors-1) or serpins; thrombin inhibitors, for example hirudin, hirulog, agratroban, PPACK; interleukin-10;
- (Group 3:) sirolimus, rapamycin, SDZ RAD (40-O-(2-hydroxyethyl)rapamycin or other rapamycin derivatives; PDGF antagonists; paclitaxel or 7-hexanoyl-taxol; cisplatin; vinblastine;
- 35

mitoxantrone; combretastatin A4; topotecan;
methotrexate; flavopiridol;

actinomycin D; Rheopro/abciximab or probucol,

5

in particular is selected from

(Group 1:) molsidomine, linsidomine, sodium
nitroprusside, nitroglycerin or general NO
donors; stimulators of soluble guanylate
10 cyclase (sGC), for example BAY 41-2272 (5-
(cyclopropyl-2-[1-(2-fluorobenzyl)-1H-
pyrazolo[3,4-n]pyridin-3-yl]pyrimidin-4-
ylamine); captopril, enalapril, lisinopril,
quinapril or other inhibitors of angiotensin
15 converting enzymes (angiotensin converting
enzyme inhibitors); losartan, candesartan,
irbesartan, valsartan or other antagonists of
the angiotensin II receptor;

(Group 2:) dexamethasone, betamethasone,
20 prednisone or corticosteroids; FK506
(tacrolimus); VEGF, VEGF receptor activators;
inhibitors of plasminogen activator 1
(plasminogen activator inhibitors-1) or serpins;

25

(Group 3:) sirolimus, rapamycin, SDZ RAD (40-O-
(2-hydroxyethyl)rapamycin or other rapamycin
derivatives; PDGF-antagonists; paclitaxel or
7-hexanoyl-taxol; mitoxantrone; combretastatin
30 A4; flavopiridol.

36. The use of an implant as claimed in any of
claims 1 to 27 for the treatment or prophylaxis of
coronary or peripheral vascular constrictions or
occlusions, in particular of constrictions or
35 stenoses or restenoses, preferably for the
prophylaxis of restenosis.

37. The use of FK506 for the coating or for the production of an implant for the treatment or prophylaxis of coronary or peripheral vascular constrictions or occlusions, in particular of constrictions or stenoses or restenoses, preferably for the prophylaxis of restenosis.
- 5
38. The use as claimed in claim 37, characterized in that the implant is a stent, a stent graft, a graft, a graft connector, a guide wire, a catheter or a catheter pump, preferably a stent, a stent graft, a graft or a graft connector, in particular a stent or a stent graft or a polymeric surface stent.
- 10
- 15
39. The use as claimed in either of claims 37 or 38, characterized in that the FK506 is bound or attached to the implant in such a way that it is released, preferably in a delayed manner, from the implant after implantation.
- 20
40. The use of FK506 for the treatment or prophylaxis of coronary or peripheral vascular constrictions or occlusions, in particular of constrictions or stenoses or restenoses, preferably for the prophylaxis of restenosis.
- 25
41. A polymeric surface stent comprising at least one physiologically and/or pharmaceutically active agent in chemically covalently bound or non-covalently bound or physically immobilized form.
- 30
42. The polymeric surface stent as claimed in claim 41, characterized in that the active agent is selected from pharmaceutically active agents such as, for example, immunosuppressants or antibiotics, is preferably selected from the following active agents and derivatives thereof
- 35

- 59 -

(Group 1:) molsidomine, linsidomine, sodium nitroprusside, nitroglycerin or general NO donors; stimulators of soluble guanylate cyclase (sGC), for example BAY 41-2272 (5-(cyclopropyl-2-[1-fluorobenzyl]-1H-pyrazolo[3,4-n]pyridin-3-yl]pyrimidin-4-ylamine); hydralazine, verapamil, diltiazem, nifedipine, nimodipine or other Ca²⁺ channel blockers; captopril, enalapril, lisinopril, quinapril or other inhibitors of angiotensin converting enzymes (angiotensin converting enzyme inhibitors); losartan, candesartan, irbesartan, valsartan or other antagonists of the angiotensin II receptor;

(Group 2:) dexamethasone, betamethasone, prednisone or corticosteroids; 17-beta-estradiol; cyclosporin; mycophenolic acid; VEGF, VEGF receptor activators; tranilast; meloxicam, celebrex, viox or other COX-2 antagonists; indomethacin, diclofenac, ibuprofen, naproxen or other COX-1 inhibitors; inhibitors of plasminogen activator-1 (plasminogen activator inhibitors-1) or serpins; thrombin inhibitors, for example hirudin, hirulog, agratroban, PPACK; interleukin-10;

(Group 3:) sirolimus, rapamycin, SDZ RAD (40-O-(2-hydroxyethyl)rapamycin or other rapamycin derivatives; PDGF antagonists; paclitaxel or 7-hexanoyl-taxol; cisplatin; vinblastine; mitoxantrone; combretastatin A4; topotecan; methotrexate; flavopiridol;

actinomycin D; Rheopro/abciximab or probucol,

in particular is selected from

- 60 -

(Group 1:) molsidomine, linsidomine, sodium nitroprusside, nitroglycerin or general NO donors; stimulators of soluble guanylate cyclase (sGC), for example BAY 41-2272 (5-
5 (cyclopropyl-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-n]pyridin-3-yl]pyrimidin-4-ylamine); captopril, enalapril, lisinopril, quinapril or other inhibitors of angiotensin converting enzymes (angiotensin converting
10 enzyme inhibitors); losartan, candesartan, irbesartan, valsartan or other antagonists of the angiotensin II receptor;

