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PATENTS ACT 1952

DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT

In support of the Application made for a patent for an invention

Insert title of invention

entitled: "Tubular Articles"

Insert full name(s) and address(es) of declarant(s) being the applicant(s) or person(s) authorized to sign on behalf of an applicant company.

I, William Gwyn Cole of
Smith & Nephew plc
2 Temple Place,
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London, WC2R 3BP,
United Kingdom

do solemnly and sincerely declare as follows :-

Cross out whichever of paragraphs 1(a) or 1(b) does not apply
1(a) relates to application made by individual(s)
1(b) relates to application made by company; insert name of applicant company.

1. (a) ~~I am the applicant for the patent~~

or (b) I am authorized by

Smith & Nephew plc

the applicant for the patent to make this declaration on its behalf.

Cross out whichever of paragraphs 2(a) or 2(b) does not apply
2(a) relates to application made by inventor(s)
2(b) relates to application made by company(s) or person(s) who are not inventor(s); insert full name(s) and address(es) of inventors.

2. (a) ~~I am~~

or (b)

Richard MILNER
of 3 Ashdale,
Thorley Park,
Bishops Stortford,
CM23 4EA
United Kingdom

is the actual inventor of the invention and the facts upon which the applicant is entitled to make the application are as follows :- the invention was made by the said inventor in course of his employment by Smith & Nephew Research Ltd., and that company has assigned its rights in the invention to the Applicant whereby the Applicant, would, if a patent were granted upon an application made by the said inventor, be entitled to have a patent assigned to it.

State manner in which applicant(s) derive title from inventor(s)

Cross out paragraphs 3 and 4 for non-convention applications. For convention applications, insert basic country(s) followed by date(s) and basic applicant(s).

3. The basic application was defined by Section 141 of the Act made

in United Kingdom on the 7th September 1988
by Smith & Nephew plc
in United Kingdom on the 23rd August 1989
by Smith & Nephew plc
in ... on the ...
by ...

4 The basic application referred to in paragraph 3 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

Insert place and date of signature.

Declared at Harlow, UK this 25th day of October 1990

Signature of declarant(s) (no attestation required)

Dr. William Gwyn Cole

Note Initial all alterations.

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TUBULAR ARTICLES

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(56) Prior Art Documents
AU 41965/89 A61L 031/00, A61B 019/04
AU 52834/86 A61L 031/00, A61L 025/00

(57) Claim

1. A method for the manufacture of an antimicrobially effective tubular article which comprises including an antimicrobially effective amount of a sparingly water soluble antimicrobial agent which is non-ionic at neutral pH in an aqueous dispersion of the article material prior to forming the article.

6. A tubular article produced by the inclusion of an antimicrobially effective amount of a sparingly water soluble antimicrobial agent which is non-ionic at neutral pH in an aqueous dispersion of the article material prior to forming the article.

7. An article as claimed in claim 6 wherein the antimicrobial agent is 2,4,4^{1}-trichloro-2^{1}-hydroxydiphenyl ether.

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(54) Title: TUBULAR ARTICLES

(57) Abstract

Tubular articles such as condoms or catheters are rendered antimicrobially effective by incorporating therein an effective amount of a non-ionic sparingly water soluble antimicrobial agent. Preferably the antimicrobial is triclosan and the tubular article is a condom made from natural rubber latex. A method of manufacturing the tubular articles is described in which the antimicrobial agent is incorporated into the material forming the article before the article is formed.

TUBULAR ARTICLES

This invention relates to tubular articles such as condoms or catheters rendered antimicrobially effective by incorporating therein an effective amount of a non-ionic sparingly water soluble antimicrcbial agent such as triclosan into the material such as natural rubber from which the article is made.

