Coating formulation for medical coating

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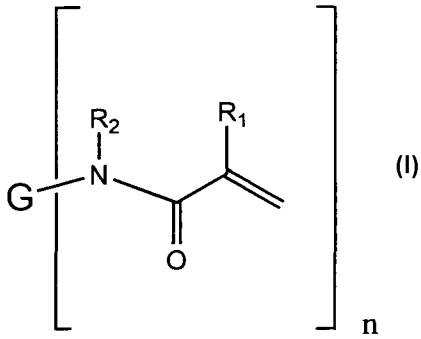

(I)

(57) Abstract: The invention relates to a coating formulation for preparing a medical coating, which coating formulation comprises (a) at least one multifunctional polymerizable compound according to formula (I), wherein G is a residue of a polyfunctional compound having at least n functional groups, wherein each R_1 and each R_2 independently represents hydrogen or a group selected from substituted and unsubstituted hydrocarbons which optionally contain one or more heteroatoms, and wherein n is an integer having a value of at least 2; and (b) at least one initiator.

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COATING FORMULATION FOR MEDICAL COATING

The invention relates to a coating formulation for preparing a medical coating, a medical coating obtainable by curing said coating formulation, a hydrophilic coating, a lubricious coating obtainable by wetting said hydrophilic coating, a coating system, use of a multifunctional polymerizable compound in a medical coating, an article comprising at least one medical, hydrophilic or lubricious coating and a method of forming on a substrate a medical, hydrophilic or lubricious coating.

People have continually attempted to impart certain functional properties to a surface by applying coatings to it. Many medical devices, such as urinary and cardiovascular catheters, syringes, membranes, imaging devices, drug-eluting devices, stents and implants therefore have a coating applied to the outer and/or inner surface. For instance, a hydrophobic surface may be made hydrophilic by applying a hydrophilic coating to it. Anti-microbial properties may be provided by including active substances, for example metal ions and/or other anti-microbial agents in the coating. Similarly, drug-eluting coatings and imaging coatings may be obtained by including drugs and imaging materials in the coating, respectively.

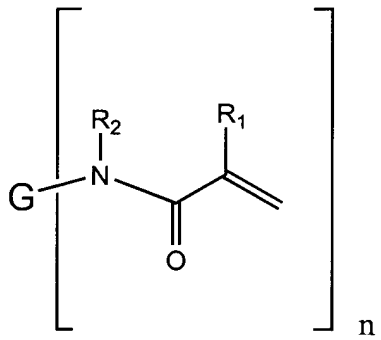
For most medical applications robustness of the coating is one of the most important requirements. In order to achieve sufficient robustness, multifunctional polymerizable compounds are frequently applied in the coating formulation, which are polymerized upon curing in the presence of an initiator. Apart from improved robustness, the use of a multifunctional polymerizable compound may offer a controllable network which will allow tuned release of active substances, for example metal ions, other anti-microbial agents and drugs. In particular for functional coatings, good results have been achieved by physically or covalently entrapping functional components, e.g. functional polymers, into a network of a multifunctional polymerizable compound that provides the necessary adherence to the surface. In that way the functional, e.g. imaging, drug-eluting, protecting or lubricious properties of the functional component are mostly well maintained. When the functional component is a functional polymer, these coatings are often referred to as interpenetrating networks or IPNs. IPNs thus consist of a functional polymer that provides the desired properties to the coating and a multifunctional polymerizable compound that is polymerized in order to form a network of polymers.

The inventors have found that many coatings comprising a multifunctional polymerizable compound show inferior coating performance. Typically

such coatings tend to degrade within a given time, particularly in a hydrated environment causing increase in extractables or leachables. Such extractables or leachables may comprise low molecular and/or polymeric compounds and/or particles which may be vital to the function of the coating. The extractables or leachables may have for example an antimicrobial, anti-thrombogenic, imaging, bioactive, and/or signalling function. Degradation of said coatings typically results in loss of properties such as ability to hydrate and maintain hydration, loss of lubricious properties, loss of patient comfort, loss of imaging properties, increased risk of infection due to the residue being left on the tissue surface, uncontrolled release and co-elution problems for biologically active components, and/or lack of mechanical robustness, as demonstrated by the fact that parts of the coating are easily removed from the coated article upon rubbing.

The problem to be solved is therefore to provide a coating formulation which comprises a multifunctional polymerizable compound and an initiator, and which results in robust and consistent coatings.

It has now surprisingly been found that such coating formulations can be obtained by using a multifunctional polymerizable compound according to formula (1)

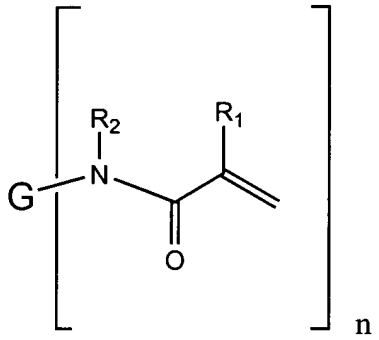


wherein G is a residue of a polyfunctional compound having at least n functional groups, wherein each R_1 and each R_2 independently represent hydrogen or a group selected from substituted and unsubstituted hydrocarbons which optionally contain one or more heteroatoms, preferably hydrogen or a C1-C20 hydrocarbon, more preferably hydrogen or a C1-C20 alkyl; and wherein n is an integer having a value of at least 2, preferably 2-100, more preferably 2-8, in particular 2 or 3.

The invention thus relates to a coating formulation for preparing a

medical coating, which coating formulation comprises:

(a) at least one multifunctional polymerizable compound according to formula (1)



wherein G is a residue of a polyfunctional compound having at least n functional groups, wherein each R_1 and each R_2 independently represent hydrogen or a group selected from substituted and unsubstituted hydrocarbons which optionally contain one or more heteroatoms, preferably hydrogen or a C1-C20 hydrocarbon, more preferably hydrogen or a C1-C20 alkyl; and wherein n is an integer having a value of at least 2, preferably 2-100, more preferably 2-8, in particular 2 or 3; and

(b) at least one initiator.

It has surprisingly been found that the coating formulation according to the invention results in better coating performance compared to conventional coating formulations.

The multifunctional polymerizable compound (a) may be used in more than 0 %, based on the total weight of the dry coating, for example more than 1 %, or more than 2%. The multifunctional polymerizable compound can be present in the coating formulation up to 100%, 90 %, 80 %, 70 %, 60 % or 50, based on the total weight of the dry coating. The skilled person can vary the amount of multifunctional polymerizable compound within the above ranges to obtain the desired properties for his application.

Hereinafter all percentages of components given in the application are based on the total weight of the dry coating.

Generally multifunctional polymerizable compound (a) has a number average molecular weight (Mn) of 500 g/mol or more, preferably 750 g/mol or more, more preferably 1000 g/mol or more. Generally multifunctional polymerizable compound (a) has a number average molecular weight (Mn) of 100,000 g/mol or less,

preferably 10,000 g/mol or less, more preferably 6,000 g/mol or less, in particular 2,000 g/mol or less. Multifunctional polymerizable compounds with an Mn within the preferred ranges show a favorable cross-link density, i.e. open enough to give room to functional components and dense enough to provide sufficient mechanical robustness.

Apart for multifunctional polymerizable compound (a) as defined above, i.e. with n ≥2, the composition may also comprise species according to formula (1) wherein n = 1, i.e. molecules comprising only one reactive moiety. These mono-functional molecules may also be part of the network formed after curing. The average number of reactive moieties per molecule according to formula (1) is preferably in the range of about 1.2 to about 64, more preferably in the range of about 1.2 to about 16, most preferably in the range of about 1.2 to about 8.

In one embodiment of the invention multifunctional polymerizable compound (a) is soluble in a polar solvent. Within the context of the invention this means that according to this embodiment at least 1 g, preferably at least 3 g, more preferably at least 5 g, in particular at least 10 g of multifunctional polymerizable compound (a) can be dissolved in 100 g of the polar solvent at 25 °C. Examples of suitable polar solvents include water and C1-C6 alcohols, in particular methanol, ethanol, propanol, isopropanol, butanol, isobutanol and t-butanol.

In one embodiment of the invention multifunctional polymerizable compound (a) comprises at least one moiety containing a heteroatom. Within the context of the invention a heteroatom is understood to be a non-carbon, non-hydrogen atom. Examples of suitable hereoatoms include oxygen atoms (O), nitrogen atoms (N), sulfur atoms (S) and phosphor atoms (P).

In one embodiment of the invention G is a residue of a hydrophilic polyfunctional compound, preferably chosen from the group consisting of polyethers, polyesters, polyurethanes, polyepoxides, polyamides, poly(meth)acrylamides, poly(meth)acrylics, polyoxazolidones, polyvinyl alcohols, polyethylene imines, polypeptides and polysaccharides, such as cellulose or starch or any combination of the above, more preferably a polymer comprising at least one polyethylene glycol or polypropylene glycol block. The use of a hydrophilic polyfuctional compound is particularly advantageous if the coating needs to have hydrophilic and/or lubricious properties.

