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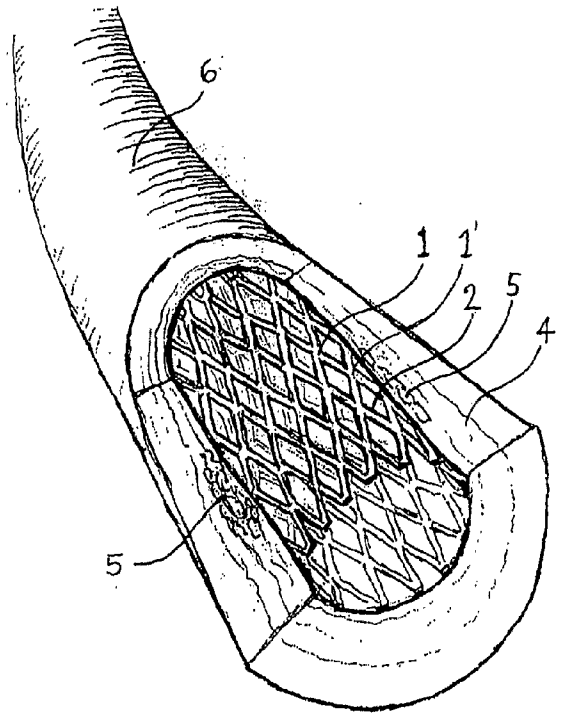
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(54) Title: DRUG-ELUTING STENT WITH ATHEROSCLEROTIC PLAQUES DISSOLVING PHARMACOLOGICAL PREPARATION



(57) Abstract: A drug eluting stent for release over time of a detergent in loco at the site of an angioplasty procedure for the dissolution of the fatty component of the atherosclerotic plaque. The detergent has the capability of passing thru the fibrous cap and of targeting the fatty components of the plaque. The detergent is aimed at dissolving the cholesterol aggregates of the plaque post angioplasty procedure, plaque which is fractured, compressed, locally redistributed by the angioplasty procedure but that it is still present within the artery wall post angioplasty procedure. Numerous other pharmacological compounds with different targeted functions can be combined with the detergent in the stent including Antineoplastics, Immnunosuppressants, Migration inhibitors, Enhanced Healing Factors, Collagen and Proteoglycan degrading enzymes. The drug eluting stent by providing the dissolution of one of the major plaque components i.e. the fatty component is expected to greatly reduce the chance of restenosis.

WO 2007/084549 A2

Drug -Eluting Stent with Atherosclerotic Plaques Dissolving Pharmacological Preparation

TECHNICAL FIELD

The invention consists of a drug-eluting arterial stent in which the eluting drug is a lipid/cholesterol dissolving pharmacological compound aimed at the solubilization of the lipid component of the atherosclerotic plaque.

BACKGROUND ART

Coronary stents are expandable metal tube mesh-like stents of variable length that are placed in the arteries of patients at the site of balloon angioplasty. Stents provide additional support to the wall of the artery after the procedure of angioplasty, aiming at preserving its patency.

Stents have shown to decrease the chance of re-narrowing of the arterial lumen. However, despite stent placement, re-stenosis is common. Up to 30%-40% if no more of patients develop re-stenosis in the long term at the site of the stent placement, the re-stenosis process starting just days after the angioplasty procedure.

Drug-eluting stents were introduced with the intent to obviate the re-stenosis problem.

Drug-eluting stents are stent coated with a thin polymer containing medications aimed at the prevention of re-stenosis of the artery by preventing formation of scar tissue at the site of an angioplasty procedure.

The drugs that may be useful in preventing re-stenosis fall in four major categories: antineoplastic, antiproliferative, migration inhibitors, enhanced healing factors.

Despite their superior performance in respect to the bare stents, still re-stenosis occurs in a significant number of cases with morbidity and mortality consequences.

A search in the Patent Office and in the world medical literature has revealed no drug-eluting stent which addresses the issue of atherosclerotic plaque dissolution.

