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- (56) Fremdragne publikationer:
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DESCRIPTION

Field of the Invention

[0001] The invention is directed to a photo-stable coating. In particular, the invention is an antimicrobial photo-stable composition used for coating a variety of medical materials. The invention also contemplates methods of making such composition, methods of forming coatings on medical materials and medical materials coated with the coating composition.

Background to the Invention

[0002] Throughout this application, various references are cited in parentheses to describe more fully the state of the art to which this invention pertains.

[0003] Anti-microbial agent(s) such as acetohydroxamic acid and magnesium ammonium phosphate hexahydrate have been added to a surface polymer coating as is disclosed for example in U.S. Pat. No. 5,788,687.

[0004] Silver is known to have general anti-microbial properties directed against a wide range of bacteria and fungi and has been used for many years in clinical settings and on medical devices which include coatings for catheters, cuffs, orthopedic implants, sutures, dental amalgams and wound dressings. Silver has been demonstrated to reduce the incidence of infection associated with the use of such devices. Silver alloy and silver oxide have been used to coat urinary catheters and are somewhat effective in preventing urinary tract infections.

[0005] The general use of silver as a prophylactic against infection has not found widespread application because of problems associated with the inadequate coating of device surfaces. Such problems include: poor solubility of metallic silver and silver oxides; short half-life; rapid binding of silver ions; inactivation by proteins; light-mediated inactivation and discoloration; and slow release of silver ions from the metallic complex. While not subscribing to any particular theory, colorless cationic silver may be photoreduced to metallic silver with subsequent dark discoloration. The ensuing discoloration of the ionic silver when coated onto medical devices results in undesirable coloration of the material or surface of the device.

[0006] U.S. 4,646,730 discloses polyvinylpyrrolidone (PVP)/silver sulfadiazine hydrogel dressings, where the gel is formed by utilizing electron beam irradiation to crosslink the PVP. Photo-stabilization of the silver component is accomplished by adding magnesium tri-silicate to the gel and by also adding hydrogen peroxide and/or polyacrylic acid.

[0007] U.S. 6,468,521 discloses a stabilized silver composition in which the silver compound is a complex with a primary, secondary or tertiary amine and the complex is associated with a hydrophilic polymer.

[0008] U.S. 4,906,466 and 5,413,788 disclose antimicrobial silver compositions in which photo-stability is enhanced by use of titanium oxide.

[0009] U.S. 6,669,981 discloses methods for enhancing the photo-stability of silver comprising an organic solution containing silver where the silver is subsequently photo-stabilized by treatment with ammonia, ammonium salts, thiosulfates, chlorides and/or peroxides.

[0010] Nomiya et al. (Inorganic Chemistry: 39:3301-3311, 2000) disclose the synthesis of water-soluble silver-pyrrolidone carboxylic acid (silver-PCA) complexes with antimicrobial activity. The material so produced shows discoloration caused by photoreduction of the silver-PCA complex.

[0011] JP 2001335405 and JP 2000256365 describe compounds that form a photostable complex with silver. The most effective was a silver- 2-pyrrolidone-5-carboxylic acid complex (silver-PCA). However, photo-reduction and discoloration of the complex remains a problem.

[0012] WO 2005/049101 describes an antimicrobial photo-stable coating composition comprising a silver salt and a dye, such as, for example, methylene blue, crystal violet or brilliant green, malachite green and ethyl violet.

[0013] There remains a need to develop a hydrophilic silver-complex that deters photo-induced discoloration of the silver-PCA

complex on the surface of medical devices such as catheters, wound dressings and the like.

Summary of the Invention

[0014] The present invention is an antimicrobial photo-stable coating composition. The coating composition comprises a silver salt complexed to pyrrolidone carboxylic acid (PCA) and dye, wherein the dye is Brilliant Green. The coating composition of the invention deters photo-induced discolouration, does not stain tissue and can be applied to the surface of a variety of medical materials.

[0015] Further aspects of the invention are defined in the appended claims.