In multifunctional polymerizable compound (a) of formula (1) R_1 preferably represents hydrogen, CH_3 or CH_2OH. Particularly suitable are multifunctional polymerizable compounds wherein R_1 and R_2 both represent hydrogen or wherein R_1

represents CH_3 and R_2 represents hydrogen.

Examples of suitable multifunctional polymerizable compounds according to the invention are polyether based (meth)acrylamides, for example polyethylene glycol diacrylamide and polyethylene glycol dimethacrylamide. Commercially available polyether multifunctional amines which can be used to produce multifunctional (meth)acrylamide multifunctional polymerizable compounds include poly(ethylene glycol) bis(3-aminopropyl) terminated, Mw = 1500 (Aldrich); PEG diamine (purely ethylene oxide units) P2AM-2 (molecular weight 2K), P2AM-3 (3.4K), P2AM-6 (6K), P2AM-8 (8K) and P2AM-10 (10K) (Sunbio), JEFFAMINE® D-230 polyetheramine, JEFFAMINE® D-400 polyetheramine, JEFFAMINE® D-2000, JEFFAMINE® D-4000, JEFFAMINE® XTJ-500 (ED-600), JEFFAMINE® XTJ D501 (ED-900), JEFFAMINE® XTJ-502 (ED-2003), JEFFAMINE® XTJ-590 diamine, JEFFAMINE® XTJ-542 diamine, JEFFAMINE® XTJ-548 diamine, JEFFAMINE® XTJ-559 diamine, JEFFAMINE® XTJ-556 diamine, JEFFAMINE® SD-231 (XTJ584), JEFFAMINE® SD401 (XTJ-585), JEFFAMINE® T-403 polyetheramine, JEFFAMINE® XTJ-509 polyoxypropylenetriamine, JEFFAMINE® T-5000 polyetheramine, and JEFFAMINE® ST-404 polyetheramine (XTJ-586).

The coating formulation according to the invention can be cured in the presence of initiator (b). The term "to cure" includes any way of treating the formulation such that it forms a firm or solid coating. In particular “curing” is understood to refer to physical or chemical hardening or solidifying by any method, for example heating, cooling, drying, crystallization or curing as a result of a chemical reaction, such as radiation-curing or heat-curing. In the cured state all or part of the components in the coating formulation may be cross-linked forming covalent linkages between all or part of the components, for example by using UV or electron beam radiation. However, in the cured state all or part of the components may also be ionically bonded, bonded by dipole-dipole type interactions, via Van der Waals forces or hydrogen bonds.

The coating formulation according to the invention can for example be cured using electromagnetic radiation, for example visible or UV light, electro-beam, plasma, gamma or IR radiation, in the presence of an initiator, for example a photo-initiator or thermal initiator, to form the medical coating. Examples of photo-initiators that can be used in the medical coating are free-radical photo-initiators, which are generally divided into two classes according to the process by which the initiating radicals are formed. Compounds that undergo unimolecular bond cleavage upon irradiation are termed Norrish Type I or homolytic photo-initiators. A Norrish Type II

photo-initiator interacts with a second molecule, i.e. a synergist, which may be a low molecular weight compound of a polymer, in the excited state to generate radicals in a bimolecular reaction. In general, the two main reaction pathways for Norrish Type II photo-initiators are hydrogen abstraction by the excited initiator or photo-induced electron transfer. The mechanisms are further explained in WO06/056482.

Examples of suitable Norrish Type I or free-radical photo-initiators are benzoin derivatives, methylolbenzoin and 4-benzoyl-1,3-dioxolane derivatives, benzilketals, α,α-dialkoxyacetophenones, α-hydroxy alkylphenones, α-aminoalkylphenones, acylphosphine oxides, bisacylphosphine oxides, acylphosphine sulphides, halogenated acetophenone derivatives, and the like. Commercial examples of suitable Norrish Type I photoinitiators are Irgacure 2959 (2-hydroxy-4'-(2-hydroxyethoxy)-2-methyl propiophenone), Irgacure 651 (benzildimethyl ketal or 2,2-dimethoxy-1,2-diphenylethanone, Ciba-Geigy), Irgacure 184 (1-hydroxy-cyclohexyl-phenyl ketone as the active component, Ciba-Geigy), Darocur 1173 (2-hydroxy-2-methyl-1-phenylpropan-1-one as the active component, Ciba-Geigy), Irgacure 907 (2-methyl-1-[4-(methylthio)phenyl]-2-morpholino propan-1-one, Ciba-Geigy), Irgacure 369 (2-benzyl-2-dimethylamino-1-(4-morpholinophenyl)-butan-1-one as the active component, Ciba-Geigy), Esacure KIP 150 (poly {2-hydroxy-2-methyl-1-[4-(1-methylvinyl)phenyl]propan-1-one}, Fratelli Lamberti), Esacure KIP 100 F (blend of poly {2-hydroxy-2-methyl-1-[4-(1-methylvinyl)phenyl]propan-1-one} and 2-hydroxy-2-methyl-1-phenyl-propan-1-one, Fratelli Lamberti), Esacure KTO 46 (blend of poly {2-hydroxy-2-methyl-1-[4-(1-methylvinyl)phenyl]propan-1-one}, 2,4,6-trimethylbenzoyldiphenyl-phosphine oxide and methylbenzophenone derivatives, Fratelli Lamberti), acylphosphine oxides such as Lucirin TPO (2,4,6-trimethylbenzoyl diphenyl phosphine oxide, BASF), Irgacure 819 (bis (2,4,6-trimethylbenzoyl)-phenyl-phosphine-oxide, Ciba-Geigy), Irgacure 1700 (25:75% blend of bis (2,6-dimethoxybenzoyl)2,4,4-trimethyl-pentyl phosphine oxide and 2-hydroxy-2-methyl-1-phenyl-propan-1-one, Ciba-Geigy), and the like. Also mixtures of type I photo-initiators can be used.

Examples of Norrish Type II photo-initiators that can be used in the medical coating formulation according to the invention include aromatic ketones such as benzophenone, xanthone, derivatives of benzophenone (e.g. chlorobenzophenone), blends of benzophenone and benzophenone derivatives (e.g. Photocure 81, a 50/50 blend of 4-methyl-benzophenone and benzophenone), Michler's Ketone, Ethyl Michler's Ketone, thioxanthone and other xanthone derivatives like Quantacure ITX (isopropyl thioxanthone), benzil, anthraquinones (e.g. 2-ethyl anthraquinone),

coumarin, or chemical derivatives or combinations of these photoinitiators.

Preferred is a photo-initiator that is water-soluble or can be adjusted to become water-soluble. Polymeric photo-initiators may also be used.

In one embodiment of the invention the coating formulation further comprises a functional species (c), which is capable of providing a function to a coating. Examples of such functional species include functional polymers, e.g. hydrophilic polymers, imaging materials, drugs, and anti-thrombogenic materials. If the functional species is a functional polymer it may be synthetic or bio-derived and can be a blend or a copolymer.

Within the context of the invention the term polymer is used for a molecule comprising two or more repeating units. In particular it may be composed of two or more monomers which may be the same or different. As used herein, the term includes oligomers and prepolymers. Usually polymers have a number average weight (Mn) of about 500 g/mol or more, in particular of about 1000 g/mol or more, although the Mn may be lower in case the polymer is composed of relatively small monomeric units. Herein and hereinafter the Mn is defined as the Mn as determined by light scattering.

In one embodiment of the invention the functional species (c) is a hydrophilic polymer, which is capable of providing hydrophilicity to a coating and may be synthetic or bio-derived and can be a blend or a copolymer. As a hydrophilic polymer in principle any polymer may be used that is suitable to provide a hydrophilic coating. In particular, suitable is such a polymer that is polymerisable, graftable and/or cross-linkable in the presence of an initiator.

The presence of a hydrophilic polymer is particularly useful in case a coating is required that is hydrophilic and, upon wetting with a wetting fluid, lubricious. For some medical applications, such as urinary or cardiovascular catheters, such a coating preferably acts as a lubricant to facilitate insertion of the device into and removal from the body and/or to facilitate drainage of fluids from the body. Lubricious properties are also required so as to minimize soft tissue damage upon insertion or removal. Especially, for lubrication purposes, such medical devices may have a hydrophilic surface coating or layer which becomes lubricious and attains low-friction properties upon wetting, i.e. applying a wetting fluid for a certain time period prior to insertion of the device into the body of a patient.

Within the context of the invention "lubricious" is defined as having a slippery surface. A coating on the outer or inner surface of a medical device, such as a

catheter, is considered lubricious if (when wetted) it can be inserted into the intended body part without leading to injuries and/or causing unacceptable levels of discomfort to the subject. In particular, a coating is considered lubricious if it has a friction as measured on a Harland FTS5000 Friction Tester (HFT) of 20 g or less, preferably of 15 g or less, at a clamp-force of 300 g, a pull speed of 1 cm/s, and a temperature of 22 °C. The protocol is as indicated in the Examples.