While all drug -eluting stents aim at preventing re-stenosis by impeding formation of scar tissue at the site of the angioplasty, none of the present drug-eluting stents addresses the fundamental issue of aiming at plaque dissolution.

In vivo studies have confirmed that during the angioplasty procedure the atherosclerotic plaque is fractured, compressed, but its components, including its major component, the cholesterol aggregates, remain in situ within the arterial wall at the angioplasty site.

Although fractured, compressed, minimally displaced and redistributed locally at the angioplasty site, the plaque components do not go away from the arterial wall. As a matter of fact, they remain within the arterial wall with their unaltered mass, and, as such, they exert constant pressure toward lumen re-stenosis.

DISCLOSURE OF THE INVENTION

With this invention Applicants propose a drug-eluting stent in which the eluting drug is an anionic detergent such as a biliary acid or any suitable lipid/cholesterol

solubilizer / biological emulsifier / detergent / surfactant, ionic, either anionic such as biliary salts or cationic, non-ionic, zwitterionic, capable of crossing the fibrous cap of the atherosclerotic plaque and of dissolving its fatty component.

Applicants have unequivocally demonstrated in vitro that a detergent, such as a biliary acid, when placed in contact with an atherosclerotic plaque is capable of dissolving it in matter of hours. The detergent, such as a biliary acid, is capable of passing thru the fibrous cap of the atherosclerotic plaque, capable of attacking the plaque and dissolving it. The detergent compound, such as deoxycholic acid, literally melts, dissolves the fatty component of the plaque. The dissolved component, namely cholesterol, filters out thru the cap into the bloodstream in micro particles.

The atherosclerotic plaque dissolving properties of a detergent/lipid solubilizer such as a biliary acid or salt is the subject matter of Applicants US Provisional Patent Application: "Dissolution of Arterial Cholesterol Plaques by Pharmacological Preparation", No. 60/739,143 filed on 11/22/2005.

The pharmacological compound with which the drug-eluting stent is coated can be any biliary acid or salt alone or in combination or any precursor or derivative of such bile acid or salt alone or in combination, such as Cholic acid or Chenodeoxycholic acid or Deoxycholic acid or Lithocholic acid Hyodeoxycholic acid or Glycocholic acid or Taurocholic acid.

As above disclosed, any type of suitable biological/biocompatible lipid / cholesterol solubilizer / detergent can be used alone or in combination.

Applicants believe that the local elimination /dissolution of the post-angioplasty atherosclerotic plaque lipid component , atherosclerotic plaque which is compressed/fractured by the angioplasty procedure , releases the constant pressure toward re-stenosis exerted when the plaque is compressed, fractured and left with its

total mass unaltered. As result of the release of such pressure, it is likely that also scar tissue formation at the plaque site become less probable.

In addition to biliary acids or salt alone or in combination or precursors or derivatives of the biliary acids or salts, alone or in combination, such as Cholic acid or Chenodeoxycholic acid or Deoxycholic acid or Lithocholic acid Hyodeoxycholic acid or Glycocholic acid or Taurocholic acid, a lipid solubilizer such as a Triton compound or a Fatty Acid Bile Acid Conjugate such as Arachidyl amido cholanoic acid known as Aramchol can be used. Applicants propose generally any pharmacological compound belonging to the class of biocompatible detergent / emulsifiers/surfactants/ lipid solubilizers/cholesterol solvents having the property of disaggregating, emulsifying, or dissolving cholesterol aggregates as a drug for drug-eluting stent.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 is a partially cross sectioned perspective view of a drug-eluting stent coated with a biocompatible detergent in place deployed within the artery, after angioplasty.

