

COMMONWEALTH OF AUSTRALIA

635843

Patents Act 1952

CONVENTION APPLICATION FOR A STANDARD PATENT

We, BECTON, DICKINSON AND COMPANY

One Becton Drive, Franklin Lakes, New Jersey 07417-1880, United States of America, hereby apply for the grant of a Standard Patent for an invention entitled

"METHOD FOR RENDERING A SUBSTRATE SURFACE
ANTITHROMBOGENIC AND/OR ANTI-INFECTIVE"

which is described in the accompanying complete specification.

Details of basic application:-

Number of basic application:- 07/563,653

Name of Convention country in which basic application was
filed:- United States of America

Date of basic application:- 6 August 1990

Our address for service is:

F.B. RICE & CO.,
28A Montague St,
Balmain N.S.W. 2041

8022043 27/05/91

Dated this 27 day of May 1991

BECTON, DICKINSON AND COMPANY

By: 

Registered Patent Attorney

TO: The Commissioner of Patents,
COMMONWEALTH OF AUSTRALIA

P1233 25

Commonwealth of Australia
The Patents Act 1952
DECLARATION IN SUPPORT

In support of the (Convention) Application made by: BECTON, DICKINSON AND COMPANY
One Becton Drive, Franklin Lakes, New Jersey 07417-1880, United
States of America.

for a patent for an invention entitled: " METHOD FOR RENDERING A SUBSTRATE SURFACE
ANTITHROMBOGENIC AND/OR ANTI-INFECTIVE "

I ~~(We)~~ Raymond P. Ohlmuller

of and care of the applicant company do solemnly and sincerely declare as follows:

a) I am ~~(We are)~~ the applicant(s) for the patent
or

b) I am ~~(We are)~~ authorised by the applicant(s) for the patent to make this declaration on its behalf.

Delete the following if not a Convention Application.

The basic application(s) as defined by section 141 ~~(142)~~ of the Act was ~~(were)~~ made

on 6 AUGUST 1990 in United States of America

~~on~~

~~in~~

~~on~~

~~in~~

by Fidelis C. Onwumere, Donald D. Solomon, Stanley C. Wells.

The basic application(s) referred to in this paragraph is ~~(are)~~ the first application(s) made in
a Convention country in respect of the invention the subject of the application.

a) I am ~~(We are)~~ the actual inventor(s) of the invention.

~~of~~ Fidelis C. Onwumere, 2211 Woodedge Court, Miamisburg, Ohio 45342 USA

b) Donald D. Solomon, 9660 Quailwood Trail, Spring Valley, Ohio 45370
USA, and Stanley C. Wells, 185 Poinciana Drive, Dayton, Ohio 45459
USA.

~~is (are)~~ the actual inventor(s) of the invention and the facts upon which

the applicant

is ~~(are)~~ entitled to make the application are as follows:

The applicant is the assignee of the invention from the said actual
inventors.

Franklin Lakes,
New Jersey, USA
Declared at this 16th day of May, 1991

Signed



Status

BECTON, DICKINSON AND COMPANY
Vice President and Secretary

Declarant's Name Raymond P. Ohlmuller

F. B. RICE & CO PATENT ATTORNEYS

This form is suitable for any type of Patent Application. No legalisation required.



AU9177339

(12) PATENT ABRIDGMENT (11) Document No. AU-B-77339/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 635843

- (54) Title
METHOD FOR RENDERING A SUBSTRATE SURFACE ANTITHROMBOGENIC AND/OR ANTI-INFECTIVE
- International Patent Classification(s)
(51)⁵ **A61L 033/00 A61L 027/00**
- (21) Application No. : **77339/91** (22) Application Date : **27.05.91**
- (30) Priority Data
- (31) Number (32) Date (33) Country
563653 06.08.90 US UNITED STATES OF AMERICA
- (43) Publication Date : **13.02.92**
- (44) Publication Date of Accepted Application : **01.04.93**
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- (56) Prior Art Documents
US 4822615
US 4678660
- (57) Claim

1. A method for applying a temperature sensitive bioactive agent to the surface of a shaped polymeric substrate comprising:

(a) combining a matrix polymer having a melting point of about 100°C or lower with a bioactive agent having a thermal decomposition point above said melting point;

(b) melt compounding said polymer and agent within the temperature range between said melting point and said decomposition point to give a homogeneous composition; and

(c) extrusion coating said composition onto the surface of a shaped polymeric substrate at a temperature within said range.