The term "wetted" is generally known in the art and – in a broad sense – means "containing water". In particular the term is used herein to describe a coating that contains sufficient water to be lubricious. In terms of the water concentration, usually a wetted coating contains at least 10 wt% of water, based on the dry weight of the coating, preferably at least 50 wt%, based on the dry weight of the coating, more preferably at least 100 wt% based on the dry weight of the coating. For instance, in a particular embodiment of the invention a water uptake of about 300-500 wt% water is feasible. Examples of wetting fluids are treated or untreated water, water-containing mixtures with for example organic solvents or aqueous solutions comprising for example salts, proteins or polysaccharides. In particular a wetting fluid can be a body fluid.

Generally the functional, in particular hydrophilic polymer has a number average molecular weight (Mn) in the range of about 8,000 to about 5,000,000 g/mol, and preferably is a polymer with a Mn in the range of about 20,000 to about 3,000,000 g/mol and more preferably in the range of about 200,000 to about 2,000,000 g/mol. The Mn is the value as determined by light scattering.

The functional polymer may for instance be a prepolymer, *i.e.* a polymer comprising one or more polymerisable groups, in particular one or more radically polymerisable groups such as one or more vinyl groups.

However, also a functional polymer which is free of such polymerisable groups may be cured in the presence of an initiator, in particular by the formation of grafts when the formulation is exposed to light.

The functional, in particular hydrophilic, polymer may be non-ionic or ionic or a mixture of non-ionic and ionic polymers.

Non-ionic polymers include but are not limited to poly(lactams), for example polyvinylpyrollidone (PVP), polyurethanes, homo- and copolymers of acrylic and methacrylic acid, polyvinyl alcohol, polyvinylethers, maleic anhydride based copolymers, polyesters, vinylamines, polyethylene imines, polyethylene oxides,

poly(carboxylic acids), polyamides, polyanhydrides, polyphosphazenes, cellulosics, for example methyl cellulose, carboxymethyl cellulose, hydroxymethyl cellulose, and hydroxypropyl cellulose, heparin, dextran, polypeptides, for example collagens, fibrins, and elastin, polysacharrides, for example chitosan, hyaluronic acid, alginates, gelatin, and chitin, polyesters, for example polylactides, polyglycolides, and polycaprolactones, polypeptides, for example collagen, albumin, oligo peptides, polypeptides, short chain peptides, proteins, and oligonucleotides.

In particular for polyvinylpyrrolidone (PVP) and polymers of the same class, a polymer having a molecular weight corresponding to at least K15, more in particular K30, even more in particular K80 is preferred. Particular good results have been achieved with a polymer having a molecular weight corresponding to at least K90. Regarding the upper limit, a K120 or less, in particular a K100 is preferred. The K-value is the value as determinable by the Method W1307, Revision 5/2001 of the Viscotek Y501 automated relative viscometer. This manual may be found at www.ispcorp.com/products/hairscin/index_3.html.

If an ionic polymer is used for (c) it may be a polyelectrolyte chosen from the group as defined below for component (d).

If a functional, in particular hydrophilic polymer (c) is present, it may be used in more than 0 wt% of the coating formulation, for example more than 1 wt%, more than 2 wt%, or more than 10 weight %, based on the total weight of the dry coating. The functional polymer can be present in the coating formulation up to 99 wt%, however, more often the functional polymer will be used up to 50, 60, 70, 80 or 90 wt%, based on the total weight of the dry coating.

In one embodiment of the invention the coating formulation according to the invention may comprise an ionic compound (d), such as a low molecular weight salt or a polyelectrolyte, preferably a polyelectrolyte, in order to further improve the dry-out time of a hydrophilic coating. Herein "ionic" may also refer to "ionizable", as long as at least part of the ionizable groups is in the ionized form in the hydrophilic coating. Hereinafter such groups are named after their ionized form. Herein polyelectrolytes are defined as a high molecular weight linear, branched or cross-linked polymers composed of macromolecules comprising constitutional units, in which between 5 and 100 % of the constitutional units are in the ionized form in the hydrophilic coating. Herein a constitutional unit is understood to be for example a repeating unit, for example a monomer. A polyelectrolyte herein may refer to one type of polyelectrolyte

composed of one type of macromolecules, but it may also refer to two or more different types of polyelectrolytes composed of different types of macromolecules.

Polyelectrolytes can for example be used to improve the dry-out time of a lubricious coating. Considerations when selecting a suitable polyelectrolyte are its solubility and viscosity in aqueous media, its molecular weight, its charge density, its affinity with the supporting network of the coating and its biocompatibility. Herein biocompatibility means biological compatibility by not producing a toxic, injurous or immunological response in living mammalian tissue. Preferably the polyelectrolytes have a number average molecular weight (Mn) of between 1,000 to 1,000,000 g/mol.

Examples of ionic groups that may be present in the polyelectrolyte are ammonium groups, phosphonium groups, sulfonium groups, carboxylate groups, sulfate groups, sulfinic groups, sulfonic groups, phosphate groups, and phosphonic groups. Such groups are very effective in binding water. In one embodiment of the invention the polyelectrolyte also comprises metal ions. Metal ions, when dissolved in water, are complexed with water molecules to form aqua ions $[M(H_2O)_x]^{n+}$, wherein x is the coordination number and n the charge of the metal ion, and are therefore particularly effective in binding water. Metal ions that may be present in the polyelectrolyte are for example alkali metal ions, such as Na^+ or K^+. When the polyelectrolyte comprises quaternary ammonium groups, anions such as halogenides, for example Cl^-, Br^-, I^- and F^-, and also sulphates, nitrates, carbonates and phosphates may be present.

Suitable polyelectrolytes are for example salts of homo- and co-polymers of acrylic acid, methacrylic acid, maleic acid, fumaric acid, and sulfonic acid, and quaternary ammonium salts and mixtures and/or derivatives thereof. Examples of suitable polyelectrolytes are polyacrylamide-co-acrylic acid sodium salt, polyacrylic acid sodium salt, polymethacrylic acid sodium salt, polyacrylamido-2-methyl-1-propanesulfonic acid sodium salt, poly(4-styrene sulfonic acid) sodium salt, poly(acrylamide-co-dialkyl ammonium chloride), quaternized poly[bis-(2-chloroethyl)ether-alt-1,3-bis[3-(dimethylamino)propyl]urea], polyallylammonium phosphate, poly(diallyldimethylammonium chloride), poly(sodium trimethyleneoxyethylene sulfonate), poly(dimethyldodecyl(2-acrylamidoethyl) ammonium bromide), poly(2-N methylpyridiniumethylene iodine), polyvinylsulfonic acids, and salts of poly(vinyl)pyridines, polyethyleneimines, and polylysines.

The ionic compound may also be a low molecular weight salt. In principle any salt can be used as long as it does not negatively affect the performance

of the coating composition or the coating.

The coating formulation according to the invention may comprise 0-90 wt%, 1-80 wt%, 5-50 wt%, or 10-30 wt% of an ionic compound based on the total weight of the dry coating.

In one embodiment of the invention the coating formulation comprises both a functional polymer (c), being a hydrophilic polymer, and an ionic compound (d). In said embodiment the weight to weight ratio of the ionic compound (d) to the hydrophilic polymer (c) is preferably in the range of 1:9 to 9:1, more preferably 1:30 to 1:1, even more preferably 1:10 to 1:5.

It has formerly been found that coatings comprising an ionic compound, in particular a polyelectrolyte, are particularly vulnerable to inferior coating performance. Therefore it is surprising that the coating according to the invention show better properties even in the presence of an ionic compound (d).

The invention relates to a coating formulation for preparing a hydrophilic coating. In one embodiment of the invention coating formulation refers to a liquid coating formulation, e.g. a solution or a dispersion comprising a liquid medium. Herein any liquid medium that allows application of the coating formulation on a surface would suffice. The coating formulation thus further comprises a liquid medium in a sufficient amount to disperse or dissolve the other components of the formulation. The concentration of the liquid medium is usually at least 25 wt. %, preferably at least 40 wt. %, more preferably at least 68 wt.%, 75 wt. %, 80 wt. %, or 85 wt. % of the total weight of the liquid coating formulation. 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 liquid medium in the composition is preferably relatively high. For that reason the total solids content is preferably 20 wt% or less.

The liquid medium may be a single liquid medium or a mixture. It is chosen such that the components can be dissolved or at least dispersed therein. In particular for dissolving or dispersing the functional polymer, if present, it is preferred that the liquid medium comprises a polar solvent. In particular, a liquid is considered polar if it is soluble in water. Preferably it comprises water and/or an organic solvent soluble in water, for example an alcohol, acetone, methylethyl ketone, tetrahydrofuran, dichloromethane, and aqueous mixtures or emulsions thereof, preferably an alcohol, more preferably a C1-C4 alcohol, in particular methanol and/or ethanol. In case of a mixture, the ratio water to organic solvent, in particular one or more alcohols, may be in

the range of about 25:75 to 75:25, in particular 40:60 to 60:40, more in particular 45:55 to 55:45.

