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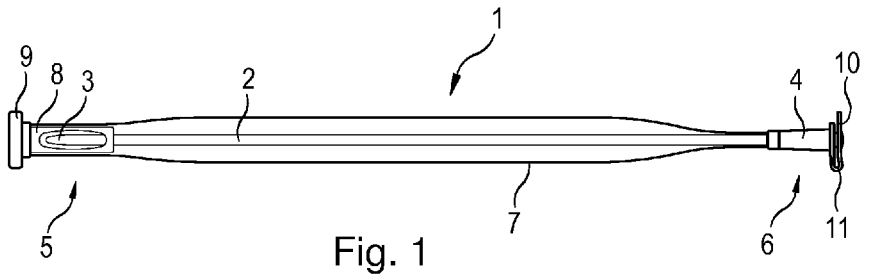


Fig. 1

(57) Abstract: The present invention relates to a method of producing a ready-to-use medical device with a functional coating comprising the steps of bringing the medical device, at least with its functional coating, in contact with a composition which prevents or retards degradation of the functional coating and sterilizing the medical device and the composition via radiation. It is the object of the invention to provide a method which leads to an improved product, namely an improved ready-to-use medical device which does not suffer a loss of quality during sterilization and storage. To solve this object, the composition comprises carboxymethyl cellulose or a derivative or salt thereof and/or an antioxidant selected from gallic acid or a derivative thereof.

WO 2018/029279 A1

Method for Sterilizing a Medical Device

The present invention relates to a method of producing a ready-to-use medical device with a functional coating comprising the steps of bringing the medical device, at least with its functional coating, in contact with a composition which prevents or retards degradation of the functional coating, and sterilizing the medical device and the composition via radiation.

It is well-known to coat medical devices with a lubricant on the outer surface, in particular to facilitate insertion into or removal from the body, e.g. blood vessels, digestive organs and the urinary system. Such lubricious properties are also desired to minimize tissue damage during insertion or removal. Usually, medical devices may be provided with a hydrophilic coating on which a wetting fluid is applied so that the hydrophilic coating is activated and obtains its highly lubricious properties. The wetting fluid protects the coating from drying out and thereby maintains the lubricious properties of the coating. Examples of wetting fluids are water, mixtures of water and organic solvents, a body fluid, and aqueous solutions of salts, e.g. a saline solution having physiological osmolarity.

Medical devices can be wetted immediately prior to use or can be stored in the wetting liquid. In particular, it is desirable to provide a ready-to-use medical device, wherein the medical device with a hydrophilic coating is in a sterile package that contains enough wetting liquid to keep the coating wetted and thereby lubricious. Such ready-to-use medical devices offer high convenience for the user because they do not require any preparation steps prior to use.

Suitable sterilization techniques for medical devices, such as autoclaving or radiation, are well-known to the skilled person. During sterilization, reactive intermediates can be formed which may attack the hydrophilic coating of the medical device. Furthermore, most hydrophilic coatings lose their water retention and lubricious properties when the coatings are stored for an extended period of time and/or after sterilization using autoclaving or radiation.

WO-A-00/30696 describes a method for sterilizing a medical device comprising a hydrophilic coating by irradiation. It was found that the water retention can be increased and the coefficient of friction can be kept low by adding hydrophilic polymers to the wetting liquid.

WO-A-2007/137669 discloses the use of a compound selected from aliphatic compounds, alicyclic compounds and antioxidants for protecting a hydrophilic coating which is sterilized by irradiation, in particular γ-radiation or Electron-beam (E-beam) radiation.

WO-A-2013/017547 is directed to the use of a wetting liquid which may comprise water in an amount of 0 to 4.9 wt% and has a boiling point higher than 100 °C and a viscosity lower than 500 mPa × s.

WO-A-2006/037321 is directed to a medical device having a wetted hydrophilic coating and which is in a ready-to-use form. The wetted hydrophilic coating comprises a coating composition comprising a hydrophilic polymer and a wetting agent comprising water and one or more lubricants.

WO-A-2006/117372 describes sterilization of medical devices having a wetted hydrophilic coating using radiation. It was found that when adding hydrophilic polymers to the storage medium prior to sterilization a high water retention and low friction is maintained when the medical device is stored in water.

WO-A-2011/076217 discloses a medical device having a hydrophilic coating and having been sterilized while in contact with a swelling medium comprising a low molecular polyol and a separate buffer and a method for sterilizing the set. The pH is in the range of from 4 to 7.4. Furthermore, ascorbic acid may be added as a stabilizing agent but that depends on the substrate, type of hydrophilic coating and gamma irradiation dosage.

WO-A-2010/003419 relates to a medical device having a hydrophilic coating and having been sterilized while in contact with a liquid comprising a hydrophilic polymer and a separate buffer and to a method for sterilizing a medical device.

WO-A-2012/085107 is directed to a hydrophilic catheter assembly including a wetting fluid. The wetting fluid is preferably an aqueous liquid such as sterile water or saline.

WO-A-2008/151074 discloses a lubricant for medical devices which is suitable for radiation sterilization.

WO-A-00/47494 relates to a storage package which contains a medical device having a coated surface which exhibits a reduced friction when wetted.

WO-A-2007/065721 and WO-A-2007/065722 describe a hydrophilic coating composition which when cured results in a hydrophilic coating. It was found that a lubricious coating with a prolonged and improved dry-out time may be obtained when a polyelectrolyte is included in the hydrophilic coating composition from which said lubricious coating is formed.

However, the compositions of the above-cited prior art are highly specific and can only be used for a limited group of hydrophilic coatings. Furthermore, the particular components present in the composition have to be selected depending on the hydrophilic coating or the base solution.

The object of the present invention is to provide a method of producing a ready-to-use medical device with a functional coating which overcomes the disadvantages of the prior art and which results in a medical device with a functional coating that does not degrade during sterilization and has a hydrolytic stability so that a high quality is ensured during the intended shelf-life of the wetted medical device. Furthermore the method and the components used in the method should be non-toxic, easy to prepare, radiation sterilizable, inexpensive and cost effective, and usable for a large variety of functional coatings.

This object is achieved by using a composition which comprises carboxymethyl cellulose (CMC) or a derivative or salt thereof and/or an antioxidant selected from gallic acid or a derivative thereof.

This object is further achieved by the use of a wetting agent comprising the composition comprising carboxymethyl cellulose or a derivative or salt thereof and/or an antioxidant selected from gallic acid or a derivative thereof.

Preferred embodiments are set forth in the subclaims 2 to 19.

With the method according to the present invention, a variety of ready-to-use medical devices with different hydrophilic coating systems, gels and material substrates can be produced. A variation in the additional components of the composition according to the present invention allows further enhancement of the wetting agent performance in relation to solubility stability and coating stability.

The composition is used as wetting agent that activates the functional coating of the medical device so that the desired low friction properties of the functional coating are achieved.

Bringing the medical device in contact with the composition which prevents or retards degradation of the functional coating may be achieved by dipping, or by spraying, or vaporizing the composition and contacting the medical device with the vaporized composition.

