



(86) Date de dépôt PCT/PCT Filing Date: 2008/05/15
(87) Date publication PCT/PCT Publication Date: 2008/11/20
(85) Entrée phase nationale/National Entry: 2009/11/10
(86) N° demande PCT/PCT Application No.: GB 2008/001675
(87) N° publication PCT/PCT Publication No.: 2008/139200
(30) Priorités/Priorities: 2007/05/15 (US60/917,972);
2007/05/15 (GB0709332.1); 2007/10/03 (GB0719321.2)

(51) Cl.Int./Int.Cl. *A61L 27/10* (2006.01)
(71) Demandeur/Applicant:
CHAMELEON BIOSURFACES LIMITED, GB
(72) Inventeurs/Inventors:
PICKETT, CHRISTOPHER JOHN, GB;
BOOTE, TIMOTHY JAMES, GB;
IBRAHIM, SAAD KHALIL, GB;
KNOTT, JANE MARIE, GB;
TOLLAND, JOHN DOUGLAS, GB
(74) Agent: BERESKIN & PARR LLP/S.E.N.C.R.L.,S.R.L.

(54) Titre : REVETEMENTS POLYMERES SUR DISPOSITIFS MEDICAUX
(54) Title: POLYMER COATINGS ON MEDICAL DEVICES

(57) **Abrégé/Abstract:**

A medical device, for example a stent, has a surface which in use contacts body tissue, wherein said surface has on it a biocompatible coating layer comprising a polymer having covalently bound allyl-terminated pendent groups, said pendent groups comprising a moiety selected from $-O-CH_2-CH=CH_2$ $-S-CH_2-CH=CH_2$ $-S(=O)-CH_2-CH=CH_2$ $-Se-CH_2-CH=CH_2$ and $-Se(=O)-CH_2-CH=CH_2$. This surface has good biocompatibility and can bind strongly to a metallic surface. The polymer may be made from an electropolymerisable monomer, e.g. a pyrrole.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
20 November 2008 (20.11.2008)(10) International Publication Number
WO 2008/139200 A3(51) International Patent Classification:
A61L 27/10 (2006.01)(74) Agents: **PAGET, Hugh** et al.; Mewburn Ellis LLP, 33
Gutter Lane, London EC2V 8AS (GB).(21) International Application Number:
PCT/GB2008/001675(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ,
EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO,
NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG,
SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG,
US, UZ, VC, VN, ZA, ZM, ZW.(22) International Filing Date:
15 May 2008 (15.05.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0709332.1 15 May 2007 (15.05.2007) GB
60/917,972 15 May 2007 (15.05.2007) US
0719321.2 3 October 2007 (03.10.2007) GB(71) Applicant (*for all designated States except US*):
CHAMELEON BIOSURFACES LIMITED [GB/GB];
Merlin Place, Milton Road, Cambridge, Cambridgeshire
CB4 0DP (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **PICKETT,**
Christopher John [GB/GB]; c/o Chameleon BioSurfaces
Limited, Merlin Place, Milton Road, Cambridge Cam-
bridgeshire CB4 0DP (GB). **BOOTE, Timothy James**
[GB/GB]; c/o Chameleon BioSurfaces Limited, Merlin
Place, Milton Road, Cambridge Cambridgeshire CB4
0DP (GB). **IBRAHIM, Saad Khalil** [GB/GB]; c/o
Chameleon BioSurfaces Limited, Merlin Place, Milton
Road, Cambridge Cambridgeshire CB4 0DP (GB).
KNOTT, Jane Marie [GB/GB]; c/o Chameleon BioSur-
faces Limited, Merlin Place, Milton Road, Cambridge
Cambridgeshire CB4 0DP (GB). **TOLLAND, John Dou-**
glas [GB/GB]; c/o Chameleon BioSurfaces Limited, Mer-
lin Place, Milton Road, Cambridge Cambridgeshire CB4
0DP (GB).(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).**Declarations under Rule 4.17:**— *of inventorship (Rule 4.17(iv))***Published:**— *with international search report (Art. 21(3))*— *before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments (Rule 48.2(h))*(88) Date of publication of the international search report:
29 October 2009

(54) Title: POLYMER COATINGS ON MEDICAL DEVICES

(57) Abstract: A medical device, for example a stent, has a surface which in use contacts body tissue, wherein said surface has on it a biocompatible coating layer comprising a polymer having covalently bound allyl-terminated pendent groups, said pendent groups comprising a moiety selected from -O-CH₂-CH=CH₂ -S-CH₂-CH=CH₂ -S (=O) -CH₂-CH=CH₂ -Se-CH₂-CH=CH₂ and -Se (=O) J-CH₂-CH=CH₂. This surface has good biocompatibility and can bind strongly to a metallic surface. The polymer may be made from an electropolymerisable monomer, e.g. a pyrrole.

WO 2008/139200 A3

POLYMER COATINGS ON MEDICAL DEVICESField of the Invention

The present invention relates to polymer coatings on
5 medical devices.

Background of the Invention

In the field of medicine, many devices are employed which
contact body tissue and fluids. These include for example
10 implanted devices, components of blood dialysis devices and
blood storage containers. It is important that the surfaces
which contact body tissue have certain properties to make them
suitable for their function. One of the most important of
these is biocompatibility, and non-toxicity to cells. When
15 the device is intended for contact with blood, it is important
that the surface of the device does not induce thrombosis.
Other considerations are important, depending on the intended
use of the device.

For example, in the case of coronary stents, it is
20 desirable that the surface of the stent does not induce
inflammatory response, does not promote thrombosis and is
rapidly endothelialised. In earlier practice, bare metal
stents made from medical steel or other alloys in various
designs were predominantly used in coronary stenting
25 procedures. However, following the arterial vessel damage
inevitably associated with the stenting operation, smooth
muscle cell proliferation and migration into the lumen occurs.
This is called restenosis. In 15-20% of operations using a
bare metal stent, restenosis leads to serious loss of lumen
30 volume. This requires further medical intervention, commonly
re-stenting of the vessel.

In recent years, coronary stents have been modified with
polymer coatings which are loaded with drugs, commonly
paclitaxel, rapamycin and closely related drugs. These drugs
35 elute from the polymer and inhibit cell migration and
neointimal thickening of the arterial wall. Such devices are

known as drug-eluting stents. The use of such stents has led to a dramatic reduction in the occurrence of restenosis.

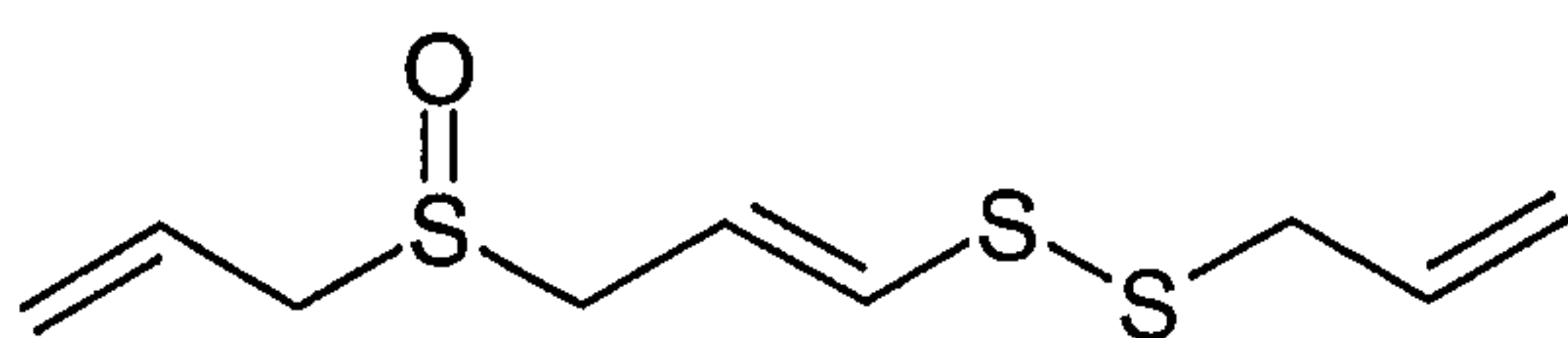
However, certain concerns about the safety of drug-eluting stents have emerged. Late-onset thrombosis leading to death occurs in some patients between 1 and 4 years after implantation of drug eluting stents. For this reason, the proportion of drug eluting stents used in coronary stenting operations has declined in favour of bare metal stents.

The cause of this late onset thrombosis is likely to be that the polymer coating or the combination of polymer and residual drug induces an inflammatory response, leading to platelet adhesion and activation, which triggers the thrombogenic cascade. Paclitaxel and rapamycin diminish restenosis, but they also inhibit endothelial cell proliferation which is necessary for healing of the damaged artery and is protective against thrombosis.

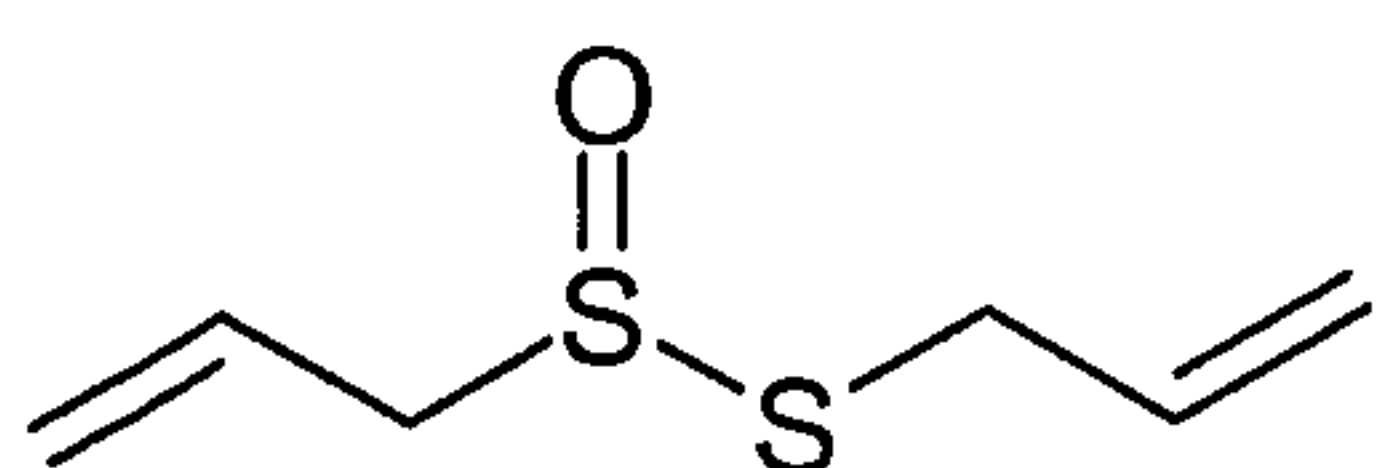
In the light of these problems, the aim of the present invention is to provide improved biocompatible polymeric coatings on stents and other medical devices which are in contact with body tissue.

It is known that extracts of *Allium sativum* (garlic) have a platelet inhibiting effect (1). In a double-blind, placebo-controlled study on 60 voluntary subjects with cerebrovascular risk factors and constantly increased platelet aggregation, it was demonstrated that the daily ingestion of 800 mg of powdered garlic (in the form of coated tablets) over four weeks led to a significant inhibition of the pathologically increased ratio of circulating platelet aggregates and of spontaneous platelet aggregation.

