(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 September 2014 (18.09.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/138885 A1

(51) **International Patent Classification**:
A61L 29/10 (2006.01) *A61L 15/42* (2006.01)
A61L 15/18 (2006.01) *A61L 29/16* (2006.01)
A61L 15/22 (2006.01)

(21) **International Application Number**:
PCT/CA2014/000211

(22) **International Filing Date**:
12 March 2014 (12.03.2014)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/778,388 12 March 2013 (12.03.2013) US
61/844,679 10 July 2013 (10.07.2013) US

(71) **Applicant**: **INNOVOTECH INC.** [CA/CA]; Suite 101, 2011 94 Street, Edmonton, Alberta T6N 1H1 (CA).

(72) **Inventors**: **OMAR, Amin A.**; Suite 212, 11615 Ellerslie Road, Edmonton, Alberta T6W 0J3 (CA). **NADWORNY, Patricia L.**; 65 Manor Drive, Sherwood Park, Alberta T8A 0P9 (CA). **ROMANCHUK, Janelle A.**; 73-54418 Rge Road, Sturgeon County, Alberta T8T 0C7 (CA). **PROSPERI-PORTA, Graeme**; 2401-10180 104 Street, Edmonton, Alberta T5J 1A7 (CA). **UNRAU, Kevin R.**; Unit 607, 179 George Street, Ottawa, Ontario K1N 1J8 (CA).

(74) **Agent**: **PARLEE MCLAWS LLP**; 1500 Manulife Place, 10180 - 101 Street, Edmonton, Alberta T5J 4K1 (CA).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

WO 2014/138885 A1

(54) **Title**: POLYMERIC COATINGS HAVING ANTIMICROBIAL PROPERTIES

(57) **Abstract**: The present invention is compositions, methods of use, methods of treating, and articles of manufacture that include at least one silver iodate for imparting antimicrobial properties, particularly as it relates to the manufacture, use, and properties of medical devices, including but not limited to catheters. The silver (I) iodates of the present invention are particularly suited for use with or incorporation into polymers and/or the monomers used to make polymers.

Polymeric Coatings Having Antimicrobial Properties

I. Field of the Invention

[0001] This invention relates to silver iodate compounds and their use in preventing or reducing microbial contamination. The compositions and methods are suitable for treating or preventing microbial contamination on any surface (i.e. surfaces used for production, handling, transport, storage, processing, or packaging).

[0002] This invention also relates to antimicrobial compositions and the use of these compositions with various devices, preferably devices such as medical devices, in which having an antimicrobial property is beneficial.

[0003] The invention also relates to articles produced or formed using the antimicrobial compositions of the present invention. For example, these compositions may be used in the making of or coating of articles, such as medical devices.

[0004] The invention also relates to coatings and/or ingredients in the manufacture of devices where having an antimicrobial property is beneficial, e.g., a medical device or an implant.

II. Background of the Invention

[0005] Silver is known for its antimicrobial use with medical devices, such as catheters, cannulae, and stents. One conventional approach for obtaining antimicrobial medical devices is the deposition of metallic silver directly onto the surface of the substrate, for example, by vapor coating, sputter coating, or ion beam coating. However, these noncontact deposition coating techniques suffer many drawbacks, including poor adhesion, lack of coating uniformity, and the need for special processing conditions, such as preparation in darkness due to the light sensitivity of some silver salts. One particular drawback of these coatings is that the processes by which the coatings are formed do not adequately coat hidden or enclosed areas, such as the interior lumen of a catheter or stent. Additionally, these methods produce coatings that are very much like metallic silver in that they do not release silver from the coating and require contact with the coating to provide antimicrobial action.

[0006] Though high concentrations of silver may be deposited on the substrate, very little free ionic silver is released on exposure to aqueous fluid. As a result, these coatings provide only limited antimicrobial activity. They essentially retard colonization of microbial agents on the surface of the device. However, because they do not release sufficient silver ions into aqueous fluids, they offer little or no protection from bacteria carried into the body upon application of the device and do not inhibit infection in the surrounding tissue.

[0007] Therefore, there is a long felt need in the art to increase the antimicrobial properties of substrates, such as medical devices, increasing resistance to infection on the surface of the device or in tissue surrounding the device, or in both locations.

[0008] Another conventional approach for obtaining antimicrobial medical devices is the incorporation of silver, silver salts, and other antimicrobial compounds into the polymeric substrate material from which the article is formed. An oligodynamic metal may be physically incorporated into the polymeric substrate in a variety of ways. For example, a liquid solution of a silver salt may be dipped, sprayed, or brushed onto the solid polymer, for example, in pellet form, prior to formation of the polymeric article. Alternatively, a solid form of the silver salt can be mixed with a finely divided or liquefied polymeric resin, which is then molded into the article. Further, the oligodynamic compound can be mixed with monomers of the material prior to polymerization.

[0009] There are several disadvantages to these approaches. One disadvantage is that larger quantities of the oligodynamic material are required to provide effective antimicrobial activity at the surface of the device. A second disadvantage is that it is difficult to produce articles that allow the release of the oligodynamic material because most device polymers absorb little, if any, water to aid in the diffusion and release of the oligodynamic material, resulting in articles that provide only a limited antimicrobial effect.

[0010] Yet another approach for obtaining antimicrobial medical devices is the incorporation of oligodynamic agents into a polymeric coating which is then applied to the surface of the article. Typically, an oligodynamic agent is incorporated into the coating solution in the form of a solution or a suspension of particles of the oligodynamic agent. Problems associated with this approach include poor adhesion of the coating to the

substrate, settling and agglomeration of the oligodynamic particles, and inadequate antimicrobial activity over time.

[0011] There is also a need in the art for compositions which can be incorporated into articles to provide antimicrobial activity. Further, there is a need for compositions which can be employed as coatings for articles that exhibit improved adhesion. There is also a need for compositions that overcome the solubility, settling, and agglomeration problems of conventional oligodynamic compositions, and exhibit enhanced, sustained release of oligodynamic agents. There is further a need for compositions that allow delivery of one or more active agents to locations.

[0012] In view of this, there is also a need for antimicrobial compositions that are stable, e.g., thermally stable, and are not inactivated in the environment of their intended use.

III. Summary of the Invention

[0013] The compositions and methods of the present invention comprise one or more silver iodate compounds or compositions and their use in or with polymers as antimicrobial agents. The invention also includes articles of manufacture that include one or more of these compounds incorporated into an article or as a polymeric layer or polymeric coating on the article.

[0014] The compositions and methods of the present invention have applicability in a wide variety of agricultural, industrial, and medical environments, e.g., disinfecting any surface, particularly disinfecting work or processing surfaces (e.g., tables); in antimicrobial coatings; in medical devices and implants, particularly where having an antimicrobial property or characteristic would be beneficial; and in treating human, plant, and animal diseases and conditions.

[0015] In some embodiments of the invention, the compositions and methods may be used to treat or prevent one or more biofilms. In some embodiments of the invention, the compositions and methods may be used to treat and/or prevent one or more human, animal, or plant diseases, conditions, infections, or contaminations. Typically these diseases and infections, etc., are caused by microbes associated with or residing in the biofilm.

IV. Detailed Description of the Invention

[0016] The present invention involves silver iodate compounds and their use as antimicrobial agents. Some embodiments of the invention include one or more silver iodate compound as an active agent, imparting an antimicrobial property or properties on or in a polymer.

[0017] In accordance with the present invention, the active agent includes a family of silver (I) periodate compounds. All of the members of the family are silver (I) combined with a higher oxidation state iodine and coordinated with oxygen atoms. These compounds include but are not limited to silver (I) iodate; pentasilver hexaoxoiodate; Ag_5IO_6; silver orthoperiodate; silver periodate (VII); silver iodate (VII); 5 $Ag_2O{\cdot}I_2O_7$; $Ag_2H_3IO_6$; $Ag_xH_yIO_6$, where x + y = 5; $Ag_xM_yIO_6$, where the total cationic charge of x + y = 5 and M is one or more cations; and combinations thereof. In preferred embodiments of the invention, the cation may be selected from the group consisting of K, Na, Mg, Ca, Au, Pt, Cu, and Fe. The most preferred cations are potassium and sodium.

