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(54) Title: A LUBRICIOUS COATING, A METHOD FOR COATING AND A COATED ARTICLE

(57) Abstract: There is disclosed a lubricious coating formed by a reaction of a compound comprising at least two thiol- groups or a disulfide derivative thereof, and a compound comprising at least two vinyl-groups, which compound is selected from the group consisting of a divinylether compound, a diacrylate compound, a dimethacrylate compound, a diallyl compound, and a vinyl alcohol copolymer wherein a hydrophilic polymer is associated to said coating. There is further disclosed a method for coating and a coated article. The coating technology is non-toxic, biocompatible and tissue friendly. The friction is reduced and the durability of the friction reduction is improved. The manufacturing process as well as the coating itself is more environmental friendly. According to the present invention there is also an option to include an active agent in the coating.

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A lubricious coating, a method for coating and a coated article

Field of the invention

- 5 The present invention relates to the field of friction reducing tissue friendly coatings, optionally comprising an active agent.

Background

- 10 For many medical articles it is desirable to have a friction reducing coating. In particular it is desirable to have a tissue and environmentally friendly friction reducing coating. Examples of such articles include various medical and surgical instruments including
15 catheters and probes. In the past many different friction-reducing coatings have been developed and used.

- Existing polymeric friction reducing coatings for medical devices are often based on a formula comprising
20 isocyanate. Examples of coatings comprising isocyanate are given in US patents Nos 5,160,790, 5,290,585, and 5,776,611 to C.R. Bard, Inc.

- US 6,017,577 to Schneider, Inc. and US 6,299,980 to
25 Medtronic AVE, Inc. disclose a friction reducing hydrogel composition involving an isocyanate.

- US 5,804,318 discloses an approach involving primary and tertiary amine functionalities.

- 30 US 6,238,799 and US 6,866,936 disclose a supporting cross linked polymer and a hydrophilic polymer associated with the supporting polymer. The supporting polymer can be built up of groups comprising sulfhydryl groups.

Poly(ethylene oxide) is mentioned as an example of a hydrophilic polymer.

US 2006229635 discloses a coating for lenses. It describes
5 the use of poly(ethylene oxide) in a cross linked matrix being built up of functional groups comprising sulfhydryl (SH) groups.

US 5,693,034 discloses a coating composition for
10 angioplasty catheters and shows a reaction product which are coated with a composition comprising a reaction product of vinyl monomers selected from the group consisting of mono-, di-, and tri- acrylates, styrene and divinylbenzene. The composition further comprises a
15 polymerisation inhibitor and an uncrosslinked water soluble hydrogel such as polyethylene oxide.

US 5,041,100 discloses a plastic catheter with a friction reducing coating comprising a mixture of a structural
20 plastic material and poly(ethylene oxide)

Even though some of the above described coatings are used today for catheters, there is still room for an improvement regarding the biocompatibility, the friction
25 reduction, the durability of the friction reduction, the toxicity, the environmental friendliness, and the capability to include active agents.

Short summary of the present invention

30 The inventors have found that by selecting certain ingredients for the coating, it is possible to manufacture a better coating, which improves at least some of the properties described above. According to the present invention there is disclosed a lubricious coating formed

by a reaction of (i) a compound comprising at least two thiol-groups or a disulfide derivative thereof, and (ii) a compound comprising at least two vinyl-groups, which compound is selected from the group consisting of a
5 divinyloether compound, a diacrylate compound, a dimethacrylate compound, a diallyl compound, and a vinyl alcohol copolymer, wherein a hydrophilic polymer is associated to said coating.

10 The novel coating technology is non-toxic, biocompatible and tissue friendly. The friction is reduced and the durability of the friction reduction is improved compared to prior art. The manufacturing process as well as the coating itself is more environmental friendly compared to
15 the coatings described in the prior art. According to the present invention there is also the option to include an active agent in the coating. The present invention has the advantage of providing a mild route to include an active agent in a coating.

20

Definitions

Before the invention is disclosed and described in detail, it is to be understood that this invention is not limited to particular configurations, process steps and materials
25 disclosed herein as such configurations, process steps and materials may vary. It is also to be understood that the terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting since the scope of the present invention is
30 limited only by the appended claims and equivalents thereof.

It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and

"the" include plural referents unless the context clearly dictates otherwise.

The following terms are used throughout the description
5 and the claims.

"Associated" is used herein to denote a binding and a spatial proximity.

10 "Biocompatible" is used herein to denote the ability of a material to perform with an appropriate host response in a specific application.

"Coating" is used herein to denote matter that is applied
15 to either a part of an object or an entire object.

"Copolymer" is used heren to denote a polymer derived from two or more types of monomers. Copolymer includes all types of copolymers such as alternating copolymers with
20 regularly alternating monomer units, periodic copolymers with monomers arranged in repeating sequences, random copolymers with random sequences of monomer, statistical copolymers in which the ordering of the distinct monomers within the polymer sequence obeys known statistical rules,
25 and block copolymers comprised of two or more homopolymer subunits linked by covalent bonds. The union of the homopolymer subunits may require an intermediate non-repeating subunit, known as a junction block. Diblock copolymers and triblock copolymers are examples of block
30 copolymers.

"Disulfide bond" is used heren to denote a single covalent bond between two sulphur atoms.

"Disulfide derivative" is used heren to denote a derivative comprising a disulfide bond. A disulfide derivative may be formed by oxidation of two thiol groups. Typically a disulfide derivative may be reduced to obtain one or more compounds comprising thiol groups.

"Lubricious" is used heren to denote the property to reducing friction and wear between moving surfaces.

10 Detailed description of the present invention

In a first aspect of the present invention there is provided a lubricious coating formed by a reaction of: (i) a compound comprising at least two thiol-groups or a disulfide derivative thereof, and (ii) a compound comprising at least two vinyl-groups, which compound is selected from the group consisting of a divinylether compound, a diacrylate compound, a dimethacrylate compound, a diallyl compound, and a vinyl alcohol copolymer, wherein a hydrophilic polymer is associated to said coating.

The compound comprising at least two vinyl groups is chosen from a divinylether compound, a diacrylate compound, a dimethacrylate compound, a diallyl compound and a vinyl alcohol copolymer.

Examples of divinylether compounds according to the present invention include tri(ethylene glycol) divinylether, tetra(ethylene glycol) divinylether, and poly(ethylene glycol) divinylether. Note that the term "poly(ethylene glycol) divinylether" includes molecules of different lengths.

Examples of diacrylate compounds according to the present invention include tri(ethylene glycol) diacrylate, tetra(ethylene glycol) diacrylate, and poly(ethylene glycol) diacrylate. Note that the term "poly(ethylene glycol) diacrylate" includes molecules of different lengths.