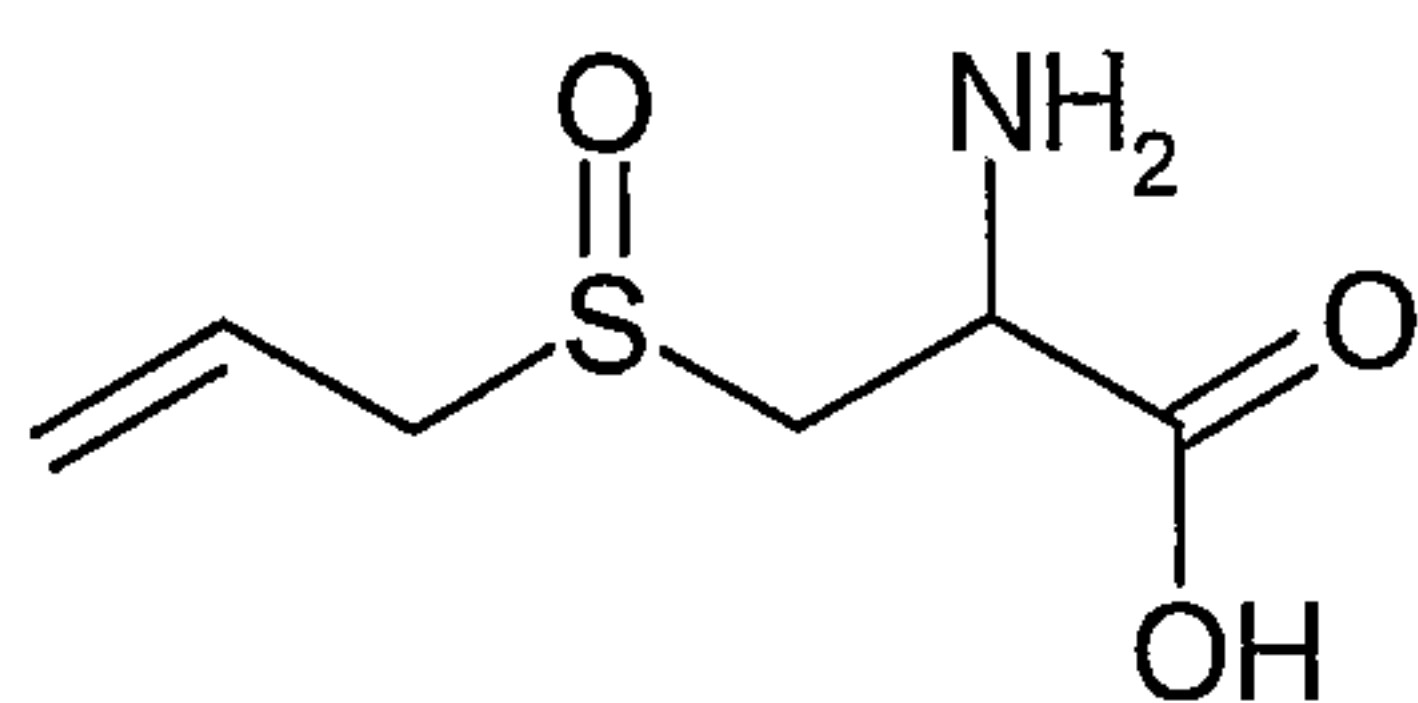
Some of the compounds in extracts of garlic with anti-inflammatory and platelet inhibiting effects are ajoene, allicin, alliin and ethiin, shown below



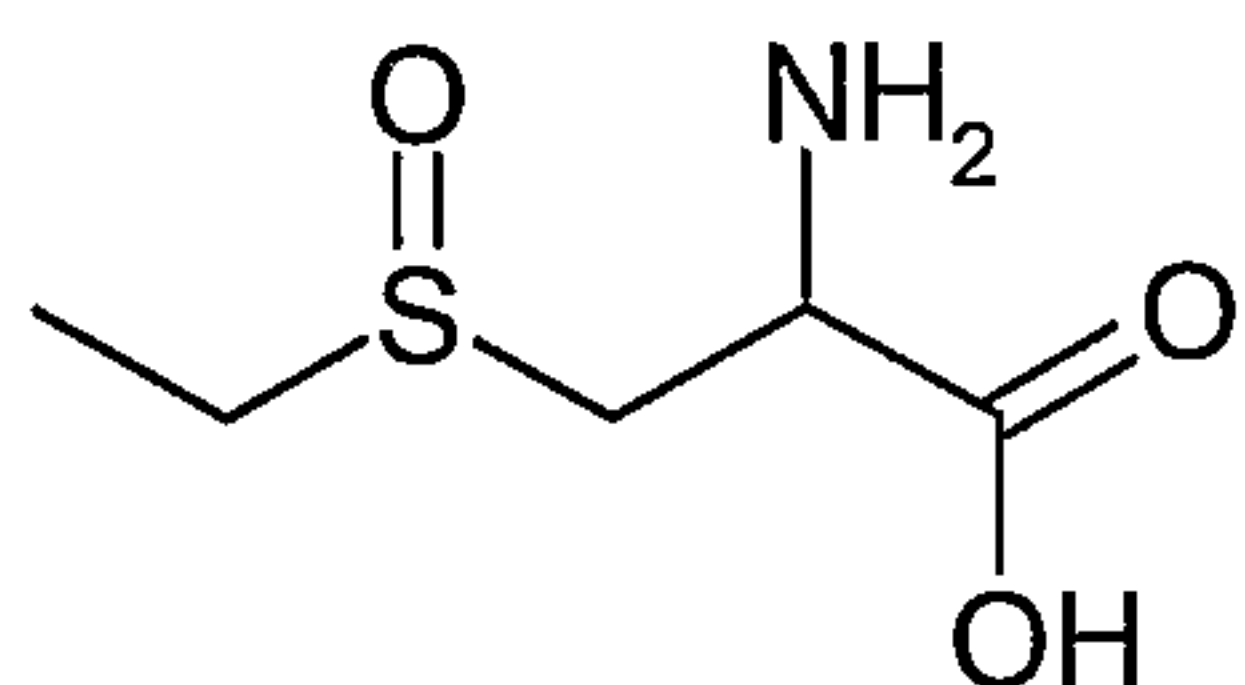
Ajoene



Allicin



Alliin



Ethiin

See: Bioactive S-alk(en)yl cysteine sulfoxide metabolites in
 5 the genus *Allium* : the chemistry of potential therapeutic
 agents.

P. Rose, M. Whiteman, P.K. Moore and Y Z Zhu.

Nat. Prod. Rep., 2005, 22, 351-368

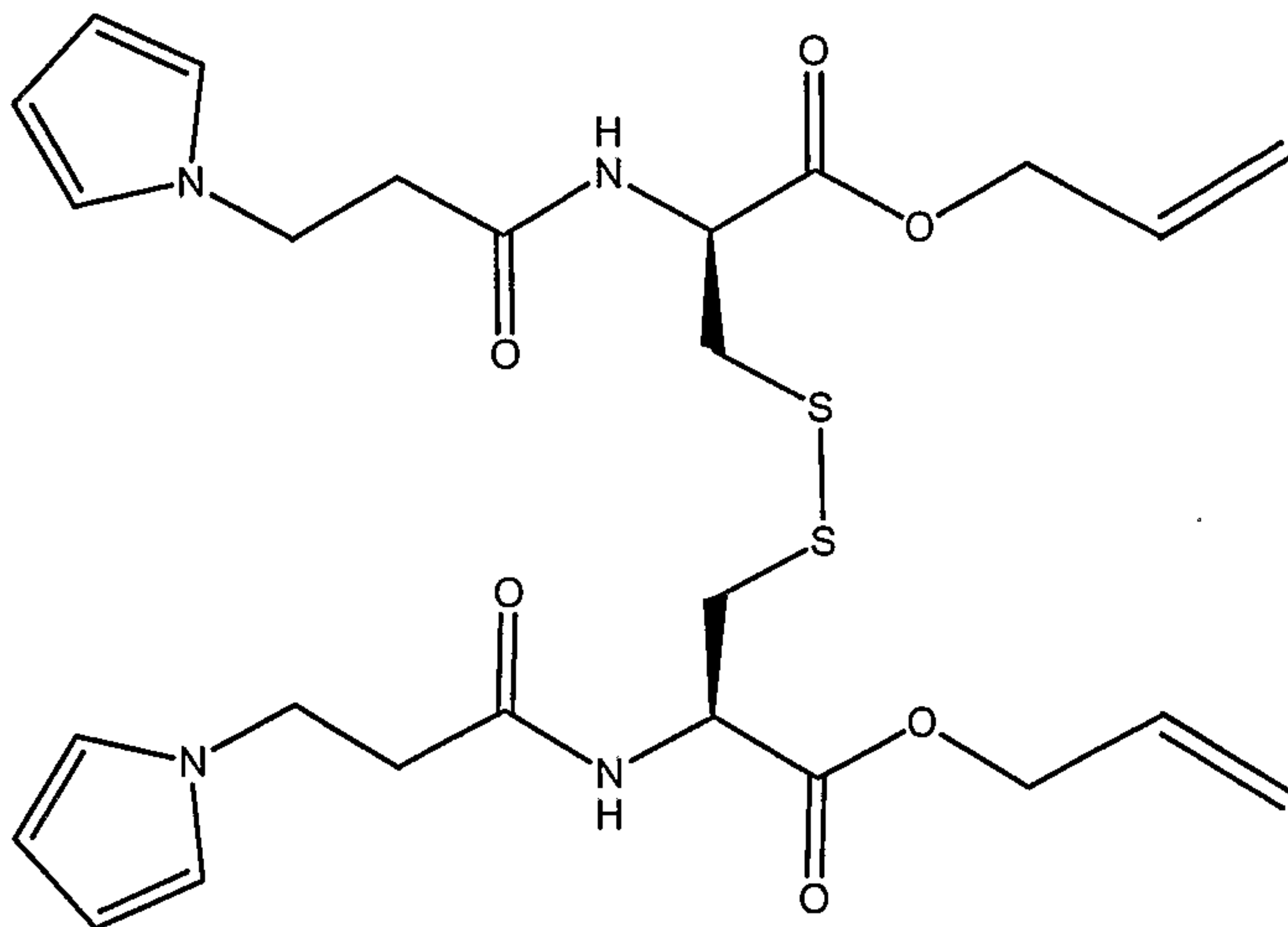
WO03/018082 discloses an implantable medical device, such
 10 as a stent, comprising a substrate and a biocompatible
 polymeric coating, wherein the coating contains ajoene and/or
 allicin or isomers, analogues, homologues or derivatives
 thereof. The biocompatible coating has a composition which
 permits the ajoene and/or allicin to be controllably released
 15 in a predetermined manner and over a prolonged period of time.
 Therefore, the medical devices disclosed in this document are
 in the "drug-eluting" category.

US4917921 discloses antithrombogenic and antibiotic
 compositions for use as coatings on artificial prostheses and
 20 implants which remain in contact with blood or other
 physiological fluids. The compositions are copolymers of 2-
 vinyl-4H-1,3-dithiin with a biocompatible monomer. The
 dithiin is a garlic extract having an allyl functionality.
 Thermal initiation using free-radical initiators,
 25 photochemical initiation using photoinitiators, or chemical
 initiation using group transfer polymerisation with activated
 methyl-methacrylate are disclosed as possible routes for

generating the copolymer. The allyl group is the polymerising part of the monomer, and is therefore not present in the polymer.

The monomer

5



has been disclosed, as an intermediate in a synthesis of other derivatised pyrroles (2). It is mentioned that this intermediate, along with a number of others, is electropolymerisable.

10

Summary of the Invention

The object of the present invention is to provide medical devices with improved biocompatible polymeric coatings.

15

According to the present invention, there is provided a medical device having a surface which in use contacts body tissue, wherein said surface has on it a biocompatible coating layer comprising a polymer having covalently bound allyl-terminated pendent groups, said pendent groups comprising a moiety selected from

20

- O-CH₂-CH=CH₂
- S-CH₂-CH=CH₂
- S(=O)-CH₂-CH=CH₂
- Se-CH₂-CH=CH₂ and
- Se(=O)-CH₂-CH=CH₂.

25

Medical devices according to the present invention can provide a number of advantages. For example, they may have low platelet adhesion and platelet activation properties, and so may be non-thrombogenic or anti-thrombogenic. They may support endothelialisation, so promote the healing process after implantation. They may have low cytotoxicity, may be haemocompatible and are generally well tolerated in biological systems. The coating layer may also exhibit strong adhesion to metallic surfaces.

The coating layer may include a drug, incorporated in a releasable or non-releasable manner. The drug may be bound to the polymer by for example covalent bonding, ionic bonding, coordinate bonding, or attached by a weak interaction such as hydrogen bonding or Van der Waal's force.

It is thought to be the allyl-terminated pendent groups in the polymeric coatings on medical devices according to the present invention which confer the beneficial effects, augmented by neighbouring O, S or Se atom. Therefore, in principle the nature of the polymer is not limited in the present invention, except that pendent groups comprising a moiety selected from those given above must be present. Examples of possible polymers are polypyrroles, polythiophenes, polyanilines, polyamides, poly-aminoacids, polysaccharides, polyesters, polyalkenes, polyamines, polyethers, polyethyleneterephthalates, polyimides, polysiloxanes, polyphosphazines, polylactides, polyglycolides, polycaprolactones, polydioxanones, polygluconates, polyanhydrides, polyphosphoesters, polyorthoesters and polyphosphate esters. Polymeric coatings on medical devices according to the present invention may comprise copolymers.