For many elastomeric tubular articles which are used in the medical or veterinary sciences it is often desirable to treat them so they can prevent the passage of bacteria or virus or even have a microbiocidal effect at least at their surfaces. Such articles include catheters such a urethral catheters, condoms, wound drains, endotracheal tubes and the like. Heretofore such articles have been treated with antimicrobial agents by washing with a solution of the agent or by treating it with a cream or lubricating oil or powders which contain an antimicrobial agent.

It would be useful if the aforementioned articles could be manufactured with the antimicrobial agent in situ. Unfortunately it has proved to be extremely difficult to produce articles made of rubbers such as natural rubber latex or the like incorporating an antimicrobial agent. For example, the agents have tendency to

destabilise the materials from which the article is formed, for example by causing gelling of a latex. However, a method has now been discovered which allows articles to be formed which incorporate an antimicrobially effective amount of an agent which reduces the tendency for bacteria to grow on the surface of the article and then improves the barrier properties of the article against transmission of bacteria and even of viruses such as the HIV and hepatitis B virus.

The present invention provides a method for the manufacture of an antimicrobially effective tubular article which comprises including an antimicrobially effective amount of a sparingly water soluble antimicrobial agent which is non-ionic at neutral pH in an aqueous dispersion of the article material prior to forming the article.

The present invention also provides a tubular article produced by the inclusion of an antimicrobially effective amount of a sparingly water soluble antimicrobial agent which is non-ionic at neutral pH in an aqueous dispersion of the article material prior to forming the article.

The antimicrobial agent is non-ionic at neutral pH values and only sparingly soluble in water. By sparingly water soluble it is meant that the antimicrobial agent has a solubility in water at 20°C

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of less than 0.1gm/litre, preferably less than 0.05gm/litre.

The article material will contain (ie within its body as opposed to residing only on its surface) an antimicrobially effective amount of antimicrobial agent. Suitably the article material may contain from 0.1 to 10% w/w of antimicrobial agent, more suitably 1 to 5% w/w and preferably about 1.0%ww.

The material which forms the article can be any one of those which are conventionallly used for forming such articles especially condoms and include natural rubber, polyvinyl chloride and polyurethane. The use of a natural rubber latex to form the article material is preferred. The use of a non-ionic sparingly soluble antimicrobial agent in a natural rubber latex article offers a method of overcoming many of the potential problems which could occur with natural rubber latex articles if they are susceptible to penetration by virus such as those responsible for AIDS and Hepatitis B.

From the foregoing it will be appreciated that in a preferred aspect this invention provides a natural rubber latex tubular article which contains a non-ionic, sparingly soluble antimicrobial agent.

The preferred antimicrobial agent is 2,4,4'-trichloro-2'-hydroxydiphenyl ether (triclosan).

Thus in a preferred aspect the present invention provides a natural rubber latex tubular article which contains 2,4,4'-trichloro-2'-hydroxydiphenyl ether.

These antimicrobial agents are particularly suitable for incorporation into catheters and condoms formed from natural rubber latex. It has been observed that natural rubber latices may be coagulated by ionic antimicrobial agent. If articles formed from natural rubber latices are to be treated with such antimicrobial agentsin the prior art, it is only after the rubber has been vulcanised that this can be achieved. The nature of the surface of cured rubber articles is such as to be not readily coated or impregnated with for example an antimicrobial agent. Methods of overcoming this problem have included coating the article with the antimicrobial agent in a binding agent modifying the rubber surface to make it responsive to binding the antimicrobial agent or by treating the surface with a solvent to cause the rubber to swell and then impregnating with the antimicrobial agent in the same or another solvent and finally removing the solvent. These processes are difficult to

carry out and do not give a consistent product. Surprisingly it has been found that non-ionic, sparingly water soluble antimicrobial agents do not coagulate natural rubber latex. This enables the antimicrobial agent to be uniformly mixed with the rubber latex in the fluid pre-cured state which makes manufacture of rubber articles made therefrom easier as it requires no post-cure operations on the article and can also provide a more consistent product. The low solubility of the antimicrobial agent means that it is not removed during the leaching step in the tubular article manufacturing process yet the antimicrobial agent is found to be effectively released from both the inside and outside of the article under conditions of which simulate wear.