Detailed Description of the Invention

[0016] The coating composition of the invention comprises silver ions that are complexed with pyrrolidone carboxylic acid (silver-PCA). This complex may be synthesized and isolated as silver salt white powder. The complex concentration in the solution may be in the range from 1 to 20 mM. As the maximum solubility of silver-PCA in water is about 300 mM it is understood by one of skill in the art that the complex concentration may vary somewhat from the 1 to 20 mM as desired. In some aspects of the invention, about 5 mM of the complex is desired to obtain desirable antimicrobial effects. In other aspects, 1 mole of silver nitrate per 2 moles of PCA provides desirable results; however, other ratios could be used to obtain the silver-PCA complex.

[0017] Silver cations may be provided from soluble silver salts, such as but not limited to silver nitrate, silver acetate, silver lactate and mixtures thereof, and form a complex with PCA in solution. The silver salt concentrations are in the range from 1 mM to 20 mM, and the PCA concentration should be about twice the silver salt concentration for the solution used to prepare the solid silver/PCA complex. The dye is added in concentration from 0.02 mM to 2 mM in the final solution containing the silver complex.

[0018] The dye for use in the present invention is a cationic triarylmethane dye, Brilliant Green, which is commercially available from Sigma-Aldrich, U.S.A. The dye is added to the silver-PCA complex to absorb light in the wavelength range of about 550-680 nm and about 380-450 nm ranges and protect the silver ion complex from undesirable chemical reduction and consequent colour changes.

[0019] The coating composition of the invention is made generally in one aspect by admixing the silver source with the PCA to form a complex that is then dried to form a silver salt powder. To this is added the dye solution. Any desired medical material is then dipped into, or the composition applied thereon as desired for a time sufficient to provide a coating. For example, the medical material may be dipped into the composition for seconds up to several minutes. Furthermore, the medical material can be dipped into the composition or the composition otherwise applied to the medical material such as by spraying for a non-limiting example. It is also within the scope of the invention to re-apply the coating composition to an already coated medical material substrate as desired as many times as desired. The coated medical material is then dried.

[0020] The coating composition of the invention can be used to treat a variety of medical materials, by treat it is meant to coat or impregnate if water absorbent materials are used to allow entry of the silver/PCA solution beyond surface regions as is understood by one of skill in the art. The medical materials may be selected from the group consisting of but not limited to hydrophilic materials and polymeric materials. Hydrophilic materials may be selected from the group consisting of but not limited to cotton gauze, polymer tubes such as urological catheters, wound drains, vascular grafts, endotracheal tubes, hemodialysis catheters, tissue coverings composed of proteins and carbohydrates. The materials so coated are photo-stable which assists in maintaining the silver in the ionic state. Polymeric materials may be selected from the group consisting of medical devices selected from the group consisting of but not limited to catheters, wound drains, endotracheal tubes and other polymeric liquid flow conduits and polymeric sheet materials.

[0021] In further embodiments of the invention, the antimicrobial coating composition of the invention can be effectively used to coat polymeric medical devices treated with hydrophilic coatings as described in Applicant's U.S. 6,808,738. Briefly, this patent describes that the surfaces of chemically inert polymers are permanently modified with a coating derived from a mixture of carboxylate-containing monomers and another vinyl co-monomer such as N-vinylacetamide, N-methylvinylacetamide, or methyl acrylate that can be made lubricious and then can be further endowed with a coating of the present invention. As such, the present invention provides for a polymeric composite that has a photostable hydrophilic silver-PCA-dye coated-surface possessing the characteristics of lubricity and antimicrobial properties.