In addition, the composition used in the method according to the present invention is non-toxic, can be easily prepared and can be sterilized via radiation. Furthermore, the composition can be used in a variety of different wetting agents irrespective of the base solutions. The wetting agents the comprise a base solution, the composition and may comprise further components. Unexpectedly, the composition according to the present invention prevents or retards the

degradation of a functional coating on a medical device due to reactive species formed during exposure to radiation even at high irradiation energy levels.

When a medical device with a functional coating is sterilized by radiation, highly reactive intermediates may be formed from water, e.g. •OH, H_2O^+, superoxide (HO_2/O_2^-), H_2O_2. These reactive moieties may cause reactions that are detrimental to the coating of the medical device. The composition used in the method of the present invention is more reactive to a reactive moiety formed from water due to the irradiation than the coating. Furthermore, the composition used in the method of the present invention may be able to inactivate a radical which may be formed in a polymer in the coating thereby preventing uncontrolled and/or excessive crosslinking of the coating, and/or chain scission of the coating polymer, and/or delamination from the substrate.

The composition used in the method of the present invention is formulated to act as a highly protective agent for all types of functional coating systems subjected to high radiation levels when the coated substrate, i.e. the medical device, is subjected to or exposed in a wetted environment comprising the composition. Furthermore, because the composition according to the present invention acts as protective agent, the functional coating of the medical device can be formed by crosslinking via an UV initiator, heat, γ-ray, X-ray or E-beam. The composition of the present invention is not limited to a particular coating material type or curing system, but it can be used for any functional coating.

In addition, the composition in accordance with the present invention also acts as highly protective agent for hydrolytic degradation, in particular long term hydrolytic degradation. The wetting agent in accordance with the present invention is particularly suitable for protecting a gel like low delicate (hydrated) interpenetrating polymer network from irradiation and also provides hydrolytic stability.

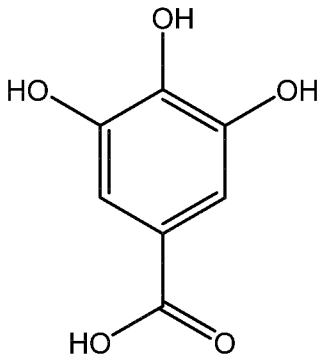
The method according to the present invention uses a composition and a wetting agent comprising the composition which is mobile and in a liquid state, preferably the wetting agent is an aqueous wetting agent containing fully dissolved gallic acid or an ester, amide or oxadiazole derivative of gallic acid and/or CMC or a salt thereof and provides intimate contact with free moving hydrophilic polymer chains of the coating of a medical device. The composition used in the method in accordance with the present invention is mobile and free flowing at the surface of the coating.

The composition of the present invention allows preventing or retarding degradation of a functional coating from both, irradiation and hydrolytic degradation. In particular, the composition and the wetting agent of the present invention are capable of protecting even

polymers such as gel networks, e.g. lightly crosslinked gel networks, and hydrophilic coatings, while in an aqueous environment and under extreme irradiation conditions. The composition and the wetting agent of the present invention further provide hydrolytic stability during the intended shelf-life of a wetted coated product.

The composition of the present invention can comprise carboxymethyl cellulose or a derivative or salt thereof and/or an antioxidant selected from gallic acid or a derivative thereof.

Gallic acid is a benzoic acid having the following structure:



The IUPAC name is: 3,4,5-trihydroxybenzoic acid.

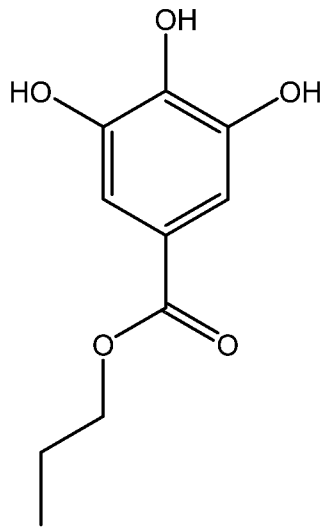
In a variant of the method, the derivative of gallic acid of the composition used in the method is an ester, amide or oxadiazole derivative of gallic acid.

The term “ester derivative of gallic acid” refers to an ester reaction product of an alcohol and gallic acid. The term “amide derivative of gallic acid” refers to the reaction product of an amine and gallic acid. The term “oxadiazole derivative of gallic acid” refers to the reaction product of oxaidazole and gallic acid.

In a preferred embodiment in combination with any of the above or below embodiments, the ester derivative of gallic acid present in the composition which is used in the method is a reaction product of gallic acid and an aliphatic C1 to C16 alcohol, more preferably a reaction product of gallic acid and an aliphatic C1 to C12 alcohol. Most preferably, the ester derivative of gallic acid is selected from propyl gallate, methyl gallate, ethyl gallate, octyl gallate and lauryl gallate or mixtures thereof, in particular, the ester derivative of gallic acid is propyl gallate.

The term “aliphatic alcohol” refers to a saturated linear or branched alcohol.

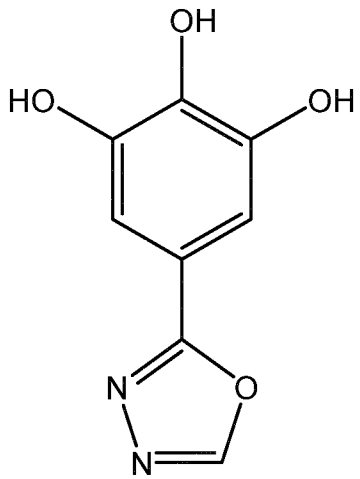
Propyl gallate is the reaction product of gallic acid and propanol and has the following structure:



Other commonly used names are: n-propyl gallate, propyl 3,4,5-trihydroxybenzoate, gallic acid propyl ester, 3,4,5-trihydroxybenzoic acid propyl ester, 3,4,5-trihydroxybenzene-1-propylcarboxylate, CAS No 121-79-9.

In a preferred embodiment in combination with any of the above or below embodiments, in the composition which is used in the method of the present invention, the amide derivative of gallic acid is selected from gallic N,N-dimethylamide, gallic naphtylamide or mixtures thereof.

The oxadiazole derivative of gallic acid has the following structure:

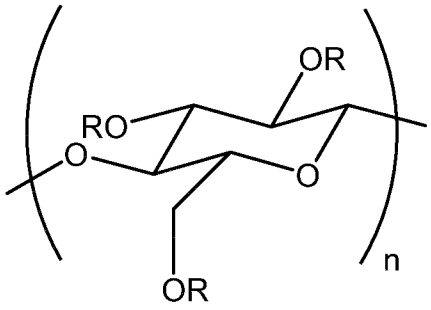


In a preferred embodiment in combination with any of the above or below embodiments, in the composition which is used in the method of the present invention, gallic acid or a derivative thereof is present in an amount of 0.001 to 5% by weight, more preferably 0.01 to 2% by weight, most preferably 0.05 to 0.5% by weight, in particular 0.1 to 0.2% by weight, based on the total

weight of the composition. This is the case if only gallic acid or a derivative thereof is present in the composition and no carboxymethyl cellulose.

Carboxymethyl cellulose (CMC) is a cellulose derivative, wherein some of the hydroxyl groups of the glucopyranose monomers that form the cellulose backbone are replaced with carboxymethyl groups (-CH_2-COOH). It is often used as its sodium salt, sodium carboxymethyl cellulose.