The invention also relates to a medical coating obtainable by applying coating formulation according to the invention to a substrate and curing it. The invention further relates to a hydrophilic coating and to a lubricious coating obtainable by wetting said hydrophilic coating applying a wetting fluid, and to the use of a multifunctional polymerizable compound according to formula (1) in a medical coating. Further the invention relates to a medical, hydrophilic or lubricious coating comprising a polymer network comprising multifunctional polymerizable compound (a). In the medical, hydrophilic or lubricious coating multifunctional polymerizable compound (a) is present in its polymerized form, i.e. at least part of the vinyl groups have reacted. In the context of the application "multifunctional polymerizable compound (a)" also refers to the reacted (i.e. polymerized) multifunctional polymerizable compound. Further the invention relates to an article, in particular a medical device or a medical device component comprising at least one medical, hydrophilic or lubricious coating according to the invention and to a method of forming on a substrate the medical, hydrophilic or lubricious coating according to the invention, wherein the coating formulation according to the invention is applied to at least one surface of the substrate, wherein the coating formulation is allowed to cure by exposing the formulation the electromagnetic radiation or heat thereby activating the initiator, and wherein, in case of a lubricious coating, the coating is subsequently wetted in a wetting fluid.

In an embodiment of the invention the medical coating comprises a multifunctional polymerizable compound (a) and at least one functional polymer (c). In the coating formulation which is used to produce said functional coating, the weight ratio of functional polymer (c) to multifunctional polymerizable compound (a) may for example vary between 5:95 and 95:5. In one embodiment of the invention the multifunctional polymerizable compound and the polyelectrolyte(s) are covalently linked and/or physically bound to each other to form a polymer network after curing.

In an embodiment of the invention the functional coating comprises a multifunctional polymerizable compound (a), a functional (e.g. non-ionic hydrophilic) polymer (c) and a polyelectrolyte (d). In the coating formulation which is used to produce said hydrophilic coating, the weight ratio of the sum of polyelectrolyte and non-ionic hydrophilic polymer to multifunctional polymerizable compound may for example vary between 5:95 and 95:5. In one embodiment of the invention the multifunctional polymerizable compound, the non-ionic hydrophilic polymer, and the polyelectrolyte are

covalently linked and/or physically bound to each other to form a polymer network after curing.

The invention also relates to a coating system for preparing a lubricious coating, said coating system comprising a coating formulation according to the invention and a wetting fluid comprising an ionic compound, preferably a polyelectrolyte or a low molecular weight salt.

The invention also relates to a medical, hydrophilic or lubricious coating comprising a multifunctional polymerizable compound comprising a polymer network comprising multifunctional polymerizable compound (a). Said coating may further comprise a functional species (c), e.g. a functional polymer and an ionic species (d), which may originate from the coating formulation or from a wetting fluid.

In an embodiment of the invention the coating formulation according to the invention further comprises at least one surfactant, which can improve the surface properties of the coating. Surfactants constitute the most important group of detergent components. Generally, these are water-soluble surface-active agents comprised of a hydrophobic portion, usually a long alkyl chain, attached to hydrophilic or water solubility enhancing functional groups. Surfactants can be categorized according to the charge present in the hydrophilic portion of the molecule (after dissociation in aqueous solution): ionic surfactants, for example anionic or cationic surfactants, and non-ionic surfactants. Examples of ionic surfactants include Sodium dodecylsulfate (SDS), Sodium cholate, Bis(2-ethylhexyl)sulfosuccinate Sodium salt, Cetyltrimethylammoniumbromide (CTAB), Lauryldimethylamine-oxide (LDAO), N-Laurylsarcosine Sodium salt and Sodium deoxycholate (DOC). Examples of non-ionic surfactants include Alkyl Polyglucosides such as TRITON™ BG-10 Surfactant and TRITON CG-110 Surfactant, Branched Secondary Alcohol Ethoxylates such as TERGITOL™ TMN Series, Ethylene Oxide / Propylene Oxide Copolymers, such as TERGITOL L Series, and TERGITOL XD, XH, and XJ Surfactants, Nonylphenol Ethoxylates such as TERGITOL NP Series, Octylphenol Ethoxylates, such as TRITON X Series, Secondary Alcohol Ethoxylates, such as TERGITOL 15-S Series and Specialty Alkoxylates, such as TRITON CA Surfactant, TRITON N-57 Surfactant, TRITON X-207 Surfactant, Tween 80 and Tween 20.

Typically 0.001 to 1 wt% of surfactant is applied, preferably 0.05-0.5 wt%, based on the total weight of the dry coating.

One or more other additives which may be present in the coating formulation according to the invention are for example amine compounds, for example

diallylamine, diisopropylamine, diethylamine, and diethylhexylamine; antioxidants; water-soluble radical stabilizers; UV absorbers; light stabilizers; (silane) coupling agents; coating surface improvers; heat polymerization inhibitors; leveling agents; surfactants; colorants, for example a pigment or a dye; discolorants; preservatives; dispersing agents; plasticizers; lubricants; solvents; fillers; wettability improvers; urea; and chain transfer agents. The colorant can be a pigment or dye.

The medical coating according to the invention can be coated on an article. The medical coating can be coated on a substrate which may be selected from a range of geometries and materials. The substrate may have a texture, such as porous, non-porous, smooth, rough, even or uneven. The substrate supports the medical coating on its surface. The medical coating can be on all areas of the substrate or on selected areas. The medical coating can be applied to a variety of physical forms, including films, sheets, rods, tubes, molded parts (regular or irregular shape), fibers, fabrics, and particulates. Suitable surfaces for use in the invention are surfaces that provide the desired properties such as porosity, hydrophobicity, hydrophilicity, colorisability, strength, flexibility, permeability, elongation abrasion resistance and tear resistance. Examples of suitable surfaces are for instance surfaces that consist of or comprise metals, plastics, ceramics, glass and/or composites. The medical coating may be applied directly to the said surfaces or may be applied to a pretreated or coated surface where the pretreatment or coating is designed to aid adhesion of the medical coating to the substrate.

In one embodiment of the invention the medical coating according to the invention is coated on a biomedical substrate. A biomedical substrate refers, in part, to the fields of medicine, and the study of living cells and systems. These fields include diagnostic, therapeutic, and experimental human medicine, veterinary medicine, and agriculture. Examples of medical fields include ophthalmology, orthopedics, and prosthetics, immunology, dermatology, pharmacology, and surgery; nonlimiting examples of research fields include cell biology, microbiology, and chemistry. The term "biomedical" also relates to chemicals and compositions of chemicals, regardless of their source, that (i) mediate a biological response in vivo, (ii) are active in an in vitro assay or other model, e.g., an immunological or pharmacological assay, or (iii) can be found within a cell or organism. The term "biomedical" also refers to the separation sciences, such as those involving processes of chromatography, osmosis, reverse osmosis, and filtration. Examples of biomedical articles include research tools, industrial, and consumer applications. Biomedical

articles include separation articles, implantable articles, and ophthalmic articles. Ophthalmic articles include soft and hard contact lenses, intraocular lenses, and forceps, retractors, or other surgical tools that contact the eye or surrounding tissue. A preferred biomedical article is a soft contact lens made of a silicon-containing hydrogel polymer that is highly permeable to oxygen. Separation articles include filters, osmosis and reverse osmosis membranes, and dialysis membranes, as well as bio-surfaces such as artificial skins or other membranes. Implantable articles include catheters, and segments of artificial bone, joints, or cartilage. An article may be in more than one category, for example, an artificial skin is a porous, biomedical article. Examples of cell culture articles are glass beakers, plastic petri dishes, and other implements used in tissue cell culture or cell culture processes. A preferred example of a cell culture article is a bioreactor micro-carrier, a silicone polymer matrix used in immobilized cell bioreactors, where the geometry, porosity, and density of the particulate micro-carrier may be controlled to optimize performance. Ideally, the micro-carrier is resistant to chemical or biological degradation, to high impact stress, to mechanical stress (stirring), and to repeated steam or chemical sterilization. In addition to silicone polymers, other materials may also be suitable. This invention may also be applied in the food industry, the paper printing industry, hospital supplies, diapers and other liners, and other areas where hydrophilic, wettable, or wicking articles are desired.

The medical device can be an implantable device or an extracorporeal device. The devices can be of short-term temporary use or of long-term permanent implantation. In certain embodiments, suitable devices are those that are typically used to provide for medical therapy and/or diagnostics in heart rhythm disorders, heart failure, valve disease, vascular disease, diabetes, neurological diseases and disorders, orthopedics, neurosurgery, oncology, ophthalmology, and ENT surgery.

Suitable examples of medical devices include, but are not limited to, a stent, stent graft, anastomotic connector, synthetic patch, lead, electrode, needle, guide wire, catheter, sensor, surgical instrument, angioplasty balloon, wound drain, shunt, tubing, infusion sleeve, urethral insert, pellet, implant, blood oxygenator, pump, vascular graft, vascular access port, heart valve, annuloplasty ring, suture, surgical clip, surgical staple, pacemaker, implantable defibrillator, neurostimulator, orthopedic device, cerebrospinal fluid shunt, implantable drug pump, spinal cage, artificial disc, replacement device for nucleus pulposus, ear tube, intraocular lens and any tubing used in minimally invasive surgery.

Articles that are particularly suited to be used in the present invention include medical devices or components such as catheters, guidewires, stents, syringes, metal and plastic implants, contact lenses, medical tubing, and extracorporeal devices.