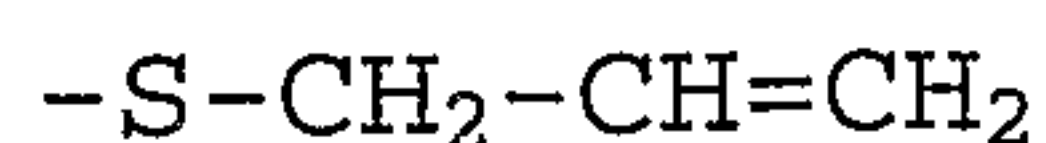
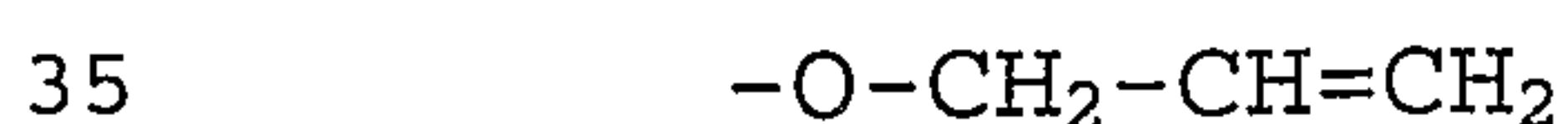
Polymers according to the present invention include polymers of two or more types of monomer, in which one or more of the types of monomeric residue includes the allyl terminated pendent group. Preferably at least 10%, more preferably at least 30%, of the monomeric residues in the polymer include the allyl terminated pendent group. Yet more

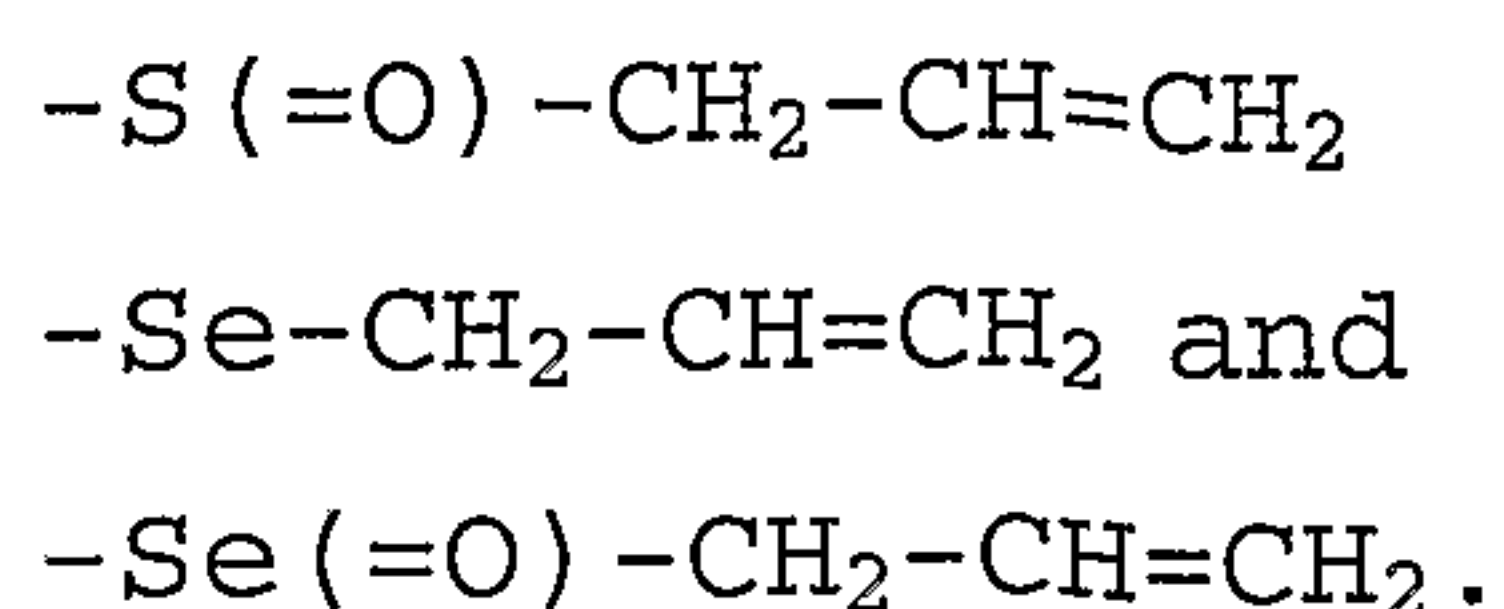
preferably, at least 50% of the monomeric residues in the polymer include the allyl terminated pendent group. Even more preferably, at least 70% of the monomeric residues in the polymer include the allyl terminated pendent group. 100% of the monomeric residues in the polymer may include the allyl terminated pendent group.

The polymeric coatings on medical devices of the present invention may be formed by any polymerisation method, including electropolymerisation, ring-opening polymerisation, radical polymerisation, coordination polymerisation, functional group (step growth) polymerisation, metathesis polymerisation and cationic polymerisation. The allyl-terminated pendent group may be present in the monomer prior to polymerisation. If necessary, the allyl-terminated pendent group may be protected during polymerisation, for example by attaching a protecting group. Alternatively, the allyl-terminated pendent group may be covalently bonded to the polymer after polymerisation.

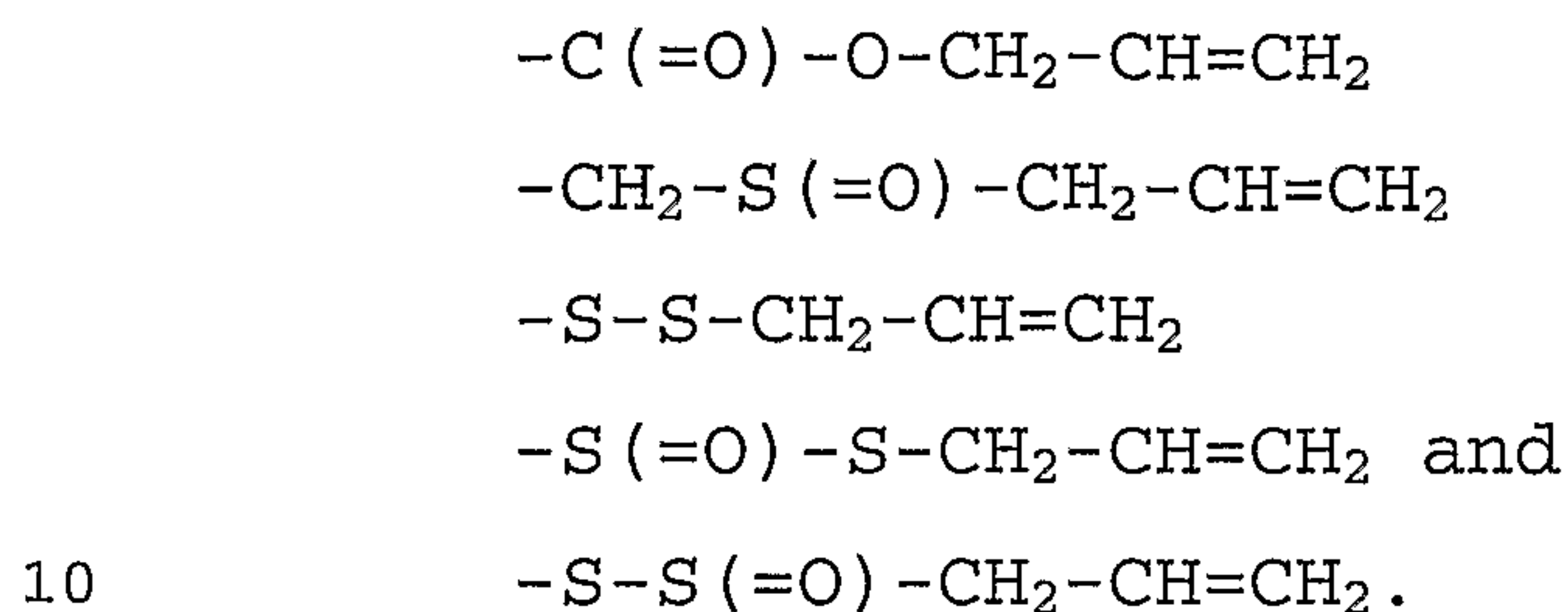
Preferably, the polymeric coatings on medical devices according to the present invention are electropolymerised. This is because allyl groups in monomers are not involved in polymerisation when the polymerisation is electropolymerisation, so it is facile to ensure that the allyl pendent group remains present in the polymer product. Therefore, preferably the polymer or polymers forming the polymeric coating on a medical device according to the present invention are selected from polypyrroles, polythiophenes and polyanilines. Most preferably, the polymeric coating according to the present invention comprises a polypyrrole.

It is believed that the presence of an allyl terminal group in the pendent groups confers the beneficial properties of medical devices having polymeric coatings according to the present invention. The pendent groups comprise a moiety selected from:

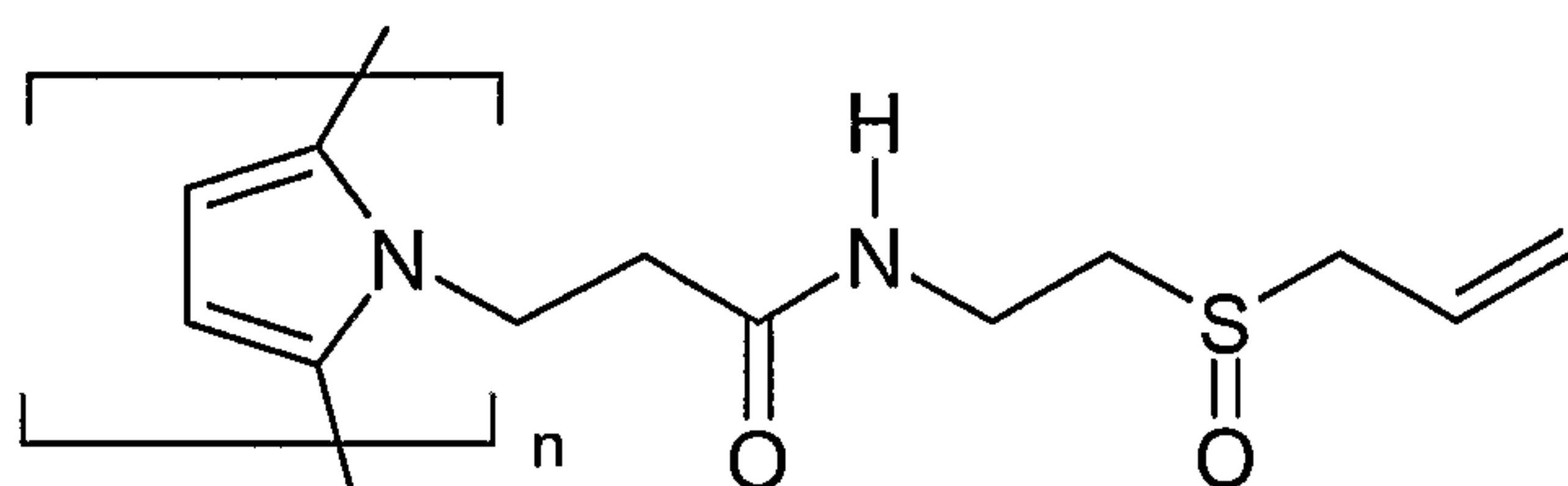




More preferably, the pendent groups comprise a moiety selected
 5 from:



The pendent groups are covalently attached, directly or
 via a linker, to the polymeric chain (backbone). The nature
 of the attachment is not crucial in conferring the beneficial
 properties of the invention. Typically, the pendent groups
 15 are attached to the residue of the polymerisable component of
 the monomer. For example:



where the pendent group is attached to the pyrrole ring
 residue in the polypyrrole polymer.

20 When the polymer is a polypyrrole the pendent groups may
 be attached, directly or via a linker, to N atoms in the
 pyrrole rings, or to C atoms in the 3-position in the pyrrole
 rings. Preferably, the pendent groups are attached to N
 atoms in the pyrrole rings.

25 When the polymer is a polythiophene the pendent groups
 may be attached, directly or via a linker, to C atoms in the
 3-position in the thiophene rings.

When the polymer is a polyaniline the pendent groups may
 be attached, directly or via a linker, to the aromatic ring.