Carboxymethyl cellulose has the following structure:



R = H, CH_2CO_2H

In a preferred embodiment in combination with any of the above or below embodiments, the composition comprises a salt of carboxymethyl cellulose, more preferably the sodium salt of carboxymethyl cellulose. In sodium carboxymethyl cellulose R of the above structural formula is CH_2CO_2Na. Other commonly used names are sodium cellulose glycolate, Na-CMC, cellulose gum, sodium CMC, CAS No 9004-32-4.

The chemical formula of sodium CMC is $[C_6H_7O_2(OH)_x(OCH_2COONa)_y]_n$, where n is the degree of polymerization; x is 1.50 to 2.80; y is 0.2 to 1.50; x + y is 3.0 (y = degree of substitution).

In a further preferred embodiment in combination with any of the above or below embodiments, carboxymethyl cellulose or a derivative or salt thereof is present in an amount of 0.1 to 10 % by weight, more preferably 0.2 to 7 % by weight, particularly preferably 0.2 to 5 % by weight, in particular 1 to 5 % by weight, based on the total weight of the composition. Preferably, carboxymethyl cellulose is present as the sodium salt, i.e. Na-CMC.

In still a further embodiment, the composition comprises carboxymethyl cellulose or a derivative or salt thereof and an antioxidant selected from gallic acid or a derivative thereof, selected from an ester, amide or oxadiazole derivative of gallic acid, more preferably propyl gallate. In this case, gallic acid or a derivative thereof is present in the composition in an amount of 0.001 to 1

% by weight, more preferably 0.01 to 0.5 % by weight, in particular 0.02 to 0.2% by weight, based on the total weight of the composition.

In a preferred embodiment in combination with any of the above or below embodiments, the composition used in the method of the present invention further comprises an aqueous or oil based base solution or a lipid media or a combination thereof.

The term "aqueous solution" refers to any solution having water as its main component, i.e. water is present in an amount at least 50% by weight based on the total weight of the aqueous solution.

The term "oil based solution" refers to a solution comprising one or more oils. Preferably, the oil based solution comprises polyethylene glycol, propylene glycol, glycerol and/or polyvinyl alcohol. Essential oils may be included in an amount up to 0.5% by weight based on the oil based solution. If an oil based solution is used, the oil based solution may be present in an amount of up to 49.8% by weight based on the total composition.

In a preferred embodiment in combination with any of the above or below embodiments, the aqueous base solution of the composition used in the method is selected from distilled water, deionized water, reverse osmosis water, filtered water or a saline solution. More preferably, the aqueous base solution is a saline solution, in particular a saline solution having physiological osmolarity.

In a further preferred embodiment in combination with any of the above or below embodiments, the aqueous base solution is present in the composition used in the method in an amount of 50 to 99.99% by weight, more preferably 85 to 99.8% by weight, in particular 85 to 94% by weight based on the total weight of the composition.

In a further preferred embodiment in combination with any of the above or below embodiments, the aqueous base solution of the composition used in the method is a saline solution having physiological osmolarity. The saline solution is present in the composition in an amount of 85 to 94% by weight based on the total weight of the composition.

In a preferred embodiment in combination with any of the above or below embodiments, the composition used in the method of the present invention is present as a suspension within and/or around the functional coating at least during and after sterilization of the medical device. The term "around" as used herein has the meaning of "in the vicinity" of the coating.

In a further preferred embodiment in combination with any of the above or below embodiments, the composition used in the method of the present invention further comprises a stabilizer, a solution enhancer and/or a buffer solution.

In another preferred embodiment in combination with any of the above or below embodiments, the stabilizer is selected from polylactams, such as polyvinylpyrrolidone (PVP), polyurethanes, homo- and copolymers of acrylic and methacrylic acid, polyvinyl alcohols, polyvinylethers, maleic anhydride based copolymers, polyesters, such as polylactides, polyglycolides, polycaprolactones, and polynucleotides, vinylamines, polyethyleneimines, polyethyleneoxides, polycarboxylic acids, polyamides, polyanhydrides, polyphosphazenes, cellulosics, such as methyl cellulose, carboxymethyl cellulose, hydroxymethylcellulose, hydroxyxpropylcellulose and other polysaccharides, such as chitosans, hyaluronic acids, alginates, gelatins, chitins, heparins, and dextrans, polypeptides/proteins, such as collagens, fibrins, elastins, and albumin. Of these, PVP is particularly preferred.

In a further preferred embodiment in combination with any of the above or below embodiments, the stabilizer is present in the composition used in the method of the present invention in an amount of 0.1 to 40% by weight, more preferably 3 to 20% by weight, most preferably 4 to 12% by weight, and in particular 7 to 12% by weight based on the total weight of the composition.

Because gallic acid and derivatives thereof have a limited solubility in water, a solution enhancer may be added to the composition used in the method of the present invention. In a preferred embodiment in combination with any of the above or below embodiments, the solution enhancer is selected from a polyol, more preferably ethylene glycol, diethylene glycol, propylene glycol, glycerol, in particular propylene glycol.

Under certain conditions and concentrations, carboxymethyl cellulose or the derivative or salt thereof and/or the esters of gallic acid may recrystallize out of the solution over time. When a stabilizer, in particular in the above-mentioned concentrations, is added, no recrystallization occurs and homogeneity of the solution is maintained.

In a further preferred embodiment in combination with any of the above or below embodiments, the solution enhancer, preferably propylene glycol, is present in the composition of the present invention in an amount of 0.1 to 49.8% by weight, more preferably 1 to 20% by weight, in particular 2 to 10% by weight based on the total weight of the composition.

As indicated above, the esters of gallic acid have limited solubility in water, e.g. the solubility of propyl gallate is 3.5 mg/mL. Furthermore, the dissolution rates are slow at room temperature. When adding a polyol such as propylene glycol, the dissolution rate significantly increases

without the necessity of heat. In a preferred embodiment in combination with any of the above or below embodiments, the weight ratio of water or saline solution to propylene glycol is 1.0 to 0.3 to 1.0 to 1.3, preferably 1.0 : 0.7.

If a wetting agent is heated to 45 °C or more, the miscibility of propyl gallate increases. However, propyl gallate can precipitate out of the solution after cooling to form low-order structure entities that resemble needle lattice structures. The addition of propylene glycol prevents or eliminates the necessity of elevating the temperature of the solution. Adding a component to a solution at an elevated temperature can generate a super-saturated solution, i.e a solution which contains more of the dissolved component than it would under normal room temperature conditions. When cooling a super-saturated solution, the dissolved component can precipitate out of the solution. With the addition of propylene glycol, elevating the temperature is no longer required because the propylene glycol increases the dissolvability of the solution for that component. The addition of propylene glycol therefore permits dissolving gallic acid or a derivative thereof at low and ambient temperatures.

If glycerol is employed, it may be necessary to add some heat to the solution in order to achieve full dissolution of the propyl gallate. Furthermore, the sequence of the mixing steps and its effect on the relative dissolution of propyl gallate when all component concentrations and temperatures are kept constant, is as follows:

- addition of propylene glycol to propyl gallate, then addition of saline or distilled water: fast reaction (high rate of dissolution of propyl gallate);
- addition of saline/distilled water to propyl gallate, then addition of propylene glycol: slow reaction (low rate of dissolution of propyl gallate);
- addition of propylene glycol to saline/distilled water, then addition of propyl gallate: fast reaction (high rate of dissolution of propyl gallate);
- employing glycerol instead of propylene glycol: slow reaction (low rate of dissolution of propyl gallate).