(Group 2:) dexamethasone, betamethasone, prednisone or corticosteroids; FK506
15 (tacrolimus); VEGF, VEGF receptor activators; inhibitors of plasminogen activator 1 (plasminogen activator inhibitors-1) or serpins;

(Group 3:) sirolimus, rapamycin, SDZ RAD (40-0-
20 (2-hydroxyethyl)rapamycin or other rapamycin derivatives; PDGF-antagonists; paclitaxel or 7-hexanoyl-taxol; mitoxantrone; combretastatin A4; flavopiridol;

25 and/or in that the polymeric surface stent comprises at least two, preferably 2 or 3, physiologically and/or pharmaceutically active active agents selected from one of groups 1 to 3,
30 preferably a maximum of one active agent from one group.

43. The polymeric surface stent as claimed in claim 42, characterized in that if the other
35 active agent is selected from group 1 this active agent is released from the implant within the first 24-72 h after implantation, and/or, if the other active agent is selected from group 2, this active agent is released from the implant within

- 61 -

the first 48 h-21 days after implantation, and/or, if the other active agent is selected from group 3, this active agent is released from the implant within 14 days to 3 months after implantation.

5

Figure 1/7

Release of FK506 from a coronary stent graft (CSG)

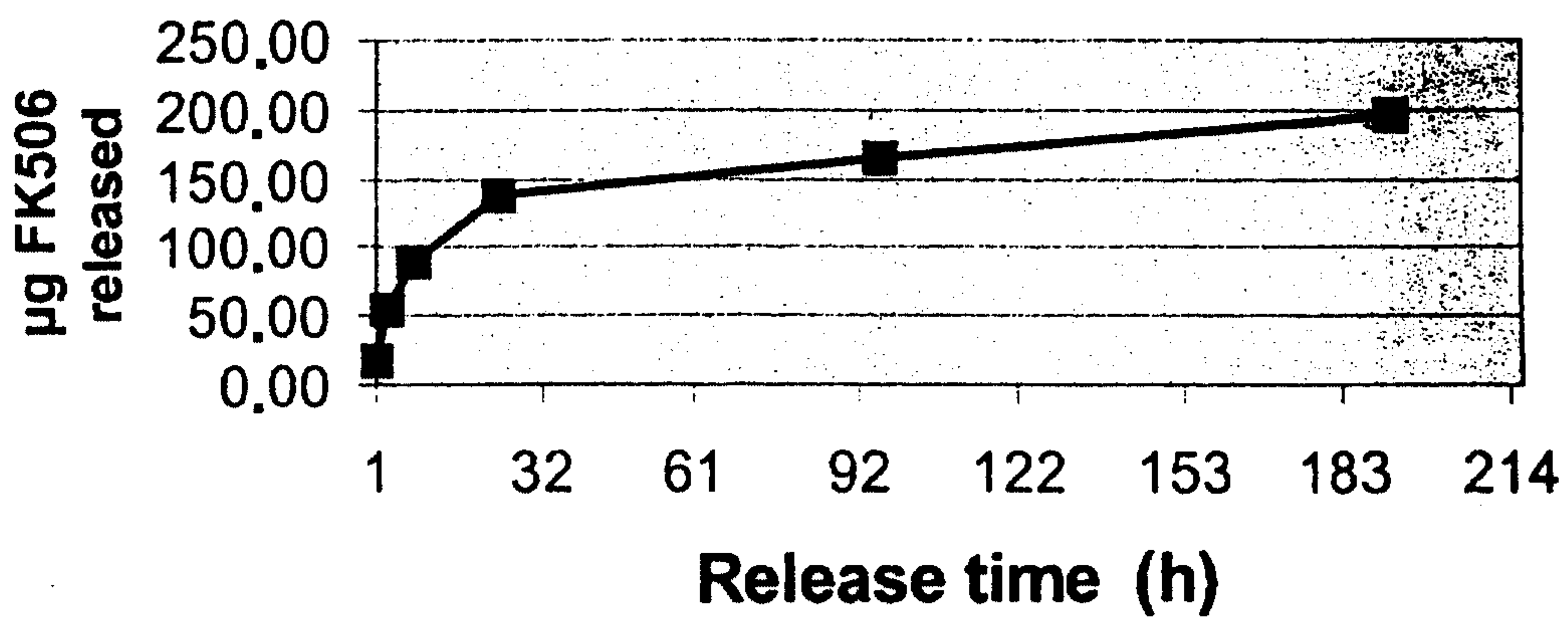
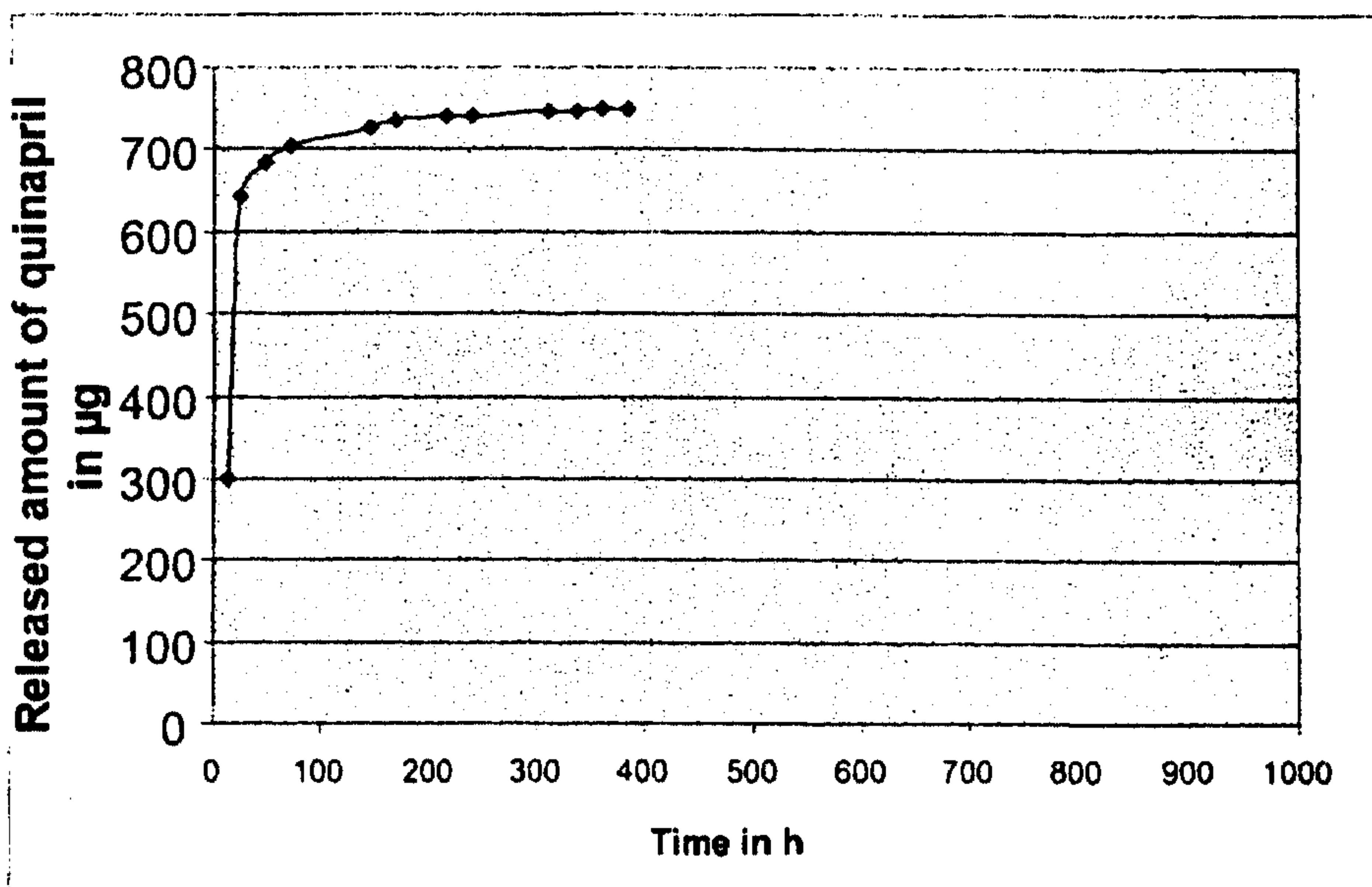
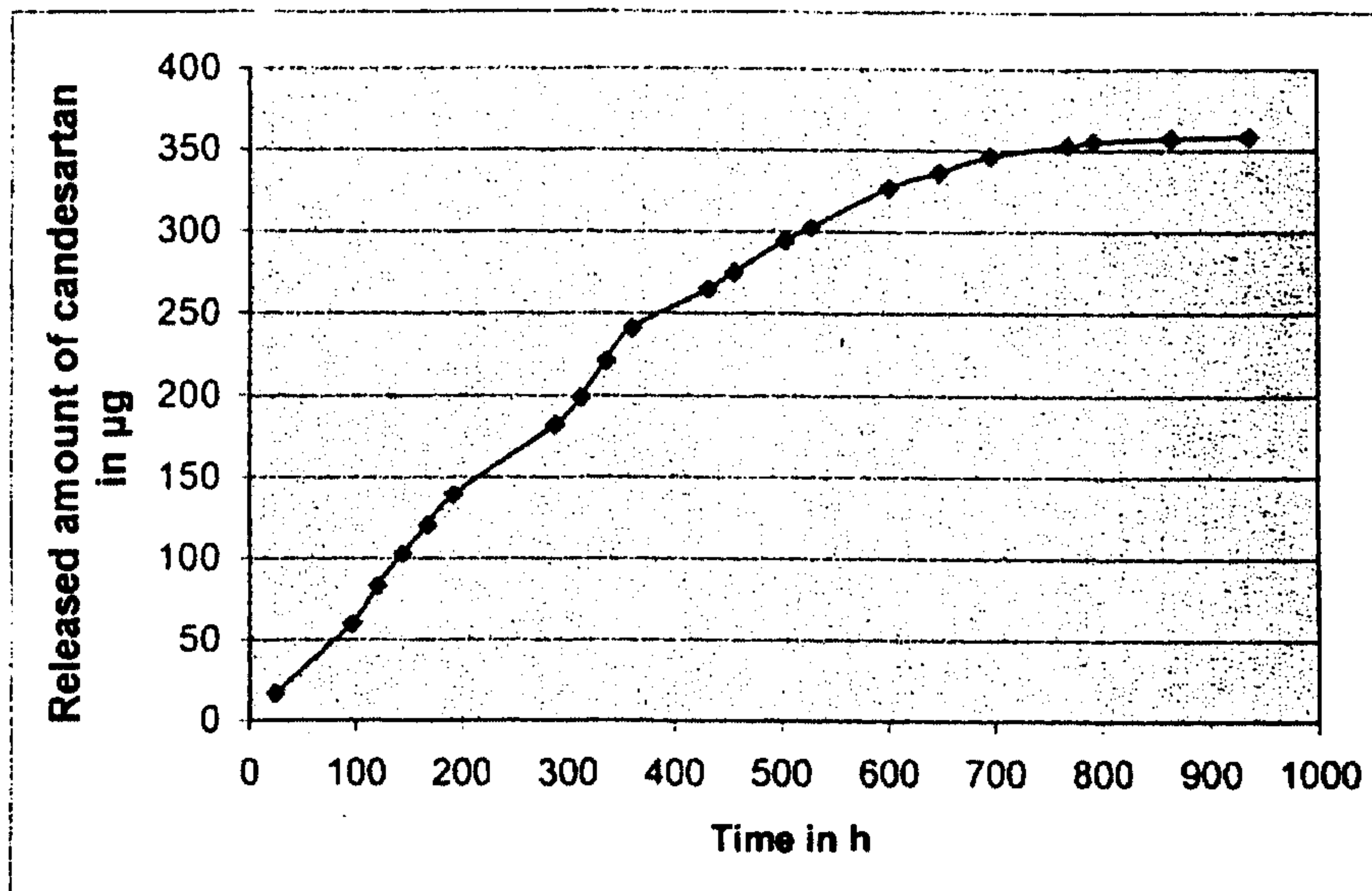


