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(54) Title: LOCAL DRUG DELIVERY SYSTEM IN CORONARY STENTS

(57) Abstract: The invention provides an implantable medical device comprising a substrate and a biocompatible polymeric coating which covers at least a portion of the said substrate, and wherein the coating contains ajoene and/or allicin or isomers, analogues, homologues or derivatives thereof, a composition comprising biocompatible polymer/s and ajoene and/or allicin suitable for use in coating the implantable medical device.

LOCAL DRUG DELIVERY SYSTEM IN CORONARY STENTS

Technical field:

This invention relates to the field of cardiology and, more particularly, to a system for the localised delivery of a drug for use following coronary angioplasty or stenting. The invention provides a stent, or other implantable medical device, which has a coating that contains ajoene and/or allicin. Ajoene and allicin are derived from garlic and have been found to be effective in the prevention or inhibition of restenosis following angioplasty.

Background:

The field of interventional cardiology has seen radical changes and has metamorphosed into a specialized branch of medicine in recent years. Exciting innovations through research have created myriad arenas where improvements are possible in the existing knowledge about this field of medicine. Researchers have zeroed in on the interface between the blood components (namely, the platelets, the red blood cells and the leukocytes) and the vessel wall as the potential area for research, where a series of physico-chemical events are triggered by vascular injury and that restore the lost anatomy of the vasculature.

When interventional cardiologists deal with the coronary vessels in disease, they are faced with the unenviable task of handling stenosed blood vessels with small diametric lumina, narrowed further by atherosclerotic plaques and vasospasm, leading to near-total, or total blockage of the arteries. Cardiac intervention in such cases, in the form of coronary angioplasty or stenting, causes endothelial damage leading to thrombosis, inflammation, proliferation and remodelling of the vasculature.

In a small percentage of cases (about 3.7%), cardiac intervention is followed by exuberant thrombus formation, or, as a late complication (in about 22% of cases), neointimal hyperplasia (i.e. the overgrowth of the vascular lining endothelium), both of which cause restenosis. The problem of coronary restenosis has been a matter of concern to interventional cardiologists and a great deal of research is being conducted to prevent and/or treat this complication.

Several steps in the coagulation cascade as well as the cell cycle are being looked at where they can be blocked to control the process of restenosis. Such selective coagulation inhibitors or anticoagulants and antiproliferative drugs or agents have been isolated from biological sources, such as animals and plants, or have been synthesized in the laboratory in the past few years. Secondly, the latest advance in pharmacology, namely the local drug delivery technique, where drug molecules are packaged with polymers or are bonded to the surface of a device by using biologically derived materials, such as serum, and delivered at the desired site by using a "time-release technique" (i.e. to achieve sustained release of the drug in a controlled manner over a predetermined and prolonged period of time), is nvisaged as the ideal method to locally manage the restenosis problem.

Stents are tubular structures that are implanted within blood vessels and other passageways within the human or animal body for the purpose of treating disease conditions such as aneurysms, occlusions and stenosis. They function to physically support and, if necessary, expand the wall of the blood vessel or other passageway into which they have been implanted. Stents can have either solid or lattice-like walls and may be either self-expandable or expanded by means of inflating a balloon positioned within them.

Stents and other implantable medical devices are also commonly used to carry and deliver therapeutic substances, such as anticoagulants, antiplatelet agents and cytostatic agents. These therapeutic substances are often carried in a polymer coating on the stent and then released over a period of time once it has been implanted in the blood vessel or other passageway. US Patent Nos. 5994341, 5869127, 6168619, 6179817, 6203551, 6231600, 6254632, 6258121 and 6280411 describe stents and other implantable medical devices which may have a biocompatible polymeric coating that contains a therapeutic agent.

Garlic (Allium sativum) has been used in traditional medicine for thousands of years; for example, for the prevention of strokes, coronary thrombosis and atherosclerosis, as well as for the treatment of various infectious diseases and vascular disorders. Some components of garlic are known to have antibiotic properties, while others are potent inhibitors of platelet aggregation (one of the initial stages of blood clot formation or

thrombosis). US Patent No. 4917921 teaches the combination of a component of garlic called dithiin (a monomeric organosulphur compound that has antibiotic and antithrombogenic properties) with a biocompatible polymer, and the use of the resulting composition in a method for coating polymeric articles.

It is an object of the present invention to provide an improved means of preventing or inhibiting restenosis following a stent angioplasty. The invention resulted from the finding that ajoene and allicin, which are two components of garlic, have antithrombotic, antibiotic, antiinflammatory and antiproliferative properties and are effective (both individually and together) for preventing or inhibiting restenosis.

Description of the invention:

According to the present invention there is provided an implantable medical device, such as a stent, comprising a substrate and a biocompatible polymeric coating which covers at least a portion of the said substrate, and wherein the coating contains ajoene and/or allicin or isomers, analogues, homologues or derivatives thereof.