The coating formulation can be applied to the substrate by for example dip-coating. Other methods of application include spray, wash, vapor deposition, brush, roller, curtain, spin coating and other methods known in the art.

The thickness of the medical coating according to the invention may be controlled by altering soaking time, drawing speed, viscosity of the coating formulation and the number of coating steps. Typically the thickness of a medical coating on a substrate ranges from 0.05-300 μm, preferably 0.1-200 μm.

To apply the medical coating on the substrate, a primer coating may be used in order to provide a binding between the medical coating and the substrate. The primer coating is often referred to as the primary coating, base coat or tie coat. Said primer coating is a coating that facilitates adhesion of the medical coating to a given substrate, as is described in for example WO02/10059. The binding between the primer coating and the medical coating may occur due to covalent or ionic links, hydrogen bonding, physisorption or polymer entanglements. These primer coatings may be solvent based, water based (latexes or emulsions) or solvent free and may comprise linear, branched and/or cross-linked components. Typical primer coatings that could be used comprise for example polyether sulfones, polyurethanes, polyesters, including polyacrylates, as described in for example US6,287,285, polyamides, polyethers, polyolefins and copolymers of the mentioned polymers.

In particular, the primer coating comprises a supporting polymer network, the supporting network optionally comprising a functional, for example hydrophilic, polymer entangled in the supporting polymer network as described in WO2006/056482 A1. The information with respect to the formulation of the primer coating is herewith incorporated by reference.

A primer layer as described in WO2006/056482 A1 is in particular useful for improving adherence of a coating comprising a hydrophilic polymer such as a polylactam, in particular PVP and/or another of the above identified hydrophilic polymers, on a surface having about the same or a lower hydrophilicity.

One embodiment of the invention relates to an article - in particular a medical device, more in particular a catheter - comprising a coating, which coating comprises at least two layers: an inner and an outer layer, of which the inner layer (*i.e.*

a layer between the outer layer and the surface) is a primer layer, comprising a supporting polymer network which is composed of a supporting polymer selected from the group consisting of polyethers, polyesters, polyurethanes, polyepoxides, polyamides, poly(meth)acrylamides, poly(meth)acrylics, polyoxazolidones, polyvinyl alcohols, polyethylene imines, polypeptides and polysaccharides, such as cellulose or starch or any combination of the above, more preferably a polymer comprising at least one polyethylene glycol or polypropylene glycol block, including copolymers comprising a polyether and/or polythioether moiety, and the outer layer is a functional layer comprising a multifunctional polymerizable compound (a) according to the invention, optionally a hydrophilic polymer, and optionally a surfactant. The hydrophilic polymer may advantageously be chemically coupled (cross-linked and/or grafted) to each other, to the multifunctional polymerizable compound and/or the primer layer.

In an embodiment of the invention the surface of the article is subjected to oxidative, photo-oxidative and/or polarizing surface treatment, for example plasma and/or corona treatment in order to improve the adherence of the coating which is to be provided. Suitable conditions are known in the art.

Application of the formulation of the invention may be done in any manner. Curing conditions can be determined, based on known curing conditions for the photo-initiator and polymer or routinely be determined.

In general, curing may be carried out at any suitable temperature depending on the substrate, as long as the mechanical properties or another property of the article are not adversely affected to an unacceptable extent.

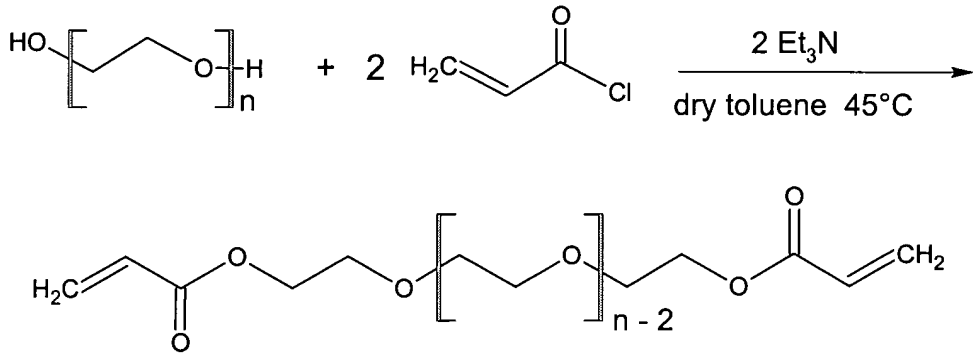
Intensity and wavelength of the electromagnetic radiation can routinely be chosen based on the photo-initiator of choice. In particular, a suitable wavelength in the UV, visible or IR part of the spectrum may be used.

The invention will be further illustrated by the following examples.

Examples

1. Synthesis of multifunctional polymerizable compounds

1.1 Synthesis of PEG-diacrylate; PEGDA



$PEG_{4000}DA$

PEG (150 g, 75 mmol OH, Biochemika Ultra from Fluka [95904], #427345/1, OH-value: 28.02 mg KOH/g, 499.5 meq/kg, Mn: 4004 mol/g) was dissolved at 45°C in 350 mL of dry toluene (Merck, pro analysis, dried on molsieves (4Å)) under nitrogen atmosphere, Irgacure 1035 (0.2 g ~ 0.15 w%, Ciba Specialy Chemical) was added as a radical stabilizer. The PEG/toluene solution was distilled azeotropically overnight (50°C / 70 mbar) leading the condensing toluene over 4Å mol sieves. It is important to determine accurately the hydroxyl value for each batch of PEG by OH titration (see analysis) to calculate the amount of acryloyl chloride (Merck, for synthesis, stored at 5°C and used as received) to be added and to determine the conversion during the reaction.

Triethylamine (9.10 grams, 90 mmol, Aldrich, 99.5%, kept under nitrogen atmosphere and is used as received) was added to the reaction mixture, followed by the drop wise addition over 1 h of acryloyl chloride (8.15 grams, 90 mmol, (Merck, for synthesis, is stored at 5°C and used as received) dissolved in 50 mL of dry toluene. The Acryloyl chloride and triethyl amine used should be colorless liquids. The reaction mixture was stirred for 2 to 4 hours at 45°C under nitrogen atmosphere. During the reaction the temperature was kept at 45°C to prevent crystallization of PEG.

To check the conversion a sample was withdrawn from the reaction mixture, dried and dissolved in deuterated chloroform, trifluoro acetic anhydride (TFAA) was added and a ^{1}H-NMR spectrum was recorded. TFAA reacts with any remaining hydroxyl groups to form a trifluoro acetic ester, which can be easily detected using

^{1}H-NMR spectroscopy (see analysis). When the conversion was < 98% (± 0.5 %) an additional 10 mmol of acryloyl chloride and triethylamine were added to the reaction mixture allowing it to react for one additional hour.

At a conversion > 98% (± 0.5 %) the warm solution was quickly filtrated to remove triethyl amine HCl salts. Approximately 300 mL of toluene was removed under vacuum (50°C, 20 mbar). The remaining solution was kept at 45°C in a heated dropping funnel and added drop wise to a 1 L of diethyl ether (cooled on an ice bath, Merck). The ether suspension was cooled for 1 additional hour before the PEG diacrylate product was obtained by filtration. The product was dried overnight at room temperature under reduced air atmosphere (300 mbar). Yield: 80-90 % as white crystals.

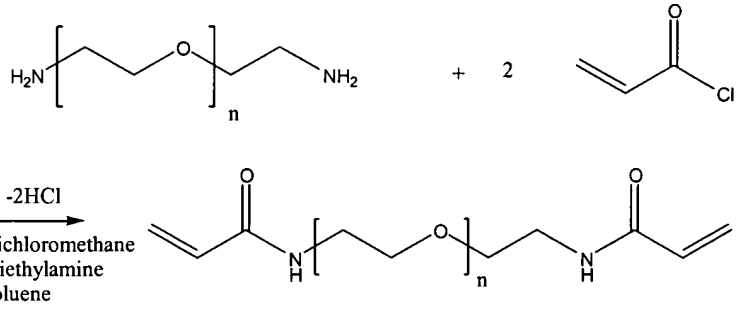
NMR: 300 MHz ^{1}H-NMR spectrum of $PEG_{4000}DA$ in $CDCl_3$ (TMS). 6.40 (doublet, 2H), 6.15 (multiplet, 2H), 5.8 (doublet, 2H), CH_2=CH- and CH_2=C*H*-; 4.3 (triplet, 4H), -(C=O)OCH_2-; 3.75 (triplet, 4H), -(C=O)OCH_2CH_2-; 3.65 (multiplet, 370H), -OCH_2CH_2O-.

The NMR pattern confirmed the formation of $PEG_{4000}DA$.

The IR pattern confirmed the formation of $PEG_{4000}DA$.

The synthesis and characterization of $PEG_{2000}DA$ was similar to synthesis and characterization of $PEG_{4000}DA$. Instead of PEG_{4000} (M_r 3500-4500; Biochemika Ultra from Fluka), PEG_{2000} (M_r 1900-2200; Biochemika Ultra from Fluka) was used.