Examples of dimethacrylate compounds according to the present invention include tri(ethylene glycol) dimethacrylate, tetra(ethylene glycol) dimethacrylate, and poly(ethylene glycol) dimethacrylate. Note that the term "poly(ethylene glycol) dimethacrylate" includes molecules of different lengths.

One example of a diallyl compound is trimethylolpropane diallylether.

If the compound comprising at least two vinyl groups is a copolymer of polyvinyl alcohol it has in one embodiment at least one side chain

Copolymers of polyvinyl alcohol compounds according to the present invention include copolymers comprising side chains comprising at least one group selected from the group consisting of a vinylether group, an acrylate group, a methacrylate group, an allyl group. The polyvinyl alcohol compound has a functionalization degree from 0.5% to 50%. The polyvinyl alcohol copolymer includes molecules of different lengths (M_n 1000-500000).

Examples of the polyvinyl alcohol compound of according to the present invention include alternating copolymers, periodic copolymers, random copolymers, and statistical copolymers.

In one embodiment the compound comprising at least two vinyl groups is chosen from tri(ethylene glycol)divinylether, trimethylolpropane diallyl ether, tetra(ethylene glycol) diacrylate, poly(ethylene glycol) diacrylate, trimethylolpropane diallyl ether, and poly(ethylene glycol dimethacrylate).

In one embodiment the compound comprising at least two thiol groups comprises at least one mercaptopropionate group.

In one embodiment a compound comprising at least two thiol groups is reacted with a compound comprising at least two vinyl-groups, which compound is selected from the group consisting of a divinylether compound, a diacrylate compound, a dimethacrylate compound, a diallyl compound, and a vinyl alcohol copolymer, wherein a hydrophilic polymer is associated to said coating.

In an alternative embodiment a disulfide derivative of a compound comprising at least two thiol groups is reacted with a compound comprising at least two vinyl-groups, which compound is selected from the group consisting of a divinylether compound, a diacrylate compound, a dimethacrylate compound, a diallyl compound, and a vinyl alcohol copolymer, wherein a hydrophilic polymer is associated to said coating. This particular embodiment may include reduction of the disulfide bond to thiol groups.

In one embodiment the compounds comprising at least two thiol groups is chosen from pentaerytritol tetrakis(3-mercaptopropionate) and trimethylolpropane tris(3-mercaptopropionate).

In one embodiment the compound comprising at least two thiol-groups is selected from the group consisting of ((mercaptopropyl) methylsiloxane) - dimethylsiloxane copolymer, and poly(mercaptopropyl)methylsiloxane.

5

Examples of compounds comprising at least two thiol groups include tetradecane-1,14-dithiol, (+/-)-trans-1,2-bis(2-mercaptoacetamido)cyclohexane, (E)-S,S'-bis(10-mercaptodecyl)-4,4'-(diazene-1,2-diyl)bis(4-cyanopentanethioate), bis(2-mercaptoethyl)sulfone, 2,5-dimercaptomethyl-1,4-dithiane, 1,4-butanediol-bis(3-mercaptopropionate), 1,16-hexadecanedithiol, undecane-1,11-dithiol, heptane-1,7-dithiol, 1,12-dimercaptododecane, octadecane-1,18-dithiol, 1,2,4,5-benzenetetramethanethiol, (5-mercaptomethyl-2,4-dimethyl-phenyl)-methanethiol, (3-mercaptomethyl-5-methyl-phenyl)-methanethiol, 1,3-benzenedimethanethiol, 1,2-benzenedimethanethiol, (4R,5R)-4,5-bis(mercaptomethyl)-2,2-dimethyl-1,3-dioxolane, tetraethyleneglycol-bis(3-mercaptopropionate), trimethylolpropane-tris(3-mercaptopropionate), 3-bis(2-mercaptoethylthio)propane, ethanethiol, dipentaerythritol-hexakis(3-mercaptopropionate), ethyleneglycol-bis(3-mercaptopropionate), aceticacid-mercapto-1,2,6-hexanetriyl ester, L-1,4-dithiothretol, glycerylthioglycolate, 3,6-dioxa-1,8-octanedithiol, 1,2-dimethyl-4,5-bis(mercaptomethyl)benzene, pentaerythritol-tetrakis(mercaptoacetate), trimethylolpropane-tris(mercaptoacetate), 1,4-butanediol-bis(mercaptoacetate), 2,4-bis(mercaptomethyl)-1,3,5-trimethylbenzene, 2,3-butanediol-1,4-dimercaptopentaerythritol-tetrakis(3-mercaptopropionate), ethanethiol-2,2',2''-nitrilotris, 2,2'-thiodiethanethiol, 1,9-nonanedithiol, 2,2'-

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oxydiethanethiol, 10-decanedithiol, 1,6-hexanedithiol, 1,4-butanedithiol, 1,5-pentanedithiol, ethyleneglycol bis(mercaptoacetate), and 1,4-benzenedimethanethiol.

Disulfide derivatives of the above mentioned thiol

5 compounds are also included in the present invention.

In one embodiment the compound comprising at least two thiol-groups is a polymer. Examples of such polymers include

- polyethyleneglycol, di-thiol terminated, Mw 3,000-
10 20,000,
- polyethyleneoxide, di-thiol terminated,
- polyethyleneglycol, 4-arm, thiol terminated, Mw
10,000-20,000, and
- polyethyleneoxide, 4-arm, thiol terminated.

15

Disulfide derivatives of the thiol terminated polymers are also encompassed within the present invention.

The hydrophilic polymer associated with the coating gives
20 the desired lubrication. In one embodiment the hydrophilic polymers is poly(ethylene oxide).

The hydrophilic polymer has a molecular weight M_w in the range 3000 to 5000000, preferably 5000 to 3000000, more
25 preferably 10000 to 1000000, even more preferably 50000 to 500000 and most preferably 100000 to 300000. A low molecular weight gives a good adhesion of the coating to the substrate, but not perfect lubricating properties. On the other hand a high molecular weight gives good
30 lubrication but not very good adhesion of the coating to the substrate. Thus the molecular weight of the hydrophilic polymer has to be adjusted to achieve the desired properties. A person skilled in the art can in the

light of this description by routine experiments determine suitable lengths of the lubricating polymer.

The association of the hydrophilic polymer means that it
5 is bound to the coating. The binding may be accomplished
with one or several different types of bindings including
binding through an interpenetrating network, binding
through van der Waal forces, binding through charged
groups, binding through polar groups, binding with
10 covalent bonding.

In a second aspect of the present invention there is
described an article coated with the coating according to
the invention. The article can either be completely coated
15 with the coating or alternatively partially coated. Non
limiting examples of articles which can be coated
according to the present invention include a medical
device, a medical instrument, a surgical instrument, a
catheter, and a medical probe. It must be noted that the
20 mentioned examples of articles which can be coated
according to the present invention are illustrative
examples and that many other types of articles also can be
coated according to the present invention.