[0018] The inventors believe that the iodine facilitates silver transfer, in a form such as $[Ag_2IO_6]^{3-}$, through the biofilm structure or matrix. The inventors also believe that the silver ions, which are present in both the cation ($[Ag_3]^{3+}$) and the anion ($[Ag_2IO_6]^{3-}$), and iodine ions provide multiple antimicrobial mechanisms of action, thus providing improved antimicrobial activity as compared to conventional compounds, and potentially helping reduce the risk of microorganisms developing resistance to the active agents.

[0019] The compounds of the present invention may be used by themselves, may be an ingredient in a composition, or may be a part, element, coating, or layer of an article of manufacture (e.g., a wound dressing, a medical grade metal, or a catheter). The compounds of the present invention may be combined with and/or formulated into a composition.

[0020] Any of the active agents of the present invention may be used to impart antimicrobial properties to a substrate. For example, one or more active agents may be incorporated into the structure of substrate or as a coating or the like. Exemplary substrates include metals; wound dressings; medical devices and instruments, including

polymeric medical devices and instruments; and plants, including seeds and leaves.

[0021] Some embodiments of the invention include forming an article including an active agent of the present invention, thereby forming an article having one or more antimicrobial properties.

[0022] The silver (I) periodate family of compounds of the present invention may be produced or synthesized by following processes already known to those skilled in the art. Examples of these processes include:

(1) Kovalevskiy, A., and Jansen, M. Synthesis, Crystal Structure Determination, and Physical Properties of Ag_5IO_6. Z Anorg Allg Chem 2006;632:577-581.

(2) Cignini, P., Icovi, M., Panero, S., and Pistoia, G. On the possibility of using silver salts other than Ag_2CrO_4 in organic lithium cells. J Power Source 1978; 3:347-357.

(3) Chapter 9. Oxysalts of Iodine. In: High Temperature Properties and Thermal Decomposition of Inorganic Salts. ©2001, CRC Press LLC.

(4) Mackay, Mackay, and Henderson. Introduction to modern inorganic chemistry, pg. 489.

(5) Gyani, P. Periodic Acid and Periodates. II The system silver oxide-periodic acid-water at 35°C. J Phys Chem 1951;55(7):1111-1119.

(6) International Patent Application No. PCT/CA2011/000941, filed 22 August 2011, incorporated herein by reference in its entirety.

[0023] The silver compositions of the present invention may be used with or incorporated into an article where antimicrobial properties are desirable and/or beneficial. Examples include, but are not limited to, medical and surgical devices and/or environments, such as implants. Other examples are provided below.

[0024] Some embodiments of the present invention also include pharmaceutically acceptable salts, or solvates and hydrates, and compositions and formulations of silver iodate compounds, silver iodate reaction products, and active agents produced from a starting material such as sodium diperiodatoargentate (III) or potassium diperiodatoargentate (III).

[0025] The present invention also includes methods of coating a metal substrate with an active agent of the present invention, said methods resulting in imparting an antimicrobial characteristic to the substrate. The present invention also includes methods of coating a wound dressing substrate with an active agent of the present invention, said methods resulting in imparting an antimicrobial characteristic to the substrate. As used herein, wound dressing substrate includes, but is not limited to, a wide variety of wound dressing substrates, including polymer-based substrates such as high density polyethylene and polyester, and organic based substrates such as cotton and rayon.

[0026] The present invention also includes methods of coating a substrate with an active agent of the present invention, said methods resulting in imparting an antimicrobial characteristic to the substrate. The substrate may be any substrate; preferred substrates include but are not limited to polymers used in the manufacture of catheters and/or one or more monomers used to make a polymer.

[0027] The compositions and methods may also include one or more other active agents.

[0028] For one or more of the active agents of the present invention, the small grain size combined with a larger particle size contribute to enhanced or improved antimicrobial activity. For example, Ag_5IO_6 has a grain size of about 15Å (fifteen angstroms), that is, nano sized, and a particle size that is much larger (typically between about 2 and 20 μm, that is, not nano). The grain size may increase with some forms of processing or post-synthesis processing, e.g., heating, exposure to solvents or solutions, grains growing together, grains combining into a single larger grain, and the like.

[0029] Some embodiments of the invention include a coating, layer, or the like on an article, said coating, etc., comprising one or more active agents of the present invention (including but not limited to silver (I) iodate compounds, and imparting improved antimicrobial characteristics to the article or a portion of the article.

[0030] Some embodiments of the invention include incorporating one or more active agents of the present invention, e.g., a silver (I) iodate compound into or on the medical device. In these embodiments of the invention, the silver composition may be any form that does not inactivate the silver, including but not limited to a gel, ointment, or cream.

[0031] In some embodiments of the invention, the active agent or a composition containing the active agent may be any form that does not inactivate the silver, including but not limited to a layer, or ingredient in a metal, a polymer, or a carrier.

[0032] In some embodiments of the invention, the compositions and methods are used for treating a microbial contaminant using an antimicrobial agent comprising silver ions or silver-containing complexes. The compositions and methods may also include one or more other active agents. The compositions and methods are antimicrobial, e.g. against biofilm, similar structures, or precursors formed by bacteria, fungi, viruses, algae, parasites, yeast, and other microbes. A microbial contaminant or infection may be found in a variety of species, including but not limited to humans, pigs, ruminants, horses, dogs, cats, and poultry.

[0033] In some embodiments of the invention, the active agent(s) may be incorporated into or onto packaging for an article, such as a medical device or a needle.

[0034] In some embodiments of the invention, one or more active agents or one or more starting materials may be used for the manufacture of a medicament intended to treat or prevent infections or contamination, particularly infections caused by bacteria, bacteria-like organisms, or biofilms.

[0035] The silver compositions of the present invention may be used to coat, or may be incorporated into, any article, including those comprising a metal or metal alloy. Typical metals and alloys include, but are not limited to titanium, titanium containing alloys, aluminum, stainless steel, mild steel, and copper. In preferred embodiments of the invention, the metal is titanium (grade 2), titanium (grade 5), aluminum, stainless steel, stainless steel needles, titanium (grade 5) pins, and other titanium (grade 5) implants.

[0036] In another embodiment, the composition optionally contains additional antimicrobial metals or salts of these antimicrobial metals, such as zinc, gold, copper, cerium, and the like. In yet another embodiment, the composition optionally comprises additional noble metals or salts of one or more noble metals to promote galvanic action. In still another embodiment, the composition optionally comprises additional platinum group metals or salts of platinum group metals such as platinum, palladium, rhodium, iridium, ruthenium, osmium, and the like.

[0037] In some embodiments, the compositions optionally contain other components that provide beneficial properties to the composition, that improve the antimicrobial effectiveness of the composition, or that otherwise serve as active agents to impart additional properties to the composition. The compositions are also used to inhibit algal, fungal, mollusk, or microbial growth on surfaces. The compositions of the invention are also used as herbicides, insecticides, antifogging agents, diagnostic agents, screening agents, and antifoulants.

[0038] In another embodiment, the composition may be applied as a coating to a preformed article, part of an article, a plant or portion thereof (e.g., a seed or a leaf), or a substrate. The coating may be produced, for example, by dipping the article, etc., into the composition or by spraying the article with the composition and then drying the coated article.

[0039] In some embodiments, the present invention relates to an article of manufacture which comprises the antimicrobial compositions of the present invention. In one embodiment, the composition is used to form an article or a portion of the article, for example by molding, casting, compounding, extruding, etc. Thus, at least part of the formed article is composed of one or more of the compositions of the present invention, alone or in admixture with other components. In another disclosed embodiment, the composition is applied to a preformed article or part of an article as a coating. The coated article may be produced, for example, by dipping the article into the composition or by spraying the article with the composition and then drying the coated article. This may be done in the presence of a solvent or a combination of solvents that promotes incorporation of the composition into the preformed article. In some embodiments of the present invention, a silver (I) iodate powder (e.g., Ag_5IO_6) is slurried into one or more solvents or mixtures thereof, a polymer (or monomer constituent) is then contacted with or exposed to the slurry, and the polymer is allowed to swell, thereby allowing the silver (I) iodate to coat or be incorporated into or onto the polymer.