10. A method for applying a temperature sensitive bioactive agent to the surface of a shaped polymeric substrate comprising:

a) combining a matrix polymer having a melting point of about 100°C or lower with a bioactive

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agent selected from the group consisting of heparin, chlorhexidine, a salt of chlorhexidine, benzalkonium chloride and methyl paraben;

b) melt compounding said polymer and agent within the temperature range between said melting point and the decomposition point of said agent to give a homogeneous composition; and

c) extrusion coating said composition onto the surface of a shaped polymeric substrate at a temperature within said range.

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AUSTRALIA

Patents Act 1990

BECTON, DICKINSON AND COMPANY

ORIGINAL

**COMPLETE SPECIFICATION
STANDARD PATENT**

Invention Title:

**"Method for Rendering a
Substrate Surface Antithrombogenic
and/or Anti-Infective"**

The following statement is a full description of this invention including the best method of performing it known to us:-



1. Field of the Invention. This invention relates to biomedical devices, and more specifically relates to a method for coating a substrate with an antithrombogenic and/or an anti-infective agent.

5 2. Background of the Invention. Extensive investigations have been undertaken over many years to find materials that will be biologically and chemically stable toward body fluids. This area of research has become increasingly important with the development of
10 various objects and articles which must be in contact with blood, such as artificial organs, vascular grafts, probes, cannulas, catheters and the like.

15 Synthetic plastics have come the fore as preferred materials for such articles. However, these materials have the major drawback of being thrombogenic. In addition, devices such as catheters provide a pathway for entrance of microorganisms into the body and thus often are a source of infection. Accordingly, much effort has been directed toward
20 methods to render plastic medical devices antithrombogenic and anti-infective.

25 Thrombogenicity has conventionally been counteracted by the use of anticoagulants such as heparin. Various procedures for attachment of heparin to otherwise thrombogenic polymeric surfaces have been disclosed. U.S. Patent Number 4,521,564 to Solomon et



al. discloses coating a polymeric article with an amine-rich surface and covalently conjugating aldehyde-actuated heparin to the amino groups thereof. Leininger et al., in U.S. Patent Number 3,617,344
5 discloses a method in which a polymeric surface is chemically modified to include a chloromethyl group. Amination of the chloromethyl group provides a quarternary ammonium halide. Reaction of the halide with sodium heparin results in ionic bonding of the
10 heparin to the surface.

A related approach has been described by Eriksson et al. in U.S. Patent Number 3,634,123. An article having a plastic surface is heated to near or above its softening point in an aqueous solution of a cationic
15 surface active agent, such as a long chain alkylamine or alkylenediamine hydrohalide. The solution is preacidified to a pH of 7.0 or lower. Subsequent digestion of the plastic article with an aqueous solution of heparin results in an article having about
20 0.12 International Unit of heparin thereon. Improvements in the surface active agent method are described in U.S. Patent No. 3,810,781 to Eriksson et al.; U.S. Patent No. 4,349,467 to Williams et al.; U.S. Patent No. 4,865,870 to Hu et al. and U.S. Patent No.
25 4,713,402 to Solomon et al.

Attempts to solve the problem of infection have likewise been directed toward adherence of an antibacterial agent to the plastic article. Shepard et al., in U.S. Patent No. 3,695,921, discloses dipping a
30 catheter into a syrup containing a hydrophilic polymer and absorbing an antibiotic into the hydrophilic



coating. Shepard et al. teach that most antibiotics are not sufficiently heat stable to be added to the syrup during the dipping step.

5 Fox et al. in U.S. Patent No. 4,581,028, teaches infection resistant plastic medical articles, such as vascular grafts, having incorporated antimicrobial agents, such as silver sulfadiazine and piperacillin. The articles are prepared by dipping procedures.