25 In a third aspect of the present invention there is
described a method of producing a lubricious coating
comprising the steps of a) dissolving i) a hydrophilic
polymer, ii) a compound comprising at least two thiol
groups or a disulfide derivative thereof and (iii) a
30 compound comprising at least two vinyl groups, which
compound is selected from the group consisting of a
divinylether compound, a diacrylate compound, a
dimethacrylate compound, a diallyl compound and a vinyl
alcohol copolymer in a solvent, b) applying said solution

to at least a part of the surface of an article, and
c) initiating a polymerisation reaction. The sequence in
which the ingredients are dissolved in step a) is not
critical, they may be dissolved in any sequence.

5

In one embodiment the method comprises addition of an
active agent.

The initiator system used for the polymerization reaction
10 is any suitable initiator system. Examples of initiator
systems include a thermal initiator and an UV-initiator.
In one embodiment there is used the thermal initiator AIBN
(2,2'-azobis(2-methylpropionitrile) in conjunction with
heating. In another embodiment there is used the thermal
15 initiator ACVA 4,4'-Azobis(4-cyanovaleric Acid) in
conjunction with heating.

Examples of suitable solvents include THF,
dichloromethane, chloroform, acetonitrile and toluene. In
20 one embodiment the solvent is chosen from THF and toluene.
In another embodiment the solvent is THF. THF and toluene
are advantageous to use regarding the environment. For
hydrophilic polymers with high molecular weight it is
often necessary to stir and/or to heat in order to
25 dissolve the polymer. When the hydrophilic polymer is
dissolved the compound comprising at least two thiol-
groups or a disulfide derivative thereof and the compound
comprising at least two vinyl-groups are added and
dissolved in the solvent. The order of addition is not
30 critical. In alternative embodiments the compound
comprising at least two thiol-groups or a disulfide
derivative thereof or the compound comprising at least two
vinyl-groups is added first and then the hydrophilic
polymer is dissolved. If an initiator system requiring

addition of a substance is used, that substance is also dissolved in the solution at any point.

In one embodiment other substances are incorporated in the coating according to the present invention. In one embodiment at least one active agent is incorporated in the coating. Examples of incorporation of an active agent in the coating include addition of an active agent during the manufacture of the coating and addition of an ingredient covalently bound to an active agent. In one embodiment the added active agent is bound to the coating. The binding is accomplished with one or several different types of bindings including binding through an interpenetrating network, binding through van der Waal forces, binding through charged groups, binding through polar groups, binding with covalent bonding. In one embodiment at least one active agent is covalently bound to at least one compound chosen from i) the compound comprising at least two vinyl-groups, ii) the compound comprising at least two thiol-groups or the disulfide derivative thereof, and iii) the hydrophilic polymer. In one embodiment the method for manufacturing the coating comprises the addition of at least one active agent. In another embodiment the method for manufacturing the coating according to the present invention comprises a step of addition of at least one active agent covalently bound to at least one of the ingredients, where the ingredients include i) the compound comprising at least two vinyl-groups, ii) the compound comprising at least two thiol-groups, iii) the hydrophilic polymer and iv) further optional ingredients which are added to the polymerization reaction.

Non-limiting examples of active agents include peptides such as antiviral peptides, antifungal peptides, antibacterial peptides and anticancer peptides. Non-limiting examples further include cathelicidin, bacteriocins, and bacteriophages. Further non-limiting examples include antimicrobial agents such as beta-lactams (penicillins and cephalosporins) (Ex. penicillin G, cephalothin), semisynthetic penicillin (Ex. ampicillin, amoxycillin), clavulanic acid (Ex. clavamox is clavulanic acid plus amoxycillin), monobactams (Ex. aztreonam), carboxypenems (Ex. imipenem), aminoglycosides (Ex. streptomycin), gentamicin, glycopeptides (Ex. vancomycin), lincomycins (Ex. clindamycin), macrolides (Ex. erythromycin), polypeptides (Ex. polymyxin), bacitracin, polyenes (Ex. amphotericin), nystatin, rifamycins (Ex. rifampicin), tetracyclines (Ex. tetracycline), semisynthetic tetracycline (Ex. doxycycline), chloramphenicol (Ex. chloramphenicol), pyrazinamide, and sulfa drugs (ex. sulfonamide), antiseptic agents such as chlorhexidine, iodine/iodophors, and triclosan. Still further non-limiting examples include quaternary ammonium compounds, phosphate imidazolinium compounds, dimethyl benzyl ammonium chloride compounds, dimethyl ethylbenzyl ammonium chloride, alkyl dimethyl ammonium chloride, paradiisobutylphenoxyethoxyethyl dimethyl benzyl ammonium chloride, poly(hexamethylene biguanide hydrochloride), and tetramine compounds. Further non-limiting examples include essential oils such as oregano oil, tea tree oil (melaleuca Oil), mint oil, sandalwood oil, clove oil, nigella sativa (black cumin) oil, onion oil (allium cepe) - phytoncides, leleshwa oil, lavender oil, lemon oil, eucalyptus oil, peppermint oil, and cinnamon oil. Further non-limiting examples include nitrofuranes such as nitrofurantoin and nitrofurazone. Further non-limiting

examples include antithrombogenic substances such as heparin group (platelet aggregation inhibitors), methacryloyloxyethyl phosphorylcholine polymer, polyphloretholphosphate, heparin, heparan sulphate, 5 hirudin, lepirudin, dabigatran, bivalirudin, fondaparinux, ximelagatran, direct thrombin inhibitors, argatroban, melagatran, ximelagatran, desirudin, defibrotide, dermatan sulfate, fondaparinux, rivaroxaban, antithrombin III, bemiparin, dalteparin, danaparoid, enoxaparin, nadroparin, 10 parnaparin, reviparin, sulodexide, tinzaparin, vitamin K antagonists, acenocoumarol, clorindione, dicumarol (dicoumarol), diphenadione, ethyl biscoumacetate, phenprocoumon, phenindione, tiocloamarol, warfarin, platelet aggregation inhibitors, abciximab, 15 acetylsalicylic acid (aspirin), aloxiprin, beraprost, ditazole, carbasalate calcium, cloricromen, clopidogrel, dipyridamole, eptifibatide, indobufen, iloprost, picotamide, prasugrel, prostacyclin, ticlopidine, tirofiban, treprostinil, triflusal, enzymes, alteplase, 20 ancrod, anistreplase, brinase, drotrecogin alfa, fibrinolysin, protein C, reteplase, saruplase, streptokinase, tenecteplase, urokinase, chelators, citrate, EDTA, and oxalate. Further non-limiting examples include anti-inflammatory substances, non-steroidal anti-inflammatory drugs, salicylates (such as aspirin 25 (acetylsalicylic acid), diflunisal, ethecamide), arylalkanoic acids (such as diclofenac, indometacin, sulindac), 2-arylpropionic acids (profens) (such as carprofen, flurbiprofen, ibuprofen, ketoprofen, ketorolac, 30 loxoprofen, naproxen, tiaprofenic acid), N-arylanthranilic acids (fenamic acids) (such as mefenamic acid), pyrazolidine derivatives (such as phenylbutazone), oxicams (such as meloxicam, piroxicam), coxibs (such as celecoxib, etoricoxib, parecoxib, rofecoxib, valdecoxib),

