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(54) Title: COATING ON METAL

(57) Abstract: The invention relates to a coating formulation suitable for coating metal substrates obtainable by a. Reacting a phosphoric acid or a derivative thereof with a polyepoxy compound, obtaining a reaction product comprising more than 10 mol% epoxy groups, b. Reacting the reaction product with an amine or a derivative thereof and optionally in the presence of a calcium phosphate salt.

COATING ON METAL

The invention relates to an anti-microbial coating formulation for coating a substrate comprising a metal.

Many medical devices, such as hip and knee prosthesis, comprise metal components. Examples of metals used in medical devices include titanium. Such medical devices require a number of challenging properties. In particular, they need to be biocompatible and anti-microbial. In order to make a metal-containing medical device biocompatible it can be coated with hydroxyapatite. However, to have a long lasting durability it is necessary to apply the hydroxyapatite in such a way that it is strongly and durably fixed in a coating composition, without deteriorating the biocompatibility of the system by the coating. Consequently, the coating should be acceptable for the body and compatible with hydroxyapatite. Coverage of titanium with a coating comprising hydroxyapatite will most likely result in a good biocompatibility, but this will obviously not result in antimicrobial properties.

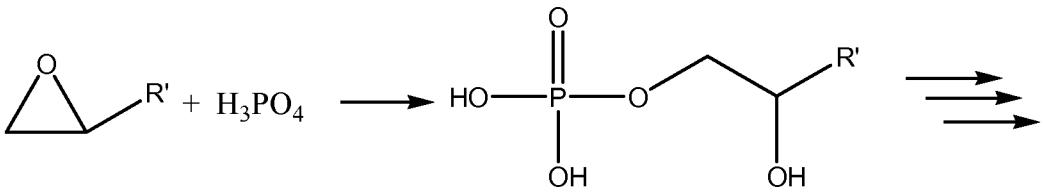
The problem to be solved is therefore to provide a coating that can be used on a metal, in particular titanium, and makes the medical device biocompatible and also provides antimicrobial properties.

The above problem is solved according to the invention by providing a coating formulation suitable for coating metal substrates obtainable by

a. Reacting a phosphoric acid or a derivative thereof with a polyepoxy compound, obtaining a reaction product comprising more than 10 mol% epoxy groups,
b. Reacting the reaction product with an amine or a derivative thereof and optionally in the presence of a calcium phosphate salt.

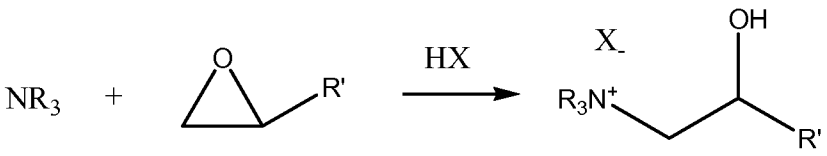
Phosphoric acid, H_3PO_4, and its derivatives have a high affinity for metal substrates. Optionally, the metal surface can be oxidized first to improve adhesion even further.

H_3PO_4 can form a bridge between the metal surface and the polyepoxy compound, yielding esters. The first step in the reaction between H_3PO_4 and the polyepoxy compound is depicted below:



The reaction product comprises more than 10 mol% epoxy groups, preferably more than 25 mol%, more preferably more than 50 mol% epoxy groups.

The reaction product can react with tertiairy amines to yield quaternary ammonium compounds, which have antibacterial properties, as depicted below.



wherein R and R' independently represent a group selected from substituted and unsubstituted hydrocarbons which optionally contain one or more heteroatoms, preferably a C1-C20 hydrocarbon, more preferably a C1-C20 alkyl, X^- represents $-O_3PO^-$, OH^-, Cl^-, Br^-, I^-. $-O_2SO^-$, $-O_3SO^-$, NO_3^-, or $RCOO^-$.

Examples of suitable polyepoxy compounds include diglycidyl ether of bisphenol A, ELO (epoxidized linseed oil) , ESO (epoxidized soybean oil), TGIC (triglycidyl isocyanaurate), diglycidyl ester of terephthalic acid, vinyl cyclohexane diepoxides, e. g. , 4-oxiranyl-cyclohexane (ERL-4206 from Union Carbide Corp.) ; (3, 4-epoxycyclohexyl) methyl 3,4-epoxycyclohexanecarboxylate (ERL-4221 from Union Carbide Corp.) ; bis [(3, 4-epoxycyclohexyl) methyl] dicarboxylates, e. g. , the adipate (ERL-4229 from Union Carbide Corp.), the succinate, and so forth; bis [(3, 4-epoxy-6- methylcyclohexyl) methyl] dicarboxylates, e. g. , the adipate (ERL-4289 from Union Carbide Corp.), the pimelate, and so forth; bis (2,3-epoxycyclopentyl) ether (ERL-0400 from Union Carbide Corp.); 2- (3, 4-epoxycyclohexyl) -5,5-spiro (2,3-epoxycyclohexane)-m-dioxane; 2- (3,4-epoxycyclohexyl)-5, 5-spiro (3,4-epoxy cyclohexane) -m-dioxane (ERL-4234 from Union Carbide Corp.); (3,4-epoxy-6-methylcyclohexyl) methyl 3,4-epoxy-6-methylcyclohexane carboxylate (ERL-4201 from Union Carbide Corp.); limonene dioxide (ERL-4269 from Union Carbide Corp.); dicyclopentadiene dioxide; and 1, 2-bis (2,3-epoxycyclopentyl) ethane.