10 Mustacich et al., in U.S. Patent No. 4,479,795, discloses medical devices of permeable polymers including a releasably incorporated coating of a carboxylate antimicrobial agent. The device is made by a dipping process.

15 PCT published application no. WO 86/02561 teaches a medical device of a hydrophobic thermoplastic polymer having up to 1% chlorhexidine base coated thereon or incorporated therein.

20 McGary et al, in U.S. Patent No. 4,678,660 discloses a method for preparing a polyurethane article having coated thereon a layer of polyurethane alloy containing a dispersed complex of a quaternary salt with either an antithrombogenic agent or an antibiotic. The method includes dipping the article in a solvent solution of the alloy.

25 Although all of the above disclosures have addressed the problems of infection and thrombogenesis during use of medical articles, satisfactory solutions have not yet been disclosed, particularly for medical



articles, such as a catheter, to be introduced and advanced through body passages. In particular, there is a need for a method for preparation of medical articles coated with temperature sensitive materials which avoids dipping procedures using potentially toxic solvents. The present invention fulfills this need.

SUMMARY OF THE INVENTION

A method for applying a bioactive agent to the surface of a polymeric substrate includes preparing a composition having a bioactive agent uniformly dispersed in a melt of a matrix polymer and extrusion coating the composition onto the polymeric substrate. The uniform dispersion of the bioactive agent may be a solution or a suspension. In a preferred method, the composition is prepared by melt compounding the matrix polymer and bioactive agent.

The extrusion coating may be carried out within a processing temperature range defined herein as the temperature range between the melting point of the matrix polymer and the thermal decomposition point of the bioactive agent. The melting point of the matrix polymer is defined as the temperature at which the polymer becomes sufficiently fluid for extrusion.

Preferred matrix polymers have a melting point of about 120, most preferably about 100°C or less and preferred bioactive agents are temperature sensitive, anti-infective and antithrombogenic agents which undergo thermal decomposition at a temperature above the melting point of the matrix polymer.



Prior to the present invention, the only method known for coating medical devices with temperature sensitive bioactive agents was by solvent coating. Solvent coating has many drawbacks which are eliminated by the extrusion coating of the invention. Solvent coating is a multi-step process which adds time and expense to a production line. Since most bioactive agents are not water soluble, expensive, high boiling organic solvents, such as dimethylacetamide must be used. The high boiling points of these solvents cause difficulty in removal. High vacuum is usually required, and this often leads to pitting of an article surface because of bubble formation. Such surfaces are rough and may lead to patient discomfort. Further, these solvents are generally toxic and complete removal is thus mandatory for medical articles intended for contact with a patient's tissue or body fluid.

In general terms, the method of the invention is an economical and efficient means of modifying surfaces to improve oxidation resistance, moisture resistance, gas impermeability, bacterial or fungal resistance, UV resistance and other forms of "host" plastic breakdown. For example, food or tissue contact plastics do not have good barrier properties against fungi and bacteria. However, extrusion coating with a polymer containing a suitable bioactive agent in accordance with the invention produces excellent fungal/bacterial barrier properties.

The extrusion coating method of the invention is of particular value in the coating of medical articles. With the method of the invention, the



article may be extrusion fabricated of any high melting base polymer to provide desired mechanical properties, then extrusion coated with a bioactive agent at low temperature to modify the surface. Conventional
5 extrusion of base polymer compounded with the bioactive agent cannot be carried out if the bioactive agent is temperature sensitive. Conversely, conventional coextrusion of base polymer with a low melting matrix polymer cannot be performed when there is a wide
10 difference in processing temperatures between the base polymer and the matrix polymer. The method of the invention makes it possible to thermally coat the shaped base polymer without changing its configuration.

DETAILED DESCRIPTION

15 While this invention is satisfied by embodiments in many different forms, there will herein be described in detail preferred embodiments of the invention, with the understanding that the present disclosure is to be considered as exemplary of the principles of the
20 invention and is not intended to limit the invention to the embodiments illustrated and described. The scope of the invention will be measured by the appended claims and their equivalents.