[0040] Some embodiments of the present invention include providing compositions that provide antimicrobial, antibacterial, antiviral, antifungal, or antibiotic activity, or any combination thereof.

[0041] Some embodiments of the present invention include providing compositions that reduce encrustation, inhibit coagulation, improve healing, inhibit restenosis, or impart antiviral, antifungal, antithrombogenic, or other properties to coated substrates.

[0042] Some embodiments of the present invention include providing compositions that inhibit the growth of algae, mollusks, bacteria, bioslime, or some combination thereof on surfaces.

[0043] As described in more detail below, the methods and compositions of the present invention may be used wherever planktonic bacteria and/or biofilm or similar structures may be found, including but not limited to microorganisms growing and/or floating in liquid environments. The antimicrobial or anti-biofilm effect may be biostatic or biocidal.

[0044] The present invention includes any method of contacting with an antimicrobial agent of the present invention. Typical mechanisms of contacting include, but are not limited to, coating, spraying, immersing, wiping, and diffusing in liquid, powder, or other delivery forms (e.g., injection, tablets, washing, vacuum, or oral). In some embodiments of the invention, the compositions and methods may include applying the anti-biofilm agent to any portion of an article or an ingredient of an article. Further, any structure or hard surface (e.g., tools or machinery surfaces associated with harvesting, transport, handling, packaging, or processing) can be sanitized, disinfected, impregnated, or coated with the anti-biofilm agent of the present invention.

[0045] The Examples provide experimental confirmation that the silver (I) periodate compounds of the present invention release silver over time, typically over fourteen or more days. These Examples therefore demonstrate that stable, slow release silver-containing compounds can be used as long-lasting antimicrobials against bacterial and fungal pathogens, including biofilms growing on a substrate or layer.

[0046] These compositions exhibit antimicrobial activity and/or anti-biofilm activity against a variety of microbes, including both bacteria and fungi, and provide a sustained release of silver ions or silver containing complexes from silver compounds.

[0047] The preferred composition of the present invention comprises an active agent that results in slow release of an ionic silver species or silver-containing complex. Silver

complexes or compounds, as used herein, refers to a composition containing silver having a valent state of one. Finally, it is believed that the compositions of the present invention may be comprised of a silver-containing substance or a plurality of silver containing substances that may react over time to form other silver containing substances which may exhibit differing antimicrobial properties.

[0048] In preferred embodiments of the invention, antimicrobial properties may be achieved by contacting an antimicrobially active silver species within or at the surface of a substrate, or diffusing from the surface of a substrate into an aqueous environment.

[0049] The silver compounds may be used in any of the following formats: silver deposition coatings, liquid, suspension, powder, capsule, tablet, coating, and similar configurations. In a preferred embodiment of the present invention, active agents are incorporated or coated directly onto or into a material, or may be incorporated or coated by sequentially adding components or precursors of the active agent to the material, and having the precursors of the active agent in or on the coating. Other forms also include films, sheets, fibers, sprays, and gels.

[0050] Examples of additional antimicrobial agents that may be used in combination with the composition of the present invention are known to those skilled in the art and include, but are not limited to: streptomycin, tetracycline, erythromycin, ciprofloxacin, doxycycline, ampicillin, penicillin, gentamicin, and heavy metals including, but not limited to, gold, platinum, silver, zinc, and copper, and their combined forms including salts, such as chloride, bromide, iodide, iodate, nitrate, sulphate, bisulphate, and periodate, complexes with carriers, and other forms.

[0051] Multiple inactive ingredients may be optionally incorporated in the formulations. Examples of such ingredients are emulsifiers, thickening agents, solvents, anti-foaming agents, preservatives, fragrances, coloring agents, emollients, fillers, and the like.

[0052] The compositions and methods of the present invention may be used to treat planktonic microorganisms and/or biofilm in a wide range of environments and places. Treating biofilm, as used herein, refers to contacting a biofilm or similar structure with an anti-biofilm agent wherever biofilm may be found, is expected to be found, or is postulated to be found. One skilled in the art will readily recognize that the areas and industries for

which the present invention is applicable include a vast number of processes, products, and places.

[0053] The active agent(s) incorporated into the matrices and devices of the present invention may be used for a variety of applications where there is a need for or benefit from the presence of the active agent.

[0054] In this aspect of the invention, the compositions and methods are suitable for treating against one or more microbial infections, including but not limited to diseases or conditions caused by *Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella pneumoniae, Clostridium difficile, Candida albicans, Staphylococcus epidermidis, Escherichia coli* and other *Escherichia* spp, *Streptococcus* spp, *Pseudomonads,* and *Xanthomonads*.

[0055] The active agents of the present invention may also be used to treat plant pathogens, including but not limited to *Pseudomonas syringae pv. syringae*, *Pseudomonas syringae* pv. *phaseolicola*, and *Curtobacterium flaccumfaciens* pv. *flaccumfaciens*.

[0056] The compositions may be used to coat substrate materials. Thus, another aspect of the invention is a coating containing the composition of the invention. These coatings may comprise either a single layer or multiple layers. The compositions of the present invention are used alone or in combination with polymer coatings to provide advantageous properties to the surface of the substrate. These compositions are used, for example, to deliver pharmaceutical agents that, for example, prevent infection, reduce encrustation, inhibit coagulation, improve healing, inhibit restenosis, or impart antiviral, antifungal, antithrombogenic, or other properties to coated substrates.

[0057] Any polymer may be employed in the present invention, including hydrophilic polymers, hydrophobic polymers, and mixtures of these two types of polymers, provided that the active agent(s) retains all or a portion of its anti-microbial effectiveness. The use of hydrophilic polymers is preferred because such polymers have additional benefits. These benefits include increased lubricity for patient comfort, increased absorption of aqueous fluids from the body which aids in the release of oligodynamic ions from the composition, inhibition of bacterial attachment, and improved solubility for some metal

salts. Hydrophilic polymers best suited to the invention are those that are soluble in water or in organic solvents containing water. The ability to add water to the polymer composition without precipitating the polymer facilitates the addition of water-soluble salts directly to the coating composition. However, the use of water is not limiting, as salt colloids can also be formed using alcohols, organic solvents, or both, that contain little or no water.

[0058] Examples of polymers which may be used to form the compositions include, but are not limited to, polyurethanes, including polyether polyurethanes, polyester polyurethanes, polyurethaneureas, and their copolymers; polyvinylpyrrolidones; polyvinyl alcohols; polyethylene glycols and their copolymers; polypropylene glycols and their copolymers; polyoxyethylenes and their copolymers; polyacrylic acid; polyacrylamide; carboxymethyl cellulose; glycoproteins; proteoglycans; glycosaminoglycans; lipoproteins; liposaccharides; cellulose and its derivatives; dextrans and other polysaccharides; starches; guar; xantham and other gums and thickeners; collagen; gelatins; other naturally occurring polymers; polytetrafluoroethylene; polyvinyl chloride (PVC); polyvinylacetate; poly(ethylene terephthalate); silicone; polyesters; polyamides; polyureas; styrene-block copolymers; polymethyl methacrylate; acrylic-butadiene-styrene copolymers; polyethylene; polystyrene; polypropylene; natural and synthetic rubbers such as latex rubbers; acrylonitrile rubber; and mixtures and copolymers of any of the above. The preferred polymer depends upon the substrate to be coated. In some preferred embodiments, the polymer is a polyurethane, polyvinyl chloride, silicone, or natural latex rubber. In some embodiments, hydrophobic polymers that are chemically similar or identical to the substrate are used alone or in combination with hydrophilic polymers to form coatings that enhance adhesion of the coating to the substrate.

[0059] One skilled in the art will recognize that the silver species of the present invention may be incorporated into an article, medical device, implant, or the like. As used herein, incorporating refers to using an ionic silver species, such as pentasilver hexaoxoiodate, in the manufacture of the article, as a coating or layer of the article, or as a lubricant or the like when using the article.