The polyol, e.g. propylene glycol, additionally functions as antimicrobial and antifungal agent and therefore delivers antimicrobial and antifungal properties to the composition used in the method of the present invention.

In another preferred embodiment in combination with any of the above or below embodiments, the buffer solution has a pH of 2.0 to 7.4, more preferably 3.0 to 6.5, in particular 3.0 to 4.0. The buffer solution is added to generate solution stability with regard to pH and prevent the

esters of gallic acid from recrystallization. Suitable buffers include monocarboxylic acids such as formic acid, acetic acid, propionic acid, 3-hydroxypropionic acid, 2,3-dihydroxypropionic acid, gluconic acid, benzoic acid, cinnamic acid, lactic acid, mandelic acid, glycolic acid, phenylacetic acid, chlorobenzoic acid, naphtoic acid, toluic acid, N-acetylglycine; dicarboxylic acids such as oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, phthalic acid, isophthalic acid, terephthalic acid, malic acid, tartaric acid, itaconic acid, and fumaric acid; tri- and tetracarboxylic acids such as citric acid and 1,2,3,4-butanetetracarboxylic acid; amino acids such as tryptophan, aspartic acid, glutamic acid, aminobenzoic acid, glycylglycine, glycylglycylglycine, glutathione, N-phenylglycine, carnosine, niacin; aminosulfonic acids; and inorganic acids such as hydrofluoric acid, cyanic acid and nitrous acid.

In another embodiment in combination with any of the above or below embodiments, the composition used in the method of the present invention can comprise 0.01 to 2% by weight of propyl gallate, 0.1 to 40% by weight of PVP, and 0.1 to 49.8% by weight of propylene glycol; more preferably 0.05 to 0.5% by weight of propyl gallate, 3 to 20% by weight of PVP, and 1 to 20% by weight of propylene glycol; in particular 0.1 to 0.2% by weight of propyl gallate, 4 to 12% by weight of PVP, and 2 to 10% by weight of propylene glycol. Particularly preferable is a composition comprising 0.1 to 0.2% by weight of propyl gallate, 4 to 12% by weight of PVP, and 2 to 10% by weight of propylene glycol and a buffer having a pH of 4 to 5.

In still another embodiment in combination with any of the above or below embodiments, the composition in accordance with the present invention comprises 0.1 to 10% by weight of sodium carboxymethyl cellulose, 0 to 1% by weight of propyl gallate, and 1 to 20% by weight of propylene glycol; more preferably 0.2 to 7% by weight of sodium carboxymethyl cellulose, 0.01 to 1% by weight of propyl gallate, and 1 to 15% by weight of propylene glycol; in particular 0.2 to 5% by weight of sodium carboxymethyl cellulose, 0.02 to 0.2% by weight of propyl gallate, and 2 to 10% by weight of propylene glycol, based on the total weight of the composition. Particularly preferable is a composition comprising 0.2 to 2% by weight of sodium carboxymethyl cellulose, 0.02 to 0.2% by weight of propyl gallate, and 2 to 10% by weight of propylene glycol, based on the total weight of the composition, and a buffer having a pH of 4 to 5. Alternatively, particularly preferable is an embodiment composition comprising 2 to 5% by weight of sodium carboxymethyl cellulose, 0% by weight of propyl gallate, and 2 to 10% by weight of propylene glycol, based on the total weight of the composition, and a buffer having a pH of 4 to 5.

In a further preferred embodiment in combination with any of the above or below embodiments, the composition used in the method of the present invention further comprises an antibacterial agent such as a silver salt, an acceptable iodine source such as povidone iodine, chlorhexidine

salts such as the gluconate, actetate, hydrochloride or quaternary antibacterial agents such as benzalkonium chloride or other antiseptics or antibiotics. The presence of antibacterial agents reduces the risk of infection. The composition according to the present invention may further comprise an osmolarity increasing agent such as urea, sodium chloride and/or any salt or organic low molecular weight compound being physiological acceptable and non-irritating for adjusting the ion strength of the coating approximately to the physiological range, the coating preferably being isotonic in use. The composition according to the present invention may also comprise preservatives and pharmaceuticals such as antimicrobial agents and antithrombogenic agents or plasticizers.

In a further embodiment in combination with any of the above or below embodiments, the energy dose of radiation during radiation sterilization is in a range from 1 to 50 kGy, preferably 15 kGy to 45 kGy, more preferably 25 kGy to 45 kGy. Even at high radiation energies up to 50 kGy the composition used in the method of the present invention prevents or retards the degradation of the functional coating on the medical device due to reactive species formed during exposure to radiation.

According to a further variant, the method additionally comprises the following steps:

- providing the medical device;
- coating the medical device at least in parts with the functional coating;
- activating the functional coating of the medical device by bringing it into contact with the composition which prevents or retards degradation of the functional coating; and
- packing the medical device and the composition into a vapour-tight package.

In still a further variant of the method, the medical device is a catheter. Even though the medical device produced by the method and having a functional coating may be any device that should be able to move against body tissue such as an inner wall of a body vessel or the outer surface of the eye, for example a medical tubing, guidewire, canula, stent, stent graft, anastomotic connector, synthetic patch, lead electrode, needle, sensor, surgical instrument, angioplastic balloon, wound drain, shunt, tubing, infusion sleeve, urethal 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, tubing used in minimally

invasive surgery, it is preferred that the medical device is a catheter such as an intraluminal catheter, e.g. a cardiovascular catheter or an intermittent catheter.

Preferably, the functional coating is a hydrophilic coating. However, the term "functional coating" also includes antithrombogenic coatings, gel coatings, hydrophilic polymer coatings, polyvinylalcohol coatings, coatings for contact lenses, coatings based on water soluble polymers used especially in drug delivery systems such as hydrogels, cellulose ethers, povidone, polyethylene glycol, polyacrylamides, polyacrylic acid copolymers, Polylactide-co-Glycolide (PGLA) and derivatives thereof.

In a further variant of the method, the catheter comprises a catheter shaft which is coated with a hydrophilic coating at least along its insertable length and which is tightly surrounded by a retractable sleeve and wherein the retractable sleeve and/or the catheter have a liquid-tight closure at a distal end and at a proximal end so that any liquid present in the retractable sleeve or the catheter shaft remains within the retractable sleeve and the catheter as long as the closure is not broken. In this case, only a small amount of the composition/wetting agent is needed to activate the hydrophilic coating and it can be ensured that the hydrophilic coating stays in the wetted condition during storage.

The composition according to the present invention is able to prevent or retard degradation of functional coatings on a medical device. The composition of the present invention can be easily prepared from non-toxic components and can be used during radiation sterilization. When used during the sterilization of a medical device, no degradation of the functional coating on the medical device from reactive species generated during exposure of radiation occurs in the presence of the composition of the present invention.

Further, the composition in accordance with the present invention is also able to prevent or retard hydrolytic degradation and is particularly suitable for wetted environments.

The following examples further describe the present invention.