30 The pendent groups are covalently attached to the polymer
 in polymeric coatings on medical devices according to the
 present invention. There may be a direct covalent bond

between a pendent group selected from those listed above and the polymer. However, preferably the pendent groups are attached to the polymer via a covalent linker. The linker is not limited in the present invention. It may be a saturated or unsaturated alkyl moiety. Preferably, the covalent linker comprises a moiety selected from amido, ester and ether. More preferably, the covalent linker comprises a moiety selected from amido or ester. Most preferably, the covalent linker comprises an amido moiety. When the covalent linker comprises an amido moiety, it is preferable that the pendent group is closer to the N atom of the amido moiety than to the C atom of the amido moiety.

Typically a monomer for forming polymeric coatings on implantable devices according to the present invention can be defined as



where:

A is the polymerisable component, for example a pyrrole ring, a thiophene ring or an aniline ring;

B is C₁₋₂₀ alkyl chain. The alkyl chain may be branched or unbranched, and optionally substituted;

C is amido (-CO-NH-), ester (-CO-O-) or ether (-O-), preferably amido;

D is C₁₋₂₀ alkyl chain. The alkyl chain may be branched or unbranched, and optionally substituted; and

E is the pendent group.

Components B and D are each optional.

Components A, B (if present), C, D (if present) and E are covalently attached as shown above. Components B (if present), C and D (if present) together are the covalent linker.

Preferred optional substituents on B and/or D, when present, are any of

-COOH or -COO⁻

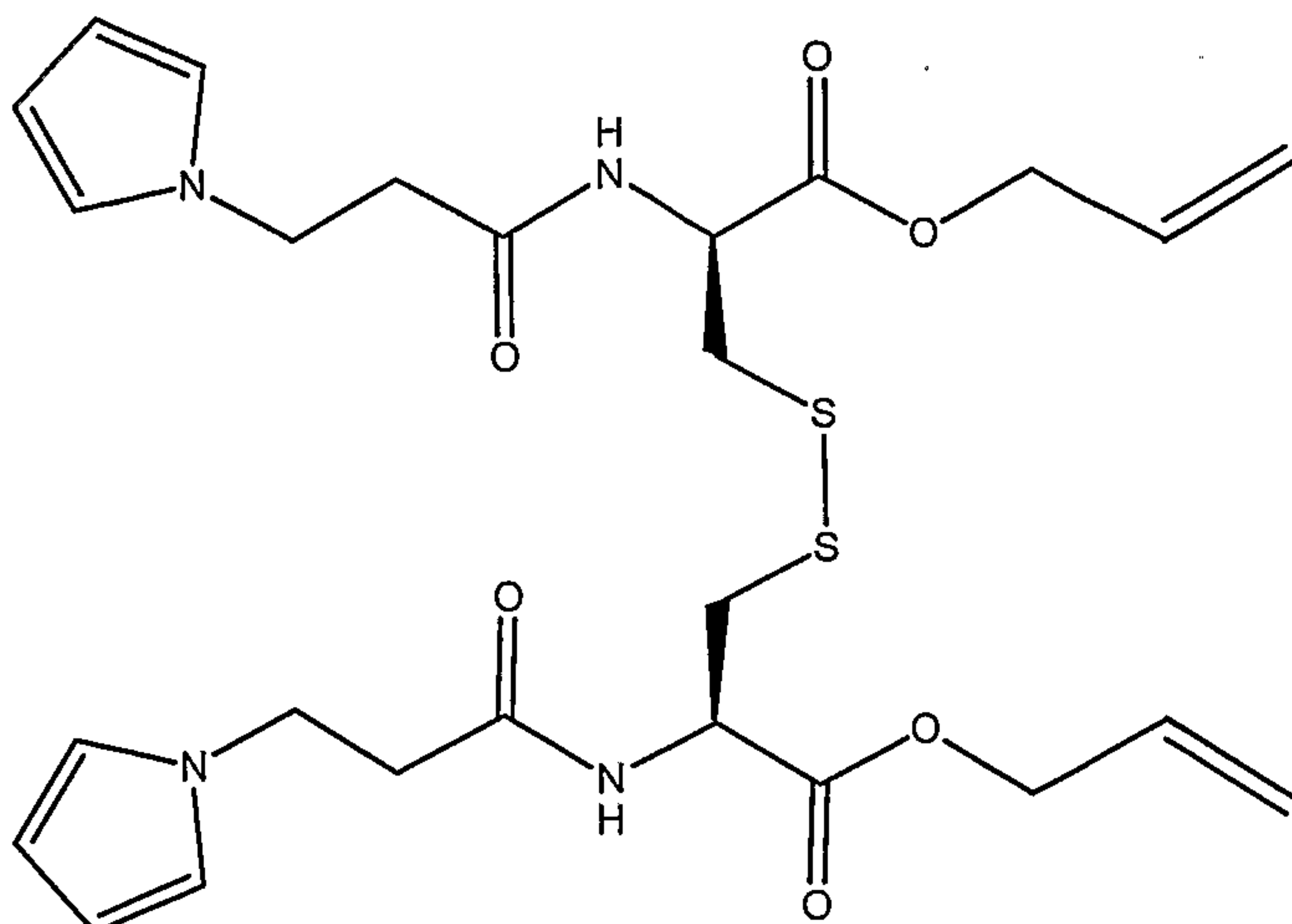
-COOR'

-CONH₂

-CONHR'
 -CON(R')₂
 -COR'
 -F, -Cl, -Br, -I
 5 -CN
 -NO₂
 -OH
 -OR'
 -SH
 10 -SR'
 -O-CO-R'
 -NH₂
 -NHR'
 -NH(R')₂
 15 N(R')₃⁺ e.g. (N(CH₃)₃)⁺
 -NH-CO-R'
 -NH-CO-H
 -NR'-CO-R'
 -NR'-SO₂H
 20 -NR'-SO₂R'
 -SO₂R'
 -OSO₂R'
 -C₅₋₂₀aryl
 -C₁₋₇alkyl-C₅₋₂₀aryl
 25 -C₁₋₇alkenyl-C₅₋₂₀aryl,

wherein R' is alkyl or alkenyl of 1 to 6 C atoms, preferably 1 to 4 C atoms.

Preferably D is unsubstituted, or is substituted by a charged group such as -COO⁻ or N(R')₃⁺ e.g. N(CH₃)₃⁺ which may
 30 bind a charged drug moiety. The covalent linker or pendant group may be covalently attached to another covalent linker or pendant group. An example of a monomer for forming polymeric coatings on medical devices according to the present invention is:



Medical devices according to the present invention have a surface which in use contacts body tissue, wherein said surface has on it a biocompatible coating layer comprising a polymer as described above. The medical device may be one of
5 a stent, an orthopaedic implant, a pump, a heart valve, a blood dialysis device, a blood storage container and a catheter guide wire. Preferably, the medical devices according to the present invention are adapted to be implanted into a mammalian body. Preferably, they are adapted to be in
10 contact with blood. Most preferably, the medical device is a stent. The invention is applicable to devices used in veterinary medicine. The invention extends to devices used in blood storage and blood treatment, for example of blood to be
15 used in transfusion.

Definitions

The term "electropolymerised" as used herein pertains to a polymer which is formed by the electropolymerisation of
20 electropolymerisable monomers. They are synthesised by applying a potential across a solution of the monomer.

When referring to a type of polymer, for example "polypyrroles", the term "polypyrroles" (or equivalent), as used herein, pertains to derivatives of polypyrrole, insofar
25 as the such polymers are not excluded by other limitations. For example, polymers according to the present invention must have pendent groups according to the present invention.

The term "body tissue" as used herein pertains to a collection of viable cells which are within a living body or are intended to be put into a living body. The term includes body fluids, such as blood.

5

Brief Description of the Drawings

Figure 1 shows the platelet shape distribution of human platelets adhering to uncoated and coated medical steel surfaces.

10

Figure 2 is a photomicrograph showing a lawn of coronary endothelial cells on a polymer coated stainless steel disc.

Figure 3 shows a coated stent according to the present invention after incubation in saline at 37°C for 14 days with 30 rpm shaking.