Examples of derivatives of phosphoric acid include phosphonic acids,

phosphinic acid, and phosphorous acid (H_3PO_3).

Examples of tertiary amines include tri(alkyl) amines, such as trimethyl amine, triethyl amine, and dimethyl dodecyl amine, and tri(aryl) amines.

The use of a calcium phosphate salt is optional but may attribute to the biocompatibility of the coating, particularly to bone compatibility. Preferably hydroxyapatite is used as the calcium phosphate salt.

The coating formulation may further comprise other components, such as hydrophilic polymers, additives or fillers. Optionally one or more additives may be present in a formulation respectively coating of the invention. Such additives may in particular be selected from antioxidants, surfactants, UV-blockers, stabilisers such as anti-sagging agents, discolourants, lubricants, plasticizers, organic antimicrobial compounds, pigments, and dyes. Such components may be selected from those known in the art, e.g. the prior art identified above. If present, the total concentration of such additives is usually less than 10 wt. % based on dry weight, in particular 5 wt. % or less.

Suitable antioxidants in particular include anti-oxidative vitamins (such as vitamin C and vitamin E) and phenolic antioxidants.

The surfactant may be an ionic (anionic/cationic), non-ionic or amphoteric surfactant. Examples of ionic surfactants include alkyl sulphates (such as sodium dodecylsulphates), sodium cholate, bis(2-ethylhexyl)sulphosuccinate sodium salt, quaternary ammonium compounds, such as cetyltrimethylammonium bromide or chloride, lauryldimethylamine oxide, N-lauroylsarcosine sodium salt and sodium deoxycholate. Examples of non-ionic surfactants include alkylpolyglucosides, branched secondary alcohol ethoxylates, octylphenol ethoxylates. If present, the surfactant concentration is usually 0.001-1 wt. %, preferably 0.05-0.5 wt. % of the liquid phase.

The formulation further comprises a carrier liquid in a sufficient amount to disperse or dissolve the other components of the formulation. The carrier liquid concentration is usually at least 68 wt. %, preferably at least 75 wt. %, more preferably at least 80 wt. %, even more preferably at least 85 wt. % of the total weight of the composition. In view of handling properties (low viscosity) and/or in order to facilitate the application of the composition such that a coating with the desired thickness is obtained, the amount of solvent in the composition is preferably relatively high. For that reason the total solids content is preferably 20 wt. % or less.

The carrier liquid may be a single solvent or a mixture. It is chosen such that the components can be dissolved or at least dispersed therein. Preferably it

comprises water and/or an organic liquid soluble in water, preferably an alcohol, more preferably a C1-C4 alcohol, in particular methanol and/or ethanol.

As described above, the invention further relates to a method for coating an article and to a coated article. In principle, the formulation can be used to provide any article with an antimicrobial coating. In particular, the formulation may be used to coat an article and the article is a medical device

If desired, the metal surface can be pre-treated in order to improve adherence of the antimicrobial coating, for instance a chemical and/or physical pre-treatment. Suitable pre-treatments are known in the art for specific combinations of materials for the surface of the article. Examples of pre-treatments include plasma treatment, corona treatment, gamma irradiation, chemical washing, polarisation and oxidation.

Application of the formulation of the invention may be done in a manner *per se.*

In general, curing is preferably carried out at elevated temperature, for example between 80 and 150 °C or up to 200 °C or up to 300 °C as long as the mechanical properties or another property of the article and the coating are not adversely affected to an unacceptable extent.

The invention will now be illustrated by the following examples.

EXAMPLES

Example 1

To 9.8 g (0.1 mol) H_3PO_4 dissolved in 100 ml water in a glass flask of 500 ml were added 34 g (0.1 mol) di-glycidyl ether of bisphenol A, 2.97 g (0.01 mol) triglycidyl isocyanurate (TGIC), 21.3 g (0.01 mol) dimethyl dodecyl amine and 10 g hydroxyapatite. The mixture was stirred for 20 minutes at room temperature, resulting in a viscous solution.