[0022] The hydrophilic coating can be provided in a variety of configurations for different surfaces. The chemically inert polymers for use in the invention are those that are used and desirable to fabricate various types of in-dwelling devices. Examples of in-dwelling devices include but are not limited to implants, catheters, stents, vascular grafts, wound dressings, cardiac valves, pins, clamps, tubings and the like can be used in the practice of the invention. Polymers that can be surface modified according to the present invention include all polymeric substrates such as polyurethanes, polyamides, polyesters, polyethers, polyorganosiloxanes, polysulfones, polytetrafluoroethylene, polysiloxanes, carbohydrate materials including cellulose fibers such as cotton and chitosan ; proteins, such as gelatin, collagen, including combinations of polymers, carbohydrates and proteins.

[0023] In providing a hydrophilic coating on the surface of polymer materials such as liquid flow conduits, the method specifically involves adding hydrophilic co-polymers derived from vinyl monomers such as N-vinylacetamide, N-methylvinylacetamide, or methyl acrylate and carboxylic acid-containing monomers to the surface of inert substrates such as poly (dimethylsiloxane)-based polymers (silicone) through the use of long wavelength UV radiation (300-400 nm) and photoinitiators in a solution containing for example, tert-butylperoxybenzoate (TPB), and benzophenone (BP). Ratios of the photoinitiators can be 1:3; 1:2; 1:1; 2:1 and 3:1 with the preferred ratios 1:2; 1:1 and most preferred ratio being 1:1. In the preferred ratio of 1:1 of the photoinitiators, the concentration of the photoinitiators may be in the range of 25mM-300mM with the preferred range being 100-200mM and the most preferred concentration being 200mM at concentrations of 200mM each (1:1). The method comprises an initial step of free radical-mediated graft polymerization of acrylic acid or various other acrylates and N-vinylacetamide on photo-initiator-coated polymer surfaces placed in aqueous solutions of monomer and exposed to UV light (365 nm). While UV light is used herein, it is readily appreciated by those familiar with the art that photo-initiators that absorb light and other wavelengths may be used. The photo-initiator is coated onto the surface of selected polymeric material by incubating the polymeric material in an ethanolic or methanolic solution of photo-initiator for a time sufficient that the photo-initiator will adhere to the polymeric surface. Any means of providing a photo-initiator coated polymeric material will suffice in the method of the present invention; this is followed by air-drying of the photo-initiator coated polymeric material. One skilled in the art can appreciate that the level of grafting may be controlled by adjustment of photo-initiator and monomer concentrations, as well as duration of irradiation. The variance of time of UV-irradiation can be in the range of 1-15 min with the preferred range being 2-10 min and the most preferred time of UV-irradiation is 6 min.

[0024] To summarize, the coating composition of the present invention can be provided on any type of medical material whether hydrophilic or polymeric. Furthermore, the medical material may already have a hydrophilic coating thereon as described herein and in Applicant's U.S. Patent 6,808,738.

Examples

Example 1 <not according to the invention>- Silver-pyrrolidone carboxylic acid complex (Ag-PCA complex) synthesis:

[0025]

1. 1. Make a 0.5 M AgNO₃ and 1 M PCA solution in distilled water
2. 2. Titrate with NH₄OH to pH = 5.0
3. 3. Pour into filtration funnel and filter through 0.45 µm filter paper.
4. 4. Dry the white powder (preferably in dark).
5. 5. Yield with respect to silver is 96 %.

Example 2 - Coating of Cotton fibers

[0026] Cotton gauze bandages were coated with silver-PCA (Ag-PCA) complex and Brilliant Green. While certain durations are presented it is well known by those skilled in the art that an increase or decrease in the durations presented is sufficient to effect the embodiment of the present invention.

1. 1. Silver-PCA complex and Brilliant Green: 2.4 g/L was dissolved in distilled water.
2. 2. A cotton gauze was dipped into the solution for 1 second to 60 minutes, more preferably from 10 seconds to 10 minutes

and most favourably from 1 min to 5 min.

3. 3. Sample was rolled between two rubber rollers to press out non-absorbed solution.
4. 4. Sample was washed 1 min in distilled water and pressed to remove excess water.
5. 5. Sample dried at room temperature.