Suitable non-ionic, sparingly soluble antimicrobial agents include phenol derivatives such as chlorophene, dichloroxylenol, hexachloraphane; diphenyl derivatives, halogenated hydroxy diphenyl derivatives such as diphenyl ethers for example 2,4,4'-trichloro-2'-hydroxy diphenyl ether (triclosan); and agents such as diacetylamino-azotoluene and triclocarban. The preferred antimicrobial agent is triclosan.

The articles containing antimicrobial agent may be prepared by mixing the required amount of agent with

the article material, for example an aqueous dispersion such as a natural rubber latex. The agent may have been previously formed into a dispersion by mixing with a little of the latex or by mixing with water and dispersing agents. The rest of the latex may be gradually mixed with this dispersion until a homogenous mixture results. The article is then formed in the usual manner.

Thus, a former may be first dipped into a coagulant solution and allowed to dry. Thereafter the coated former is dipped into the latex, removed, dried and immersed in a leaching bath. After drying the article may then be 'cured'. Alternatively, condoms or catheters may be prepared by conventional processes not employing coagulatants, for example acid gellation or heat gellation as well as multivalent cation gellation. Condoms are most aptly prepared by the conventional double dipping process.

In a process described above the antimicrobial agent may be distributed through the whole of the article material if desired so that the agent may be released from both the inside and the outside of the article. However, it may be desirable for some purposes to have the agent available only on the inside or wearer-contacting surface of the article. The agent

may be present therefore in the material which forms the last coat on the former, that is becomes the inside of the article when the article is removed from the former. Thus with a condom the vaginal flora is less likely to be disturbed. Reversing the method when producing a catheter means that a product can be produced where most of the antibacterial agent can be available on the outside of the catheter.

It will be understood that in a preferred aspect this invention provides a thin polymer condom which contains $2,4,4^1$ - trichloro - 2^1 - hydroxydiphenyl ether (triclosan).

Such condoms incorporating a non-ionic sparingly water soluble antimicrobial agent offer the user a higher degree of protection from common infecting organisms that might penetrate through any discontinuity in the condom.

The present invention provides a method of reducing the risk of infection which comprises using thin polymer condom which contain $2,4,4^1$ - trichloro - 2^1 - hydroxydiphenyl ether (triclosan). The condom contains an antimicorbially effective amount of triclosan. The triclosan provides a protection for the period of use by improving the barrier property of the condom, for example with respect to HIV.

In a further preferred aspect the present invention provides a condom which contains a non-ionic, sparingly water soluble antimicrobial agent and which has at least on the inside surface thereof a powder containing triclosan.

The powder may contain an antimicrobially effective amount of triclosan. The powder may suitably contain from 0.1 to 10% w/w of triclosan, more suitably may contain from 0.5 to 8% w/w and preferably contains about 1% w/w.

The powder containing an antimicrobially effective amount of triclosan may be obtained by methods which comprise mixing of the ingredients. Suitable methods include (a) mixing a solution of triclosan in acetone with the powder, drying, grinding and sieving the resulting powder to remove large particles and (b) mixing the dry powders together.

The powder containing triclosan may be coated onto the inside of the condom incorporating the non-ionic, sparingly water soluble antimicrobial agent such as triclosan itself in the way lubricating powders are conventionally applied.

The article according to this invention may also contain a further antibacterial agent is desired, for example chlorhexidine digluconate.

The following examples illustrate the invention.