sulphonanilides (such as nimesulide), diclofenac, flurbiprofen, ibuprofen, indometacin, ketoprofen, naproxen, piroxicam, and eicosanoids. Further non-limiting examples include any of a group of substances that are
5 derived from arachidonic acid, including leukotrienes, thromboxanes, and prostaglandins. Further non-limiting examples include immunosuppressive drugs. Further non-limiting examples include analogues of rapamycin, such as tacrolimus (FK-506), sirolimus and everolimus, paclitaxel,
10 docetaxel, and erlotinib.

The article to be coated can be made of a variety of materials or combinations of materials. The article to be coated is a substrate for the coating. In one embodiment
15 of the present invention the substrate is a polymeric substrate.

In one embodiment the substrate is chosen from latex, vinyl, polymers comprising vinyl groups, polyurethane
20 urea, silicone, polyvinylchloride, polypropylene, styrene, polyurethane, polyester, copolymers of ethylene vinyl acetate, polystyrene, polycarbonate, polyethylene, polyacrylate, polymethacrylate, acrylonitrile butadiene styrene, polyamide, polyimide, and mixtures thereof.

25

In another embodiment of the present invention the substrate is chosen from a natural polymer, a degradable polymer, an edible polymer, a biodegradable polymer, an environmental friendly polymer, a crosslinked polymer, a
30 medical grade polymer, and mixtures thereof.

In another embodiment of the present invention the substrate is a metal.

In one embodiment the metal for the substrate is chosen from stainless steel, medical grade steel, titanium, medical grade titanium, cobalt, chromium, aluminium, and mixtures thereof.

5

In another embodiment of the present invention the substrate is chosen from glass, minerals, zeolites, stone ceramics, and mixtures thereof.

10 In another embodiment of the present invention the substrate is chosen from paper, wood, woven fibres, fibres, cellulose fibres, leather, carbon, carbon fibres, graphite, polytetrafluoroethylene, polyparaphenyleneterephthalamide, and mixtures thereof.

15

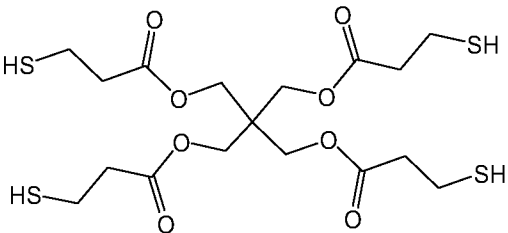
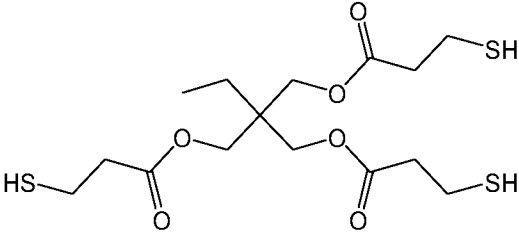
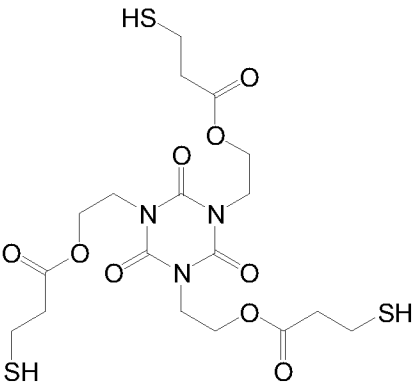
The article to be coated is immersed in the solution described above. In one embodiment a part of an article is contacted with the solution to achieve a partial coating. Alternatively another method of contacting the article
20 with the solution is used. Alternative methods of contacting the article with the solution include spraying and pouring the solution onto the article.

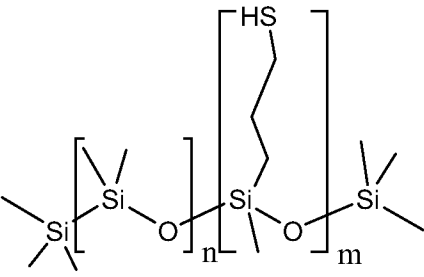
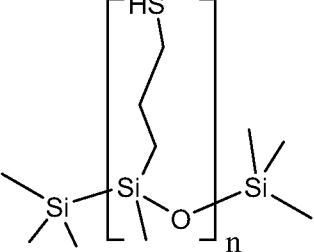
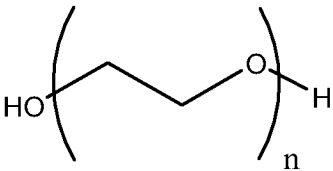
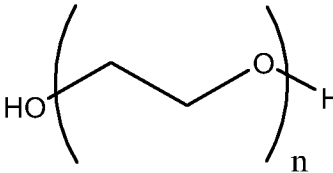
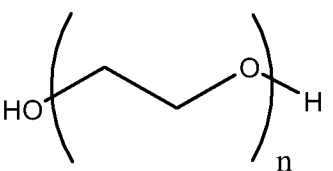
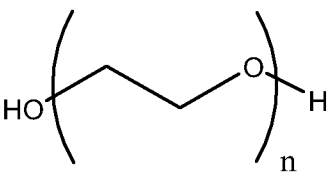
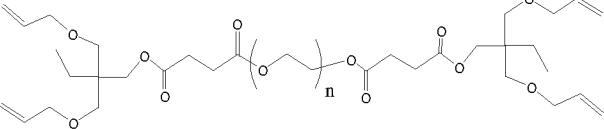
The article is then removed from the solution, and if a
25 thermal initiator is used the article is heated to a suitable temperature. The heating will also evaporate the solvent. Optionally the article is dried after the curing.

The curing will give a cross linked coating, which coating
30 encompasses a hydrophilic polymer. The coating is attached to the underlying substrate with an interpenetrating polymer network.