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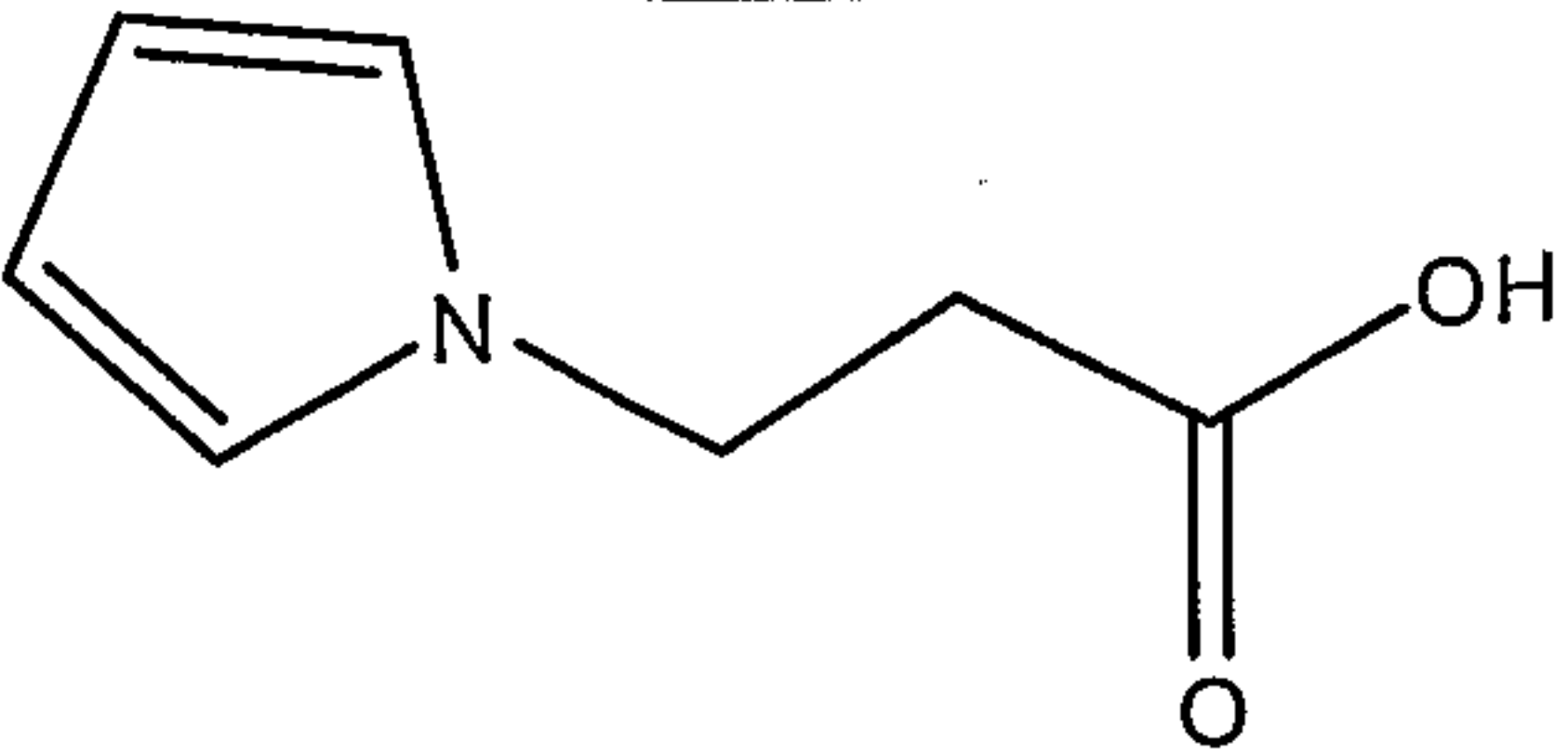
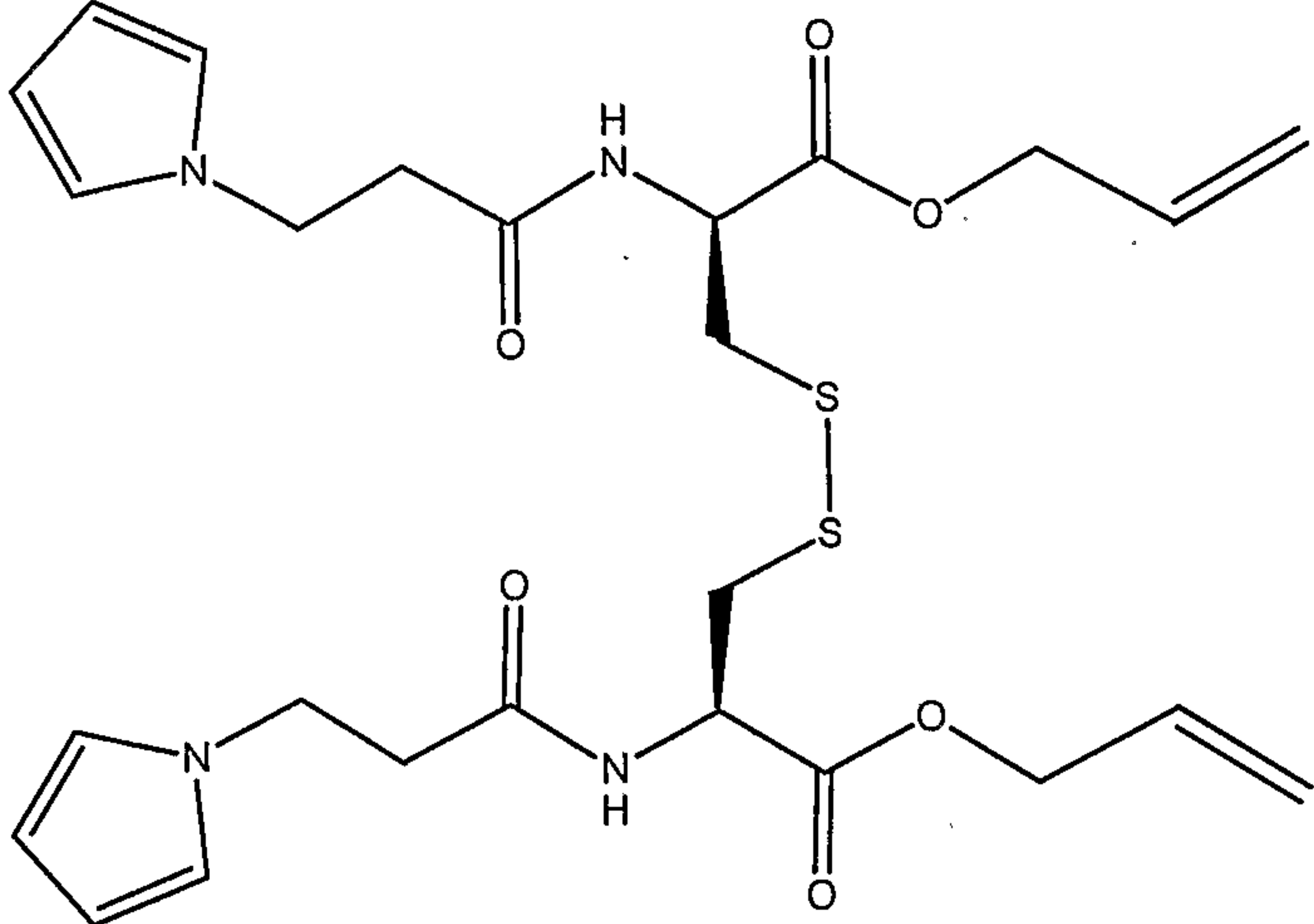
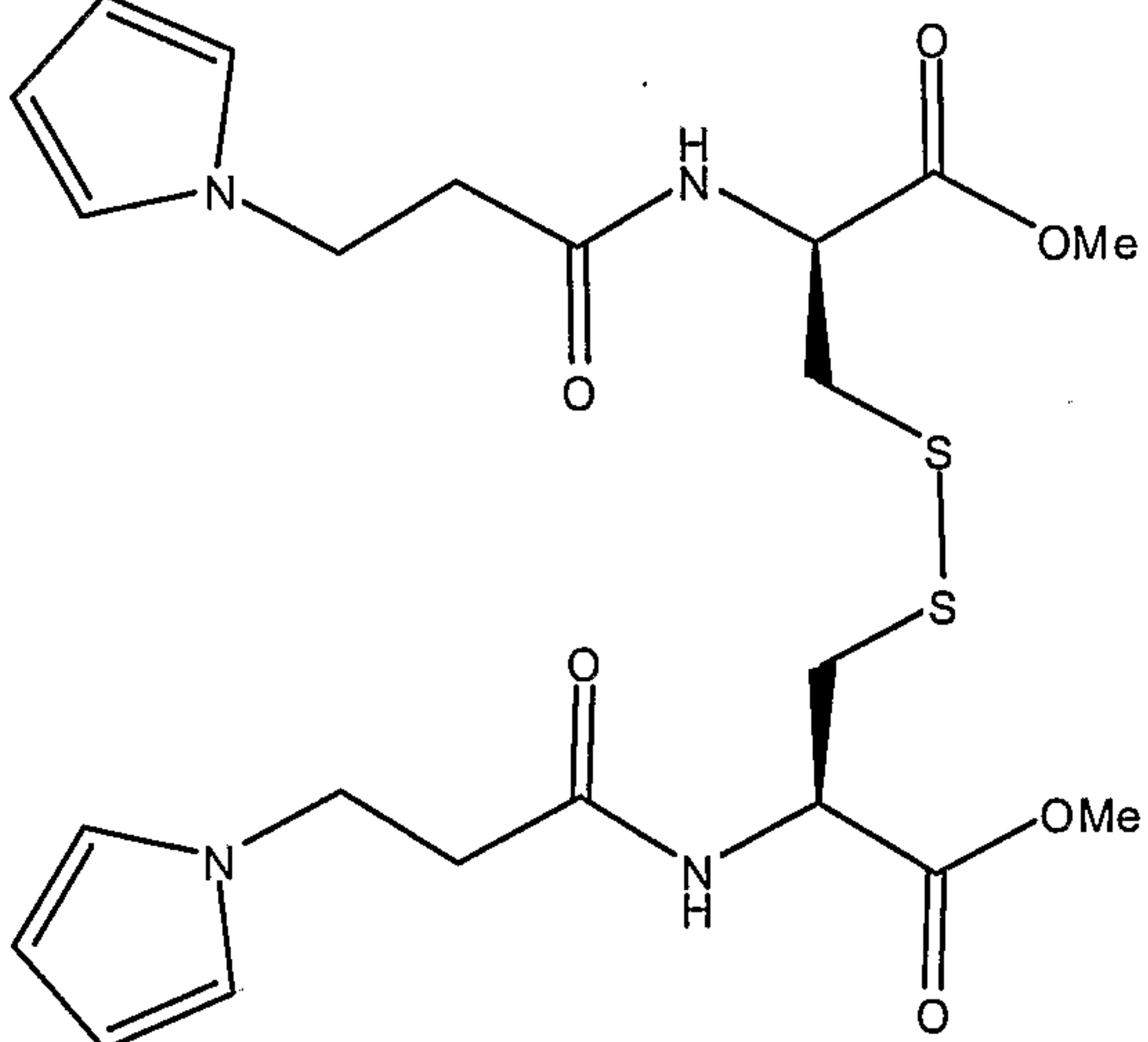
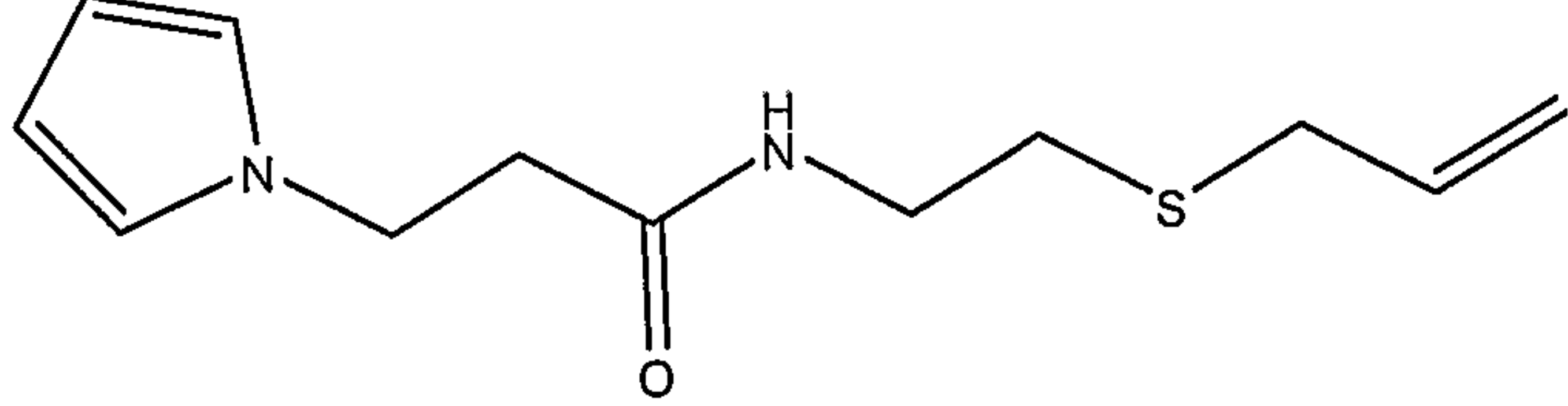
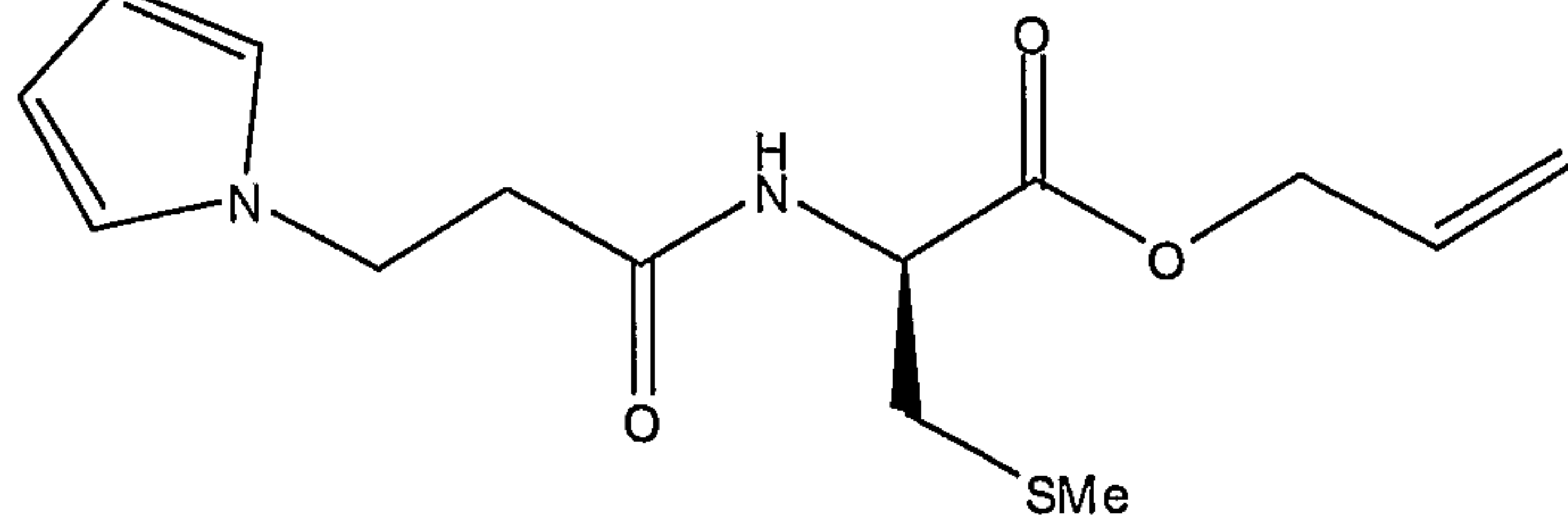
Figure 4 shows an expanded stent according to the present invention coated with poly E.