[0060] Materials commonly used to make catheters include, but are not limited to natural

rubber latexes, silicones, polyvinyl chlorides, polyurethanes, plastisols, polyvinyl acetate, and methacrylate copolymers. Natural rubber latexes, polyurethanes, polyvinyl chlorides, and silicones are preferred materials. Any combination of the foregoing materials may also be used in making catheters.

[0061] The above list of materials that can be used in making catheters is not intended to be exhaustive and any other materials that can be used are within the scope of the invention. In addition, catheters of the present invention are not limited in terms of the number of layers of material. For example, one or more additional coatings may be applied to the surface of the catheters to provide lubricity, to reduce risk of infection, or for any other purpose. Any combination of layers can be used.

[0062] The compounds of the present invention and/or their reaction products may be incorporated into any metal article, e.g., a metallic medical device, including but not limited to various grades of titanium, titanium alloys, stainless steel, mild steel, aluminum, copper, etc.

[0063] The active agents of the present invention also exhibit good storage stability. Ag_5IO_6 powder is stable at 90°C for >28 days, which correlates to stability for greater than two years at room temperature.

[0064] The active agents of the present invention also exhibit good photostability. Ag_5IO_6 powder is photostable, and therefore does not need to be stored in the absence of light.

[0065] The active agents of the present invention are also thermally stable. Ag_5IO_6 powder is stable up to 440°C, indicating that the active agents of the present invention may be used under the high heat thermal processing required in the manufacture of some medical devices.

[0066] The active agents of the present invention may also be formulated into a composition comprising a solvent with short term stability. Exemplary solvents include, but are not limited to, water, saline (where some initial breakdown occurs but appears to be self-limited), methanol, ethanol, acetone, acetonitrile, tetrahydrofuran, chloroform, 1,2,4-trichlorobenzene, and 3M Novec Engineered Fluids such as HFE-7100 and HFE-71DE. The active agent can then be incorporated into or coated onto polymers by

exposing the polymers to the active agents in slurried or solution form in these solvents within the time period for which the components are stable together.

[0067] The active agents of the present invention exhibit improved and commercially valuable antimicrobial activity and longevity. As shown in the Examples, silver(I) periodate exhibits bacteriostatic longevity on wound dressings for greater than 10 days *in vitro* using day-to-day transfer corrected zone of inhibition testing, and bactericidal longevity on wound dressings greater than 14 days *in vitro* with continuous exposure to saline followed by a challenge in human serum and media in saline.

[0068] The active agents of the present invention also exhibit broad range antimicrobial activity. As shown in the Examples, would dressings coated with an active agent of the present invention are antimicrobial against fungi, bacteria (Gram-positive and Gram-negative pathogens, including *C. difficile*), both against planktonic forms and as anti-adherent/anti-biofilm agents. Further, these active agents retain their antimicrobial activity in environments that reduce or eliminate the antimicrobial effect of some silver species, e.g., in the presence of bodily fluids such as human serum and physiological saline.

[0069] The active agents of the present invention may be used in the agricultural industry as an antimicrobial agent or composition. One or more agents are suitable for use as an antimicrobial seed coating or in a foliar spray. Agents have demonstrated bactericidal activity (anti-adherence and anti-planktonic) against plant pathogens, including after exposure to soil.

[0070] The compounds of the present invention and/or their reaction products may be incorporated into any gel, ointment, or cream.

[0071] Definitions The following definitions are used in reference to the invention:

[0072] As used herein, active agent describes a silver-containing chemical substance, compound, or complex that exhibits antimicrobial activity, and is Ag (I) combined with higher oxidation state iodine and coordinated with oxygen atoms. Active agent includes, but is not limited to, a silver(I) periodate; one or more reaction products of a sodium diperiodatoargentate, each of these reaction products containing silver and iodine; one or

more reaction products of a potassium diperiodatoargentate, each of these reaction products containing silver and iodine; one or more reaction products of a combination of sodium and potassium diperiodatoargentate, each of these reaction products containing silver and iodine; pentasilver hexaoxoiodate; Ag_5IO_6; silver orthoperiodate; silver periodate (VII); silver iodate (VII); 5 $Ag_2O \circ I_2O_7$; $Ag_2H_3IO_6$; and other combinations of $Ag_xH_yIO_6$ where x+y=5; $Ag_xM_yIO_6$, where the total cationic charge of x + y = 5 and M is one or more cations; and combinations thereof. One skilled in the art will readily recognize that the cation can be any of a large number of cations. Exemplary cations include but are not limited to K, Na, Mg, Ca, Au, Pt, Cu, and Fe. The preferred cations are K and Na. Active agent also includes compositions comprising one or more active agents.

[0073] Reaction product, as used herein, refers to any silver containing compound or complex in the silver iodate family, formed by a number of different reaction processes. Exemplary reaction products include but are not limited to pentasilver hexaoxoiodate; Ag_5IO_6; silver orthoperiodate; silver periodate (VII); silver iodate (VII); 5 $Ag_2O \circ I_2O_7$; $Ag_2H_3IO_6$; and other combinations of $Ag_xH_yIO_6$ where x+y=5, $Ag_xM_yIO_6$, where the total cationic charge of x + y = 5 and M is one or more cations (including those specified above); and combinations thereof.

[0074] Medical device as used herein refers to any device, tool, instrument, implant, or the like, relating to medicine or the practice of human or veterinary medicine, or intended for use to heal or treat a disease or condition. A medical device of the present invention may be used for the medical benefit of a human or animal, including laboratory or hospital equipment. A medical device or a component of a medical device may include all natural and synthetic materials and both fibrous and non-fibrous materials. For example, the materials may be comprised of a metal, plastic, paper, glass, ceramic, textile, rubber, polymer, composite material or any other material or combination of materials. Exemplary medical devices include, but are not limited to, any kind of catheter; cannulae; needles; stents; guide wires; implant devices; filters; endoscopes; surgical or medical instruments; stents of any size, shape, or placement; coils of any size, shape, or placement; contact lenses; IUDs; peristaltic pump chambers; endotracheal tubes; gastroenteric feeding tubes; arteriovenous shunts; condoms; oxygenator and kidney

membranes; gloves; pacemaker leads; wound dressings; metallic pins, plates, and screws; metallic artificial hips; artificial knees; and gels, creams, and ointments.

[0075] "Sustained release" or "sustainable basis" are used to define release of atoms, molecules, ions, or clusters of a noble metal that continues over time measured in hours or days, and thus distinguishes release of such metal species from the bulk metal, which releases such species at a rate and concentration which is too low to be effective, and from highly soluble salts of noble metals such as silver nitrate, which release silver ions virtually instantly, but not continuously, in contact with an alcohol, aqueous solution, or electrolyte. The products of the present invention are superior to other commercially available silver containing compounds in part because of the slower release of silver.

[0076] Surface contamination, as used herein, refers to microorganisms growing on or relocated to a surface. The microorganisms associated with surface contamination may be actively growing or dormant, but represent a viable inoculum that can reinitiate infection, disease, or other undesirable conditions.

[0077] Antimicrobial activity is art-recognized and may be biostatic and/or biocidal. Biostatic materials are materials that inhibit the growth of all or some of the microorganism; and a biocide is a material that kills all or some of the microorganism. The active agents of the present invention are sufficiently soluble to provide biostatic and/or biocidal activity.

[0078] The term "coating" as used herein generally includes coatings that completely cover a surface, or portion thereof, as well as coatings that may only partially cover a surface, such as those coatings that after drying leave gaps in coverage on a surface. The latter category of coatings may include, but are not limited to a network of covered and uncovered portions (e.g., non-continuous covered regions of the surface). When the coatings described herein are described as being applied to a surface, it is understood that the coatings need not be applied to, or that they need not cover, the entire surface. For instance, the coatings will be considered as being applied to a surface even if they are only applied to modify a portion of the surface. The coating may be applied to a surface or impregnated within the material used to construct an item or a portion of an item.