Figure 2/7

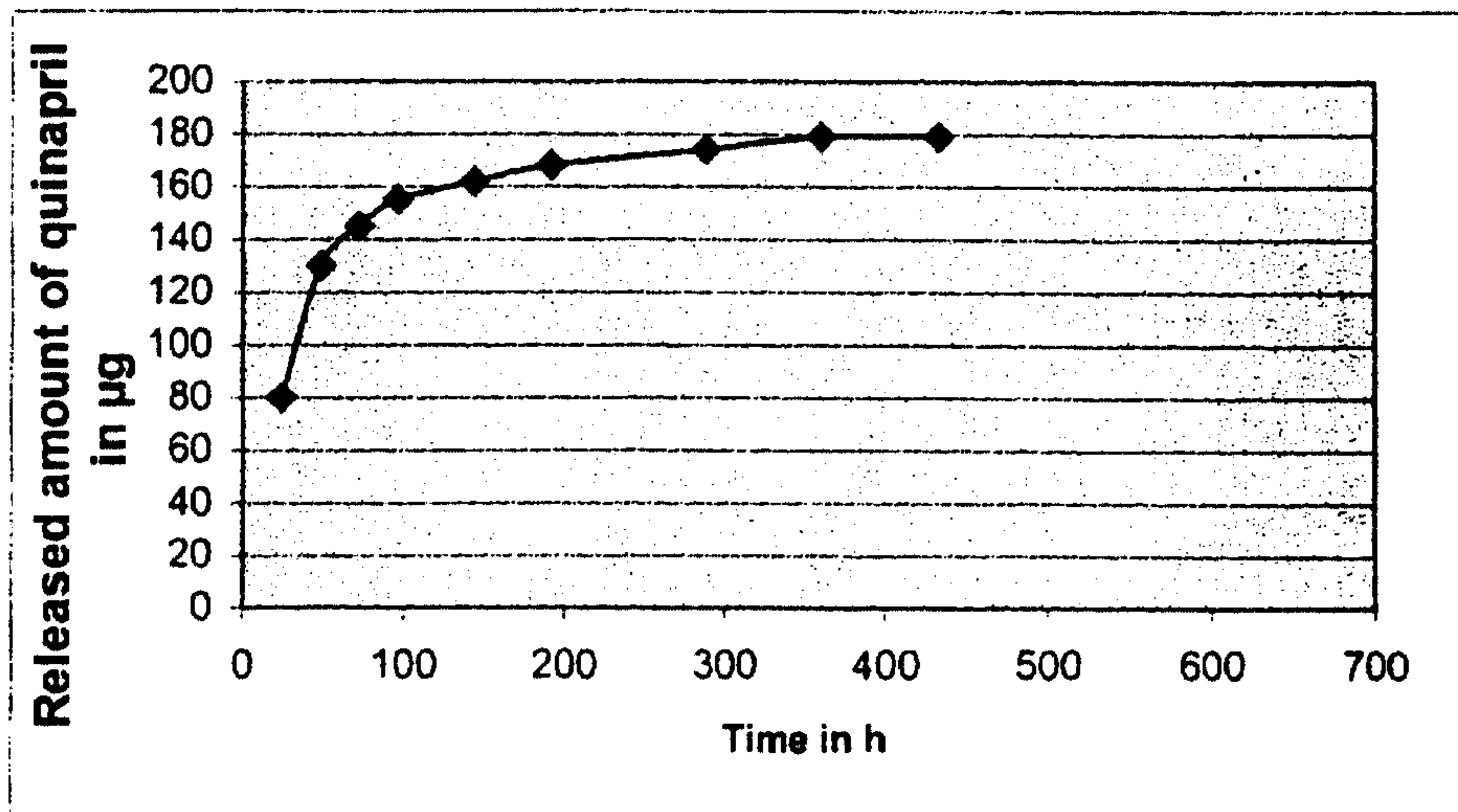
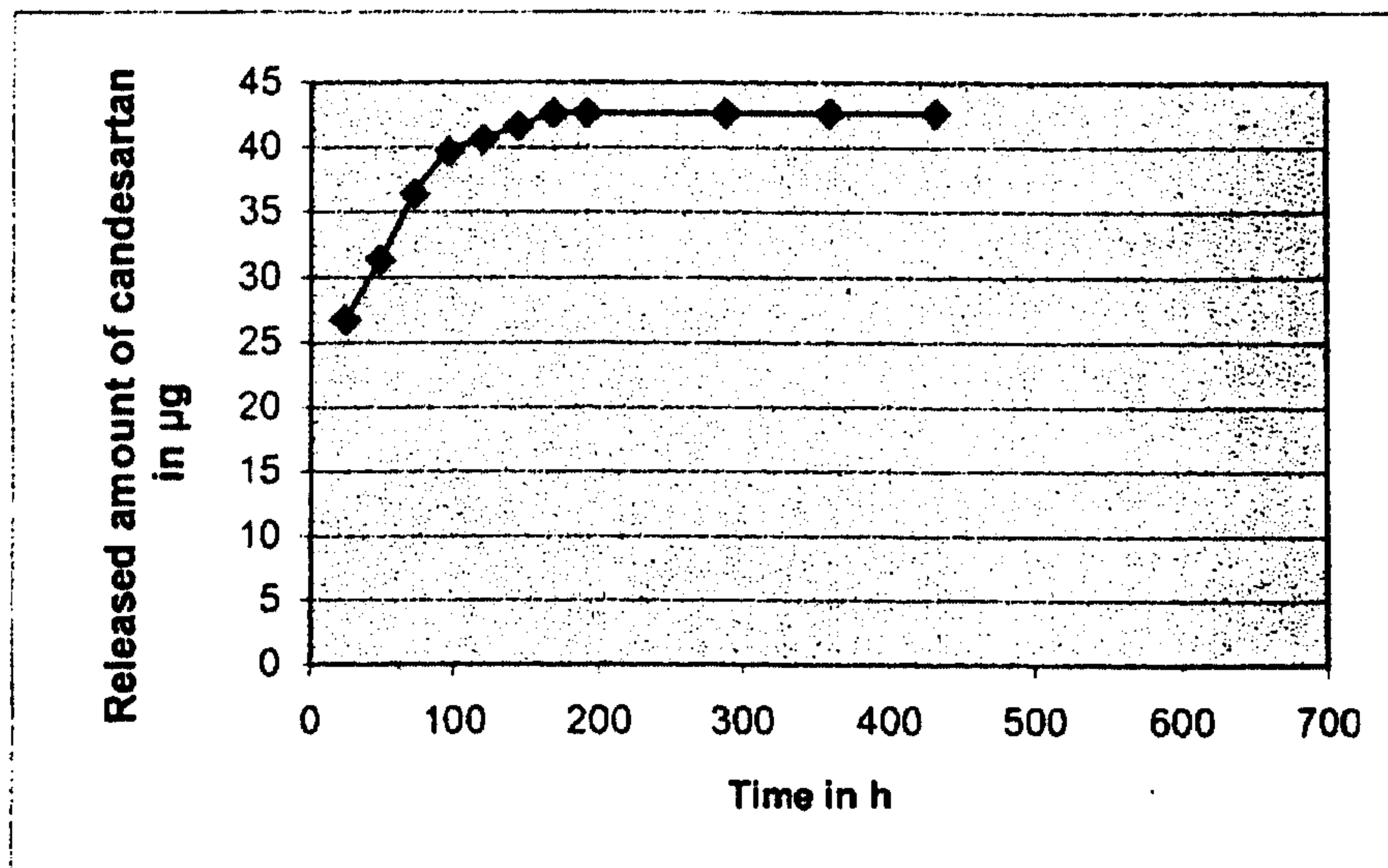
Release of candesartan and quinapril from a porous PTFE membrane