1.2 Synthesis of PEG-diacrylamide; $PEG(AM)_2$



20 g (13.3 mmol) of PEG-diamine (M_n 1500 g/mol; Aldrich) was azeotropically distilled in 400 mL of toluene under nitrogen, removing about 100 mL of toluene. The solution was cooled at room temperature under nitrogen and then cooled

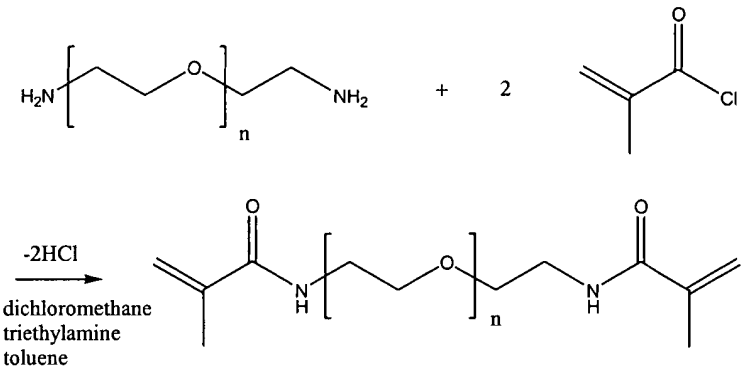
in an ice bath. 50 mL of dichloromethane (Merck) were added. 4.04 g (39.7 mmol) of triethylamine was added dropwise followed by the dropwise addition of 3.48 g (39.7 mmol) of acryloyl chloride (used without further purification). The reaction proceeded overnight under nitrogen. The solution was cooled in an ice bath to precipitate NEt_3.HCl salts and was then filtrated. After adding 1% (w/w) Irganox 1035, the filtrate was concentrated under vacuum. The concentrate was redissolved in 75 mL of dichloromethane, followed by precipitation in 1.5 L ice cold diethyl ether. The product was collected by filtration and subsequent washing with diethyl ether.

^{1}H-NMR ($CDCl_3$, 22°C) δ (TMS) = 6.7 ppm (2H, –N*H*-); 6.2 & 6.1 ppm (4 H, C*H*$_2$=CH-); 5.6 ppm (2H, CH_2=C*H*-); 3.6 ppm (164H, -O-C*H*$_2$-C*H*$_2$- and -O-C*H*$_2$-C*H*$_2$-CH_2-); 1.8 ppm (4H, -O-CH_2-CH_2-C*H*$_2$-).

The NMR spectrum confirmed the formation of PEG(AM)$_2$. From the integration of the NMR peaks at 6.2 and 6.1 ppm, respectively 1.8 ppm, about 99% of the PEG-diamine was estimated to be converted into PEG(AM)$_2$.

The IR spectrum confirmed the formation of PEG(AM)$_2$.

1.3 Synthesis of PEG-dimethacrylamide; PEG(MAM)$_2$



Synthesis: similar to synthesis of PEG-diacrylamide.

Instead of acryloyl chloride, methacryloyl chloride (Acros) was used.

^{1}H-NMR ($CDCl_3$, 22°C) δ (TMS) = 6.8 ppm (2H, –N*H*-); 5.7 & 5.3 ppm (4H, C*H*$_2$=C); 3.6 ppm (164H, -O-C*H*$_2$-C*H*$_2$- and -O-C*H*$_2$-C*H*$_2$-CH_2-); 1.95 ppm (C*H*$_3$ methacrylamide); 1.8 ppm (4H, -O-CH_2-CH_2-C*H*$_2$-).

The NMR pattern confirmed the formation of PEG(MAM)$_2$. From the integration of the NMR peaks at 5.7 and 5.3 ppm, respectively 1.8 ppm, about 90% of the PEG-diamine was estimated to be converted into PEG(MAM)$_2$.

The IR pattern confirmed the formation of $PEG(MAM)_2$.

1.4 Synthesis of $PTGL1000(T\text{-}H)_2$

In a dry inert atmosphere toluene diisocyanate (TDI or T, Aldrich, 95 % purity, 87.1 g, 0.5 mol), Irganox 1035 (Ciba Specialty Chemicals, 0.58 g, 1 wt% relative to hydroxy ethyl acrylate (HEA or H)) and tin(II) 2-ethyl hexanoate (Sigma, 95 % purity, 0.2 g, 0.5 mol) were placed in a 1 liter flask and stirred for 30 minutes. The reaction mixture was cooled to 0 °C using an ice bath. HEA (Aldrich, 96 % purity, 58.1 g, 0.5 mol) was added dropwise in 30 min, after which the ice bath was removed and the mixture was allowed to warm up to room temperature. After 3 h the reaction was complete. Poly(2-methyl-1,4-butanediol)-alt-poly(tetramethyleneglycol) (PTGL, Hodogaya, Mn = 1000 g/mol, 250 g, 0.25 mol) was added dropwise in 30 min. Subsequently the reaction mixture was heated to 60 °C and stirred for 18 h, upon which the reaction was complete as indicated by GPC (showing complete consumption of HEA), IR (displayed no NCO related bands) and NCO titration (NCO content below 0.02 wt%).

2. Formulations

Table 1. Primer formulation Example 1 and Comparative Experiment A:

Compound	Amount (%, w/w)
$PTGL_{1000}(TDI\text{-}HEA)_2$	20
Ethanol (Merck, 96 %, extra pure PH EUR, BP)	79.6
Irgacure 2959 (Aldrich)	0.4

Table 2. Primer formulation Examples 3 and 4 and Comparative Experiment C:

Compound	Amount (g)	Amount (%, w/w)
$PTGL_{1000}(TDI\text{-}HEA)_2$	29.82	5.04
PVP 1.3 M (Povidone, Sigma-Aldrich)	5.25	0.89
Ethanol	555.52	93.84
Irgacure 2959	1.40	0.23

Table 3. Coating formulation Example 1 and Comparative Experiment A:

Compound	Amount (%, w/w)
Multifunctional polymerizable compound: $PEG(AM)_2$ (Example 1) PEGDA (Comp. Exp. A)	20
Ethanol	79.6
Irgacure 2959 (Aldrich)	0.4

Table 4. Coating formulation Example 2 and Comparative Experiment B:

Compound	Amount (%, w/w)
Multifunctional polymerizable compound: $PEG(AM)_2$ (Example 2) PEGDA (Comp. Exp. B)	2
PVP 1.3 M	2
Methanol (Merck pa)	47.96
Water	47.96
Irgacure 2959	0.04
Tween 80 (surfactant, Merck)	0.04

Table 5. Coating formulation Examples 3 and 4 and Comparative Experiment C:

Compound	Amount (g)	Amount (%, w/w)
Multifunctional polymerizable compound: $PEG(AM)_2$ (Example 3) $PEG(MAM)_2$ (Example 4) PEGDA (Comp. Exp. C)	10	4.71 [4.71]
PVP 1.3 M	6.66	3.14 [3.14]
Poly(acrylamide-co-acrylic acid).Na^+ 20% (w/w) acrylamide / 14.5% (w/w) Na^+ (Aldrich)	3.34	1.58 [1.57]
Methanol	95.92	45.24 [45.20]
Water	95.92	45.24 [45.20]
Irgacure 2959	0.2	0.09 [0.09]
[Tween 80]	[0.2]	[0.09]

For the primer formulations as well as for the coating formulations the compounds were dissolved in the solvent under stirring at room temperature. To obtain the coating formulation, a formulation containing all of the compounds indicated above except the multifunctional polymerizable compound was prepared the day before the start of the experiment. The experiment was started with the dissolution of the multifunctional polymerizable compound in this formulation (within one hour the multifunctional polymerizable compound was dissolved).

3. Methods

3.1. NMR measurements

Nuclear magnetic resonance (NMR) measurements were performed on a Varian Inova 300 spectrometer.

NMR experiments were performed at 22°C for the synthesized multifunctional polymerizable compounds dissolved in deuterated chloroform.

3.2. FTIR measurements

Fourier transformed infrared (FTIR) measurements were performed by means of a Perkin Elmer Spectrum One spectrophotometer using the Spectrum software.

The synthesized multifunctional polymerizable compounds were analysed in the form of potassium bromide (Uvasol; Merck) pills.

3.3. Coating on PET film (Example 1 and Comparative Experiment A)

The primer coating formulation according to Table 1 was coated on 120 μm PET foil using Meyenbar # 12 resulting in a dry film thickness of approximately 550 nm. The primer coating formulation was cured with 1.10 J/cm^2 using a D-lamp in air. Subsequently the coating formulations of Table 3 were coated on the primer. The coatings were left for 1 min to dry at 25 °C and were exposed to a single UV pass with 1.10 J/cm^2 using a D-lamp in air. The resulting coating thickness was 2 μm.

3.4. Dip-coating (Examples 3 and 4 and Comparative Experiment C)

Dip-coating was performed with a Harland PCX coater. The intensity of the lamps was measured by means of a Harland UVR 335 (also known as IL 1400) equipped with an International Light detector SED 005#989. Input optic: W#11521, filter

wbs320#27794.