Example 3 - Coating of silicone Foley catheters

[0027]

Process 1: The process is as described in Applicant's U.S. 6,808,738 for preparing a hydrophilic catheter surface. The catheters so produced may be coated with the silver-PCA-Brilliant Green solution according to the present invention.

Process 2: Catheters are immersed in a solution of photoinitiator composed of 200 mM each of benzophenone and tert-butylperoxybenzoate for 1 - 10 min., preferably 1 min. The catheters are dried and immersed in a solution of 200 mM of acrylic acid and 50 mM of N-vinylacetamide with constant purging using nitrogen gas for 10 minutes; lesser times or more time allotted to this step is sufficient to demonstrate the embodiment of the invention. The samples in solution are irradiated with UV light (365 nm) for 5 minutes, less or more time is also effective, for surface grafting of the monomers to the silicone surfaces. The catheters are washed in ethanol, and transferred to a solution of Trizma base (pH 9; 10-100 mM). The catheters so treated are immersed in a solution of 2.5 mM silver acetate, 5 mM pyrrolidone carboxylic acid and 0.04 mM of Brilliant Green dye. Subsequently, the catheters are transferred to a solution of Trizma base (pH 8.5; 1-10 mM), and finally rinsed in deionized water and dried.

[0028] The residence time of catheters in each of the above solutions may be varied from 1 - 30 min, with 5-15 minutes being preferable and 12 minutes most preferable. However, it is easily understood by those familiar with the art that reducing or increasing the duration at each station are also embodiments of the present invention.

Example 4 - Coating of Central Venous Catheters

Process 1:

[0029] Catheters are immersed in a solution of photoinitiator composed of 200 mM each of benzophenone and tert-butylperoxybenzoate for 1 - 10 min., preferably 1 min. The catheters are dried and immersed in a solution of 200 mM of acrylic acid and 50 mM of N-vinylacetamide with constant purging using nitrogen gas for 10 minutes; lesser times or more time allotted to this step is sufficient to demonstrate the embodiment of the invention. The samples in solution are irradiated with UV light (365 nm) for 5 minutes, less or more time is also effective, for surface grafting of the monomers to the silicone surfaces. The catheters are washed in ethanol, and transferred to a solution of Trizma base (pH 9; 10-100 mM). The catheters so treated are immersed in a solution of 2.5 mM silver acetate, 5 mM pyrrolidone carboxylic acid and 0.04 mM of Brilliant Green dye. Subsequently, the catheters are transferred to a solution of Trizma base (pH 8.5; 1-10 mM), and finally rinsed in deionized water and dried.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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Patentkrav

1. Antimikrobiel fotostabil belægningssammensætning, som omfatter kompleksbundet sølv og farvestof, hvor det kompleksbundne sølv omfatter et sølv-salt, der er kompleksbundet til pyrrolidoncarboxylsyre (PCA) for at beskytte sølvet mod efterfølgende oxidations-/reduktionsreaktioner, hvor farvestoffet er brilliant-grøn, og hvor sammensætningen hindrer fotoinduceret misfarvning, ikke farver væv og kan påføres overfladen af en række medicinske materialer.
2. Sammensætning ifølge krav 1, hvor sølvsaltet er valgt fra gruppen bestående af sølvnitrat, sølvacetat, søvlactat og kombinationer deraf.
3. Sammensætning ifølge et hvilket som helst af kravene 1-2, hvor sølvsaltet forefindes i en mængde på 1 til 20 mM, og PCA forefindes i en ca. dobbelt så stor mængde som sølvsaltet.
4. Sammensætning ifølge et hvilket som helst af kravene 1-3, hvor farvestoffet forefindes i en mængde på 0,02 til 2 mM.
5. Medicinsk materiale, som er belagt eller imprægneret med sammensætningen ifølge et hvilket som helst af kravene 1-4, hvor det medicinske materiale er valgt blandt et hydrofilt materiale og et polymert materiale.
6. Medicinsk materiale ifølge krav 5, hvor det polymere materiale er en anordning valgt fra gruppen bestående af implantater, katetre, stenter, sårforbindinger, hjerteklapper, slanger, stifter og klemmer.
7. Medicinsk materiale ifølge krav 5, hvor det hydrofile materiale er valgt fra gruppen bestående af gazebind, polymerslanger, sårdræn, kartransplantater, endotrakealtuber, hæmodialysekatetre og vævsafdækning sammensat af proteiner og carbohydrater.