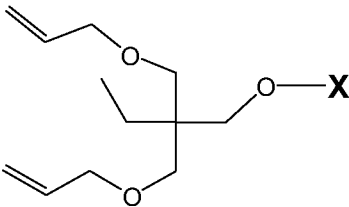
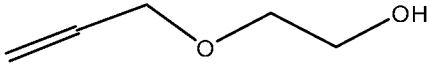
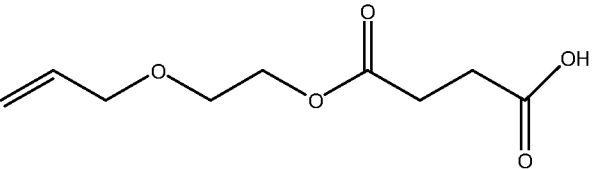
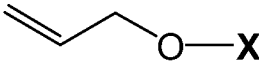
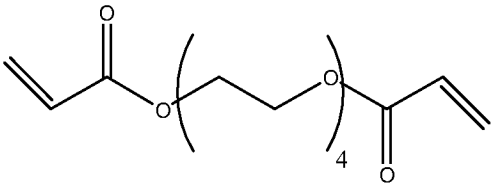
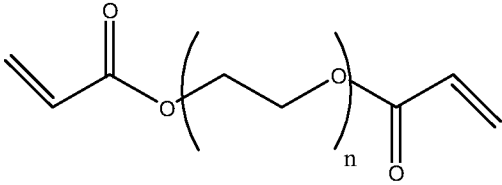
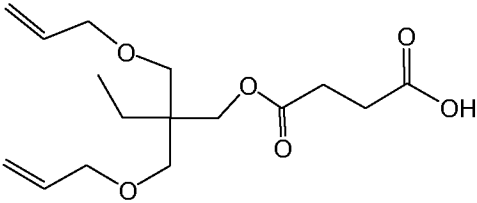
It is to be understood that this invention is not limited to the particular embodiments shown here. The following examples are provided for illustrative purposes and are not intended to limit the scope of the invention since the scope of the present invention is limited only by the appended claims and equivalents thereof.

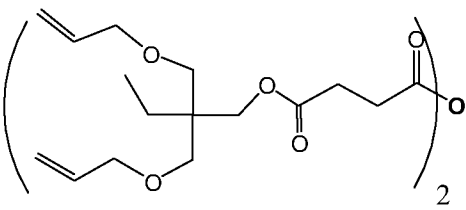
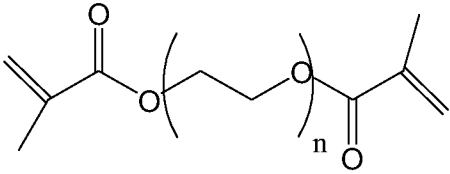
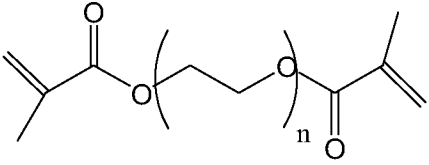
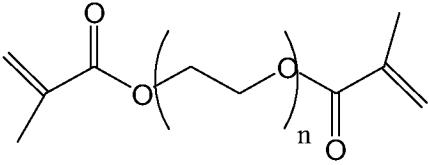
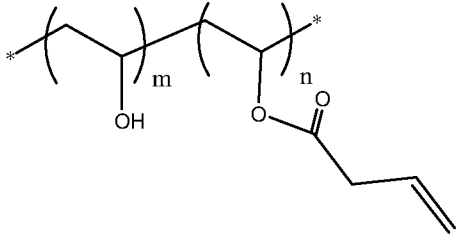
The abbreviations in the following table are used to denote substances used according to the present invention. The substances in the table below are non limiting examples of substances that may be used in the present invention.

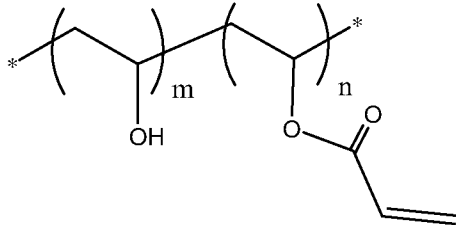
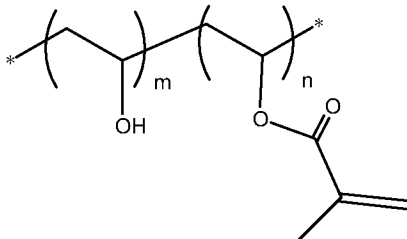
Abbreviation and name of compound	Structure
SH4 Pentaerythritol tetrakis(3- mercaptopropionate)	
SH3 Trimethylolpropane tris(3- mercaptopropionate)	
SHT3 Tris[2- mercaptopropionyloxy ethyl]isocyanurate	

PDMS-SH ((4-6% mercaptopropyl) methylsiloxane) - dimethylsiloxane copolymer;	
(PDMS-SH100) poly(mercaptopropyl) methylsiloxane	
PEO100 Poly (ethylene oxid) Mn:100000	
PEO300 Poly (ethylene oxid) Mn:300000	
PEO600 Poly (ethylene oxid) Mn:600000	
PEO1000 Poly (ethylene oxid) Mn:1000000	
Tetraallyl PEO 100-1000k Poly (ethylene oxid)-	

Allyl Mn:100000 - 1000000	
Dimethacrylate-PEO 100-1000k Poly(ethylene oxide) dimethacrylate Mn:100000 - 1000000	
Diallyl PEO 100-1000k Poly(ethylene oxide) - diallyl Mn:100000 - 1000000	
diacrylate-PEO 100-1000k Poly(ethylene oxide) dimethacrylate Mn:100000 - 1000000	
Divinyl Tri(ethylene glycol) divinyl ether	
TMPDE Trimethylolpropane diallyl ether	
TMPDE-COOH Trimethylolpropane diallyl ether	

TMPDE-O-X X is any active agent mentioned above	
2-Allyloxyethanol	
4-(2-(allyloxy)ethoxy)-4-oxobutanoic acid	
Allyl-O-X X is any active agent mentioned above	
diacrylate-3 Tetra(ethylene glycol) diacrylate	
diacrylate-7 Poly(ethylene glycol) diacrylate	
TMPDE-COOH Trimethylolpropane diallyl ether	

TMPDE-Anhydride Trimethylolpropane diallyl ether	
Dimethacrylate-PEG 3.4k Poly(ethylene glycol) dimethacrylate Mn:3400	
Dimethacrylate PEG 20k Poly(ethylene glycol) dimethacrylate Mn:20000	
Dimethacrylate PEG 100k Poly(ethylene glycol) dimethacrylate Mn:100000	
Poly (PVA1-co-Allyl) Allylic functionalized Poly (vinyl alcohol): Mn: 1000-500000 m= (50 to 99%) Substitution degree (SD) n(SD)= (1 to 50%)	

Poly (PVal-co-acrylate) Acrylic functionalized Poly (vinyl alcohol): Mn: 1000-500000 m= (50 to 99%) Substitution degree (SD) n(SD)= (1 to 50%)	
Poly (PVal-co-methacrylate) Methacrylic functionalized Poly (vinyl alcohol): Mn: 1000-500000 m= (50 to 99%) Substitution degree (SD) n(SD)= (1 to 50%)	

Examples

Examples 1-4 describe thermally prepared hydrophilic
 5 coatings based on thiol-ene chemistry and with physically
 entrapped high molecular weight (HMW) PEO.