Coating of substrates with polymers is a
25 conventional process in many industries. One common coating process applies a monomer to a substrate surface and polymerizes it in situ by exposure to a glow discharge, an electron beam, ultraviolet radiation or other procedure. In extrusion coating, on the other
30 hand, a layer of polymer is applied directly to the



substrate surface. In this process, a molten, homogeneous thermoplastic material is metered through a die directly onto a solid continuous shaped substrate surface such as paper, paperboard, film, foil, fabric or wire. General and specific descriptions of equipment and processing conditions for extrusion coating may be found in Petrothene® Polyolefins - A Processing Guide, Fifth Edition, 1986, page 73 et seq. published by USI Chemicals, Division of National Distillers and Chemical Corp. A discussion of dies and equipment suitable for extrusion coating of wires wherein a melt flows around a hollow mandril through which a wire is passed is given by Michaeli in Extrusion Dies, Page 210 et seq., Hanser Publishers, New York, New York (1984).

In accordance with the present invention, a shaped polymeric article is extrusion coated with a bioactive agent compounded in a thermoplastic matrix polymer. While the invention contemplates extrusion coating of any polymeric article, preferred substrates are shaped polymeric medical articles, most preferably articles intended for contact with a patient's tissue or body fluid. Representative non-limiting substrates are a tubing such as a catheter, a solid rod such as an obturator, and a sheet or porous membrane such as a graft or wound dressing.

The shaped medical article to be extrusion coated may be any thermoplastic or thermoset polymeric substrate. It may be fully cross-linked, slightly cross-linked or have no cross-linking. Preferred polymeric substrates have a melting point above the



processing temperature of the matrix polymer.

5 The polymeric substrate serves as a support material for the matrix polymer and provides the article with whatever mechanical properties are desired, such as tensile strength, thermoplasticity and flexibility. The invention contemplates use of any polymeric or copolymeric substrate material which provides these attributes. The particular choice of substrate polymer and the shape thereof does not
10 constitute a critical aspect of the invention. Suitable substrate polymers are polyacrylate, polystyrene, polyethylene, polypropylene, polytetrafluoroethylene, polyester, polyamide, and polyvinyl such as polyvinyl chloride and polyvinyl acetate. Preferred substrate polymers are
15 thermoplastic polyurethanes, most preferably polyurethaneureas.

20 The choice of matrix polymer depends on the thermal stability of the desired bioactive agent. If the bioactive agent is thermally stable so that no substantial thermal degradation occurs during the extrusion coating, any thermoplastic matrix polymer may be used and the extrusion coating may be carried out at any suitable processing temperature.

25 A preferred application of the method of the invention is extrusion coating of temperature sensitive bioactive agents. For such agents, the matrix polymer preferably has a processing temperature below the decomposition temperature of the bioactive agent. The
30 most preferred matrix polymers have a processing



temperature of about 100°C or less. The following list is merely representative and not limitative of matrix polymers which are suitable for extrusion coating of temperature sensitive agents. The melting points are given in parentheses.

5

	ethylene acrylic acid	
	(15%, 20%) copolymer	(90°C)
	polycaprolactone	(60°C)
	polyethylene adipate	(55°C)
10	polybutylene adipate	(54°C)
	polyethylene azelate	(55°C)
	polyethylene methacrylic acid ionomer	(83°C)

15 It is evident that any anti-infective agent as known in the art, such as antibacterials, anti-microbials and germicides may be extrusion coated onto the shaped medical article if it is stable at the processing temperature of the matrix polymer. Thus the invention contemplates extrusion coating of thermally

20 stable anti-infectives such as chlorhexidine and silver sulfadiazine. However, the method of the invention is particularly directed to anti-infectives which are temperature sensitive, most particularly those which undergo thermal decomposition during extrusion.

25 Representative temperature sensitive anti-infectives which have heretofore been applied to a substrate surface only by solvent-based coating techniques but which may be extrusion coated in accordance with the present invention are methyl, propyl and butyl paraben, benzalkonium chloride, octenidine, alexidine, phenolic

30 agents, triphenyl bismuthine, nitrophenyl acetate,



silver, cetyl pyridinium chloride, bis pyridinamines and alkyl bis biguanides.