[0079] The term "substrate" as used herein generally refers to a body or base layer or material (e.g., onto which other layers are deposited). A substrate may be organic (e.g., cotton or wool), metal, a polymer (e.g., polyvinyl chloride, high density polyethylene, polyurethane, silicone, rubber, rayon or polyester), or cellular (e.g., a plant, a seed, leaves, skin, or hide). Metal substrates include but are not limited to a wide variety of metals (e.g., titanium and stainless steel); metal alloys; and devices or products made using these metals (e.g., medical devices, needles, ports, implants, pins, etc.). In accordance with the present invention, the substrate must not inactivate the silver compound, or inactivate it to the extent that the silver is no longer suitable for use as an antimicrobial agent.

EXAMPLES

Example 1. Ag_5IO_6 Stability in Solvents

The purpose of this study was to determine whether or not Ag_5IO_6 interacts with methanol, tetrahydrofuran, acetone, and acetonitrile. 2-3 mm of Ag_5IO_6 was placed in a vial, 2 mL of the solvent was added, and the vial was placed in a TAM III for an isothermal run at room temperature for >24h with solvent only as the reference. The heat flow was measured. After the run was complete, the solvents were allowed to flash off and the solids collected were submitted to XRD. Samples exposed following essentially the same method for only 18h were also submitted for XRD.

This experiment shows that Ag_5IO_6 can be blended with all solvents for <18h without substantial reaction at room temperature. Acetone is the first to show significant reaction (onset ~14h-18h), followed by methanol (onset ~33h), then THF (onset ~56h), then acetonitrile (slower onset at ~56h).

Example 2.

This study compares Ag_5IO_6 coated dressings to uncoated control dressings and initial inoculum concentration for their ability to prevent bacterial adherence/biofilm formation. Organisms: *P. aeruginosa*, *S. epidermidis, S. aureus, K. pneumoniae, C. albicans.* Inoculum was made up in 10% MHB/SDB in 0.9% saline + 25% human serum to determine ability of Ag_5IO_6 coatings to act in the presence of human serum and saline.

24h was allowed for biofilm growth.

Dressings Coated: Source Gauze Sponges – 100% cotton; 3 ply dressings – rayon/polyester core with upper and lower HDPE layers; and Tensoplast – rayon/cotton with adhesive

All coating methods demonstrated excellent anti-adherence efficacy against all organisms, with the exception that the 3-ply dressing did not demonstrate anti-adherence efficacy against *Pseudomonas aeruginosa* ATCC 9027 when compared to the uncoated controls.

Statistical analyses were performed using one-way ANOVAs with Tukey-Kramer post-testing to compare the anti-adherence activity of the different coated dressings, within each organism, using the uncoated control data for the analysis. For the *Staphylococcus aureus*, *Candida albicans*, and *Klebsiella pneumoniae*, there were no statistically significant differences between the dressings ($p=0.7450$, $p=0.3513$, and $p=0.4841$, respectively). For the *Staphylococcus epidermidis*, there were statistically significant differences between groups ($p=0.0101$), with the sponge gauze and 3 ply dressings both generating significantly higher log reductions than the Tensoplast ($p<0.05$ each). However, it should be noted that the Tensoplast still generated a log reduction >4. For the *Pseudomonas aeruginosa*, there were statistically significant differences between groups ($p=0.0295$), with post testing indicating that the Tensoplast generated significantly higher log reductions than the 3 ply dressing ($p<0.05$).

Example 3. Biostatic longevity

This study measured day-to-day transfer corrected zones of inhibition (CZOIs) using various relevant microorganisms against Ag_5IO_6 coated materials: 316 stainless steel; Grade 2 Ti; Grade 5 Ti; Tensoplast™ ; 3-ply dressing (HDPE exterior layers, rayon/polyester interior); and 100% cotton sponge gauze.

Organisms: *P. aeruginosa* ATCC 9027, *S. aureus* ATCC 6538, *K. pneumoniae* ATCC 4352, *S. epidermidis* ATCC 35984, *C. albicans* ATCC 18804

Methods: Day-to-day transfer CZOIs, with comparison to uncoated controls.

Conclusion: Coated dressings (all 3 types) demonstrated substantial bacteriostatic longevity against a wide range of clinically relevant bacteria (gram positive and gram

negative pathogens). In some cases, the dressings were still active after 10 days. The dressings were also active against *C. albicans*, for a shorter time period (4 days).

Example 4. Incorporation of Ag_5IO_6 powder into silicones

0.4g Ag_5IO_6 was added to 10 mL each type of silicone (GE clear hardware store grade silicone, Nusil® MED 4870 liquid silicone rubber (LSR), MED 9050 silicone gel, and MED 6345 silicone gel), mixed, placed in a mold coated in Embedding Mold Release Spray (Polysciences, Inc.), and cured per manufacturer instructions for the silicones selected (at room temperature for 24h, at 165°C for 5 minutes, at room temperature, and at 60°C for 3h, respectively).

The resulting material was submitted for XRD to determine whether the Ag_5IO_6 had reacted with the silicones. For all 4 silicone samples, the only silver species detected was Ag_5IO_6.

Digestible silver content was determined by AAS. The silver released during nitric acid digest was: 0.55 mg/g GE silicone, 6.93 mg/g MED 6345, and 3.89 mg/g MED 9050. Silver release from MED 4870 was not determined.

Day-to-day transfer corrected zones of inhibition were performed using *P. aeruginosa*. The GE silicone and MED 4870 silicone did not generate zones of inhibition, even on the first day. The MED 6345 and MED 9050 silicones generated zones of inhibition for >10 days, with no statistically significant differences in zone size during those days.

This experiment shows that Ag_5IO_6 can be incorporated into silicones without reaction with the silicones, affecting neither obvious properties of the Ag_5IO_6 or those of the silicones. Also, In softer silicones, the Ag_5IO_6 can be released at an appropriate rate to generate bacteriostatic longevity for >10 days.

Example 5. Ag_5IO_6 incorporation into polymers via swelling with solvents (Part I)

The purpose of this study was to incorporate Ag_5IO_6 into polymers used in catheters via swelling pre-formed polymer tubes with solvents in the presence of Ag_5IO_6.

Method 1: Ag_5IO_6 was incorporated into silicone (S), polyvinyl chloride (C), polyurethane (U), and latex rubber (R) using the following solvents: acetone (A),

acetonitrile (B), ethanol (E), methanol (M), and tetrahydrofuran (T). Polymer tubing lengths were placed in a 5000 ppm slurry of Ag_5IO_6 in each solvent and stirred for a maximum of 18 hours. The solvent was then allowed to flash off of the polymers, the tubing pieces were briefly rinsed in ddH_2O to remove any poorly-adhered Ag_5IO_6, and then the tubing lengths were allowed to dry.

Method 2: This was performed using the same technique as Method 1, except that polymers were first placed in the pure solvent and allowed to swell for up to 2 days or until swelling equilibrium was reached, and then transferred to the Ag_5IO_6 slurry with agitation for 18h.

The resulting polymers were then analyzed using day-to-day corrected zone of inhibition (CZOI) assays against *P. aeruginosa*, silver content via digestion and subsequent AAS, and/or x-ray diffraction (XRD) to determine silver species included in the polymers.

In the results below, the sample codes are based on (polymer)(solvent)-(method); i.e. for Ag_5IO_6 incorporated into **s**ilicone using **a**cetone via method **1**, the code would be SA-1.

For CT-1, CT-2, UT-1, and UT-2, the polymer dissolved in the solvent so no further testing was performed. For CA-1, CA-2, CB-1, CB-2, CM-1, and CM-2, the polymers hardened (and in some cases, shrank) indicating poor polymer/solvent compatibility.

For the remainder of the polymers, there were no solvent/polymer compatibility issues, and in most cases, a color change of the polymer to dark brown after coating was observed, although in some cases, the polymer itself didn't appear to change color, but rather had a "dirty" appearance, suggesting a less consistent incorporation/coating of the Ag_5IO_6. In these cases, the inside of the tubes still appeared to be coated as well as the outsides.