DETAILED DESCRIPTION OF THE INVENTION

In the preferred embodiment as shown in Fig.1 drug-eluting stent 1 is shown deployed in situ within an artery with atherosclerotic lesions after angioplasty has been carried out. Drug-eluting stent 1 of generally tubular shape is composed of lattice, expandable workframe or structure 2 assembled from a variety of metals such as nitinol, stainless steel or cobalt chromium. Stent 1 is spring like and flexible. Wall 4 of artery 6, shown in partial cross section view, shows plaque 5 fractured, compressed, locally redistributed within artery wall 4 post angioplasty procedure.

Lattice structure 2 of drug-eluting stent 1 is coated with deoxycholic acid 1' which has detergent properties.

The release in situ of pharmacological compound such as deoxycholic acid 1' will dissolve the fatty components of plaque 5 after having passed through the fibrous cap of the atherosclerotic plaque.

The drug carrier which slowly releases the drug over time can be typically a polymer, although also phosphorylcholine and ceramics could be used in a single or multiple layers fashion. Also a stent with an eluting sheath could be used , as disclosed in US Patent Application number 10/334,034 "Drug-eluting stent cover and method of use" by Yip Philip S. and Al., filed on December 30, 2002. Such intravascular stent includes an eluting sheath fabricated from a mesh for controlled release of therapeutic drugs and for delivery of the therapeutic drugs in localized drug therapy in a blood vessel. The eluting sheath is attached to the outside surface area of the stent structure and is fabricated from a mesh designed to expand outwardly in unison with the radial stent expansion. The eluting sheath can be loaded with at least one therapeutic drug for its controlled release.

The above mentioned lipid-solubilizer detergent, as well as other biocompatible detergents, is capable indeed of passing thru the fibrous cap of the atherosclerotic plaque and capable of attacking the plaque for its dissolution.

A lipid solubilizer detergent compound such as the Deoxycholic acid, Cholic acid or Chenodeoxycholic acid or Lithocholic acid, Hyodeoxycholic acid or Glycocholic acid or Taurocholic acid or a biocompatible a Triton compound or a Fatty Acid Bile Acid Conjugate such as Arachidyl amido cholanoic acid 1', literally melts, dissolves the fatty components of the plaque. What is occurring is indeed a delipidization of the atherosclerotic plaque.

Such compounds, which are biological/biocompatible compounds can be classified according to several criteria.

Detergents classified according to structure:

Alkyl glycosides, which include: -D-glucopyranoside,□-D-glucopyranoside, n-octyl-□n-nonyl- -D-glucopyranoside,□-D-glucopyranoside, n-hexyl-□n-heptyl- -Dthioglucopyranoside, and□-D- maltoside, octyl-□-D-maltoside, decyl-□dodecyl-maltoside and others.

Bile acids, which include a very large number of compounds listed elsewhere in this application.

Glucamides, which include: MEGA-10, MEGA-9, MEGA-8, Deoxy Big CHAP, Big CHAP, and others.

Polyoxyethylenes, monodisperse and polydisperse which include: reduced TRITON® X-100, reduced TRITON® X-114, TRITON® X-100, NP-40, TRITON® X-114, GENAPOL® X-080, GENAPOL® X-100, C12E8, C12E9, THESIT®, LUBROL® PX, GENAPOL® C-100, BRIJ® 35, PLURONIC® F-127®, (laurate), TWEEN® 20 (oleate), TWEEN® 80, and others.

Zwittergents, which include: EMPIGEN BB® (n-dodecyl-N,Ndimethylglycine), ZWITTERGENT® 3-08, ZWITTERGENT® 3-10, ZWITTERGENT® 3-12, ZWITTERGENT® 3-14, ZWITTERGENT® 3-16, CHAPS, CHAPSO, and others.