EXAMPLE 1

A condom former of glass is thoroughly washed using dilute acid or alkali solutions. The former is rinsed in soft water and dried. The former is dipped into the natural rubber latex. The former is removed and the latex coating dried and evenly distributed over the former by rotation and agitation of the former. The former is then dipped a second time into the latex since a second layer of latex reduces the chance of any pin-holes remaining in the final product. The former is removed and the second coat dried. The article is then leached in a tank of warm water at 70°C for two minutes. After leaching the former is dipped in an aqueous solution containing 10% w/w of chlorhexidine digluconate for 20 seconds and then removed and shaken to remove any adhering water droplets.

The rubber latex contained 1% by weight of triclosan.

This was prepared as follows:-

The hydroxy halogenated biphenyl ether 2,4,4^{1}-trichloro-2^{1}-hydroxy diphenyl ether (triclosan) was incorporated into a natural rubber latex by mixing triclosan (21g) with a small quantity of latex to form a paste. The latex was gradually diluted with more latex until the required concentration was achieved. The final latex formulation was:-

Latex (42%)	4940g
Triclosan	21g

EXAMPLE 2

The procedure of Example 1 was repeated omitting the chlorhexidine step.

EXAMPLE 3

The procedure of Example 2 was repeated but the triclosan was incorporated into the first latex only.

EXAMPLE 4

A catheter is prepared by a multiple dipping process whereby a former of appropriate size is repeatedly dipped in a bath of pre-vulcanised rubber latex to build up layers of rubber to give the required wall thickness. The final latex dip incorporated 1% triclosan (based on solids content of latex).

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method for the manufacture of an antimicrobially effective tubular article which comprises including an antimicrobially effective amount of a sparingly water soluble antimicrobial agent which is non-ionic at neutral pH in an aqueous dispersion of the article material prior to forming the article.

2. A method as claimed in claim 1 wherein the antimicrobial agent is 2,4,4^1-trichloro-2^1-hydroxydiphenyl ether.

3. A method as claimed in claim 1 or claim 2 wherein the article is a condom.

4. A method as claimed in claim 1 or claim 2 wherein the article is a catheter.

5. A method as claimed in any one of claims 1 to 4 wherein the material is a natural rubber latex.

6. A tubular article produced by the inclusion of an antimicrobially effective amount of a sparingly water soluble antimicrobial agent which is non-ionic at neutral pH in an aqueous dispersion of the article material prior to forming the article.

7. An article as claimed in claim 6 wherein the antimicrobial agent is 2,4,4^1-trichloro-2^1-hydroxydiphenyl ether.

8. An article as claimed in claim 6 or claim 7 which is a condom.

9. An article as claimed in claim 6 or claim 7 which is a catheter.

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10. An article as claimed in any one of claims 6 to 9 wherein the material is natural rubber.

11. A method as claimed in claim 1 substantially as hereinbefore described with reference to any one of the examples.

12. An article as claimed in claim 6 substantially as hereinbefore described with reference to any one of the examples.

DATED this 29th day of November, 1991.

SMITH & NEPHEW PLC
By Its Patent Attorneys
DAVIES COLLISON CAVE

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INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 89/01048

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 L 31/00, A 61 L 29/00, A 61 F 6/04

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 L, C 08 J, C 08 K, A 61 F

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0229862 (TERUMO) 29 July 1987, see claims; page 3, lines 18,25; page 4, lines 1,2	1,2,4-7,9,10
P,X	FR, A, 2623087 (MEDIC 44 SARL) 19 May 1989, see page 1, lines 1-17,22-37	1,3,5,8,10
A	EP, A, 0141628 (UNITIKA) 15 May 1985	
A	US, A, 4592920 (R. MURTFELDT) 3 June 1986	
A	EP, A, 0147970 (ROHM & HAAS) 10 July 1985, see claims 1,3,10	

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* Special categories of cited documents: [10]

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27th November 1989	10. 01. 90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	K. WILLIS

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 8901048 SA 31080

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 02/01/90
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0229862	29-07-87	AU-B- 558588	05-02-87
		JP-A- 61037248	22-02-86
FR-A- 2623087	19-05-89	None	
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		JP-A- 60222063	06-11-85