Examples

General procedure for the preparation of the propyl gallate solutions:

Propyl gallate is only slightly soluble in water but, with the addition of propylene glycol, the solubility of propyl gallate increases. Propylene glycol has a great affinity to water and is also a viable alternative additive to glycerol from a cost perspective.

1. Using a standard disposable pipette, 5 g of propylene glycol or glycerol was placed in a 200 ml glass beaker.

2. 10 g of 0.9 wt% saline (9 g/L sodium chloride solution) was then added to the propylene glycol or glycerol.

3. 0.01 to 0.5 g of propyl gallate was added to the beaker and distilled water or 0.9 wt% saline (9 g/L sodium chloride solution) was added to amount to 100 ml of solution.

4. Taking the beaker by hand, the contents were gently swirled for about 2 minutes to promote mixing, resulting in the propyl gallate being visibly dissolved. This pre-mixing ratio of saline or water with propylene glycol or glycerol delivers a method that does not require heating of the beaker to achieve complete dissolution of the propyl gallate. However, if glycerol is employed, it may be necessary to add some heat to the solution in order to achieve full dissolution of the propyl gallate. While the addition of glycerol to distilled water/water/saline increases the degree of dissolution and dissolution rate of propyl gallate, it is significantly less effective than propylene glycol. For that reason, it may be necessary to add heat when using glycerol, especially when a relatively high concentration of propyl gallate is being considered (i.e. 0.15 to 0.5 wt% propyl gallate).

5. Other additives such as polyvinylpyrrolidone (PVP; Sigma Aldrich; K60, 45% in H_2O), surfactants such as Tween 20 and 80 (non-ionic agent supplied by Sigma Aldrich), buffer solutions (pH 4.00 (20°C) or citric acid/sodium hydroxide/hydrogen chloride supplied by Merck Chemicals KGaA) may optionally be added after the mixing of the propyl gallate has been accomplished.

6. A magnetic stirrer bar was placed in the beaker and the beaker was placed on a magnetic stirrer (IKA RT5 Magnetic Stirrer). The heat settings were set at zero and the rotation speed was set between the 3 and 4 mark on the stirrer equipment. The contents were stirred slowly for an hour to ensure a homogenous solution.

The amounts of the components are shown in the tables 1-5 below.

<u>General procedure for the preparation of the CMC solutions:</u>

Preparation of sodium carboxylmethyl cellulose (Na-CMC) Pre-Mix:

1. 100 g of deionized water was weighed and poured into a glass beaker.

2. The required amount of Na-CMC as specified by Tables 6 and 7 was weighed.

3. The water was placed on a magnetic stirrer and the stirrer set to 80°C to promote the dispersion and dissolution of the Na-CMC powder.

4. The Na-CMC was slowly added over 2-3 hour period until dissolved into the water (the mixing time may greatly reduce depending on the amount of CMC required).

5. The mixture was allowed to cool to room temperature while stirring of the solution was maintained.

6. When the mixture has cooled, 5 g of buffer (pH 4) was added and stirring was continued for 15-30 minutes.

Preparation of Wetting Agent Pre-mix:

1. The correct amount of propyl gallate in accordance with Tables 6 and 7 was weighed and placed into a 100 mL glass beaker.

2. 5 g of polypropylene glycol was added to the glass beaker containing the propyl gallate.

3. In short succession, 9.5 mL of saline solution was added to the glass beaker containing the mixture of propyl gallate and polypropylene glycol.

4. The glass beaker and its contents was stirred by hand for 2 minutes until all the propyl gallate has visually dissolved in the liquid mixture.

5. Where specified in Table 6 for ultrasonic agitation of the mixture, immediately after adding the 9.5 mL of saline fluid to the propyl gallate and polypropylene glycol mixture, this 100 mL glass beaker (containing all ingredients) was placed into an ultrasonic bath for 30 seconds.

Combining Pre-mixes:

1. Wetting Agent Premix was added into the CMC Premix

2. The contents were stirred employing a magnetic stirrer with no heat

3. Stirring was permitted for 2 hours.

Other additives such as Tween 20 and 80 (non-ionic agent supplied by Sigma Aldrich), buffer solutions (pH 4.00 (20°C); citric acid/sodium hydroxide/hydrogen chloride supplied by Merck

Chemicals KGaA), may optionally be added after mixing of the Na-CMC and/or propyl gallate has been accomplished.

General procedure for the preparation of the test specimen:

Extruded polymer shafts reflecting a diameter of 4.5 mm with an ID of 3.0 mm were selected for the testing. These shafts had been dipped and cured which resulted in a uniform hydrophilic coating along the polymeric tube substrate. It is important to ensure that the same processing parameters of dipping and UV curing of the coating were maintained so as to eliminate any variability in coating integrity. The shaft material used for these series of trials was polyurethane block copolymers and plasticized polyvinyl chloride. The shafts were placed on a cutting matt and the polymeric coated tubes were cut to a length of approximately 200 mm with a sharp blade. The distal end of the shaft was cut at an angle to distinguish the distal end from the proximal end (at the distal end, the coating tends to be slightly thicker and the angle cut provides information for the friction test operator). Latex gloves were worn during all handling and cutting steps of all specimens prepared for friction testing to prevent contamination of the surfaces of specimen substrates.

Friction Testing (Coefficient of Friction - COF):

1. The protocol test program option was selected to access the test parameters.

2. The following information was inputted into the program:
    a. clamp force = 300 g
    b. test speed = 180 mm/minute
    c. test distance = 60 mm.
    d. repeated friction test cycles = 25
    e. speed = 3 cm/s

3. A stainless steel mandrel of appropriate diameter to the inner lumen of the coated test specimen was completely inserted into the test specimen. The tube was positioned with a clamp on the section having a clean level cut (the angled tube cut faced the water container of the friction testing machine).

4. The clamping pads were of 60 DURO supplied by Harland (Part Number 102149).

5. This test assembly was mounted on the Harland Friction Tester FTS 5000 after it had been calibrated.

6. A container was filled with water to a predetermined mark so that the coated test specimen and clamps were submerged prior to testing. The clamp section of the specimen remained out of the water while the angled cut end of the specimen was submerged in the water.

7. The test was started after 30 seconds had elapsed to ensure that the coating was fully hydrated.

8. The force expressed into the clamps was automatically recorded as a graph showing gram force over time.

9. After the test was completed, a reading of average gram force and maximum gram force was presented by the instrument.

10. The COF was calculated by dividing the average gram force reading by 300 grams

11. After each test, a wetted cloth was used to remove any residual coating that may have accumulated on the pads.

Abbreviations:

PG = propyl gallate; supplied by Sigma Aldrich in the form of powder

Na-CMC = sodium carboxymethyl cellulose

PPG = propylene glycol

DW = distilled water

Buffer:

HPCE grade buffer solution with a pH value of 4.0 at 25°C with a concentration of 20 mM sodium citrate (supplied by Sigma Aldrich).