Detergent classified according to electric charges:

Ionic Detergents, which include:

BATC

Cetyltrimethylammonium Bromide (CTAB), Molecular Biology Grade

Chenodeoxycholic Acid, Free Acid

Chenodeoxycholic Acid, Sodium Salt

Cholic Acid, Sodium Salt

Cholic Acid, Sodium Salt, ULTROL® Grade

Deoxycholic Acid, Sodium Salt

Deoxycholic Acid, Sodium Salt, ULTROL® Grade

7a,12a-Dihydroxy-5ß-cholanic Acid

Glycholic Acid, Sodium Salt

Glycodeoxycholic Acid, Sodium Salt

Lauroylsarcosine, Sodium Salt

Sodium n-Dodecyl Sulfate (SDS)

Sodium n-Dodecyl Sulfate (SDS), High Purity

Sodium n-Dodecyl Sulfate (SDS), Molecular Biology Grade

Sodium n-Dodecyl Sulfate (SDS), 30% Solution

Taurochenodeoxycholic Acid, Sodium Salt

Taurocholic Acid, Sodium Salt

Taurocholic Acid, Sodium Salt, ULTROL® Grade

Taurodehydrocholic Acid, Sodium Salt

Taurodeoxycholic Acid, Sodium Salt

Taurolithocholic Acid, Sodium Salt

Tauroursodeoxycholic Acid, Sodium Salt

TOPPS

Non-ionic Detergents:

APO-10

APO-12

Big CHAP

Big CHAP, Deoxy

BRIJ® 35, PROTEIN GRADE® Detergent, 30% Solution

BRIJ® 35, PROTEIN GRADE® Detergent, 10% Solution, Sterile-Filtered

C12E6

C12E8

C12E9

Cyclohexyl-n-ethyl-ß-D-maltoside, ULTROL® Grade

Cyclohexyl-n-hexyl-ß-D-maltoside, ULTROL® Grade

Cyclohexyl-n-methyl-ß-D-maltoside, ULTROL® Grade

n-Decanoylsucrose

n-Decyl-ß-D-maltopyranoside, ULTROL® Grade 252718

n-Decyl-ß-D-thiomaltoside, ULTROL® Grade

Digitonin, High Purity

Digitonin, Alcohol-Soluble, High Purity

n-Dodecanoylsucrose 324374

n-Dodecyl-ß-D-glucopyranoside 324355

ELUGENT™ Detergent, 50% Solution

GENAPOL® C-100, PROTEIN GRADE® Detergent, 10% Solution

GENAPOL® X-80, PROTEIN GRADE® Detergent, 10% Solution

GENAPOL® X-100, PROTEIN GRADE® Detergent, 10% Solution

n-Heptyl-ß-D-glucopyranoside

n-Heptyl-ß-D-thioglucopyranoside, ULTROL® Grade, 10% Solution

n-Hexyl-ß-D-glucopyranoside

MEGA-8, ULTROL® Grade

MEGA-9, ULTROL® Grade

MEGA-10, ULTROL® Grade

n-Nonyl-ß-D-glucopyranoside

NP-40, PROTEIN GRADE® Detergent, 10% Solution

n-Octanoyl-ß-D-glucosylamine (NOGA)

n-Octanoylsucrose

n-Octyl-ß-D-glucopyranoside

n-Octyl-ß-D-glucopyranoside, ULTROL® Grade

n-Octyl-ß-D-maltopyranoside

n-Octyl-ß-D-thioglycopyranoside, ULTROL® Grade

PLURONIC® F-127, PROTEIN GRADE® Detergent, 10% Solution

TRITON® X-100

TRITON® X-100, PROTEIN GRADE® Detergent, 10% Solution

TRITON® X-100, Molecular Biology Grade

TRITON® X-100, Hydrogenated

TRITON® X-100, Hydrogenated, PROTEIN GRADE® Detergent, 10% Solution

TRITON® X-114, PROTEIN GRADE® Detergent, 10% Solution

TWEEN® 20

TWEEN® 20, Molecular Biology Grade

TWEEN® 20, PROTEIN GRADE® Detergent, 10% Solution

TWEEN® 80, PROTEIN GRADE® Detergent, 10% Solution

n-Undecyl-ß-D-maltoside, ULTROL® Grade

Zwitterionic Detergents:

ASB-14

ASB-16

CHAPS

CHAPSO

DDMAB

DDMAU

EMPIGEN BB® Detergent, 30% Solution

Lauryldimethylamine Oxide (LDAO), 30% Solution

ZWITTERGENT® 3-08 Detergent

ZWITTERGENT® 3-10 Detergent

ZWITTERGENT® 3-12 Detergent

ZWITTERGENT® 3-14 Detergent

ZWITTERGENT® 3-16 Detergent

Of particular interest to Applicants are: Pluronic compounds such as F68 i.e. Polaxamer 188; Tween 80 i.e. Polysorbate 80; Triton X 100; Methyl-Butyl Ether known as MBTE; Ethylpropionate known as EP; Sorbitol Anydride Monostearate known as Span; Sorbitan compounds; taurodihydrofusidate, Caprylic and capric mono-diglyceride esters known as Captex; Capmul compounds i.e. mono and di-glyceride emulsifiers prepared through the glycerolysis of select fats and oils. They can be prepared by esterification of glycerin with specific fatty acids or fatty acid radicals; Caprol® polyglycerol esters compounds so called PGE's, which are generally prepared by esterification of select polyglycerol molecules with fatty acids or by alcoholysis of a vegetable oil with a polyglycerol; fatty acids or fatty acids radicals conjugated with biocompatible/biological solvents: for instance butyric, caproic, caprylic, lauric, myristic, palmitic, stearic, arachidic, behenic, oleic, linoleic, alpha-linolenic, arachidonic, eicosapentaenoic, docosahexaenoic acid , euric acid

ASB-16

CHAPS

CHAPSO

DDMAB

DDMAU

EMPIGEN BB® Detergent, 30% Solution

Lauryldimethylamine Oxide (LDAO), 30% Solution

ZWITTERGENT® 3-08 Detergent

ZWITTERGENT® 3-10 Detergent

ZWITTERGENT® 3-12 Detergent

ZWITTERGENT® 3-14 Detergent

ZWITTERGENT® 3-16 Detergent

Of particular interest to Applicants are: Pluronic compounds such as F68 i.e. Polaxamer 188; Tween 80 i.e. Polysorbate 80; Triton X 100; Methyl-Butyl Ether known as MBTE; Ethylpropionate known as EP; Sorbitol Anydride Monostearate known as Span; Sorbitan compounds; taurodihydrofusidate, Caprylic and capric mono-diglyceride esters known as Captex; Capmul compounds i.e. mono and di-glyceride emulsifiers prepared through the glycerolysis of select fats and oils. They can be prepared by esterification of glycerin with specific fatty acids or fatty acid radicals; Caprol® polyglycerol esters compounds so called PGE's, which are generally prepared by esterification of select polyglycerol molecules with fatty acids or by alcoholysis of a vegetable oil with a polyglycerol; fatty acids or fatty acids radicals conjugated with biocompatible/biological solvents: for instance butyric, caproic, caprylic, lauric, myristic, palmitic, stearic, arachidic, behenic, oleic, linoleic, alpha-linolenic, arachidonic, eicosapentaenoic, docosahexaenoic acid , euric acid

conjugated with a suitable biocompatible solvent having the properties of being bioavailable in the systemic circulation as opposed to being available in the enterohepatic circulation ; d-limonene, which can be considered as an organic solvent belonging to the terpenes. Organic solvents are indeed lipid solubilizers, but they are also generally toxic. Among a few other exceptions besides the ones cited above, are certain terpenes, which are usually extracted from essential oils of plants, such as the mentioned d-limonene, and certain terpenoids, also of plant origins, as for instance terpenoid constituents of Ginkgo biloba extract:

The dissolved main component, namely cholesterol aggregates targeted by the lipid solubilizer, will filter out thru the cap into the bloodstream in microscopic or ultramicroscopic particles or at molecular size.