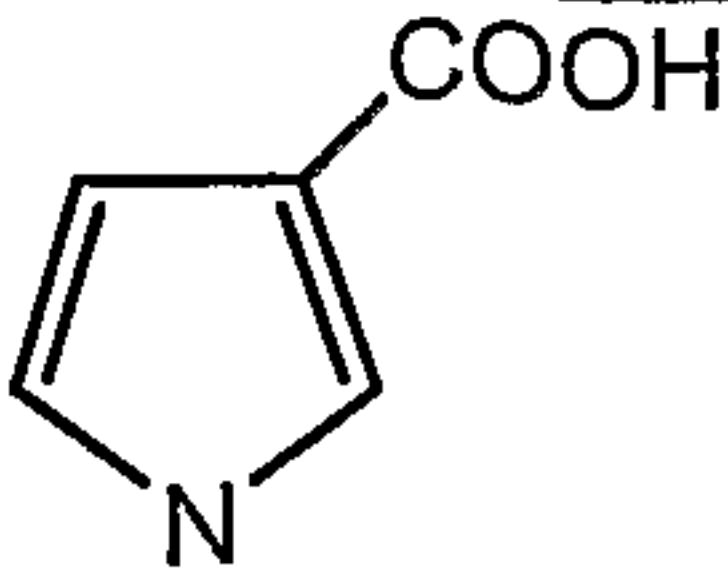
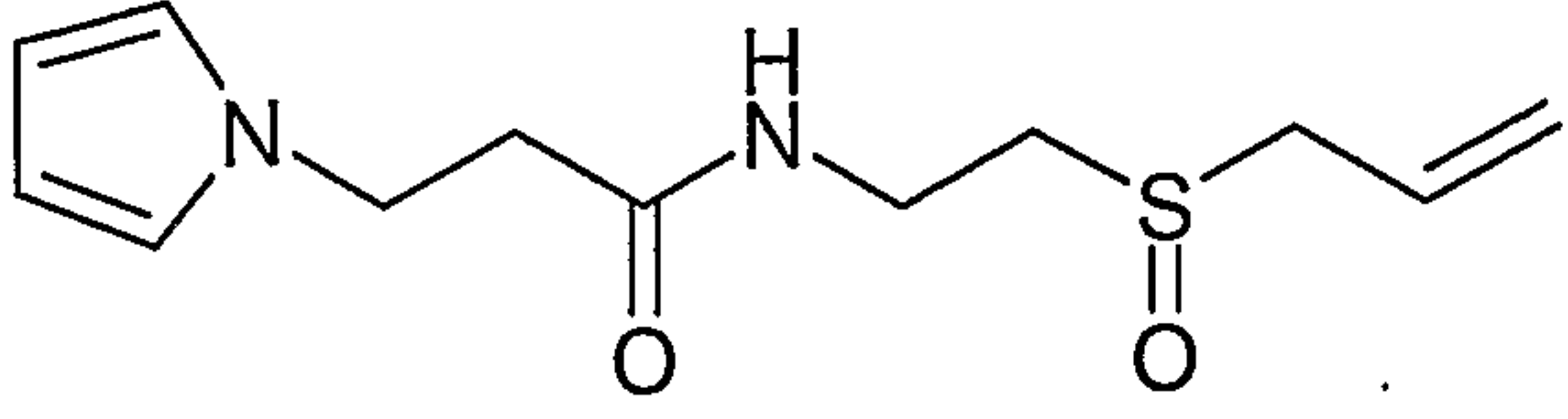
Figure 5 is a close-up view of a strut of the stent in Figure 4.

20

Detailed Description

In the following description, polymers of the following monomers are referred to. The polymer of monomer A is referred to as "poly A", the polymer of monomer E as poly E, etc.

A	
E	
G	
L	
P	

R	
T	

Poly A, poly G, poly L and poly R are outside the scope of the present invention, and are included as comparative examples. Medical devices coated with poly E, poly P and poly T are within the present invention. Poly E is discussed in detail below. Poly P and poly T are further examples of the present invention.

Electropolymerisation

Monomers for forming polymeric coatings on medical devices according to the present invention were electropolymerised according to well established procedures (2). Surface preparation of the discs, rods or stents before electrochemical coating involves, for example, degreasing with a commercial halocarbon, sonication in water for 5 minutes followed by washing with ethanol and drying. The amount of polymer on the metal surface was determined by weighing, by measuring the charge required for oxidising the polymer film or by measuring the bulk charge required to grow the film. The films were spectroscopically characterised by diffuse reflectance FTIR spectroscopy (3) when grown on discs.

The procedure for coating a stent with poly E is as follows. In their unexpanded state the stents used were 15 by 1.57 mm, with surface area of approximately 0.31 cm², made from 316 LVM stainless steel.

Prior to coating the stents underwent a strict preparation protocol. Following sonication in ethanol (>99.7% purity) for two hours and drying under a stream of compressed air, the stents were weighed on a five figure balance. They

were further cleaned by dipping in concentrated nitric acid for 15 seconds. The acid was removed by soaking in ethanol. The stents were again dried under a stream of compressed air. The last cleaning step was to thoroughly spray with ZeroTri
5 de-greaser (LPS Laboratories, USA), and then dry.

The stents were transferred to an H-type cell containing 4-6 mM monomer E in a dinitrogen sparged 200 mM tetrabutyl ammonium tetra fluoroborate in dry acetonitrile solution, such that the entire length of the stent was under the surface of
10 the solution and formed the working anode of the cell. The stent was held at a potential of about 1.1V versus the Ag/AgCl reference electrode and sufficient charge was passed to provide the desired coating thickness. After coating, the stent holder assembly was removed from the cell, and the stent
15 placed in a bath of warm acetonitrile to remove residual electrolyte. The stent was then removed, dried and re-weighed to give an estimation of coating weight.

Platelet Adhesion and Activation

Poly E and poly R were formed as polymer coatings on the
20 surface of a medical steel disc of diameter 1cm. Poly E is within the present invention, poly R is a comparative example. The platelet adhesion and activation properties of steel coated with poly E and with poly R were compared with those of
25 uncoated 316 LVM medical steel.

Platelet rich plasma (PRP) was retrieved from whole citrated human blood by gentle centrifugation at 200g for 10 minutes. The PRP was then diluted 50:50 in sterile phosphate buffered saline (PBS) containing 5.5mM of glucose (warmed to
30 37°C) and 0.5mL of this was added to each steel sample (coated with poly E, coated with poly R, uncoated). The samples were then incubated at 37°C under an atmosphere of 5% CO₂ for one hour. After incubation, the samples were rinsed three times in PBS to remove any non-adherent platelets. The samples were
35 then fixed in 2.5% SEM grade glutaraldehyde (in cocadylate buffer) for two hours at room temperature. After fixation the

samples were dehydrated through a series of increasing concentrations of ethanol (30, 50, 70, 90 and 100%) for 15 minutes at each concentration. The samples were then air dried, mounted and sputter coated with palladium for SEM analysis.

The number of platelets were counted per field of view (100 μ m x 140 μ m), and the average calculated from ten fields of view per sample on three replicate samples. Platelet shapes have been categorised into either spread (activated) or round (non-activated). Previous studies have similarly identified various stages of platelet morphological changes upon adhesion to foreign surfaces (4,5). It is commonly assumed that platelet shape changes are strongly associated with activation.

Figure 1 provides an indication of the number and morphology of adherent platelets to each material tested. These results clearly suggest that coating poly E reduces both platelet adhesion and platelet activation compared with bare steel. Also it can be seen that the poly E coated steel has significantly lower platelet adhesion than poly R coated steel. These results suggest that polymer coatings on medical devices according to the present invention significantly reduce platelet adhesion and activation, and therefore are likely to significantly reduce the thrombogenicity of such devices.

Endothelialisation

As discussed above, the ability of a coating to support endothelialisation is a desirable feature in implantable devices, particularly stents. The ability of poly E to support the growth of human coronary endothelial cells is shown by the photomicrograph in Figure 2. Figure 2 shows a monolayer lawn of coronary endothelial cells laid down on a 1 cm diameter stainless steel disc coated with approximately 1 μ m layer of poly E.

General in vivo Tolerance

Poly A, poly E, poly G and poly R coatings on stainless steel rods were implanted into rabbit dorsal muscle together with uncoated 316L stainless steel controls. These were removed and examined after implantation for periods up to 90 days as defined by EN 10993-6. The results showed that the polymers were very well tolerated and that poly E in particular behaved better than the bare metal control with respect to fibrin formation as shown in Table 1.

Table 1 Tolerance of poly E in rabbits following muscular implantation: histological findings, summary of biological parameters

	Kill Day 31		Kill Day 61		Kill Day 91	
	Control sites	Test sites	Control sites	Test sites	Control sites	Test sites
Total examined	(11)	(11)	(12)	(12)	(11)	(12)
Fibroplasia						
minimal	1	8	7	9	8	12
mild	7	3	3	3	3	0
moderate	3	0	1	0	0	0
Total	11	11	11	12	11	12
Myofibre degeneration	8	1	2	0	3	1
Lymphocytic infiltration	4	4	2	7	1	3
Polymorphonuclear infiltration	0	1	1	3	0	1
Mononuclear cell infiltration	1	0	0	0	0	0
Pigmented macrophages	3	1	1	6	0	8
Giant cells	4	2	0	1	1	0
Mineralisation	4	6	0	5	0	1
Fibrosis (distant from implant site)	5	2	4	5	2	0

5 **Cytotoxicity**

The very low cytotoxicity of polypyrroles, including those usable in the present invention, is illustrated by the data obtained for poly E. The assay protocol used MRC-5 cells followed by the procedure defined by ISO 10993 with polyethylene and latex rubber as the negative and positive controls respectively. The results in Table 2 illustrate that

poly E extracts showed no resulting cell damage to the sensitive strain.

Table 2

Dose Level (% eluate added)	Polyethylene			Latex Rubber			Poly E		
	Sample 1	Sample 2	Sample 3	Sample 1	Sample 2	Sample 3	Sample 1	Sample 2	Sample 3
0	0	0	0	0	0	0	0	0	0
6.25	0	0	0	4	4	4	0	0	0
12.5	0	0	0	4	4	4	0	0	0
25	0	0	0	4	4	4	0	0	0
50	0	0	0	4	4	4	0	0	0
100	0	0	0	4	4	4	0	0	0

- 5 Grading of toxicity: 0 = No cells showing damage
 1 = 0-25% of cells showing damage
 2 = 25-50 % of cells showing damage
 3 = 50-75% of cells showing damage
 4 = 75-100% of cells showing damage

10

Haemocompatibility

Poly A and poly E were tested for haemocompatibility under the ISO 10993 guidelines for medical implants. Both were found to be haemocompatible, as shown in table 3.

15

Table 3
Haemocompatibility Index (% Haemolysis)

<i>sample</i>	<i>Donor Blood A</i>	<i>Donor Blood B</i>	<i>Donor Blood C</i>	<i>Mean</i>	<i>Haemolytic grade</i>
poly A	0.0	0.0	0.0	0.0	Non-haemolytic
poly E	0.0	0.0	0.0	0.0	Non-haemolytic
Saline	0.0	0.0	0.0	0.0	Non-haemolytic
Saponin	84.0	86.0	57.8	75.9	Severely haemolytic

Adhesion Studies

5 Adhesion of the polymers unmodified polypyrrole, poly A, poly L and poly E to 316L polished stainless steel (surface roughness factor $R_a = 0.03$) was tested by TWI. The force per unit area required to fracture a cyanoacrylate bonded steel stub from the polymer-coated 316L stainless steel plaque was measured, and the results obtained are as shown in Table 4.

10

Table 4

Polymer	Force per unit area / MPa
Polypyrrole (unmodified)	<1
Poly A	2.4
Poly L	3.9
Poly E	>6.7

Therefore, it can be seen that polymer coatings according to the present invention (poly E) showed very strong adhesion to steel. This is desirable because it reduces the risk of the polymer coating flaking off or otherwise cracking or breaking which can lead to thrombosis or other undesirable effects.

Five stainless steel stents coated with poly E were incubated at 37 °C in blood isotonic saline solution for 14 days, with 30 rpm shaking. They were removed and photomicrographs were taken. No flaws, cracking or flaking of the coatings was observed at 20nm resolution. Figure 3 shows a stent treated as described.

Three stainless steel stents coated with poly E were each manually crimped onto a catheter balloon which was then fully expanded. The coated stents were removed and photomicrographs were taken. No flaws, cracking or flaking of the coatings was observed at 20nm resolution. This demonstrates the physical robustness of the polymer coating. Figure 4 shows an expanded stent coated with poly E. Figure 5 is a close-up view of a strut of the stent.

In vivo tests

As mentioned above, the occurrence of late-onset thrombosis in use of drug-eluting stents has caused bare metal stents to be favoured. *In vivo* tests carried out in pig coronary arteries using stents coated with a coating layer in accordance with the present invention have shown that such

stents induce no adverse vascular response compared to bare metal stents.