According to a further embodiment, the present invention provides a composition which comprises one or more biocompatible polymers and ajoene and/or allicin or isomers, analogues, homologues or derivatives thereof and which is suitable for use in coating an implantable medical device. The present invention still further provides a method of manufacturing an implantable medical device which includes the step of applying such a composition as a coating to the said device.

The coating of the stent or other implantable medical device typically contains a total of from 50 to 800 micrograms of the drug or active ingredient (i.e. of ajoene alone, allicin alone or ajoene and allicin in combination). The composition of the coating typically comprises from 60 to 80% by weight of the polymer (preferably 70%) and from 20 to 40% by weight of the drug (preferably 30%).

Thus, the invention also provides a method of manufacturing an implantable medical device which comprises applying to a substrate a coating of a composition. The composition may be prepared as a solution of ajoene and/or allicin with biodegradable and biocompatible polymers selected from lactone-based polyesters or copolyesters

such as polylactide, polycaprolactone-glycolide, polyorthoesters, polyanhydrides, poly-aminoacids, polysaccharides; polyphosphazenes; poly (ether-ester) copolymers, or blends thereof in a solovent selected from dichloromethane. Dimethyl formamide, dimethyl sulphoxide, hexafluoroisopropanol or acetone. The polymer may be non-absorbable and biocompatible.

The polymers are such as polydimethylsiloxane; poly (ethylene-vinylacetate); acrylate based polymers or copolymers, poly (hydroxyethyl methylmethacrylate, polyvinyl pyrrolidone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

The implantable medical devices of this invention include tubular scaffolding bodies, grafts, catheters and, in particular, endoluminal stents (including cardiovascular stents) designed for dealing with various intraluminal occlusions and contractions within the body. The substrate referred to above is thus typically a stent body and which may be made of, for example, metal or a polymer composition.

The biocompatible polymeric coating has a composition which permits the ajoene and/or allicin to be controllably released in a predetermined manner over a prolonged period of time. It will be appreciated that its precise composition will be chosen to produce the desired release profile. The polymeric coating may be either biodegradable or non-biodegradable. It may consist of either a single biocompatible polymer or a combination of two or more such materials. Typically, the coating comprises polyactides, polyglycolides, polycaprolactone, polydioxanone, polygluconate, polyanhydrides, polyphosphoesters, polyethyleneterpthalate, polyhydroxylbutyrate, polyphosphazene, polyorthoesters or polyphosphate esters, or mixtures or copolymers thereof.

The ajoene and/or allicin is disposed, dispersed, dissolved, embedded, micro-encapsulated or otherwise incorporated in the coating or a part of the coating. Furthermore, the coating may comprise two or more layers and which each contain one or both of these components. It will be appreciated that its precise composition will be chosen to produce the desired release profile.

The ideal agent(s) for the management of coronary restenosis would have the following properties:

1) antithrombotic and antiplatelet activity, to control the amount of thrombus formation and also to control the process of intimal regeneration, which will prevent restenosis;

2) antilipemic and antiatherosclerotic activity, which act to maintain the potency of the vascular lumen in hyperlipidemic patients and also to improve blood flow by reducing plasma viscosity (blood-thinning property);

3) antiinflammatory activity, to control the inflammation;

4) antiproliferative activity, to control neointimal hyperplasia;

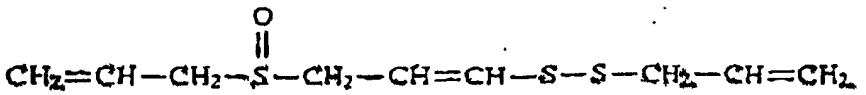
4) antiseptic activity, which may be useful in taking care of any infection introduced during the invasive procedure of angioplasty or coronary stenting; and

5) safe for use with minimal side effects (local as well as systemic).

It has been found that these multiple beneficial properties are possessed by botanical extracts from the root bulb of the much-studied and commonly used Allium sativum (garlic) called ajoene and allicin.

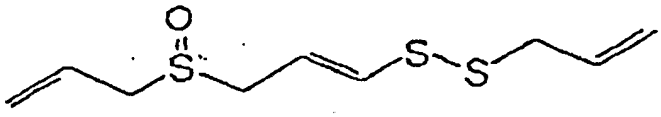
Ajoene (from "ajo", Spanish for garlic) is a sulphur-containing natural product derived from the ubiquitous and perennial bulbous herb, Allium sativum. Garlic contains 33 sulphur compounds, the chief one being allicin (diallyl thiosulphonate) which is formed only when garlic is cut or macerated or heated. This is the compound responsible for the offensive odour of garlic. Ajoene is formed by the combination of three molecules of allicin.