Commercially available medical grade PVC tubing (14 French; Raumedic) was used. The tubing was sealed at the bottom end in order to prevent the coating formulation to reach the inside of the tubing during dipping. A guide wire was inserted in the tubing to fix the tubing and to attach it in the holder of the coater. The tubing was cleaned with lens tissues (Whatman) immersed in a 96% (w/v) aqueous ethanol solution (Merck). The assembly was subsequently dipped in the primer and the topcoat formulations using the coater. The intensity of the lamps was 60 mW/cm^2 on average. The instruction manual of International Light was applied to measure the intensity of the lamps, which is available on the internet: www.intl-light.com. The tubing was dipped in the primer formulation for 10 seconds, moved up with a speed of 0.3 cm/s and cured for 15 seconds with a total dose of 0.9 J/cm^2. The tubing was then dipped in the topcoat formulation for 10 seconds, moved up with a speed of 1.5 cm/s and cured for 360 seconds with a total dose of 21.6 J/cm^2. After drying for a night at room temperature, the lubricity, wear resistance and dry-out time of the coatings were determined.

3.5. Determination of lubricity and wear resistance of coatings (Examples 3 and 4 and Comparative Experiment C)

A Harland FTS 5000 friction tester was used. Friction tester pads were used from Harland Medical Systems, P/N 102692, FTS 5000 Friction Tester Pads, 0.125*0.5*0.125, 60 durometer.

A guide wire was inserted in the tubing to fix the tubing and to attach it in the holder of the friction tester. If the test was to be run wet, the clamp was positioned over the container such that the clamp pads were submerged. The holder was moved down such that the (coated) tubing was also immersed in the water. After immersing for one minute the clamp was closed and fixed the tubing with a clamp force of 300 g. The holder moved up for 10 cm and the friction force was measured during the moving-up. The following parameters were applied: 25 testing cycles, pulling speed 1.0 cm/s, acceleration time 2.0 s. When compounds were leaching out of the coating, the clamp pads of the friction tester were cleaned before each testing cycle.

The dry-out time can be determined by measuring the lubricity (as friction in g) as a function of time. In the test to measure the dry-out time 5 testing cycles were applied with a time interval of 300 s. All other parameters are the same as in the lubricity test.

3.6. Stability tests (Example 1 and Comparative Experiment A): effect of multifunctional polymerizable compound on rub resistance

In order to test the stability of the coating formulations of Example 1 and Comparative Example A the following test was performed.

The films prepared according to 3.3. were incubated in standard phosphate buffer solutions ("PBS buffers") for 110 hours at 45 °C. The rub resistance was immediately checked after annealing using a single index finger tip using 5 drops of water. The results are shown in Table 6.

3.7. Stability tests (Example 2 and Comparative Experiment B): effect of multifunctional polymerizable compound on stability upon incubating the coating

In order to test the stability of the coating formulations of Examples 1-2 the following test was performed.

Coating formulations according to Table 3 were incubated at a temperature of respectively 50, 20, and -20 °C. The amount of respectively PEGDA and $PEG(AM)_2$ were monitored using liquid chromatography-UV (LC-UV). The results are given in Tables 7 and 8.

3.8. Stability tests (Examples 3 and Comparative Experiment C): effect of multifunctional polymerizable compound on the lubricity of the lubricious coating upon incubating the coating formulation

In order to test the stability of the coating formulations used to prepare the lubricious coating the following test was performed

Coating formulations according to Table 5, comprising respectively PEGDA and $PEG(AM)_2$, were incubated at 50°C in a closed container for 0 and 2 days (PEGDA) and 0, 2 and 7 days ($PEG(AM)_2$). Tubings were coated with the resulting coating formulations according to the method described in 3.4.

The tubings coated with the coating formulation comprising PEGDA were tested twice in a series (catheter still immersed in water). After the 25 cycles of the first test the coated tubing was kept in the water for 10 minutes before starting the second test consisting of 25 cycles. The results are given in Figure 1.

The tubings coated with the coating formulation comprising $PEG(AM)_2$ were tested only once. The results are given in Figure 2.

4. Results

4.1. Example 1 and Comparative Experiment A: Stability of the coating determined by rub tests

Table 6. Example 1 and Comparative Experiment A: stability of coatings comprising $PEG(AM)_2$ and PEGDA, respectively.

	Primer	Multifunctional polymerizable compound	Rubbing performance
Example 1	Table 1	$PEG(AM)_2$	-
sComparative Experiment A	Table 1	PEGDA	+

Table 6 shows that the coating according to Example 1, prepared form a coating formulation containing $PEG(AM)_2$, Irgacure 2959 and ethanol is much more stable against rubbing than an equivalent coating containing PEGDA instead of $PEG(AM)_2$

4.2. Example 2 and Comparative Experiment B: Stability of the multifunctional polymerizable compound in the coating formulations

Table 7. Example 2: Stability of $PEG(AM)_2$ expressed in wt% of $PEG(AM)_2$ in formulation.

Incubation time (days)	T = 50 °C	T = 20 °C	T = -20 °C
1	1.9	1.9	1.9
14	2.1	1.8	2.0
27	2.1	2.0	2.2
41	1.9	1.9	1.9
54	1.9	1.9	1.9

Table 8. Comparative Experiment B: Stability of PEGDA expressed in wt% of PEGDA in formulation.

Incubation time (days)	T = 50 °C	T = 20 °C	T = -20 °C
1	2.0	2.0	2.0
14	1.8	1.8	1.8
27	1.7	1.8	1.8
41	1.6	1.6	1.6
54	1.1	1.2	1.4
80	0.9	1.1	1.3

Comparison of the results in Tables 7 and 8 clearly show the improved stability of the coating formulation comprising $PEG(AM)_2$.

4.3. Examples 3 and 4 and Comparative Experiment C

4.3 1. Appearance of coatings

Curing fresh formulations containing $PEG(AM)_2$ (Example 3), $PEG(MAM)_2$ (Example 4) and PEGDA (Comparative Experiment C) resulted in clear coatings. Upon incubating the coating formulations containing PEGDA at 50°C in a closed container, the resulting coatings became more and more opaque. The coating made from the formulation containing $PEG(AM)_2$ and $PEG(MAM)_2$ remained clear upon incubating the formulation at 50°C. This shows the improved stability of the coating formulation.

4.3.2. Lubricity and wear resistance

Figure 1 (Comparative Experiment C) shows that the lubricity, expressed as the friction force (the higher the friction force, the lower the lubricity), is significantly reduced after incubating the coating formulations comprising PEGDA used for preparing the lubricious coatings for 2 days at 50 °C (closed triangles): friction forces in the range 40-80 g were measured. In fact, for the coatings prepared from a PEGDA containing coating formulation parts of the coating were removed by the clamp pads of the friction tester during the first cycles of the first test series. As a result, the coatings were damaged. The second test of the test series after 2 days of incubation therefore resulted in even higher friction forces (open triangles) in the range 70-140 g. This was not observed for the coatings prepared from the fresh coating formulation

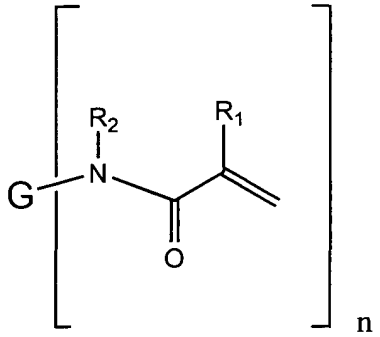
(0 days incubation) (closed and open squares): friction forces of approximately 10 g were measured in both test series.

Figure 2 (Example 3) shows much more favorable results for the lubricious coatings prepared from the formulation containing $PEG(AM)_2$. Even the coatings prepared from coating compositions incubated at 2 or 7 days still feature a high lubricity (low friction force): in all measurements the friction force was below 10 g. All coatings stayed intact during the friction test. The incubation of the formulation had no influence on the wear resistance of the resulting coating.

CLAIMS

1. Coating formulation for preparing a medical coating, which coating formulation comprises

(a) at least one multifunctional polymerizable compound according to formula (1)



wherein G is a residue of a polyfunctional compound having at least n functional groups; wherein each R_1 and each R_2 independently represents hydrogen or a group selected from substituted and unsubstituted hydrocarbons which optionally contain one or more heteroatoms, preferably hydrogen or a C1-C20 hydrocarbon, more preferably hydrogen or a C1-C20 alkyl; and wherein n is an integer having a value of at least 2, preferably 2-100, more preferably 2-8, in particular 2 or 3;

(b) at least one initiator.

2. Coating formulation according to claim 2, wherein G comprises at least one heteroatom.

3. Coating formulation according to claim 1 or claim 2, wherein the multifunctional polymerizable compound according to formula (1) has a number average molecular weight (Mn) of 500 g/mol or more.

4. Coating formulation according to any one of claims 1-3, wherein the multifunctional polymerizable compound according to formula (1) has a number average molecular weight (Mn) of 2000 g/mol or less.

5. Coating formulation according to any one of claims 1-4, wherein the multifunctional polymerizable compound according to formula (1) is soluble in a polar solvent.