5 In the same way, the invention contemplates extrusion coating of any antithrombogenic agent as known in the art. The term antithrombogenic agent or material as used herein refers to any material which inhibits thrombus formation on its surface, such as by reducing platelet adhesion and/or aggregation, dissolving fibrin, enhancing passivating protein
10 deposition, or inhibiting one or more steps within the coagulation cascade. Illustrative antithrombogenic materials may be selected from the group consisting of heparin, prostaglandins, sulfated polysaccharide, urokinase, dicumerol, warfarin, streptokinase, albumin
15 and mixtures thereof. It should be understood that these materials are used in their natural form or as salts thereof, such as the sodium, or lithium salt or as chemically modified moieties. The preferred antithrombogenic agent is heparin which is temperature sensitive and heretofore has been coated onto medical
20 devices only from solution.

25 In another embodiment of the method of the invention, extrusion coating of a quaternary ammonium salt may be carried out. Any salt, such as those disclosed in U.S. Patent No. 4,865,870 to Hu et al. for solvent coating onto a polymeric substrate may be used. Preferred salts are thermally stable at the processing temperature of the matrix polymer. Such salts are well-known to have some inherent antimicrobial activity. Preferably, they may be
30 extrusion coated onto the shaped article to serve as a



binder for antithrombogenic agents and anti-infective agents having a functional group which forms a complex with the salt.

5 Preferred antithrombogenic agents for this embodiment of the invention are sulfonated polysaccharides, such as dextran sulfate, or preferably a salt of heparin, such as sodium heparin. Preferred anti-infective agents for this embodiment of the invention are antibiotics bearing a functional group
10 reactive with the quaternary salt, such as a carboxyl functionality. Exemplary materials may be selected from the group consisting of penicillin, oxacillin, ticarcillin, carbenicillin, cephalosporins, cefoxitin, cefazolin, dicloxacillin, cloxacillin and clavulanic
15 acid, and mixtures thereof.

20 Reaction of the quaternary salt extrusion coated onto the substrate and the antithrombogenic or anti-infective agent may be carried out by steeping the article in an aqueous solution of the agent, as described in the aforementioned U.S. Patent No. 4,865,870.

25 In preparation for extrusion coating, the bioactive agent of the invention may be compounded with the matrix polymer. Any compounding procedure as known in the art which does not cause degradation of the agent may be used. For example, if the agent is soluble, it may merely be dissolved in the matrix polymer melt. If it is not soluble, it may be
30 dispersed in the melt as a suspension of finely divided particles.



In a preferred compounding technique, an intimate mixture of the bioactive agent and matrix polymer pellets is prepared by conventional procedures such as dusting or tumbling. The mixture may then be introduced into a compounding extruder from which it emerges as a homogenous melt directly into the coating extruder where it contacts the substrate.

Any desired ratio of bioactive agent and matrix polymer may be used. Preferably, the bioactive agent is combined with the matrix polymer in a weight percent ratio of about 1:5 to 1:100. Most preferably, a ratio of about 1:10 to 1:20 is used.

As is well known by those skilled in the art, the extrusion coating conditions may be adjusted to give a coating of any desired thickness. Preferred coatings are about 0.1 to 5.0 mils thick, most preferably about 1 to 2 mils.

EXAMPLE

General Procedure for Extrusion Coating

Pellets of the matrix polymer and finely powdered bioactive agent are tumbled together for about 10 minutes to give an even coating of the powder on the pellets. The coated pellets are charged into the hopper of a C.W. Brabender extruder with a mixing head and melt compounded. The melt is forced into a Killon extruder where it contacts and coats a polymeric article.



The following chart includes polyurethane tubes extrusion coated by the method of the invention and is provided merely by way of non-limiting examples.