Ajoene is (E,Z) 4, 5, 9 – trithiadodeca -1, 6, 11 -triene-9-oxide) and has the following structural formula:-



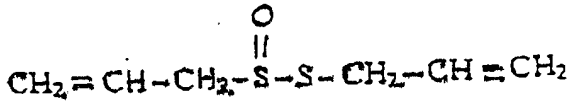
Which can be represented as:-

Z-ajoene



E-ajoene

Allicin is S-allyl-2-propenethiosulphinate and has the following structural formula:-



Ajoene and a precursor thereof can be isolated from extracts of garlic. As the garlic is crushed, allicin in the garlic comes into contact with allinase in the cell wall to form allicin. In the presence of a polar molecule (such as a lower alcohol) or even water, allicin forms ajoene.

Pharmacological actions:

A) Antithrombotic, antiinflammatory and antiplatelet activity: This effect is achieved by interfering with cyclo-oxygenase mediated thromboxane synthesis (a potential stimulant) non-competitively and irreversibly. It inhibits prostaglandin synthetase and lipoxygenase, decreasing thromboxane synthesis and inflammatory cytokines. It also reversibly inhibits platelet aggregation. Ajoene synergistically potentiates the anti-aggregatory action of prostacyclin, indomethacin and dipyridamole. It causes fibrinolysis by inhibiting thromboxane synthesis. These effects lead to reduced thrombus formation and inflammation in the damaged vasculature.

B) Antilipemic and antiatherosclerotic activity: In-vitro animal studies and in-vivo human studies have proved that ajoene is capable of reducing blood cholesterol by up to 10% and favourably altering the HDL/LDL ratios (by increasing the HDL levels and reducing LDL levels). Significant reduction in triglycerides has also been noted

following garlic administration. It also exhibits antiatherosclerotic activity by reducing lipid content of existing plaques and by significantly inhibiting the proliferative activity of smooth muscle cells from atherosclerotic plaques. These effects lead to significant improvement in plasma viscosity and capillary blood flow as evidenced by reduction in pulse wave velocity and elastic vascular resistance (two measures of arterial elasticity). Blood pressure also fell by up to 7% due to these effects.

C) Antiseptic activity: Ajoene has been proved to possess antibacterial activity against gram-positive bacteria (such as Bacillus cereus, Bacillus subtilis, Mycobacterium smegmatis, Streptomyces griseus, Straphylococcus aureus and Lactobacillus plantarum) and gram-negative bacteria (like Escherichia coli, Klebsiella pneumoniae and Xanthmonas maltophilia); ajoene also inhibited yeast growth.

D) Safety of use: Garlic is an abundantly used herb across the globe for culinary as well as medicinal purposes. Garlic and its derivatives are on the Food and Drug Administration's Generally Recognised as Safe (GRAS) list, but it is known to cause gastric irritation if taken in high doses. This effect is not expected to occur when it is administered locally at the site of endothelial injury. Chronic toxicity with garlic and its extracts is unknown. In fact it appears to protect against agents with known genotoxicity, embryotoxicity and carcinogenicity.

Acute and chronic complications following coronary stenting can be reduced by using the safe and multipotential garlic extract, ajoene, which has been proved by in-vitro and in-vivo studies to possess all the beneficial qualities required for countering the processes of thrombus formation, hyperlipemia, atherosclerosis, inflammation, proliferation and sepsis. A coronary stent can be loaded with a drug-polymer complex of a combination of a polymer and ajoene and/or allicin and their derivatives to provide for "time-release". The polymer acts as a vehicle to hold the drug and present it to the site of injury whenever required and as programmed for time-release. The released drug is then able to act locally and counter the acute and chronic complications of coronary stenting which lead to restenosis.

The present invention will now be illustrated by the following Examples (all parts are by weight unless otherwise indicated). Example 1 describes the preparation of a stent with a coating containing ajoene. A coating containing allicin or both ajoene and

allicin would be prepared in a corresponding manner. Example 2 demonstrates the time-release properties of the drug from the coating of a stent according to the present invention.

EXAMPLE 1

Pre-Treatment: Received bare stents are given an ultrasonic isopropanol washing treatment for about 30 minutes to 1 hour for better adhesion of the coating material. After that the stents are washed with sterile water and then dried with a hot air drier.