Lattice structure 2 of stent 1 can be coated with any biliary acid or salt alone or in combination or any precursor or derivative of such bile acid or salt alone or in combination, such as Cholic acid or Chenodeoxycholic acid or Deoxycholic acid or Lithocholic acid or Hyodeoxycholic acid or Glycocholic acid or Taurocholic acid or a FABC such as Arachidyl amido cholanoic acid or any of the above disclosed pharmacological compound belonging to the class of biocompatible detergents/ emulsifiers/ surfactants/lipid and cholesterol solubilizers having the property of disaggregating, emulsifying, or dissolving cholesterol aggregates.

By providing the dissolution/solubilization of the fatty component of the plaque, i. e. by delipidizing the atherosclerotic plaque of its fatty component , the eluting drug above disclosed is expected to greatly reduce the chance of re-stenosis.

Applicants propose the use of other pharmacological compounds in association with the stent detergent/lipid solubilizer to enhance the anti-re-stenosis properties of the stent, namely:

Immunosuppressive agents such as Sirolimus, Tacrolimus, Eveolimus, Levoflunomide, M-Prednisolone, Dexamethasone, Abbot ABT-578, Cyclosporine, Mychophenolic acid, Mizoribine, Interferon, Tranilast;

Antiproliferative agents such as Taxol known as paclitaxel, Actinomycin, Methrotrexate angiopeptin, Vincristine, Mitomycin, Statins, CMYC Antisense, Abbot ABT-578 , Resten ASE, 2-chloro deoxyadenosine, PCNA Ribozyme;

Migration Inhibitors such as Batimistat, Prolyl Hydrossylase, Halofunginone, C-proteinase inhibitors, Probucol;

Enhaced Healing Factors such as BCP 671, VEGF, Estradiols, NO Donor Compounds, EPC antibodies;

Collagenase and other collagen degrading enzymes aimed at the lysis of the fibrotic component of the plaque including the plaque fibrous cap;

Proteoglycan-degrading enzymes/proteinases aimed at the degradation of the proteoglycan component of the plaque;

EDTA aimed at the dissolution of the calcium deposit within the plaque;

Heparin /Acetylsalicilic acid to prevent in situ thrombosis;

Lipase directed to the digestion of the fatty component of the plaque enhancing the action of the detergent.

What we claim is:

Claims

Claim1. A drug eluting stent system for delivery of a therapeutic agent in a blood vessel having walls and a body lumen at the site of an atherosclerotic plaque with lipid component, comprising:

an intravascular expandable workframe configured to contact the walls of the body lumen to maintain the patency of the vessel and

a lipid solubilizer aimed at the solubilization of the lipid component of the plaque.

Claim 2. The stent of claim 1 wherein the lipid solubilizer comprises a biliary compound.

Claim 3. The stent of claim 2 wherein the biliary compound of Claim 2 is deoxycholic acid.

Claim 4. The stent of claim 1 including a drug carrier for release over time of the lipid solubilizer of claim 1.

Claim 5. The stent of claim 4 wherein said drug carrier is a polymer.

Claim 6. The stent of claim 4 wherein said drug carrier is a phosphorylcholine.

Claim 7. The stent of claim 4 wherein said drug carrier is a ceramic.

Claim 8. The stent of claim 1 wherein the lipid solubilizer is associated with immunosuppressive agents.

Claim 9. The stent of claim 1 wherein the lipid solubilizer is associated with antineoplastic agents.

Claim 10. The stent of claim 1 wherein the lipid solubilizer is associated with migration inhibitors agents.

Claim 11. The stent of claim 1 wherein the lipid solubilizer is associated with enhanced healing factor agents.

Claim 12. The stent of claim 1 wherein the lipid solubilizer is associated with collagenase aimed at the lysis of the fibrotic component of the plaque including the plaque fibrous cap.