8. Medicinsk materiale ifølge krav 6, hvor anordningen belægges med en hydrofil belægning, inden den belægges eller imprægneres med sammensætningen.
- 5 9. Polymer medicinsk anordning, som omfatter det medicinske materiale ifølge krav 8 med en hydrofil belægning frembragt ved fremgangsmåden, der omfatter: inkubering af et fotoinitiatorbelagt siliconemateriale, der er tilvejebragt som en anordning valgt fra gruppen bestående af implantater, katetre, stenter, sårforbindinger, hjerteklapper, slanger, stifter og klemmer, med en vandig co-monomeropløsning, som er i stand til fri radikal-polymerisering og er valgt fra den primære gruppe bestående af acrylsyre, methacrylsyre, 2-carboxyethylacrylat, 4-vinylbenzoesyre, itaconsyre og blandinger deraf og en sekundær gruppe bestående af en hvilken som helst vinylmonomer, hvor fotoinitiatoren er valgt fra gruppen bestående af p-benzoyl-tert-butylperbenzoat, benzophenon, tert-butylperoxybenzoat, 15 2,2-dimethoxy-2-phenyl-acetophenon, benzilketaler, benzoiner og derivater og blandinger deraf;
- eksponering af materialet, der inkuberes, for ultraviolet lys, så der frembringes en modificeret overflade på materialet; og
- vask og tørring af materialet med den modificerede overflade, hvor anordningen endvidere belægges eller imprægneres med sammensætningen ifølge et hvilket 20 som helst af kravene 1-4.
10. Anordning ifølge krav 9, hvor vinylmonomeren er N-vinylacetamid, N-methylvinylacetamid eller methylacrylat.
- 25 11. Fremgangsmåde til fremstilling af et antimikrobielt fotostabilt belagt medicinsk materiale, hvilken fremgangsmåde omfatter:
- (a) blanding af et sølvsalt med PCA og lyofilisering til dannelse af et tørt pulver;
- (b) tilsætning af (a) til en brilliantgrøn-opløsning;
- 30 (c) nedsækning af et medicinsk materiale i (b) i et ønsket tidsrum og
- (d) tørring af det medicinske materiale.

12. Fremgangsmåde ifølge krav 11, hvor sølvsaltet forefindes i en mængde på 1 til 20 mM, PCA forefindes i en ca. dobbelt så stor mængde som sølvsaltet, og brilliantgrøn forefindes i en mængde på 0,02 til 2 mM.
- 5 13. Fremgangsmåde ifølge krav 11 eller 12, hvor sølvsaltet er valgt fra gruppen bestående af sølvnitrat, sølvacetat, søvlactat og kombinationer deraf.
14. Fremgangsmåde ifølge et hvilket som helst af kravene 11-13, hvor det medicinske materiale er valgt fra gruppen bestående af hydrofile materialer og poly-
10 mere materialer.
15. Fremgangsmåde ifølge krav 14, hvor de hydrofile materialer er valgt fra gruppen bestående af gazebind, polymerslanger, sårdræn, kartransplantater, endotrakealtuber, hæmodialysekatetre og vævsafdækning sammensat af protei-
15 ner og carbohydrater.
16. Fremgangsmåde ifølge krav 15, hvor polymerslangen er et urinvejskateter.
17. Fremgangsmåde ifølge krav 2,
20 hvor de polymere materialer er medicinske anordninger valgt fra gruppen bestående af katetre, sårdræn, endotrakealtuber og andre polymere væskestrømningskanaler og polymere foliematerialer.