Example 2

To 2,0 g (0.02 mol) H_3PO_4 dissolved in 100 ml water in a glass flask of 500 ml were added 34 g (0.1 mol) di-glycidyl ether of bisphenol A, 2.97 g (0.01 mol) triglycidyl isocyanurate (TGIC), 21.3 g (0.01 mol) dimethyl dodecyl amine and 10 g hydroxyapatite. The mixture was stirred for 20 minutes at room temperature, resulting in a viscous solution.

Example 3

A titanium metal plate was cleaned thoroughly with an aqueous HCl solution and rinsed with demineralized water until no chlorine could be detected any more in the rinsing water. Titanium test bars (5x5 cm) were coated with the aqueous solution of the polymer according to example 1 and heated in an oven at 100 ^{o}C for 1 hour, yielding a coating of about 20 µm thick.

Five of these test samples were evaluated in the JIS Z2801 antibacterial test. All the test samples were bacteria free. Samples were heated in boiling water for 7 days, and there was no sign of deterioration of the coating.

CLAIMS

1. Coating formulation suitable for coating metal substrates obtainable by
   a. Reacting a phosphoric acid or a derivative thereof with a polyepoxy compound, obtaining a reaction product comprising more than 10 mol% epoxy groups,
   b. Reacting the reaction product with an amine or a derivative thereof and optionally in the presence a calcium phosphate salt.
2. Coating formulation according to claim 1, wherein the polyepoxy compound is chosen from the group consisting of diglycidyl ether of bisphenol A, ELO (epoxidized linseed oil) , ESO (epoxidized soybean oil), TGIC (triglycidyl isocyanaurate), diglycidyl ester of terephthalic acid, vinyl cyclohexane diepoxides, e. g., 4-oxiranyl-cyclohexane (ERL-4206 from Union Carbide Corp.); (3, 4-epoxycyclohexyl) methyl 3,4-epoxycyclohexanecarboxylate (ERL-4221 from Union Carbide Corp.); bis [(3, 4-epoxycyclohexyl) methyl] dicarboxylates, e. g., the adipate (ERL-4229 from Union Carbide Corp.), the succinate, and so forth; bis [(3, 4-epoxy-6- methylcyclohexyl) methyl] dicarboxylates, e. g., the adipate (ERL-4289 from Union Carbide Corp.), the pimelate, and so forth; bis (2,3-epoxycyclopentyl) ether (ERL-0400 from Union Carbide Corp.); 2- (3, 4-epoxycyclohexyl) -5,5-spiro (2,3-epoxycyclohexane)-m-dioxane; 2- (3,4-epoxycyclohexyl)-5, 5-spiro (3,4-epoxy cyclohexane) -m-dioxane (ERL-4234 from Union Carbide Corp.); (3,4-epoxy-6-methylcyclohexyl) methyl 3,4-epoxy-6-methylcyclohexane carboxylate (ERL-4201 from Union Carbide Corp.); limonene dioxide (ERL-4269 from Union Carbide Corp.); dicyclopentadiene dioxide; and 1, 2-bis (2,3-epoxycyclopentyl) ethane.
3. Coating formulation according to claim 1 or 2, wherein the amine is a tertiary amine.
4. Coating formulation according to anyone of claims 1-3, wherein the phosphate salt is hydroxyapatite.
5. Coating formulation accoding to anyone of claims 1-4, wherein the metal substrate is a titanium substrate.
6. Medical device coated with the coating formulation according to any one of claims 1-5.
7. Use of the coating formulation according to any one of claims 1-5 in medical applications.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L27/34 C09D163/00 C09D5/14 C08G59/14

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)
A61L C08L C09D C08G C08K

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 4 461 857 A (SEKMAKAS KAZYS [US] ET AL) 24 July 1984 (1984-07-24) column 1, lines 20-35; claim 1; example 5 column 3, lines 35-49	1-3,5
Y	GB 952 842 A (UNISEARCH LTD) 18 March 1964 (1964-03-18) page 2, line 42 - page 4, line 87; claims	1-7
Y	DE 197 55 334 A1 (AICHER WILHELM DR [DE]; GECKELER KURT E PROF DR [DE]; KUESSWETTER WOLF) 24 June 1999 (1999-06-24) claims	1-7
Y	EP 0 212 193 A (WALKER MICHAEL MONTGOMERY) 4 March 1987 (1987-03-04) column 4, line 45 - column 7, line 47; claims	1-7

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

[X] See patent family 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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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 March 2009	27/03/2009

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/051891

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94/15652 A (UNIV SOUTHAMPTON [GB]; EVANS SAMUEL LEWIN [GB]; GREGSON PETER JOHN [GB) 21 July 1994 (1994-07-21) page 3, line 4 - page 5, line 20; example 1	1-7
A	US 4 397 970 A (CAMPBELL KENT D ET AL) 9 August 1983 (1983-08-09) claims; example 1	1-3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/051891

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