Spray coating process: A solution of ajoene (the drug) is prepared in a solvent such as dichloromethane, dimethyl formamide, dimethyl sulfoxide, hexafluoroisopropanol or acetone and biodegradable and biocompatible polymers, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolactone-glycolide, polyorthoesters, polyanhydrides; poly-aminoacids; polysaccharides; polyphosphazenes; poly (ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Non-absorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiloxane; poly (ethylene-vinylacetate); acrylate based polymers or copolymers, e.g., poly (hydroxyethyl methylmethacrylate, polyvinyl pyrrolidone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters could also be used . The base coat is from 40% to 45% of the drug; about 250 micrograms of the coating. The second coat can be from 25% to 30% of the drug; about 210 micrograms of the coating. The third coat contains 30% to 35% of the drug; about 240 micrograms of coating in its layer, using a broad band ultrasonic generator attached to a nozzle and medical grade nitrogen gas as the carrier. The power at which the system is operated is 5.0 m Watts. The flow rate is adjusted to about 0.3 ml/min. The spray system is placed in a vacuum amber coloured glass box to eliminate air current and to slow down the evaporation. The stents are positioned (horizontally) 1.5 to 5.0 cm distance from the nozzle and have a dwell time in the spray cloud of about 50 to 60 seconds. The interval is of 10 to 20 seconds and the stent motion is both clockwise and anticlockwise. The room temperature is maintained at 20°C to 23°C. The stent is then dried in ambient conditions for 12 to 16 hours at 38°C. Then the drug-coated stent is stored in a sealed container.

EXAMPLE 2

Drug Release Studies:

Preparation of pH 7.5 phosphate buffer saline (IP) : According to IP procedure. In 15 ml glass, screw-capped tubes are placed 10 ml of 10 mM phosphate buffered saline (PBS), pH 7.4 and 200 micrograms of drug-loaded stent. The tubes are tumbled at 37°C and at given time intervals, centrifuged at 1500 x g for 5 mintues and the supernatant saved for analysis. Drug-loaded stents are resuspended in fresh PBS (10ml) at 37°C and reincubated. Drug concentrations are determined by extraction into 2 ml DCM followed by evaporation to dryness under a stream of medical grade nitrogen gas, reconstitution in 1 ml of acetonitrile in water and analysis using the HPLC method. 30% of the drug is released initially in 2 to 3 days, 27.5% of the drug is released within the next 7 to 10 days and the remaining 42.5% should be released in the next 35 to 40 days.

CLAIMS

1.An implantable medical device comprising a substrate and a biocompatible polymeric coating which covers at least a portion of the said substrate, and wherein the coating contains ajoene and/or allicin or isomers, analogues, homologues or derivatives thereof.

2.A device as claimed in claim 1, wherein the substrate is a stent body.

3.A device as claimed in claim 1 or claim 2, wherein the composition of the polymeric coating permits the ajoene and/or allicin to be controllably released in a localised and predetermined manner over a prolonged period of time.

4.A device as claimed in any one of the preceding claims, wherein the coating comprises polylactides, polyglycolides, polycaprolactone, polydioxanone, polygluconate, polyanhydrides, polyphosphoesters, polyethyleneterpthalate, polyhydroxylbutyrate, polyphosphazene, polyorthoesters or polyphosphate esters, or mixtures or copolymers thereof.

5.A device as claimed in any one of the preceding claims, wherein the ajoene and/or allicin is disposed, dispersed, dissolved, embedded, microencapsulated or otherwise incorporated in the coating or a part of the coating.

6.A device as claimed in any one of the preceding claims, wherein the coating comprises two or more layers and each of which contain ajoene and/or allicin.

7. A composition comprising biocompatible polymer/s and ajoene and/or allicin or isomers, analogues, homologues or derivatives thereof and which is suitable for use in coating an implantable medical device.

8. A composition as claimed in claim 7 wherein the amount of biocompatible polymer/s is 55-80% and the amount of ajoene and/or allicin, its isomers, analogues, homologues or derivatives is 20 to 45%.

9. A method of manufacturing an implantable medical device which comprises applying to a substrate a coating of a composition as claimed in claim 7.

10. A method as claimed in claim 9 wherein the composition is prepared as a solution of ajoene and/or allicin with biodegradable and biocompatible polymers selected from lactone-based polyesters or copolyesters such as polyactide, polycaprolactone-glycolide, polyorthoesters, polyanhydrides, poly-aminoacids, polysaccharides; polyphosphazenes; poly (ester-ester) copolymers, or blends thereof in a solvent selected from dichloromethane, dimethyl formamide, dimethyl sulphoxide, hexafluoroisopropanol or acetone.

11. A method as claimed in claim 9 wherein the polymer is non-absorbable.

12. A method as claimed in claim 9 wherein the polymers are such as polydimethylsiloxane; poly (ethylene-vinylacetate); acrylate based polymers or copolymers, poly (hydroxyethyl methylmethacrylate, polyvinyl pyrrolidone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

INTERNATIONAL SEARCH REPORT

Interi ıal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L31/16 A61L31/10 A61L29/16 A61L29/08 A61L27/54
A61L27/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 99 21008 A (FRIEDMAN ELLIOT P ;PHARMAPRINT INC (US); KHWAJA TASNEEM A (US); UN) 29 April 1999 (1999-04-29) claims	1-12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
29 November 2002	12/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	ESPINOSA, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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