Results:

Example 1: Propyl gallate solutions

a) Effects of glycerol on coating integrity

Table 1

Dosage (kGy)	PG (wt%)	PVP (wt%)	PPG (wt%)	pH Buffer (wt%)	Carrier Solution	Glycerol (wt%)	COF (Number of Friction Cycles; 300 g clamp force)				
							0	5	10	20	25
45	0.2	5	0	0	DW	5	4.2	4.1	4.1	4.1	4.1
45	0.2	5	0	0	DW	0	4.5	4.3	4.3	4.3	4.3

b) Effects of PG concentration on coating integrity

Table 2

Dosage (kGy)	PG (wt%)	PVP (wt%)	PPG (wt%)	pH Buffer (wt%)	Carrier Solution	Glycerol (wt%)	COF (Number of Friction Cycles; 300 g clamp force)				
							0	5	10	20	25
45	0	10	0	0	DW	5	30	90	120	160	190
45	0.2	10	0	0	DW	5	4	4.3	4.2	4.2	4.3
45	0.5	10	0	0	DW	5	4	4.3	4.3	4.3	4.3
45	0.2	5	0	0	DW	5	4.3	4.1	4.1	4.1	4.1

c) Effects of PG concentration on coating integrity

Table 3

Dosage (kGy)	PG (wt%)	PVP (wt%)	PPG (wt%)	pH Buffer (wt%)	Carrier Solution	Glycerol (wt%)	COF (Number of Friction Cycles; 300 g clamp force)				
							0	5	10	20	25
45	0	5	0	0	DW	0	30	70	130	170	220
45	0.2	5	0	0	DW	0	4.2	4.1	4.1	4.1	4.1

d) Effects of PPG concentration on coating integrity

Table 4

Dosage (kGy)	PG (wt%)	PVP (wt%)	PPG (wt%)	pH Buffer (wt%)	Carrier Solution	Glycerol (wt%)	COF (Number of Friction Cycles; 300 g clamp force)				
							0	5	10	20	25
45	0.2	0	0	4 (10)	saline	0	8.0	6.0	6.0	6.0	6.0
45	0.2	0	5	4 (10)	saline	0	6.0	4.5	4.5	4.5	4.5

e) Effects of carrier solution on coating integrity

Table 5

Dosage (kGy)	PG (wt%)	PVP (wt%)	PPG (wt%)	pH Buffer (wt%)	Carrier Solution	Glycerol (wt%)	COF (Number of Friction Cycles; 300 g clamp force)				
							0	5	10	20	25
45	0.2	0	5	4 (10)	saline	0	5.0	4.5	4.5	4.5	4.6
45	0.2	0	5	4 (10)	DW	0	7.0	7.0	6.5	6.5	6.5

As can be seen from the test results, in the absence of propyl gallate, the coefficient of friction (COF) is much higher than in the presence of propyl gallate. Furthermore, the COF increases with an increase in the number of cycles. If propyl gallate is present, the COF is low and almost constant (Table 2, Table 3).

Furthermore, the COF can be adjusted by adding additional additives or by selecting the carrier solution and/or the pH.

Example 2: CMC solutions:

Formulations based on propyl gallate (PG) and sodium carboxymethyl cellulose (Na-CMC) were developed to further enhance the wetting agent performance. The samples were prepared with polypropylene glycol and buffer content maintained constant throughout the study to demonstrate the influence of the main stabilizing component ingredients, i.e. propyl gallate and sodium carboxymethyl cellulose.

The coating integrity and hydrolytic stability of the coating were tested after subjecting the hydrated specimens to 45 kGy gamma irradiation dosages. The primary objective of the wetting

agent is to protect the hydrated hydrophilic coating during the sterilization cycles and secondarily, to provide hydrolytic stability to the coating, reflecting real-world shelf-life product indication.

The hydrolytic stability of the coating was assessed by interpreting the coating frictional stability performance over the 25 frictional cycles after subjecting coated hydrated specimens to accelerated aging for periods of 15 days (T15) and 30 days (T30), respectively, at an ageing temperatures of 50°C. All specimens were subjected to 45 kGy irradiation dosages. Time Zero (T0) directly after exposure captures the isolated effects of gamma irradiation on the coating integrity.

Table 6

Stability of wetting agent formulations after 45 kGy exposure

	Sample 1	**Sample 2**	**Sample 3***	**Sample 4**
PG (wt%)	0.02	0.20	0.02	0.10
PPG (wt%)	5.00	5.00	5.00	5.00
Na-CMC (wt%)	0.20	0	0.20	0.10
Buffer (wt%)	5.00	5.00	5.00	5.00
T0	Meta-stable	stable	stable	stable
T15	Not stable	stable	stable	stable
T30	Meta-stable	stable	stable	stable

* = ultrasonic agitation; T0 = directly after exposure; T15 = after 15 days at 50°C; T30 = after 30 days at 50°C.

After 15 days ageing at 50°C in a hydrated state after 45 kGy exposure, the data indicate that PG provides further stability within the formulation. When comparing Samples 1 and 3, the formulations are identical, but Sample 3 was ultrasonically agitated to promote the dissolution of the propyl gallate (PG) and enhances the efficacy of the PG within the solution and coating. Comparing Sample 3 to Sample 5, suggests that 0.1 wt% of PG and 0.1 wt% of CMC are sufficient to deliver coating stability after irradiation and ageing of the product specimens.

After 30 days ageing at 50°C in a hydrated state after 45 kGy exposure, the data highlights:

- PG at concentrations of 0.2 wt% provide adequate stability alone (Sample 2)
- Ultrasonic agitation enhances the efficacy of PG dissolution (Samples 1 and 3)
- A relative low 1:1 ratio of PG to Na-CMC delivers adequate coating stability (Sample 4).

Further developments were focused on increasing the percentage of Na-CMC within the

formulation. The following results depict Na-CMC concentrations of 2 wt% and 5 wt% and assessing the influence of PG.

Table 7

Stability of wetting agent formulations after 45 kGy exposure

	Sample 5	Sample 6	Sample 7	Sample 8
PG (wt%)	0.20	0	0.02	0
PPG (wt%)	5.00	5.00	5.00	5.00
Na-CMC (wt%)	2.00	2.00	5.00	5.00
Buffer (wt%)	5.00	5.00	5.00	5.00
T0	stable	stable	stable	stable
T15	stable	stable	stable	stable
T30	stable	stable	stable	stable

T0 = directly after exposure; T15 = after 15 days at 50°C; T30 = after 30 days at 50°C.

At T0 after 45 kGy exposure, all formulations exhibited optimum coating friction and wear characteristics. After 15 days ageing at 50°C in a hydrated state after 45kGy exposure, all formulations exhibited optimum coating friction and wear characteristics. After 30 days ageing at 50°C in a hydrated state after 45kGy exposure, all formulations exhibited optimum coating friction and wear characteristics.

Na-CMC delivers excellent stability to the coating and can be used in conjunction with low concentration of PG to further improve the coating stability as indicated by results obtained in Tables 6 and 7.

In the following, a ready-to-use medical device with a functional coating which is produced with the method of the present invention and the method itself are described in more detail with the aid of drawings:

Figure 1 shows a first embodiment of the ready-to-use medical device produced with the method of the present invention,

Figure 2 shows a detail of the medical device of Figure 1,

Figure 3 shows a second embodiment of a ready-to-use medical device produced with the method of the present invention, and

Figure 4 shows a detail of the medical device of Figure 3.