	Matrix Polymer	Bioactive Agent (wt. %)	Extrusion Temp (°C)	Coating Thickness (Mil)
5				
	1. polycaprolactone	heparin (5)	75	2.0
	2. polycaprolactone	warfarin (5)	115	1.5
	3. polycaprolactone	dicumerol (6)	120	1.5
	4. polycaprolactone	chlorhexidine diacetate (6)	120	1.5
10	5. ethylene acrylic acid (300 melt index)	chlorhexidine (6)	115	2.0
	6. polycaprolactone	benzalkonium chloride (6)	120	2.1
	7. ethylene acrylic acid (300 melt index)	benzalkonium chloride (6)	120	2.1
20	8. polycaprolactone	methylparaben (6)	120	1.5

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method for applying a temperature sensitive bioactive agent to the surface of a shaped
5 polymeric substrate comprising:
- (a) combining a matrix polymer having a melting point of about 100°C or lower with a bioactive agent having a thermal decomposition point above said melting point;
- 10 (b) melt compounding said polymer and agent within the temperature range between said melting point and said decomposition point to give a homogeneous composition; and
- (c) extrusion coating said composition onto
15 the surface of a shaped polymeric substrate at a temperature within said range.
2. The method of Claim 1 wherein said substrate is a rod.
- 20 3. The method of Claim 1 wherein said substrate is a tubing.
4. The method of Claim 1 wherein said
25 polymeric substrate is selected from the group of polymers consisting of polyacrylate, polystyrene, polyethylene, polypropylene, polytetrafluoroethylene, polyester, polyamide, polyvinyl compounds and polyurethane.
- 30 5. The method of Claim 1 wherein said matrix polymer is selected from the group consisting of ethylene acrylic acid copolymer, polycaprolactone, polyethylene adipate, polybutylene adipate,



polyethylene azelaate and polyethylene methacrylic acid ionomer.

5 6. The method of Claim 1 wherein said agent is selected from the group consisting of an anti-infective agent and an antithrombogenic agent.

7. The method of Claim 1 wherein said melt compounding step is performed by extrusion compounding
10 particles of said matrix polymer and particles of said agent at a temperature of 100°C or less.

8. A method for applying an agent to the surface of a polymeric article comprising:
15 a) preparing a homogeneous composition comprising a melt of a matrix polymer and a material selected from the group consisting of a bioactive agent and a binder for a bioactive agent,
b) extrusion coating said composition onto a
20 surface of a polymeric article at a temperature at which said material does not undergo any substantial thermal decomposition.

9. The method of Claim 8 wherein said binder
25 is a quaternary ammonium salt and said method further comprises reacting said salt with an aqueous solution containing a bioactive agent which forms a complex with said salt.

10. A method for applying a temperature sensitive bioactive agent to the surface of a shaped polymeric substrate comprising:

a) combining a matrix polymer having a melting point of about 100°C or lower with a bioactive



agent selected from the group consisting of heparin, chlorhexidine, a salt of chlorhexidine, benzalkonium chloride and methyl paraben;

5 b) melt compounding said polymer and agent within the temperature range between said melting point and the decomposition point of said agent to give a homogeneous composition; and

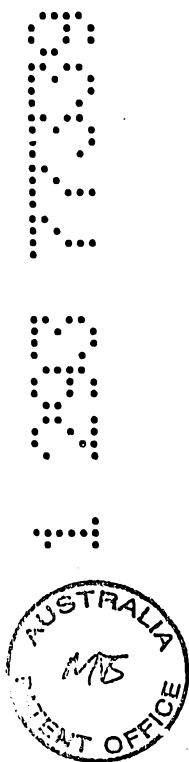
10 c) extrusion coating said composition onto the surface of a shaped polymeric substrate at a temperature within said range.

DATED THIS 27th day of January 1993.

BECTON, DICKINSON AND COMPANY

PATENT ATTORNEYS FOR THE APPLICANT

F.B. RICE & CO.



ABSTRACT OF THE DISCLOSURE

5 A shaped medical article of a polymeric substrate is extrusion coated with a composition which includes a bioactive agent dispersed in a matrix polymer. Preferred bioactive agents are temperature sensitive agents which undergo thermal decomposition at a temperature above the processing temperature of the matrix polymer. Preferred matrix polymers have a melting point of about 100°C or lower.

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