A sample of RB-1 was submitted for XRD analysis, and the only silver species detected in the polymer was Ag_5IO_6 as a minor component relative to the polymer.

AAS data indicated that Method 1 caused higher incorporation of silver than Method 2. In all cases where there were statistically significant differences between methods, Method 1 treated polymers contained more digestible silver than Method 2 treated polymers.

CZOI data indicated that Method 1 was more effective at generating an antimicrobially-active Ag_5IO_6-incorporated polymer than Method 2. On Days 1 and 2, the ethanol swelled polyurethane using Method 1 had significantly larger zones than Method 2. On Days 1 and 2, the acetonitrile and methanol swelled PVC using Method 1 had significantly larger zones than using Method 2. On Day 2, the acetonitrile swelled silicone using Method 1 had significantly larger zones than using Method 2. It was only on Day 3 that the acetone swelled latex rubber tubing using Method 2 had significantly larger zones than using Method 1. The maximum number of transfers achieved by any method was 3 days.

Improved results could be obtained by increasing the penetration of Ag_5IO_6 into the polymers, increasing the quantity coated onto/incorporated into the polymers, or improving release of Ag_5IO_6 after incorporation.

Example 6. Testing for interactions between Ag_5IO_6 and organic solvents (Part II)

This study measured interactions between Ag_5IO_6 and the solvents HFE-7100 3M Novec Engineered Fluid, HFE-71DE 3M Novec Engineered Fluid, chloroform, and 1,2,4-trichlorobenzene.

2-3 mm of Ag_5IO_6 was layered into a glass vial, 2 mL of the solvent was placed on the Ag_5IO_6, and the vial was placed in a TAM III Calorimeter, with a glass vial containing solvent only as a reference. An isothermal run was performed at room temperature for at least 24h hours, and the heat flow in μW was measured. After the run was complete, the solvent was allowed to flash off, and the solid collected was analyzed by XRD. In addition, once a window of apparent stability was determined based on the calorimetry, Ag_5IO_6 samples were exposed to the solvent for that period of time (24h), the solvent was allowed to flash off, and the solid collected was analyzed by XRD.

Results

Dissolution calorimetry interpretation: HFE-71DE – very little interaction with some heat flow; HFE-7100 – quite a bit of interaction; chloroform – neither much interaction nor much heat flow; 1,2,4-trichlorobenzene – not much interaction but some heat flow.

1,2,4-trichlorobenzene did not flash off well, so further testing was not performed.

After both 24h and the complete dissolution calorimetry run, followed by flashing off the solvents, the solid material collected was still 100 wt% Ag_5IO_6 as determined by XRD. There was some variation in crystallite size, particularly after the longer dissolution calorimetry run (>4 days), suggesting some crystal growth over the analysis period.

Chloroform, HFE-71DE, and HFE-7100 were all considered appropriate solvents for potential use for incorporation of Ag_5IO_6 into polymers, but 1,2,4-trichlorobenzene was not for the polymers tested.

Example 7. Ag_5IO_6 incorporation into polymers via swelling with solvents (Part II)

The purpose of this study was the same as Example 5 using additional solvents selected from Example 5. The methods were the same as those described in Example 5, except that the following solvents were used: HFE-7100 3M Novec Engineered Fluid (H), HFE-71DE 3M Novec Engineered Fluid (D), and chloroform (F). In addition, only Method 1 was performed.

Visual observations: The following samples had light-to-dark brown even coatings: SD, SH, UH, UF, RD, RH, and RF. The following samples showed minimal coating visually: CH and UD. The following samples showed incompatibility between the polymer and the solvent (shriveling and hardening of the polymer): CD and CF.

CD had significantly more silver than the other PVC tubing pieces as well as the other tubing materials coated using the HFE-71DE solvent ($p<0.05$ or $p<0.01$ for all cases). RH had significantly more silver than other latex rubber tubing pieces as well as the other tubing materials coated using HFE-7100 ($p<0.001$ for all cases).

On Days 1 and 2, there was no significant differences in CZOI zone size within a polymer coated using the different solvents, but in comparing different polymers using the same solvent, RH had significantly larger zones than CH ($p<0.05$) on Day 1, and RH had significantly larger zones than SH on Day 2 ($p<0.05$). On Day 3, RH had significantly larger zones than RF ($p<0.05$); and RH had significantly larger zones than SH ($p<0.05$).

A sample of RH was submitted for XRD analysis, and the only silver species detected was Ag_5IO_6 (100 wt%, crystallinity of the material estimated to be 8%, crystallite size 16±1Å).

The latex rubber tubing coated using the HFE-7100 solvent had the best results in the zone of inhibition study, lasting 5 days, and XRD confirmed that the antimicrobial activity was caused by Ag_5IO_6, as opposed to a reaction product. Although the polyurethane tubing coated using HFE-71DE solvent had a very high silver content relative to the other polymers, it only generated zones of inhibition for 3 days.

Example 8. Ag_5IO_6 incorporation into polymers via swelling with solvents (Part III)

The purpose of this study was the same as Example 5 using blends of methanol and tetrahydrofuran (THF) rather than single solvents. The methods used were the same as those described in Example 5 except that the following solvent blends (by volume) were used: 90% THF/10% methanol (9T1M), 70% THF/30% methanol (7T3M), 50% THF/30% methanol (5T5M), 30% THF/70% methanol (3T7M), and 10% THF/90% methanol (1T9M). In addition, only Method 1 was performed, and the only polymers used were silicone (S) and latex rubber (R).

In subsequent results, the samples codes are based on (polymer)(solvent blend); i.e. for Ag_5IO_6 incorporated into silicone using 90%THF/10% methanol, the code would be S9T1M.

Visual observations: Light-to-dark even coatings were achieved for all rubber samples. Visually patchier coatings were obtained with the silicone. The coating darkness increased with the quantity of THF used for both types of polymer.

The R9T1M had significantly more silver deposited per unit area than all other latex rubber samples, and significantly more silver than the S9T1M.

On Day 1, there were no significant differences in zones sizes between latex rubber tubing pieces coated with varying solvent blends. The S9T1M showed significantly larger zones of inhibition than all other silicone tubing pieces. In all cases where there was a significant difference in zone size between the silicone and latex rubber tubing pieces, the latex rubber tubing pieces had larger zones of inhibition. On Day 2, the S9T1M tubing had significantly larger zones of inhibition than all other silicone sample, and the solvent combinations containing more tetrahydrofuran had significantly larger zones of inhibition than the lower percent tetrahydrofuran containing solvent combinations for the latex rubber. On Day 3, the R9T1M had significantly larger zones of inhibition than

the R5T5M, R7T3M, and the S9T1M (all had $p<0.01$). None of the other remaining tubing pieces showed significant differences in zone size ($p>0.05$).

A sample of R9T1M was submitted for XRD analysis, and the only silver species detected was Ag_5IO_6 (100 wt%, crystallinity of the material estimated to be 10%, crystallite size 14±1Å).

The CZOI data and silver content analysis correlated, with the R9T1M having the best CZOI results and the highest digestible silver content, and the activity was due to the presence of Ag_5IO_6, as indicated by the XRD analysis. Higher THF:methanol ratios appeared to be more effective than lower THF:methanol ratios, but also to be more effective than using pure THF.

Example 9. Evaluation of Ag_5IO_6-incorporated polymers against human pathogens – BEST™ Assay

Various polymers from previous Examples, based on digestible silver content and number of days of transfer in corrected zone of inhibition assays, were tested against relevant clinical human pathogens, relative to uncoated controls, for 30 days.