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Figure 3/7

Release of candesartan and quinapril from a polyurethane coating



4/7

Figure 4/7

Release of candesartan and quinapril from a polyurethane/hydrogel blend

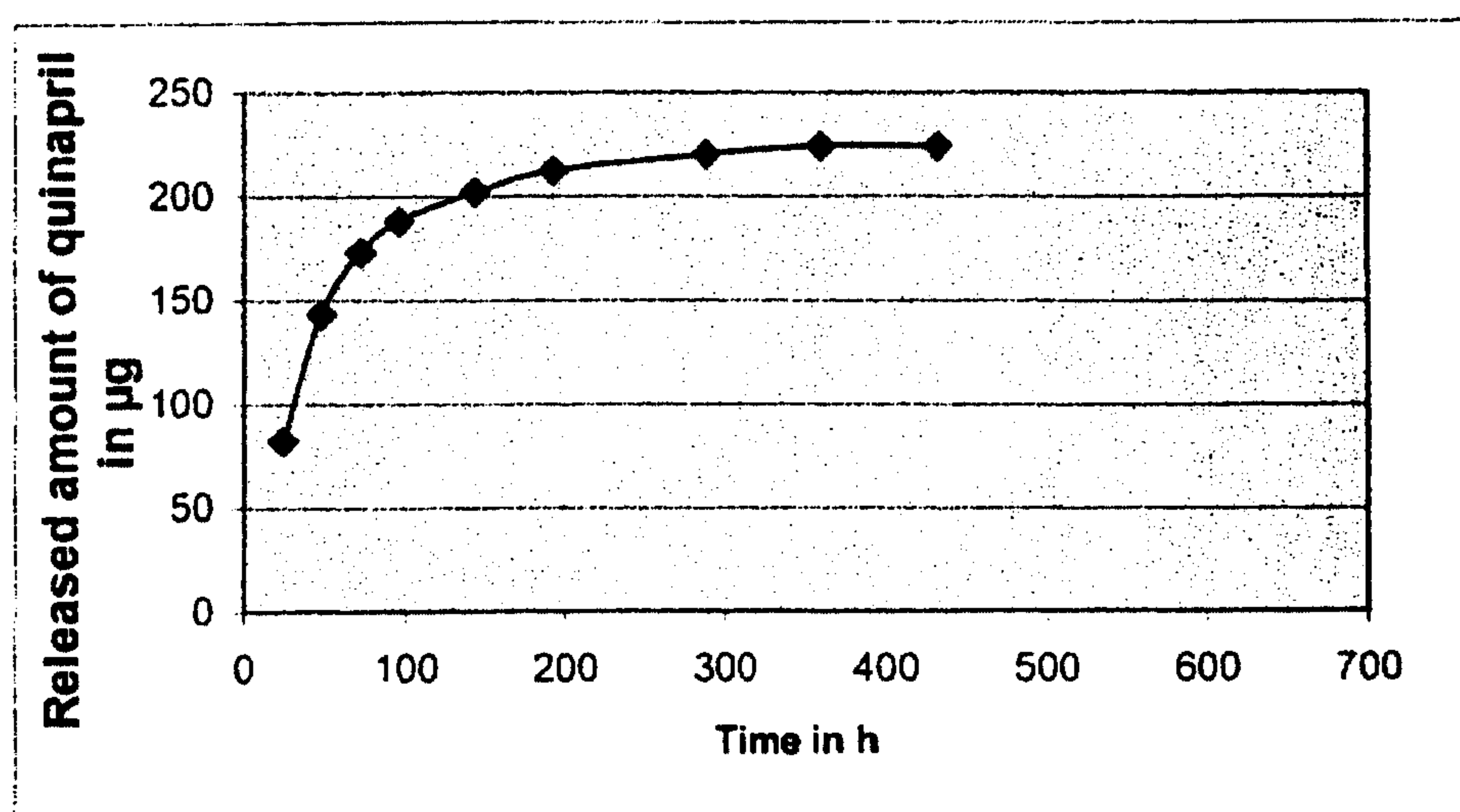
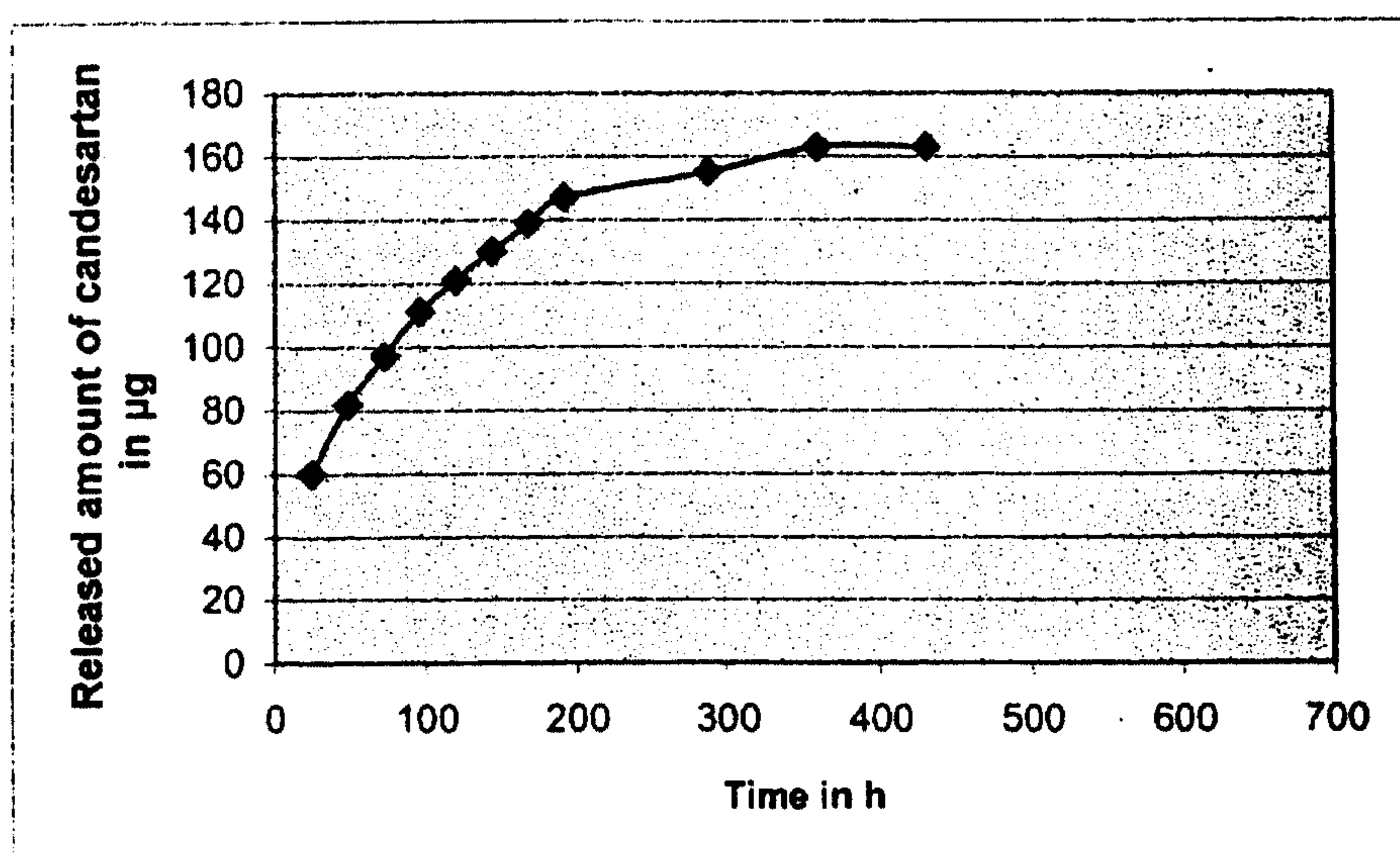