Method: Stents with a ca.1 μm thick polymer surface layer formed by electropolymerisation of the functionalised pyrrole monomer **E** (*N,N'*-Bis[3-(pyrrol-1-yl)propanoyl]-L-cystine diallyl ester) described above (Coated stents) and bare metal stents (BMS) were implanted into native coronary arteries of 17 farm pigs by standard endovascular technique (26 Coated stents, 25 BMS stents). The stents were made of 316 L stainless steel. The electropolymerisation was carried out as described in reference 2 (Le Gall et al.). At one week post-implant 6 stented arteries (N=6) and at one month post-implant 11 stented arteries (N=11) were taken for analysis. **Results:** Coated stents evoked response indistinguishable from BMS at 1-week. For 1-month implants, there were no differences in intima thickness (coated 0.28 ± 0.18 vs. BMS 0.25 ± 1.18 mm, P=NS) or % area stenosis (coated 37 ± 19 vs. BMS $32 \pm 20\%$, P=NS). Both stent types were endothelialized and vessel morphology was similar. **Conclusion:** Novel stent surface modification by introduction of an allyl cystine surface motif attached to a poly(pyrrole) backbone formed by electropolymerisation evokes a coronary artery response indistinguishable from bare metal stents in pig coronaries.

25

Syntheses

Monomer A

3-(Pyrrol-1-yl)propanoic acid was prepared according to a modification of literature procedures (6,7). Tetrabutyl ammonium hydroxide solution (1.0 M in methanol, 15.4 mL, 15.4 mmol, 0.1 equiv.) was added to pyrrole (10 g, 154 mmol, 1 equiv.) with stirring under nitrogen. Acrylonitrile (30 mL, 786.5 mmol, 5.3 equiv) was added very slowly over 2.5 hours, keeping the temperature below 50 °C. The reaction was then allowed to stir for a further hour at room temperature before the addition of potassium hydroxide (30 g, 535 mmol, 3.5

equiv.) in distilled water (45 mL) and refluxing for 1.75 hours. After cooling to room temperature, the pH of the reaction mixture was lowered to 5.5 by the addition of 2M hydrochloric acid (ca. 70 mL) and then the resultant solution
5 extracted with diethyl ether (100 mL). After a single extraction, the pH of the aqueous phase was again lowered to 5.5 followed by a further extraction with diethyl ether (100 mL). This acidification and extraction process was repeated approx. 15 to 20 times. The combined organic washings were
10 dried (MgSO_4) and the solvent evaporated *in vacuo* to yield an off white crystalline solid (10.1 g, 47 %). ν_{max} (KBr disc) 2922 (N-H), 1700 (C=O) cm^{-1} ; δ (400MHz, CDCl_3) 6.67 (2H, t, J 2.1 Hz, C(α)H pyrrole), 6.14 (2H, t, J 2.1 Hz, C(β)H pyrrole), 4.20 (2H, t, J 6.8 Hz, py- CH_2 -), 2.82 (2H, t, J 6.8 Hz,
15 - CH_2COOH).

Monomer E

In a modified literature procedure (2) CDI (carbodiimidazole, 3.00 g, 18 mmol, 2.2 equiv) was added to a solution of 3-
20 (pyrrole-1-yl) propanoic acid (2.66 g, 18 mmol, 2.2 equiv.) in dry THF (40 mL) and the reaction mixture stirred for 1.5 hours under nitrogen at room temperature. Meanwhile, L-cystine bisallyl ester bis(toluene-4-sulphonate) (6.00 g, 8.2 mmol, 1 equiv.) was dissolved in THF (60 mL) with stirring under
25 nitrogen, with the dropwise addition of sufficient triethylamine to effect the dissolution. The ester solution was then added to the activated acid solution by cannula. The resultant reaction mixture was stirred at room temperature for 68 hours followed by warming to 60°C for a further 6 hours.
30 Once cool, the solvent was evaporated under vacuum to yield a yellow oily solid. The pure product was obtained as a white solid by washing with DCM and further recrystallisation of the mother liquor from DCM/diethyl ether. White crystalline solid (m.p. 164-5 °C). Found C 55.50, H 6.19, N 9.82, $\text{C}_{26}\text{H}_{34}\text{N}_4\text{O}_6\text{S}_2$
35 requires C 55.50, H 6.09, N 9.96 %; ν_{max} (Nujol[®]) 3315 (N-H),

1733 (C=O ester), 1640 (C=O amide), 1537 (C=O amide), 731 (C-H) cm^{-1} ; δ (400MHz, CDCl_3) 6.62 (4H, t, J 2.0 Hz, C(α)H pyrrole), 6.31 (2H, d, J 7.3 Hz, NH), 6.08 (4H, t, J 2.0 Hz, C(β)H pyrrole), 5.83 (2H, m, $-\text{CH}=\text{CH}_2$), 5.28 (4H, m, $-\text{CH}=\text{CH}_2$),
5 4.80 (2H, m, $-\text{CHCH}_2\text{S}-$), 4.61 (4H, t, J 3.0 Hz, $-\text{OCH}_2\text{CH}=\text{CH}_2$), 4.17 (4H, m, $\text{py}-\text{CH}_2-$), 2.99 (4H, m, $-\text{CH}_2\text{S}-$), 2.63 (4H, t, J 6.7 Hz, $\text{py}-\text{CH}_2\text{CH}_2-$).

Monomer G

10 *N,N'*-Bis[3-(pyrrol-1-yl)propanoyl]-L-cystine dimethyl ester was prepared according to a literature procedure (3). White solid (m.p. 146-147 °C). Found C 51.70, H 5.75, N 11.00, $\text{C}_{22}\text{H}_{30}\text{N}_4\text{O}_6\text{S}_2$ C 51.75; H 5.92; N 10.97 %; ν_{max} 3327 (N-H), 1739 (C=O ester), 1643 (C=O amide) cm^{-1} ; δ (270MHz, CDCl_3) 6.63 (4H, t, J 2.0 Hz, C(α)H pyrrole), 6.36 (2H, d, J 7.3 Hz, NH), 6.09 (4H, t, J 2.0 Hz, C(β)H pyrrole), 4.79 (2H, td, J 7.5 Hz, J' 5.1 Hz, $-\text{CHCH}_2\text{S}-$), 4.21 (4H, dt, J 6.7 Hz, J' 2.6 Hz, $\text{py}-\text{CH}_2-$), 3.73 (6H, s, $-\text{OCH}_3$), 3.10 (2H, dd, J 14.5 Hz, J' 5.1 Hz, $-\text{CH}(\text{H})\text{S}-$), 3.00 (2H, dd, J 14.3 Hz, J' 5.1 Hz, $-\text{CH}(\text{H})\text{S}-$), 2.67
15 (4H, t, J 6.8 Hz, $\text{py}-\text{CH}_2\text{CH}_2-$).

Monomer L

N-(2-Mercapto-ethyl)-3-pyrrol-1-yl-propionamide (1.3 g, 6.52 mmol, 1 equiv.) was dissolved in acetonitrile (80 mL) with
25 stirring under nitrogen. Triethylamine (2.7 mL, 1.96 g, 19.4 mmol, 3 equiv.) was added dropwise followed by allyl bromide (0.6 mL, 838.8 mg, 6.93 mmol, 1.06 equiv.) and the reaction refluxed for 10 hours. After cooling, the white precipitate by product that had formed was removed by filtration and the
30 solvent evaporated to yield the crude product. Further by product was removed by stirring with ethyl acetate (100 mL) and again filtering off the solid. Removal of the solvent *in vacuo* and purification by flash chromatography on silica

eluting with ethyl acetate (R_f 0.55) afforded pure *N*-(2-Mercapto-ethyl)-3-pyrrol-1-yl-propionamide as a yellow solid.

Monomer P

5 To a stirred solution of pyrrole propanoic acid (0.8g, 5.75mmol) in thf (20ml), 1-1'carbonyl diimidazole (1g, 6.2 mmol) was added portion wise and the mixture was left stirring for 1h. Methionine allyl ester (2.3g, 6.4 mmol) in thf (30ml) was then added along with Et_3N . The reaction mixture was
10 stirred for 8h at room temperature. All solvent was removed under vacuum, and the product was extracted by Et_2O . The Et_2O phase was evaporated under vacuum. The solid was washed with hexane to give a white solid 1.2g (4mmol) 63% yield. ν_{max} (Nujol[®]) 3314 (N-H), 1745 (C=O ester), 1634 (C=O amide), 1532 (C=O amide) cm^{-1} ; δ (400MHz, CD_3CN) 6.81 (1H, br s, NH), 6.64 (2H, t, J 2.1 Hz, C(α)H pyrrole), 5.99 (2H, t, J 2.0 Hz, C(β)H pyrrole), 5.96 - 5.86 (1H, m, -CH=CH₂), 5.31 (1H, m, -CH=C(H)H_{trans}), 5.21 (1H, m, -CH=C(H)H_{cis}), 4.57 (2H, d, J 5.6 Hz, py-CH₂-), 4.52 - 4.47 (1H, m, -CHCH₂S-), 4.15 - 4.12 (2H, m, -OCH₂CH=CH₂), 2.70 - 2.55 (2H, m, -CH₂S-), 2.47 - 2.37 (2H, m, py-CH₂CH₂-), 2.01 (3H, s, -SCH₃); m/z (E.I.) 310 (M^+).

Monomer R

This material is commercially available (Aldrich).

25

Monomer T

N-(2-Allylsulfanyl-ethyl)-3-pyrrol-1-yl-propionamide (0.3704g, 1.554 mmol, 1 equiv) was taken up in 100ml of dichloromethane with stirring under nitrogen. The reaction mixture was cooled
30 to between 0-4C. Meta-chloroperoxybenzoic acid (0.4815g, 2.790 mmol, 1.8 equiv) was added to the mixture and the reaction stirred at 0-4C for 16 hours. The solvent was removed *in vacuo* and purification by flash chromatography on silica: eluting with ethyl acetate gave the by-product meta-chlorobenzoic
35 acid. Further elution with the solvent mixture was gradually

changed to a 1:1 ethyl acetate/ethanol gave the product which was isolated by removal of the solvent *in vacuo* as off-white crystals in 60% yield.

5 δ (300MHz, CDCl₃) 6.58 (2H, t, *J* 1.9 Hz, C(α)H pyrrole), 6.38 (1H, br s, NH), 6.04 (2H, t, *J* 2.1 Hz, C(β)H pyrrole), 5.76 (1H, m, -CH=CH₂), 5.41 - 5.30 (2H, m, -CH=CH₂), 4.15 (2H, t, *J* 6.5 Hz, py-CH₂-), 3.65 (2H, q, *J* 6.0 Hz, -NHCH₂), 3.48 (2H, m, -CH₂CH=CH₂), 2.81 (2H, m, -NHCH₂CH₂S-), 2.52 (2H, t, *J* 6.6 Hz, py-CH₂CH₂-), ^{m/z} (E.S.) 254.85 (M⁺).

10

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CLAIMS

1. A medical device having a surface which in use contacts body tissue, wherein said surface has on it a biocompatible coating layer comprising a polymer having covalently bound allyl-terminated pendent groups, said pendent groups comprising a moiety selected from
- 5
- 10
- O-CH₂-CH=CH₂
 - S-CH₂-CH=CH₂
 - S(=O)-CH₂-CH=CH₂
 - Se-CH₂-CH=CH₂ and
 - Se(=O)-CH₂-CH=CH₂.
2. A medical device according to claim 1 wherein said pendent groups comprise a moiety selected from
- 15
- 20
- C(=O)-O-CH₂-CH=CH₂
 - CH₂-S(=O)-CH₂-CH=CH₂
 - S-S-CH₂-CH=CH₂
 - S(=O)-S-CH₂-CH=CH₂ and
 - S-S(=O)-CH₂-CH=CH₂.
3. A medical device according to claim 1 or claim 2 wherein the pendent group is bound to the polymer via an amido, ester or ether moiety.
- 25
4. A medical device according to any of claims 1 to 3, wherein the polymer is selected from
- polypyrroles,
 - polythiophenes,
 - 30 polyanilines,
 - polyamides,
 - poly-aminoacids,
 - polysaccharides,
 - polyesters,
 - 35 polyalkenes,
 - polyamines,

polyethers,
polyethyleneterephthalates,
polyimides,
polysiloxanes,
5 polyphosphazines,
polylactides,
polyglycolides,
polycaprolactones,
polydioxanones,
10 polygluconates,
polyanhydrides,
polyphosphoesters,
polyorthoesters and
polyphosphate esters.

15

5. A medical device according to any of claims 1 to 4 wherein the polymer is formed by polymerisation of one or more types of monomer, at least one of the types of monomer comprising said pendent group.

20

6. A medical device according to any one of claims 1 to 5 wherein the polymer is an electropolymerised polymer.

25

7. A medical device according to claim 6, wherein the polymer is selected from
polypyrroles,
polythiophenes and
polyanilines.

30

8. A medical device according to any one of claims 1 to 7 wherein the surface of the medical device is a conductive surface.