6. Coating formulation according to any one of claims 1-5, wherein G is a residue of a hydrophilic polyfunctional compound, preferably chosen from the group consisting of polyethers, polyesters, polyurethanes, polyepoxides, polyamides, poly(meth)acrylamides, poly(meth)acrylics, polyoxazolidones, polyvinyl alcohols, polyethylene imines, polypeptides and polysaccharides, such as cellulose or starch or any combination of the above, more preferably a polymer comprising at least one polyethyleneglycol or polypropylene glycol block.

7. Coating formulation according to any one of claims 1-6, wherein R_1 = H and R_2 = H.

8. Coating formulation according to any one of claim 1-6, wherein R_1 is CH_3 and R_2 = H.

9. Coating formulation according to any one of claims 1-8, further comprising at least one functional component (c), preferably a functional polymer (c).

10. Coating formulation according to claim 9, wherein the functional polymer (c) is a hydrophilic polymer, preferably chosen from the group consisting of poly(lactams), for example polyvinylpyrollidone (PVP), polyurethanes, homo- and copolymers of acrylic and methacrylic acid, polyvinyl alcohol, polyvinylethers, maleic anhydride based copolymers, polyesters, vinylamines, polyethylene imines, polyethyleneoxides, poly(carboxylic acids), polyamides, polyanhydrides, polyphosphazenes, cellulosics, for example methyl cellulose, carboxymethyl cellulose, hydroxymethyl cellulose, and hydroxypropylcellulose, heparin, dextran, polypeptides, for example collagens, fibrins, and elastin, polysacharrides, for example chitosan, hyaluronic acid, alginates, gelatin, and chitin, polyesters, for example polylactides, polyglycolides, and polycaprolactones, polypeptides, for example collagen, albumin, oligo peptides, polypeptides, short chain peptides, proteins, oligonucleotides, and mixtures thereof.

11. Coating formulation according to claim 9, wherein the hydrophilic polymer is a polyelectrolyte chosen from the group consisting of polyacrylamide-co-acrylic acid sodium salt, polyacrylic acid sodium salt, polymethacrylic acid sodium salt, polyacrylamido-2-methyl-1-propanesulfonic acid sodium salt, poly(4-styrene sulfonic acid) sodium salt, poly(acrylamide-co-dialkyl ammonium chloride), quaternized poly[bis-(2-chloroethyl)ether-alt-1,3-bis[3-(dimethylamino)propyl]urea] and poly(diallyldimethylammonium chloride),

polyallylammonium phosphate, poly(diallyldimethylammonium chloride), poly(sodium trimethyleneoxyethylene sulfonate), poly(dimethyldodecyl(2-acrylamidoethyl) ammonium bromide), poly(2-N methylpyridiniumethylene iodine), polyvinylsulfonic acids, salts of poly(vinyl)pyridines, polyethyleneimines, and polylysines, and mixtures thereof.

12. Coating formulation according to any one of claims 1-11 further comprising an ionic compound, preferably a polyelectrolyte as defined in claim 10 or a low molecular salt.

13. Coating formulation according to any one of claims 1-12, further comprising at least one surfactant.

14. Coating formulation according to any one of claims 1-13, further comprising a polar solvent.

15. Coating system for preparing a lubricious coating, said coating system comprising a coating formulation according to any one of claims 10-14, and a wetting fluid comprising an ionic compound, preferably a polyelectrolyte or a low molecular weight salt.

16. Medical coating obtainable by curing a medical coating formulation according to any one of claims 1-14.

17. Medical coating according to claim 16, which medical coating is a hydrophilic medical coating.

18. Lubricious medical coating obtainable by wetting a hydrophilic medical coating according to claim 17 applying a wetting fluid.

19. Lubricious medical coating according to claim 18, wherein the wetting fluid comprises an ionic compound, preferably a polyelectrolyte or a low molecular weight salt.

20. Lubricious medical coating obtainable by curing a coating formulation and wetting the obtained coating, wherein a coating system according to claim 15 is used.

21. Medical, hydrophilic or lubricious coating comprising a polymer network comprising a multifunctional polymerizable compound (a) as defined in Claim 1.

22. Use of a multifunctional polymerizable compound according to formula (1) in a medical coating.

23. Article comprising at least one medical, hydrophilic medical or lubricious medical coating according to any one of claims 16-20.

24. Article according to claim 23, wherein the article is a medical device or component.

25. Medical device or component according to claim 24 comprising a catheter, medical tubing, guidewire, a stent or a membrane.

26. Method of forming on a substrate a medical, hydrophilic or lubricious coating, the method comprising

- applying a coating formulation according to any one of claims 1-14 to at least one surface of the article;
- allowing the coating formulation to cure by exposing the formulation to electromagnetic radiation thereby activating the initiator;
- and, in case of a lubricious coating, subsequently wetting the coating in a wetting fluid.

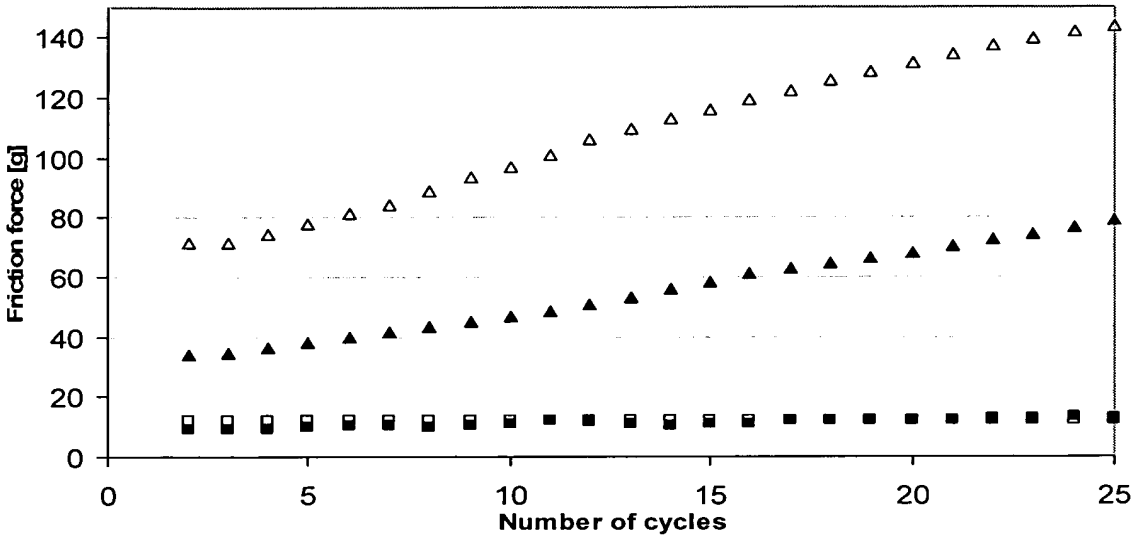


Figure 1/2: Comparative Example C. Friction forces obtained for PVC tubing coated with primer and a topcoat with PEGDA (Comparative Experiment C), immersed in distilled water. The coating was prepared from a topcoat formulation incubated at 50°C for 0 (squares) and 2 (triangles) days. The closed and open squares/triangles represent the first and second test on the coatings, respectively

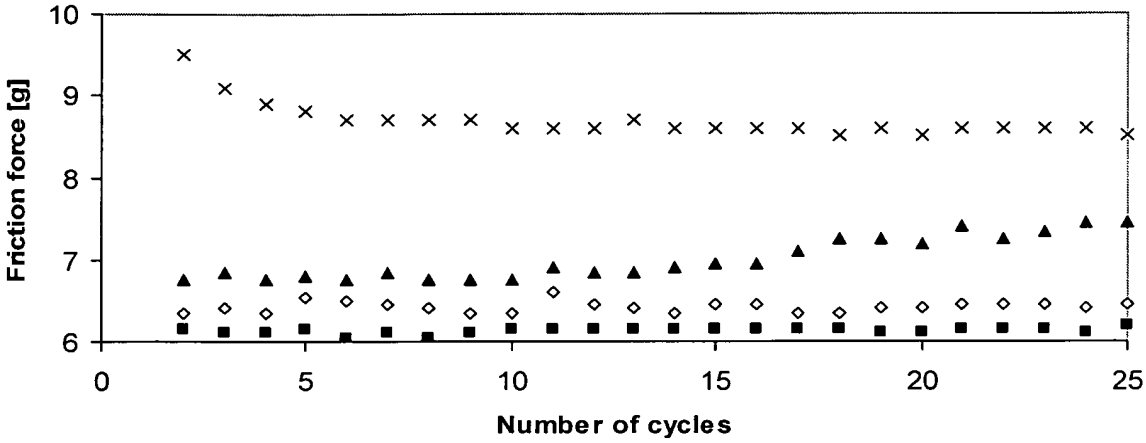


Figure 2/2: Example 3. Friction forces obtained for PVC tubing coated with primer and a topcoat without $PEG(AM)_2$ (x) and with $PEG(AM)_2$, immersed in distilled water. The coating containing $PEG(AM)_2$ was prepared from a topcoat formulation incubated at 50°C for 0 (◇), 2 (■) and 7 (▲) days.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/007985

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L27/34 C09D151/08 C08F290/06

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 C09D C08F

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

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
5 December 2007	14/12/2007

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/007985

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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