Claim 13. The stent of claim 1 wherein the lipid solubilizer is associated with a proteoglycan-degrading enzyme aimed at the degradation of the proteoglycan component of the plaque.

Claim 14. The stent of claim 1 wherein the lipid solubilizer is associated with EDTA aimed at the dissolution of the calcium deposit within the plaque.

Claim 15. The stent of claim 1 wherein the lipid solubilizer is associated with acetylsalicic acid aimed at prevent thrombosis in situ.

Claim 16. The stent of claim 1 wherein the lipid solubilizer is associated with heparin aimed at prevent thrombosis in situ.

Claim 17. The stent of claim 1 wherein the lipid solubilizer is associated with lipase directed to lysis of the fatty component of the plaque, enhancing the action of the lipid solubilizer

Claim 18. The stent of claim 1 wherein the lipid solubilizer is an ionic detergent.

Claim 19. The stent of claim 1 wherein the lipid solubilizer is a non-ionic detergent.

Claim 20. The stent of claim 1 wherein the lipid solubilizer is a zwitterionic detergent.

Claim 21. The stent of claim 1 wherein the drug eluting from the stent is a fatty acid bile conjugate compound.

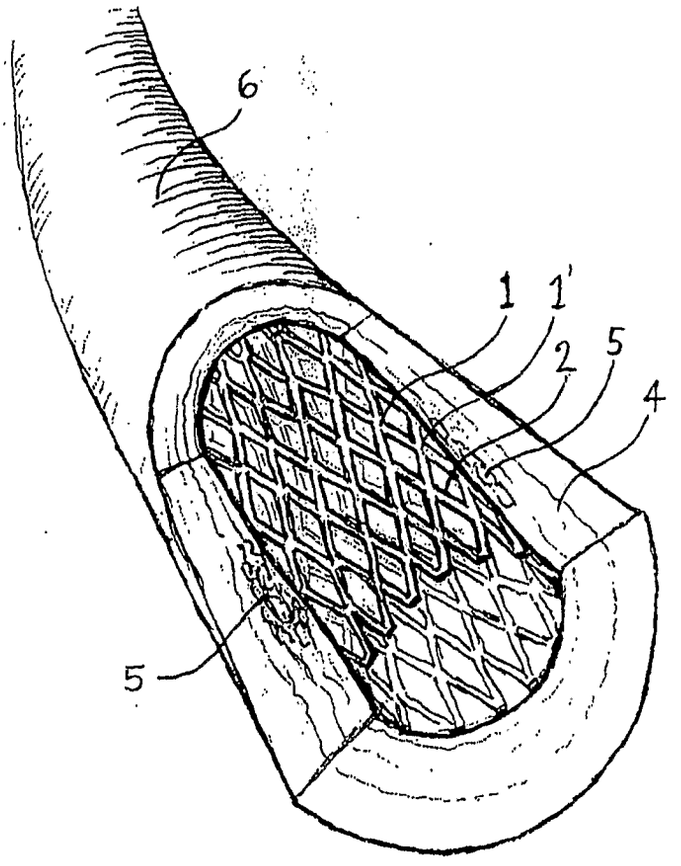
Claim 22. The stent of claim 1 wherein the drug eluting from the stent is a Methyl-Butyl
Ether compound .

Claim 23. The stent of claim 1 wherein the drug eluting from the stent is a Ethylpropionate compound.

Claim 24. The stent of claim 1 wherein the drug eluting from the stent is a terpene compound including a d-limonene.

Claim 25 . The stent of claim 1 wherein the drug eluting from the stent is a lipid solubilizer obtained by esterification of fatty acids or fatty acid radicals with a glycerol compound.

Claim 26 . The stent of claim 1 wherein the drug eluting from the stent is a lipid solubilizer obtained by conjugation of fatty acids or fatty acid radicals with a biocompatible lipid solubilizer, said lipid solubizer having the properties of being bio-available in a systemic circulation as opposed to being available in an enterohepatic circulation.



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