Test Groups:

- A-D were uncoated controls for each type of polymer tested
- E – Latex Rubber, Ag_5IO_6 coated using method 9T1M from Example 8
- F – Latex Rubber, Ag_5IO_6 coated using HFE-7100, (method from Example 7)
- G – PVC, Ag_5IO_6 coated using methanol, following Method 1 from Example 5
- H – Polyurethane, Ag_5IO_6 coated using acetone, Method 1 from Example 5
- I – Silicone, Ag_5IO_6 coated using 9T1M method from Example 8
- J – PVC, Ag_5IO_6 coated using HFE-71DE, following method from Example 7
- K – Latex Rubber, Ag_5IO_6 coated using acetone, Method 1 from Example 5
- L – Latex Rubber, Ag_5IO_6 coated using acetonitrile, Method 1 from Example 5
- M – Latex Rubber, Ag_5IO_6 coated using ethanol, Method 1 from Example 5
- N – Latex Rubber, Ag_5IO_6 coated using method 5T5M from Example 8
- O – Latex Rubber, Ag_5IO_6 coated using method 7T3M from Example 8
- P – Polyurethane, Ag_5IO_6 coating using methanol, Method 1 from Example 5

- Microorganism: *Escherichia coli* ATCC 29425
- Recovery buffer: DE neutralizer + 5 g/L L-cysteine + 5 g/L L-glutathione
- Polymers attached to BEST™ assay and saline soaks changed 3x per week up to challenge
- Challenges performed on Days 1, 7, 14, 21, and 30 in artificial urine
- Both planktonic and biofilm biomass recovery performed
- Log reductions calculated relative to uncoated control polymers that went through the same procedures

All of the latex rubber samples and the silicone sample continued to generate excellent anti-adherence properties as well as the ability to eliminate the surrounding planktonic organisms for 30 days.

Polyurethane sample H continued to prevent adherence of bacteria out to 30 days, but between 21 and 30 days lost the ability to eliminate the surrounding planktonic bacteria, suggesting insufficient silver release into the surrounding media by Day 30. Polyurethane sample P generated anti-adherence activity and the ability to eliminate surrounding planktonic bacteria for 7 days, but failed by 14 days.

PVC sample G continued to prevent adherence of bacteria out to 21 days (failed at 30 days), but was able to eliminate surrounding planktonic bacteria out to 30 days, suggesting that the material may have lost its silver coating unevenly, such that there were bare patches that allowed for bacterial adherence, but that the silver was still able to be released from other areas to kill the planktonic organisms. PVC sample J was the reverse – it was able to prevent adherence out to 30 days, but only eliminated surrounding planktonic bacteria out to 21 days (failed at 30 days).

The remaining eight coated polymers (E, F, I, K, L, M, N, and O) showed bactericidal activity and anti-adherence (anti-biofilm) properties under the same conditions for up to 30 days.

With simple methods, various polymers used in catheters had Ag_5IO_6 incorporated into them that resulted in extended activity against *E. coli* in artificial urine. The Ag_5IO_6-coated polymers performed well against E. coli, and demonstrated both anti-adherence and anti-planktonic activity.

Example 10. Bacteriostatic longevity of dressings coated at various concentrations of silver (I) periodate

In this study, wound dressings were coated at different concentrations (similar to Example 3, except that the full amount of Ag_5IO_6 was used for some dressings, 5x less material was used for others, and a third group was coated using 10x less Ag_5IO_6). Day-to-day transfer corrected zone of inhibition testing was performed using the same 5 organisms as Example 3, except that the *Pseudomonas aeruginosa* strain used was ATCC 27853. In general, using 5x less Ag_5IO_6 to coat dressings did not impact the number of days that zones of inhibition could be generated. However, for a few organisms, using 10x less Ag_5IO_6 in the coating process resulted in reduced longevity, suggesting that the dressings should be coated with at least that quantity of Ag_5IO_6 to obtain good bacteriostatic longevity.

Example 11. Efficacy at various concentrations and comparison to other silver dressings

This study evaluated the antimicrobial activity (anti-adherence and effect on surrounding planktonic bacteria) of Ag_5IO_6 incorporated into two dressing types at three different concentrations against the 5 microorganisms used in Example 10, and compared the dressings to three commercially available silver-containing dressings.

Dressings

A: Untreated 3-ply dressings (rayon/polyester core with upper and lower HDPE layers) – growth control for all B dressings below

B Full: Ag_5IO_6 treated 3 ply dressings treated at full strength

B-5x: Ag_5IO_6 treated 3 ply dressings treated at 5x less concentration

B-10x: Ag_5IO_6 treated 3 ply dressings treated at 10x less concentration

C: Untreated Tensoplast™ (cotton/rayon cloth with elastic adhesive) – growth control for all D dressings below

D Full: Ag_5IO_6 treated 3 ply dressings treated at full strength

D-5x: Ag_5IO_6 treated 3 ply dressings treated at 5x less concentration

D-10x: Ag_5IO_6 treated 3 ply dressings treated at 10x less concentration

E: Aquacel® (growth control for F)

F: Aquacel® Ag

G: Untreated 3-ply dressings wrapped around stainless steel (growth control for H)

H: Acticoat* wrapped around stainless steel so that uncoated side was not exposed

I: SeaSorb® (growth control for J)

J: SeaSorb® Ag

A BEST™ assay used, with a challenge in 10% media+25% human serum in 0.9% saline – 24h biofilm growth. Both planktonic and adhered bacteria (biofilm) recovery performed.

The results showed that the dressings with Ag_5IO_6 coating performed as well as or better than the commercial silver dressings at "full strength" coating. Typically, this was also true of the dressings with 5x and 10x less coating, but there were instances where they did not perform as well as Dressing J (SeaSorb Ag) in the adherence testing. This suggests that the 10x lower coating might be the limit in terms of how much the silver content of the dressings should be decreased.

Example 12. Efficacy after saline soaks and comparison to other silver dressings

This study compared Ag_5IO_6 coated dressings to uncoated controls and inoculum checks using a BEST™ assay. Commercial silver-containing dressings were also tested, along with their uncoated controls, for comparison. In this test, both the ability to prevent bacterial adherence/biofilm formation and the ability to kill surrounding planktonic bacteria were tested. Dressings were pre-soaked in saline for 24h, 7 days (3 saline changes), and 14 days (6 saline changes), to provide an idea of how the dressings would perform after exposure to the Cl^- present in wounds for various numbers of days. 3 organisms were tested. The challenge was performed in 10% media in 0.9% saline + 25% human serum, again to determine how the dressings performed in the presence of bodily fluids, and the biofilms were allowed 24h to grow.

Dressings Coated

A) Uncoated 3-ply dressing wrapped around stainless steel (rayon/polyester core with upper and lower HDPE layers) – control for B

B) Acticoat*

C) Aquacel® - control for D

D) Aquacel® Ag

E) Uncoated 3-ply dressing – control for F

F) 3-ply dressings coated with Ag_5IO_6

G) Uncoated Tensoplast™ (cotton/rayon cloth bandage with elastic adhesive) – control for H

H) Tensoplast™ coated with Ag_5IO_6

I) SeaSorb® - control for J

J) SeaSorb® Ag

The Ag_5IO_6-coated dressings (F and H) performed well against all three organisms (gram positive, gram negative, and yeast), and demonstrated both anti-adherence and anti-planktonic activity. Even after 14 days exposure to saline, the dressings demonstrated bactericidal activity and anti-adherence properties under most conditions.
Where there were statistically significant differences in dressing performance, the Ag_5IO_6-coated dressings out-performed the other dressings (with the exception of dressing J performing better than dressing H for adhered *S. aureus* and *C. albicans* at Day 14 only).

Example 13. Efficacy against *C. difficile*

This study compared Ag_5IO_6 coated dressings to uncoated controls and inoculum checks using a BEST™ assay. Commercial silver-containing dressings were also tested, along with their uncoated controls, for comparison. In this test, both the ability to prevent *Clostridium difficile* adherence/biofilm formation and the ability to kill surrounding planktonic *Clostridium difficile* were tested. The challenge was performed in 10% media in 0.9% saline + 25% human serum, to determine how the dressings performed in the presence of bodily fluids, and the biofilms were allowed 24h to grow.

Dressings Coated

A) Uncoated 3-ply dressing – control for B

B) 3-ply dressings coated with Ag_5IO_6

C) Uncoated Tensoplast™ (cotton/rayon cloth bandage with elastic adhesive) – control for D

D) Tensoplast™ coated with Ag_5IO_6

E) SeaSorb® - control for F

F) SeaSorb® Ag

G) Aquacel® - control for H

H) Aquacel® Ag

Only the Ag_5IO_6-coated 3-ply dressings demonstrated activity against *C. difficile*, both killing the planktonic bacteria and preventing adherence with log reductions >3, and just under 3, respectively. This indicates that Ag_5IO_6 may be an effective agent against *C. difficile* in appropriate formulations, where other commercial silver-containing dressings were not.