35

9. A medical device according to claim 8 wherein the surface of the medical device is a metal surface.

10. A medical device according to any one of claims 1 to 9 wherein the medical device is selected from

a stent
an orthopaedic implant
5 a pump
a heart valve
a blood dialysis device
a blood storage container and
a catheter guide wire.

10

11. A medical device according to any of one of claims 1 to 10 wherein the medical device is adapted to be implanted in a mammalian body.

15

12. A method of manufacture of a medical device comprising the step of forming a biocompatible polymeric layer by electropolymerisation of one or more types of monomer, wherein at least one type of monomer includes a covalently bound allyl-terminated pendent group, said pendent group comprising
20 a moiety selected from:

-O-CH₂-CH=CH₂
-S-CH₂-CH=CH₂
-S(=O)-CH₂-CH=CH₂
-Se-CH₂-CH=CH₂ and
25 -Se(=O)-CH₂-CH=CH₂.

25

1/2

Fig. 1

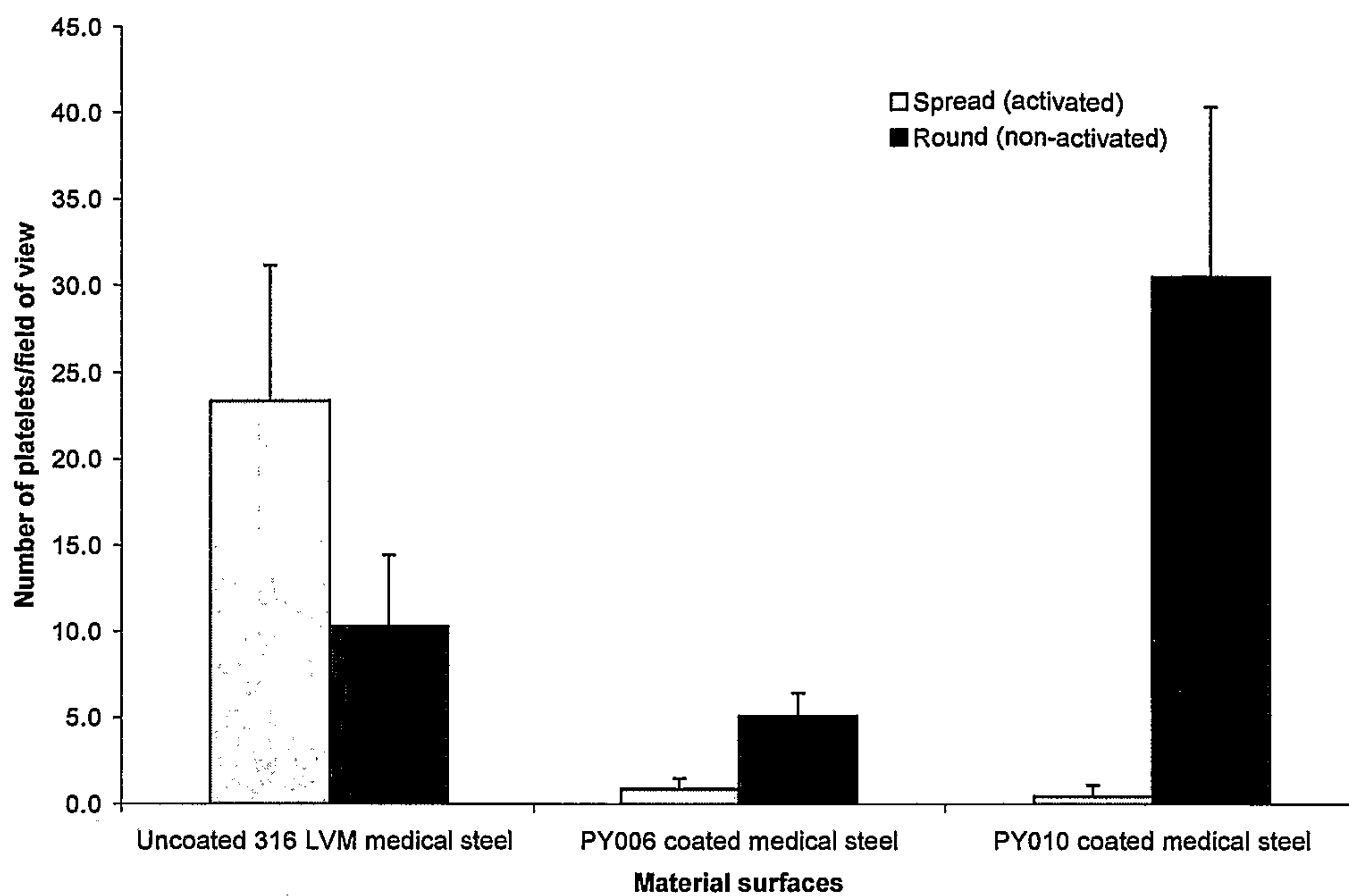
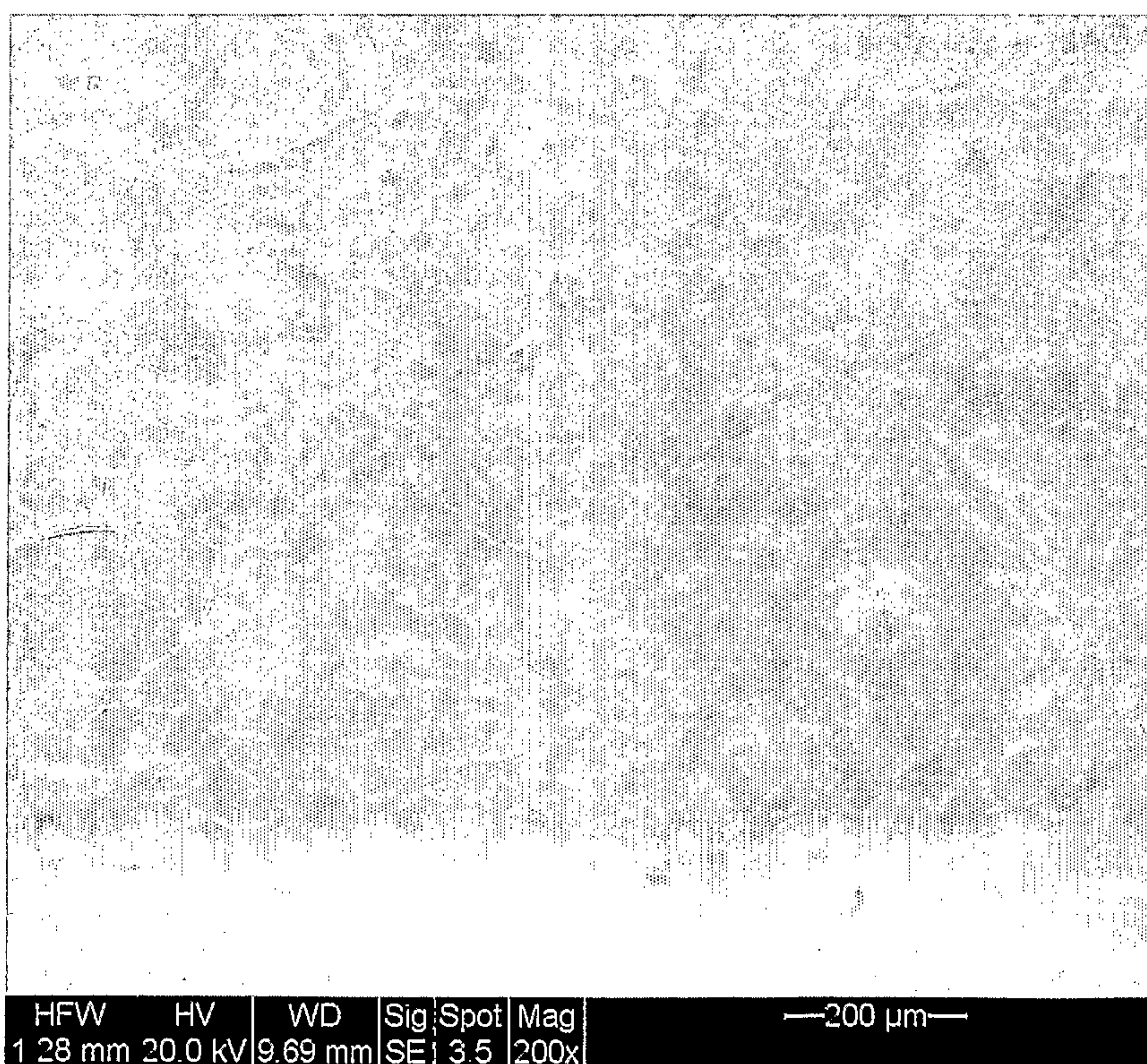


Fig. 2



Monolayer of human artery endothelial cells on surface of poly E

2/2

Fig. 3

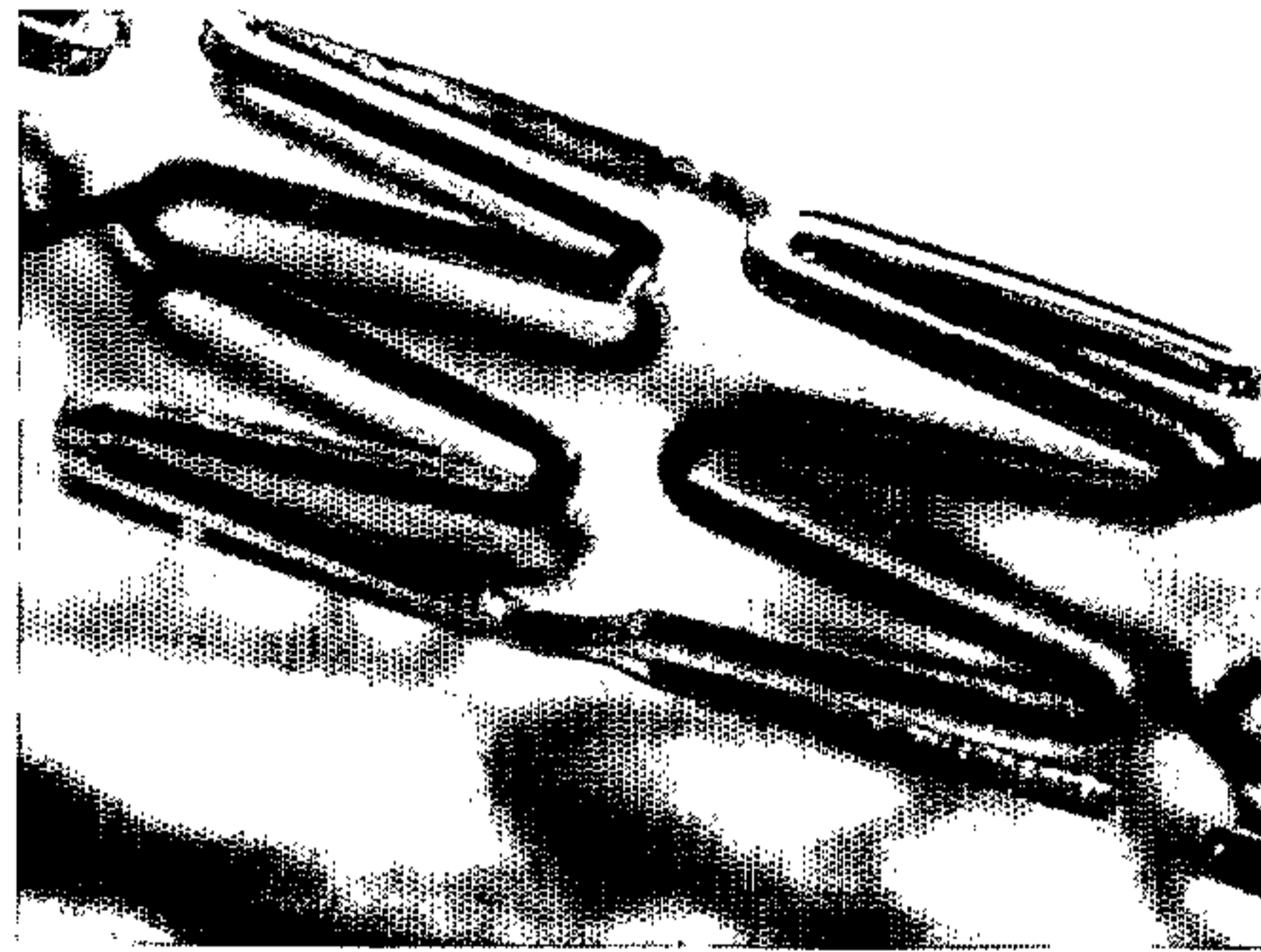


Fig. 4



Fig. 5