In Figure 1 a first embodiment of a ready-to-use medical device produced with the method of

the present invention is shown. The ready-to-use medical device of the first embodiment is a catheter 1 used for intermittent catheterization. The catheter 1 comprises a catheter shaft 2 with a catheter tip 3 at a distal end 5 and a funnel 4 at a proximal end 6. The catheter shaft 2 is covered with a hydrophilic coating at least along its insertable length. The catheter shaft 2 is surrounded by a retractable sleeve 7. At the proximal end 6, the retractable sleeve 7 is fixed to the catheter shaft 2. The retractable sleeve can also be fixed to the funnel. At the distal end 5, the catheter 1 is provided with an introduction aid 8. The introduction aid 8 is slidably arranged on the catheter shaft 2. That means that the introduction aid 8 can be slid up and down the catheter shaft without any effort. The distal end of the retractable sleeve 7 is fixed to the introduction aid 8. A plug 9 can be inserted in the end of the introduction aid 8 that faces away from the catheter shaft 7 so that a fluid-tight connection or closure between the plug 9 and the introduction aid 8 is formed. The plug 9 preferably has a T-shape. Furthermore, the plug 9 can comprise a reservoir with a wetting agent which comprises the composition as described above. The funnel 4 comprises a cap 10 which is connected to the funnel 4 via a hinge 11. The distal end 6 of the catheter 1 with the funnel 4 and the cap 10 is shown in more detail in Figure 2. For clarity reasons, the sleeve is not shown in Figure 2. The cap 10 is plugged in the funnel 4 so that a liquid-tight closure is achieved. The wetting agent is inserted into the retractable sleeve 7 via the plug 9. Because the plug 9 and the introduction aid 8 as well as the funnel 4 and the cap 10 form liquid-tight closures, the wetting agent remains inside the retractable sleeve 7 and/or the catheter shaft 2 and the outside of the retractable sleeve 7 as well as the outside of the funnel 4 remain dry and can be easily gripped by a user. This catheter set can then be placed in a vapour-tight package (not shown).

Figure 3 shows a second embodiment of a ready-to-use medical device produced with the method of the present invention. In the second embodiment, the ready-to-use medical device is also a catheter 21 used for intermittent catheterization. The catheter 21 comprises a catheter shaft 22 which is provided with a catheter tip 23 at a distal end 25 and with a funnel 24 at a proximal end 26. The catheter shaft 2 is covered with a hydrophilic coating at least along its insertable length. The catheter shaft 22 is enclosed by a retractable sleeve 27. The proximal end of the retractable sleeve 27 is connected to the proximal end 26 of the catheter 21. The retractable sleeve 27 can either be fixed directly to the catheter shaft 22 or to the funnel 24. The distal end 29 of the retractable sleeve 27 is connected to an introduction aid 28 which is slidably arranged on the catheter shaft 22. The introduction aid 28 is pushed back on the catheter shaft 22 so that the retractable sleeve 27 is retracted and the catheter shaft 22 is exposed. The catheter 21 with the catheter shaft 22 and the retractable sleeve 27 arranged thereon is arranged in a vapour-tight package 30. Furthermore, a wetting agent comprising the composition as described above is inserted in the package 30.

In both embodiments, the catheter shaft 2, 22 is coated with a hydrophilic coating, the functional coating, at least along its insertable length. The insertable length of the catheter shaft 2, 22 is the length of the catheter shaft which is inserted in the urethra when the catheter is used. Furthermore, in both embodiments, the wetting agent contacts and activates the hydrophilic coating of the catheter shaft 2, 22. The wetting agent comprises the composition as described above with carboxymethyl cellulose or a derivative or a salt thereof and/or an antioxidant selected from gallic acid or a derivative thereof as described above.

In the following, a method for a producing the catheters 1, 21 as shown above is described. In a first step, the catheter shaft 2, 22 with the catheter tip 3, 23 and the funnel 4, 24 is produced. After that, the catheter shaft 2, 22 is coated with a hydrophilic coating. The retractable sleeve 7, 27 is arranged around the catheter shaft 2, 22 and is connected to the catheter shaft 2, 22 or the funnel 4, 24 at the proximal end of the catheter 1, 21. At the distal end of the catheter 1, 21 an introduction aid 8, 28 is slidably arranged on the catheter shaft 2, 22 and connected to the distal end of the retractable sleeve 7, 27.

In the first embodiment, the funnel 4 is closed with the cap 10 and the plug 9 with the wetting agent contained therein is connected to the introduction aid 8. The complete assembly is then placed in a vapour-tight package (not shown). The wetting agent comprises the composition as described above. The wetting agent is brought into contact with the hydrophilic coating of the catheter shaft 2 so that the hydrophilic coating is activated. The complete package is then submitted to radiation, for example γ-irradiation (see page 1, second to last paragraph), so that all components are sterilized. Because the wetting agent comprises a composition as described above, degradation of the hydrophilic coating during sterilization and storage is avoided.

In the second embodiment, the catheter 21 comprising the catheter shaft 22, the catheter tip 23, the funnel 24 and the retractable sleeve 27 is placed in a vapour-tight package 30. The funnel 24 and the introduction aid 8 are open. Furthermore, the wetting agent comprising the composition as described above is added to the package 30. The wetting agent is brought into contact with a hydrophilic coating of the catheter shaft 22 so that the hydrophilic coating is activated. After that, the entire package is submitted to radiation sterilization, for example γ-irradiation, so that all components are sterilized.

In both embodiments, the energy dose of radiation during radiation sterilization lies in a range from 1 kGy to 50 kGy, preferably 15 kGy to 45 kGy, more preferably 25 kGy to 45 kGy.

CLAIMS

1. Method of producing a ready-to-use medical device with a functional coating comprising the steps of:

   - bringing the medical device, at least with its functional coating, in contact with a composition which prevents or retards degradation of the functional coating; and
   - sterilizing the medical device and the composition via radiation,

   characterized in that

   the composition comprises carboxymethyl cellulose or a derivative or salt thereof and/or an antioxidant selected from gallic acid or a derivative thereof.

2. Method according to claim 1, wherein the antioxidant of the composition is an ester, amide or oxadiazole derivative of gallic acid.

3. Method according to claim 1 or 2, wherein gallic acid or a derivative thereof is present in the composition in an amount of 0.001 to 5 % by weight based on the total weight of the composition.

4. Method according to claim 1 wherein the composition comprises the sodium salt of carboxymethyl cellulose.

5. Method according to claim 1 or 4, wherein carboxymethyl cellulose or a derivative or salt thereof is present in an amount of 0.1 to 10 % by weight based on the total weight of the composition.

6. Method according to claims 1, 4 or 5 wherein the composition comprises carboxymethyl cellulose or a derivative or salt thereof and gallic acid or a derivative thereof selected from an ester, amide or oxadiazole derivative of gallic acid, preferably propyl gallate.

7. Method according to claim 6, wherein gallic acid or a derivative thereof is present in an amount of 0.001 to 1 % by weight, based on the total weight of the composition.

8. Method according to any of claims 1 to 7, wherein the composition comprises a solution enhancer.

9. Method according to any one of claims 1 to 8, wherein the composition further comprises an aqueous or oil based base solution or a lipid media or a combination thereof.

10. Method according to claim 9, wherein the aqueous base solution of the composition is selected from distilled water, deionized water, reverse osmosis water, filtered water or a saline solution.

11. Method according to claim 9 or 10, wherein the aqueous base solution is present in the composition in an amount of 50 to 99.99 % by weight based on the total weight of the composition.