Example 1

A diacrylate-3-SH4 matrix using dichloromethane as a
 10 solvent, 5% solids.

	Example 1	5 % solids
<i>Lubrication</i>	PEO100	3.0 grams
<i>Solvent</i>	dichloromethane	190 grams
<i>Vinyl comp.</i>	diacrylate-3	3.5 grams
<i>Thiol</i>	SH4	3.5 grams
<i>Initiator</i>	AIBN	35 mg

The procedure below develops lubricous coated latex catheters:

- 5 1) The PEO100 was added to a beaker containing the dichloromethane.
- 2) The diacrylate-3, SH4 and AIBN were added to the clear solution in dark.
- 3) A latex catheter was soaked (30 cm) in the solution for
- 10 5 min at RT.
- 4). The soaked catheter was allowed to dry for 1 min to remove excess solution.
- 5) The catheter was allowed to cure for 60 min in a heated oven at 100°C.
- 15 6) The cured catheter was allowed to reach ambient temperature before testing.

Example 2

A diacrylate-7-SH3 matrix using toluene as a solvent, 2 %
20 solids.

	Example 2	2 % solids
<i>Lubrication</i>	PEO300	4.2 grams
<i>Solvent</i>	toluene	588 grams
<i>Vinyl comp.</i>	diacrylate-7	5.0 grams
<i>Thiol</i>	SH3	2.8 grams
<i>Initiator</i>	AIBN	40 mg

The procedure to develop smoothly coated latex catheters was divided in several steps:

- 1) The PEO300 was added to a beaker containing toluene.
- 2) The mixture was heated until the PEO300 was dissolved
5 and the clear solution was allowed to reach RT.
- 3) The diacrylate-7, SH3 and AIBN were added to the solution in dark.
- 4) A latex catheter was soaked (30 cm) in the solution for 1 min at RT.
- 10 5) The soaked catheter was dried for 1 min to remove excess solution.
- 6) The catheter was allowed to cure for 60 min in a heated oven at 100°C.
- 7) The cured catheter was allowed to reach ambient
15 temperature before testing.

Example 3

A diacrylate-7-SHT3 matrix using THF as a solvent, 2,5 % solids.

20

	Example 3	2.5 % solids
<i>Lubrication</i>	PEO600	0.75 grams
<i>Solvent</i>	toluene	585 grams
<i>Vinyl comp.</i>	diacrylate-7	12.25 grams
<i>Thiol</i>	SHT3	2 grams
<i>Initiator</i>	AIBN	70 mg

The procedure to develop smoothly coated latex catheters was divided in several steps:

- 1) The PEO600 was added to a beaker containing THF.
- 25 2) The mixture was heated until the PEO600 was dissolved and the clear solution was allowed to reach RT.
- 3) The diacrylate-7, SHT3 and AIBN were added to the solution in dark.

4) A latex catheter was soaked (30 cm) in the solution for 1 min at RT.

5) The soaked catheter was dried for 1 min to remove excess solution.

5 6) The catheter was allowed to cure for 60 min in a heated oven at 100°C.

7) The cured catheter was allowed to reach ambient temperature before testing.

10 *Example 4*

A Poly (PVAL-co-acrylate) Mn:30000 with 5% acrylate-tetraethyleneglycol-bis(3-mercaptopropionate) (SH-TEG-SH) matrix using water as a solvent, 2,0 % solids. In PVAL₉₅-co-acrylate₅ the numbers 95 and 5 denote the proportions of
15 different units in the copolymer. PVAL₉₅-co-acrylate₅ thus denotes a copolymer with 95% polyvinylalcohol and 5% acrylate.

	Example 4	2.0 % solids
<i>Lubrication</i>	PEO300	1.5 grams
<i>Solvent</i>	Water	588 grams
<i>Vinyl comp.</i>	(PVAL ₉₅ -co-acrylate ₅)	
	Mn:30000	7.5 grams
<i>Thiol</i>	HS-TEG-SH	3 grams
<i>Initiator</i>	ACVA	70 mg

20 The procedure to develop smoothly coated latex catheters was divided in several steps:

1) The PEO300 and (PVAL₉₅-co-acrylate₅) Mn:30000 were added to a beaker with water.

2) The mixture was stirred at room temperature until the
25 polymers were dissolved and the clear solution.

3) The HS-TEG-SH and ACVA were added to the solution in dark.

- 4) A latex catheter was soaked (30 cm) in the solution for 5 min at RT.
- 5) The soaked catheter was dried for 1 min to remove excess solution.
- 5 6) The catheter was allowed to cure for 2 hours in a heated oven at 90°C.
- 7) The cured catheter was allowed to reach ambient temperature before testing.
- 10 Examples 5-8 describe thermally prepared hydrophilic coatings based on thiol-ene chemistry and with chemically entrapped high molecular weight PEO.

Example 5

- 15 A diacrylate-3-SH4 matrix using dichloromethane as solvent, 5% solids.

	Example 5	5 % solids
<i>Lubrication</i>	PEO100-tetraallyl	2.0 grams
<i>Solvent</i>	dichloromethane	190 grams
<i>Vinyl comp.</i>	diacrylate-3	4.0 grams
<i>Thiol</i>	SH4	4.0 grams
<i>Initiator</i>	AIBN	50 mg

- The procedure below develops lubricous coated latex catheters:
- 20 1) The PEO100-A was added to a beaker containing the dichloromethane.
- 2) The mixture was stirred at room temperature until the PEO was dissolved.
- 25 3) The diacrylate-3, SH4 and AIBN were added to the clear solution in dark.
- 4) A latex catheter was soaked (30 cm) in the solution for 1 min at room temperature.

5) The soaked catheter was allowed to dry for 5 min to remove excess solution.

6) The catheter was allowed to cure for 60 min in a heated oven at 100°C.

5 7) The cured catheter was allowed to reach ambient temperature before testing.

Example 6

A diacrylate-7-SH4 matrix using toluene as a solvent, 4 %
10 solids.

	Example 6	4 % solids
<i>Lubrication</i>	PEO1000-	
	diallyl	4.0 grams
<i>Solvent</i>	Toluene	576 grams
<i>Vinyl comp.</i>	diacrylate-7	14.4 grams
<i>Thiol</i>	SH4	5.6 grams
<i>Initiator</i>	AIBN	100 mg

The procedure to develop smoothly coated latex catheters was divided in several steps:

15 1) The PEO1000-A was added to a beaker containing toluene.