Figure 5/7

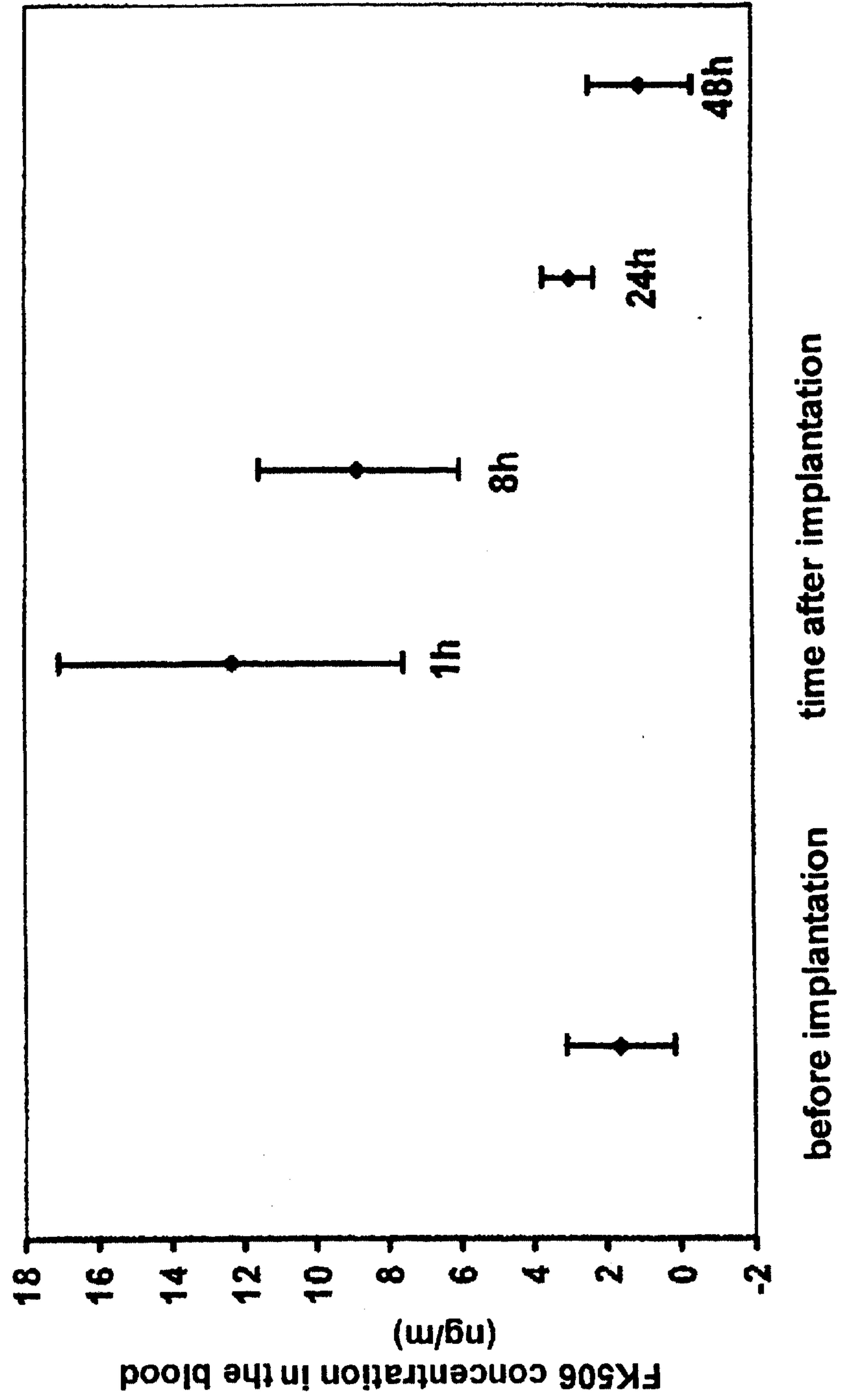
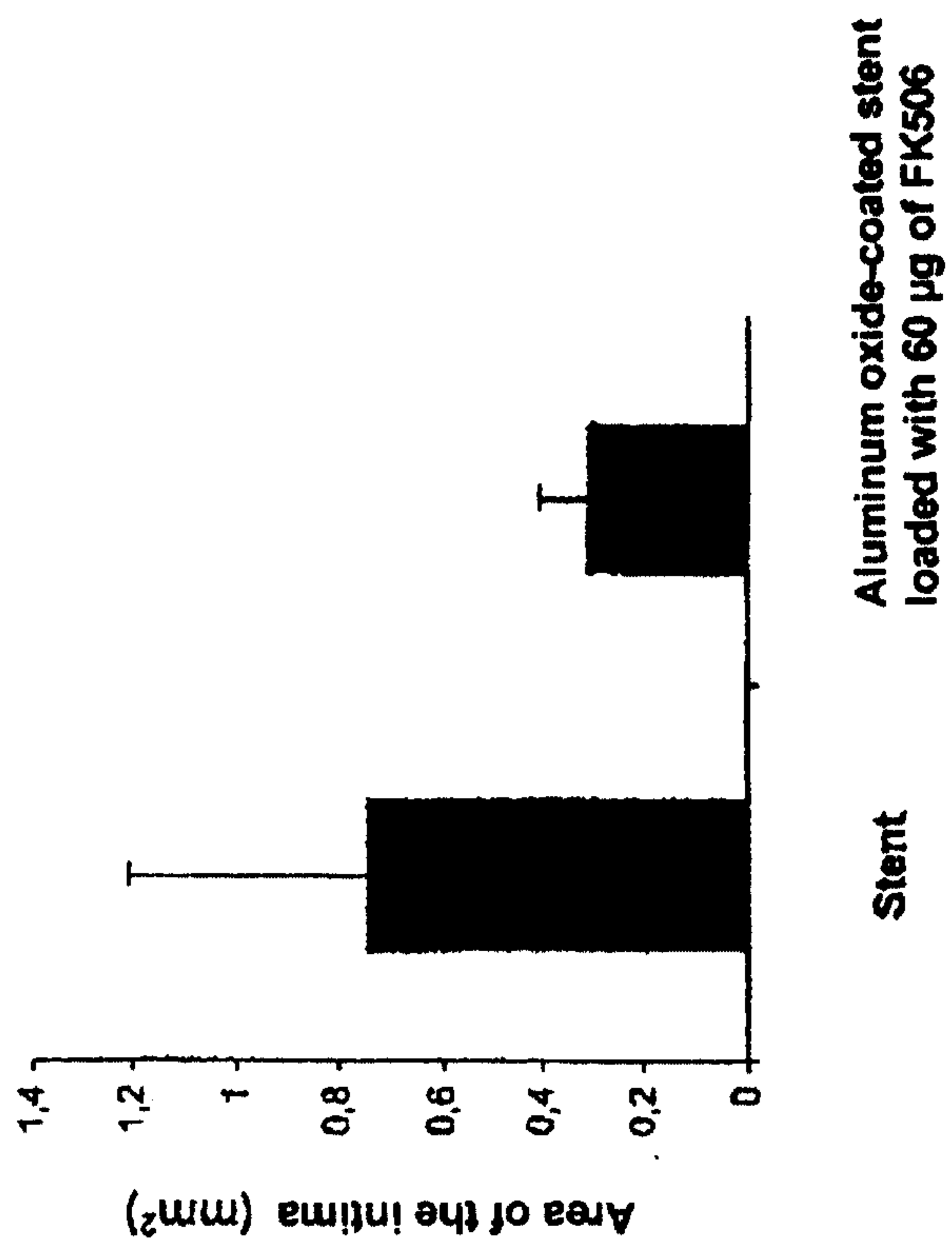


Figure 6/7



7/7

Figure 7/7