12. Method according to any one of claims 1 to 11, wherein the composition further comprises a stabilizer and/or a buffer solution.

13. Method according to any of claims 8 to 11, wherein the solution enhancer is selected from ethylene glycol, diethylene glycol, propylene glycol, or glycerol and is present in an amount of 0.1 to 49.8 % by weight based on the total weight of the composition.

14. Method according to claim 12 or 13, wherein the buffer solution has a pH of from 2.0 to 7.4.

15. Method according to any of claims 1 to 14, wherein the energy dose of radiation during radiation sterilization is in a range from 1 to 50 kGy, preferably 15 kGy to 45 kGy, more preferably 25 kGy to 45 kGy.

16. Method according to any of claims 1 to 15, further comprising the following steps:

- providing the medical device;
- coating the medical device at least in parts with the functional coating;
- activating the functional coating of the medical device by bringing it into contact with the composition which prevents or retards degradation of the functional coating, and;
- packing the medical device and the composition into a vapour-tight package (30).

17. Method according to any of claims 1 to 16, wherein the medical device is a catheter (1; 21).

18. Method according to any of claims 1 to 17, wherein the functional coating is a hydrophilic coating.

19. Method according to claim 17 or 18, wherein the catheter (1; 21) comprises a catheter shaft (2; 22) which is coated with the hydrophilic coating at least along its insertable length and which is tightly surrounded by a retractable sleeve (7; 27) and wherein the retractable sleeve (7; 27) and/or the catheter (1; 21) have a liquid-tight closure at a distal

end (5; 25) and at a proximal end (6; 26) so that any liquid present in the retractable sleeve (7; 27) or the catheter shaft (2; 22) remains within the retractable sleeve (7; 27) and the catheter as long as the liquid-tight closure is not broken.

20. Use of a wetting agent comprising a composition comprising carboxymethyl cellulose or a derivative or salt thereof and/or an antioxidant selected from gallic acid or a derivative thereof in the method according to claims 1 to 19.

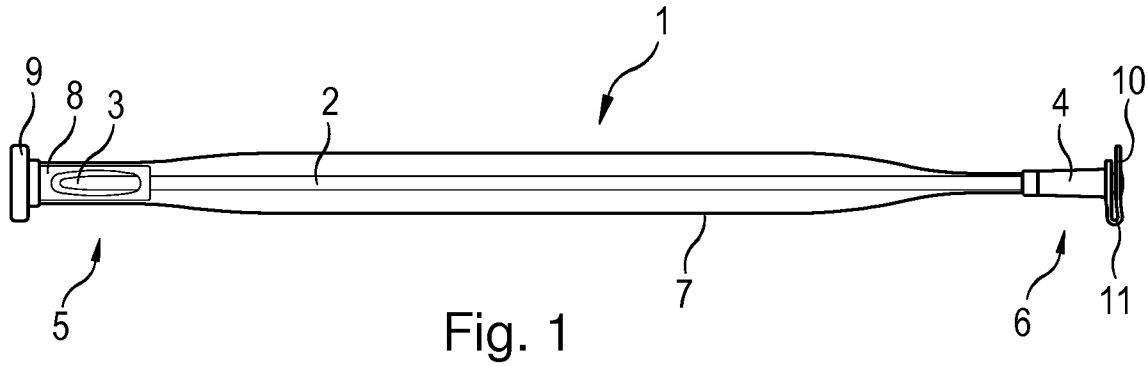


Fig. 1

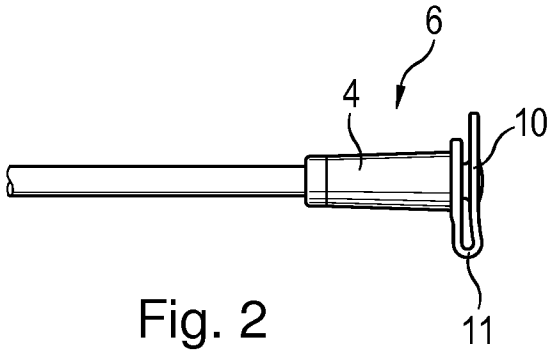


Fig. 2

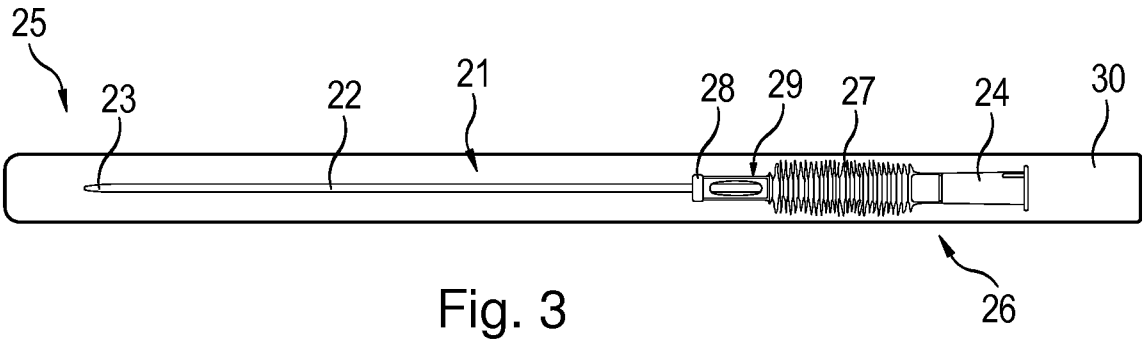


Fig. 3

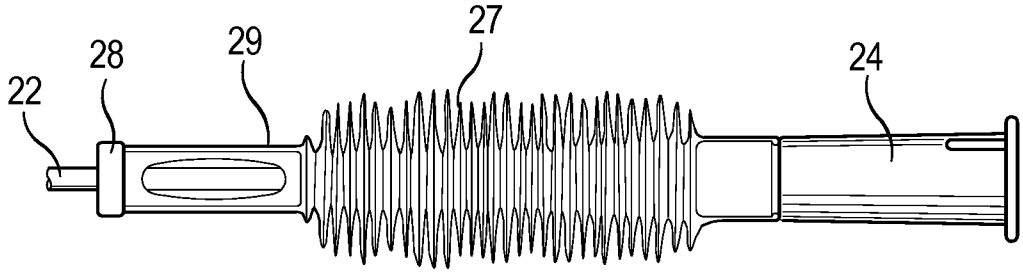


Fig. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/070249

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L27/34 A61L27/50 A61L27/52 A61L29/08 A61L29/14
ADD.

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

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 practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 8 147 769 B1 (HUANG BIN [US] ET AL) 3 April 2012 (2012-04-03) column 5, line 53 - column 7, line 67 -----	1-3, 6-12,16, 18,20
X	WO 2006/117372 A1 (COLOPLAST AS [DK]; MADSEN NIELS JOERGEN [DK]) 9 November 2006 (2006-11-09) cited in the application page 4, line 14 - line 20 page 5, line 10 - page 8, line 25 page 10, line 1 - line 22; examples ----- -/--	1,4-6, 8-20

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

[X] See patent family annex.

* Special categories of cited documents :

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

"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)

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

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 2017	14/11/2017

Name and mailing address of the ISA/	Authorized officer
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1

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International application No
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1

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