2) The mixture was heated until the PEO1000-A was dissolved and the clear solution was allowed to reach room temperature.

20 3) The diacrylate-7, SH4 and AIBN were added to the solution in dark.

4) A latex catheter was soaked (30 cm) in the solution for 1 min at room temperature.

5) The soaked catheter was dried for 1 min to remove excess solution.

25 6) The catheter was cured for 60 min at 100°C.

7) The cured catheter was allowed to reach ambient temperature before testing.

Example 7

A diacrylate-7-SHT3 matrix using THF as a solvent, 3 % solids.

5

	Example 7	3 % solids
<i>Lubrication</i>	PEO300-diallyl	1.0 grams
<i>Solvent</i>	THF	582 grams
<i>Vinyl comp.</i>	diacrylate-7	14 grams
<i>Thiol</i>	SHT3	3 grams
<i>Initiator</i>	AIBN	90 mg

The procedure to develop smoothly coated latex catheters was divided in several steps:

- 1) The PEO600 was added to a beaker containing THF.
- 10 2) The mixture was heated until the PEO600 was dissolved and the clear solution was allowed to reach room temperature.
- 3) The diacrylate-7, SHT3 and AIBN were added to the solution in dark.
- 15 4) A latex catheter was soaked (30 cm) in the solution for 1 min at room temperature.
- 5) The soaked catheter was dried for 1 min to remove excess solution.
- 6) The catheter was allowed to cure for 60 min in a heated
- 20 oven at 100°C.
- 7) The cured catheter was allowed to reach ambient temperature before testing.

Example 8

- 25 A Poly (PVA1-co-allyl) Mn:15000 with 10% allyl-tetraethyleneglycol-bis(3-mercaptopropionate) (SH-TEG-SH) matrix using water as a solvent, 1,5 % solids. In PVA1₉₀-co-acrylate₁₀ the numbers 90 and 10 denote the proportions

of different units in the copolymer. PVal₉₀-co-acrylate₁₀ thus denotes a copolymer with 90% polyvinylalcohol and 10% acrylate.

	Example 8	1.5 % solids
<i>Lubrication</i>	PEO600-diallyl	1.0 grams
<i>Solvent</i>	Water	591 grams
<i>Vinyl comp.</i>	(PVal ₉₀ -co-acrylate ₁₀)	
	Mn:15000	6.5 grams
<i>Thiol</i>	HS-TEG-SH	1.5 grams
<i>Initiator</i>	ACVA	70 mg

5

The procedure to develop smoothly coated latex catheters was divided in several steps:

- 1) The PEO600-diallyl and (PVal₉₀-co-acrylate₁₀) Mn:15000 were added to a beaker with water.
- 10 2) The mixture was stirred at room temperature until the polymers were dissolved and the clear solution.
- 3) The HS-TEG-SH and ACVA were added to the solution in dark.
- 4) A latex catheter was soaked (30 cm) in the solution for
- 15 10 min at room temperature.
- 5) The soaked catheter was dried for 1 min to remove excess solution.
- 6) The catheter was allowed to cure for 1 hour in a heated oven at 100°C.
- 20 7) The cured catheter was allowed to reach ambient temperature before testing.

Examples 9-10 describe thermally prepared hydrophilic coatings based on thiol-ene chemistry, a coating

25 comprising a chemically entrapped HMW PEO and activated functionality.

Example 9

A diacrylate-3/TMPDE-COOH/SH4 matrix using dichloromethane as a solvent, 4 % solids.

	Example 9	4 % solids
<i>Lubrication</i>	Tetraallyl PEO 100	2.0 grams
<i>Solvent</i>	dichloromethane	576 grams
<i>Vinyl comp. I</i>	diacrylate-3	13.5 grams
<i>Vinyl comp. II</i>	TMPDE-COOH	3 grams
<i>Thiol</i>	SH4	5.5 grams
<i>Initiator</i>	AIBN	90 mg

5

A one-pot procedure to develop a lubricous coating for latex catheters with ca 12,5 % of a COOH-activated monomer incorporated. The procedure was divided in several steps:

- 1) The Tetraallyl PEO 100 was added to a beaker containing dichloromethane.
- 2) The mixture was stirred until the Tetraallyl PEO 100 was dissolved and a clear solution was obtained.
- 3) The diacrylate-3, SH4, TMPDE-COOH and AIBN were added to the solution in dark.
- 4) A 30 cm latex catheter was dipped in the solution for 1 min at room temperature.
- 5) The soaked catheter was dried for 30 seconds to remove excess solution.
- 6) The catheter was cured for 60 min at 100°C.
- 7) The cured catheter was allowed to reach ambient temperature before testing.

15

20

Example 10-11 describe systems based on inorganic silicone thiols

Example 10

Matrix: Diaclylate-3 (Tetra(ethylene glycol) diallyl ether)

(PDMS-SH) ((mercaptopropyl 4-6%) methylsiloxane)
 5 dimethylsiloxane copolymer.

Solvent: THF

	Example 10	2.23 % solids
Lubrication	PEO600	1,25 grams
Solvent	THF	500 grams
Vinyl comp.	Diacrylate-7	
	(700g/mol)	5 grams
Thiol	(PDMS-SH)	5 grams
Initiator	AIBN	175 mg

10

The procedure to develop smoothly coated latex catheters was divided in several steps:

- 1) The PEO600 was added to a round-bottom flask containing THF.
- 15 2) The mixture was heated by placing the round-bottom flask in an oil bath of temperature (55-60° C) until all PEO was dissolved and the clear solution was allowed to reach RT. Both upon heating and stirring was necessary to get all PEO dissolved.
- 20 3) The diacrylate-7, PDMS-SH and AIBN were added to the solution in dark.
- 4) A latex catheter was soaked (30 cm) in the solution for 1 min at RT.
- 5) The soaked catheter was dried for 1 min to remove
- 25 excess solution.
- 6) The catheter was allowed to cure for 40 min in a heated oven at 100°C.

7) The cured catheter was allowed to reach ambient temperature before testing.

Example 11

- 5 Matrix: Diacrylate-7 (Tetra(ethylene glycol) diallyl ether)
(PDMS-SH100) poly(mercaptopropyl) methylsiloxane (100 %)
Solvent: DCM

	Example 11	2.23 % solids
Lubrication	PEO600	0,625 grams
	PEO 1million	0,625 grams
Solvent	DCM	500 grams
Vinyl comp.	Diacrylate-7	
	(700g/mol)	5 grams
Thiol	(PDMS-SH100)	5 grams
Initiator	AIBN	175 mg

10

The procedure to develop smoothly coated latex catheters was divided in several steps:

- 1) The PEO600 was added to a round-bottom flask containing THF.
- 15 2) The mixture was heated by placing the round-bottom flask in an oil bath of temperature (55-60° C) until all PEO was dissolved and the clear solution was allowed to reach RT. Both upon heating and stirring was necessary to get all PEO dissolved.
- 20 3) The diacrylate-7, PDMS-SH and AIBN were added to the solution in dark.
- 4) A latex catheter was soaked (30 cm) in the solution for 1 min at RT.
- 5) The soaked catheter was dried for 1 min to remove
- 25 excess solution.

6) The catheter was allowed to cure for 40 min in a heated oven at 100°C.

7) The cured catheter was allowed to reach ambient temperature before testing.

5

Example 12

Friction measurements

The friction coefficients for different coated objects
10 were measured. The friction was measured for a) an
untreated latex catheter (virgin latex catheter), b) a
commercial latex Foley catheter with a friction reducing
coating comprising an isocyanate based hydrogel
(commercial lubricous catheter), and c) latex catheters
15 coated according to example 1 and 3 respectively.

Friction force measurements were performed using a 5566
Instron testing machine with a 10 N load cell. The
crosshead speed was 500 mm/min. The measurements were
20 performed at standard atmosphere (23°C, 50% relative
humidity). The force values in the table are mean forces
measured during:

1. Between 50 and 200 mm travel distance for the
catheter (=starting when the catheter has reached the
25 inside of the cell and continues out on the far end of the
cell).

2. The distance after the tip of the catheter (screw
head) has reached outside the far end of the cell until
stopping (when the rubber cap reaches the cell).

30

Results:

Sample	Average Force (N) $\pm$ std dev
Virgin latex catheter	3.92
Commercial lubricous catheter	1.19 $\pm$ 0.4
Sample manufactured according to example 1	1.14 $\pm$ 0.07
Sample manufactured according to example 1	1.08 $\pm$ 0.31
Sample manufactured according to example 1	0.99 $\pm$ 0.14
Sample manufactured according to example 1	1.25 $\pm$ 0.17
Sample manufactured according to example 1	1.0 $\pm$ 0.08
Sample manufactured according to example 3	0.60 $\pm$ 0.21
Sample manufactured according to example 3	1.02 $\pm$ 0.15

Claims

1. A lubricious coating formed by a reaction of:
 - a. a compound comprising at least two thiol-groups or a disulfide derivative thereof, and
 - 5 b. a compound comprising at least two vinyl-groups, which compound is selected from the group consisting of a divinylether compound, a diacrylate compound, a dimethacrylate compound, a diallyl compound, and a vinyl alcohol copolymer,
- 10 wherein a hydrophilic polymer is associated to said coating.
2. The coating according to claim 1, wherein said compound comprising at least two thiol-groups comprises at
- 15 least one mercaptopropionate group.
3. The coating according to any one of claims 1-2, wherein said compound comprising at least two vinyl-groups is a copolymer of polyvinyl alcohol with at least one side
- 20 chain comprising at least one group selected from the group consisting of a vinylether group, an acrylate group, a methacrylate group, an allyl group.
4. The coating according to any one of claims 1-3,
- 25 wherein said compound comprising at least two vinyl-groups is selected from the group consisting of tri(ethylene glycol)divinylether, trimethylolpropane diallyl ether, tetra(ethylene glycol) diacrylate, poly(ethylene glycol) diacrylate, trimethylolpropane diallyl ether, and
- 30 poly(ethylene glycol dimethacrylate).
5. The coating according to any one of claims 1-4, wherein said compound comprising at least two thiol-groups is selected from the group consisting of pentaerythritol

tetrakis(3-mercaptopropionate), and trimethylolpropane tris(3-mercaptopropionate).

6. The coating according to any one of claims 1-4,
5 wherein said compound comprising at least two thiol-groups is selected from the group consisting of ((mercaptopropyl)methylsiloxane) - dimethylsiloxane copolymer, and poly(mercaptopropyl)methylsiloxane.

10 7. The coating according to any one of claims 1-6, wherein said hydrophilic polymer is poly(ethylene oxide).

8. The coating according to any one of claims 1-7,
15 wherein said hydrophilic polymer has a molecular weight M_w in the range 3000 to 5000000.

9. The coating according to any one of claims 1-8, wherein at least one active agent is incorporated in the coating.

20

10. The coating according to any one of claims 1-9, wherein at least one active agent is covalently bound to at least one compound selected from the group consisting of said compound comprising at least two vinyl-groups,
25 said compound comprising at least two thiol-groups, and said hydrophilic polymer.

11. An article coated with the coating according to any one of claims 1-10.

30

12. The article according to claim 11, wherein said article is selected from the group consisting of a medical device, a medical instrument, a surgical instrument, a catheter, and a medical probe.

13. A method of producing a lubricious coating comprising the sequential steps:

- a. dissolving (i) a hydrophilic polymer, (ii) a
5 compound comprising at least two thiol-groups or a
disulfide derivative thereof, and (iii) a compound
comprising at least two vinyl-groups, which compound is
selected from the group consisting of a divinylether
compound, a diacrylate compound, a dimethacrylate
10 compound, a diallyl compound, and a vinyl alcohol
copolymer, in a solvent,
b. applying said solvent to at least a part of the
surface of an article, and
c. initiating a polymerisation reaction.

15

14. The method according to claim 13, wherein said method further comprises the addition of at least one active agent.

- 20 15. The method according to any one of claims 13-14,
wherein said method further comprises the addition of at
least one active agent covalently bound to at least one of
the ingredients.

- 25 16. The method according to any one of claims 13-15,
wherein said coating is produced on an article selected
from the group consisting of a medical device, a medical
instrument, a surgical instrument, a catheter, and a
medical probe.

30 ---

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2008/051224

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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: A61L, C09D

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

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1086980 A1 (NATIONAL STARCH AND CHEMICAL INVESTMENT HOLDING CORPORATION), 28 March 2001 (28.03.2001), paragraphs [0013], [0021], [0032], [0036], [0043], [0059]	1,2,5,7-12
A	--	3,4,6,13-16
Y	US 6238799 B1 (OPOLSKI, MARGARET P.), 29 May 2001 (29.05.2001), column 2, line 43 - column 3, line 2; column 3, line 30 - line 36; column 5, line 15 - line 29	1,2,5,7-12
A	--	3,4,6,13-16

☒ Further documents are listed in the continuation of Box C.☒ 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

"E" earlier application or patent 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)

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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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"&" document member of the same patent family

Date of the actual completion of the international search

4 February 2009

Date of mailing of the international search report

10-02-2009

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2008/051224

C (Continuation). 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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International patent classification (IPC)

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A61L 29/08 (2006.01)
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