Example 19.

The purpose of this study was to test successful Ag_510_6-coated polymers for antimicrobial efficacy against relevant clinical human pathogens, compared to uncoated control polymers against a selected strain over an evaluation window of up to 30 days.

Example 9 was repeated, except that the samples were tested against three different microorganisms: *P. aeruginosa*, ATCC 27853; *C. albicans*, ATCC 18804; and *S. aureus*, ATCC 29213.

The Ag_5IO_6 coated catheters showed variable anti-adherence activity for all three strains tested. Despite the general presence of anti-adherence activity, it appears as though the Pseudomonas strain is more susceptible to the anti-microbial effects of the silver. The silver coated catheters exposed to *Pseudomonas aeruginosa* resulted in higher log reductions for both planktonic and adhered biomass compared to its controls (un-coated catheters) and the other two strains at the different time points tested.

Nevertheless, silver coated catheters exposed to *Staphylococcus aureus* showed significant log reduction for both planktonic and adhered biomass, specifically catheters F, G, H, J compared to its controls (uncoated catheters) on day 14 and 30. In the case catheters exposed to Candida Albicans on day 14, all silver tested articles showed significant log reduction for adhered biomass and anti-planktonic activity for catheters F and G compared its control. After 30 days only silver coated catheters E, F, H, I showed significant anti-adhered activity and only silver coated catheter J showed anti-planktonic activity.

While the invention has been described in some detail by way of illustration and example, it should be understood that the invention is susceptible to various modifications and alternative forms, and is not restricted to the specific embodiments set forth in the Examples. It should be understood that these specific embodiments are not intended to limit the invention but, on the contrary, the intention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the invention.

IN THE CLAIMS:

1. An article of manufacture comprising a polymer comprising an antimicrobial silver (I) periodate.

2. The article of manufacture of claim 1 wherein the silver (I) periodate is one or more compounds selected from the group consisting of silver (I) iodate; pentasilver hexaoxoiodate; Ag_5IO_6; silver orthoperiodate; silver periodate (VII); silver iodate (VII); 5 $Ag_2O{\cdot}I_2O_7$; $Ag_2H_3IO_6$; $Ag_xH_yIO_6$, where x + y = 5; $Ag_xM_yIO_6$, where the total cationic charge of x + y = 5 and M is a cation; and combinations thereof.

3. The article of manufacture of claim 2 wherein the cation M is selected from the group consisting of K, Na, Mg, Ca, Au, Pt, Cu, and Fe.

4. The article of manufacture of claim 1 wherein the polymer is one or more polymers selected from the group consisting of polyurethanes, polyesters, polyethylenes including high density polyethylene, rayons, polypropylenes, polyvinyl chlorides, silicones, and rubber.

5. The article of manufacture of claim 1 wherein the article is a wound dressing, a medical instrument, a medical device, a metallic article, or a portion thereof.

6. The article of claim 4 wherein the article is a catheter or a surface of a catheter.

7. A method of making a surface antimicrobial, comprising forming or coating the surface with a polymer comprising silver (I) periodate.

8. The method of claim 7 wherein the silver (I) periodate is one or more compounds selected from the group consisting of silver (I) iodate; pentasilver hexaoxoiodate; Ag_5IO_6; silver orthoperiodate; silver periodate (VII); silver iodate (VII); 5 $Ag_2O{\cdot}I_2O_7$; $Ag_2H_3IO_6$; $Ag_xH_yIO_6$, where x + y = 5; $Ag_xM_yIO_6$, where the total cationic charge of x + y = 5 and M is a cation; and combinations thereof.

9. The method of claim 7 wherein the surface is a portion of a wound dressing, a medical instrument, a medical device, a metallic article, a plant, a seed, or a portion thereof.

10. A method of preventing or reducing microbial contamination on a substrate comprising coating the substrate with a polymeric substrate comprising one or more silver(I) periodates.

11. A method of producing a polymer comprising a silver (I) iodate comprising selecting a polymer, and incorporating a silver (I) iodate into the polymer by contacting the iodate with the polymer.

12. The method of claim 11 wherein a solution of silver (I) iodate contacts the polymer by dipping, spraying, or brushing.

13. The method of claim 11 wherein a silver (I) iodate solid is mixed with the polymer, and the polymer/iodate mixture is then molded.

14. The method of claim 11 wherein the iodate is mixed with one or more constituents used to make a polymer, then the mixture is subject to polymerization.

15. The method of claim 10 comprising mixing a polymer with one or more silver (I) iodates, forming a coating of the polymer/iodate mixture, and applying the coating onto at least a portion of a surface of an article.

16. A method of making an antimicrobial polymer, comprising contacting a silver (I) periodate with polymer or at least one monomer used to make a polymer, and forming the polymer.

17. The method of claim 7 wherein the surface is a catheter or a portion thereof.

18. The method of claim 11 wherein a polymer or a monomer used to make a polymer is mixed with a silver (I) iodate, and the mixture is formed into slurry using a suitable solvent or mixture of solvents.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2014/000211

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61L 29/10*** (2006.01), ***A61L 15/18*** (2006.01), ***A61L 15/22*** (2006.01), ***A61L 15/42*** (2006.01), ***A61L 29/16*** (2006.01)

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: **A61L 29/10** (2006.01), **A61L 15/18** (2006.01), **A61L 15/22** (2006.01), **A61L 15/42** (2006.01), **A61L 29/16** (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database, Total Patent, SCOPUS. Keywords: silver *iodate, silver *periodate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2846278 A1 (OLSON ET AL.) 28 February 2013 (28-02-2013) Abstract; Pages 2-9; Example 2; Claims	1-18
X	CA 1341224 C (FOX ET AL.) 01 May 2001 (01-05-2001) Abstract; Pages 1-14, 21-22; Claims	1, 2 and 4-18
X	CA 2468780 A1 (TERRY, RICHARD N.) 12 June 2003 (12-06-2003) Abstract; Claims	1, 2 and 4-18

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search	Date of mailing of the international search report 05 June 2014 (05-06-2014)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Authorized officer Yara Ghazi (819) 934-0075

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2431126 C (MCGHEE, DIANE) 01 August 2002 (01-08-2002) Abstract; Claims	1, 2, 4-11 and 15-17
X	CA 2639838 A1 (MCGHEE, DIANE) 30 April 2009 (30-04-2009) Abstract; Claims	1, 2, 4-11 and 15-17

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2014/000211

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA 2846278 A1	28 February 2013 (28-02-2013)	WO2013026150A1	28 February 2013 (28-02-2013)
CA 1341224 C	01 May 2001 (01-05-2001)	US5616338A	01 April 1997 (01-04-1997)
		JP07090039B2	04 October 1995 (04-10-1995)
		DE68905939T2	05 August 1993 (05-08-1993)
		DE68905939D1	19 May 1993 (19-05-1993)
		AU636767B2	06 May 1993 (06-05-1993)
		EP328421B1	14 April 1993 (14-04-1993)
		US5133090A	28 July 1992 (28-07-1992)
		AU616472B2	28 October 1991 (31-10-1991)
		AU7922991A	03 October 1991 (03-10-1991)
		EP328421A3	01 August 1990 (01-08-1990)
		EP328421A3	01 August 1990 (01-08-1990)
		AU2989589A	17 August 1989 (17-08-1989)
		EP328421A2	16 August 1989 (16-08-1989)
CA 2468780 A1	12 June 2003 (12-06-2003)	MXPA04005332A	16 May 2005 (16-05-2005)
		CN1612804A	04 May 2005 (04-05-2005)
		JP2005511144A	28 April 2005 (28-04-2005)
		WO03047636A3	02 October 2003 (02-10-2003)
		AU2002357050A8	17 June 2003 (17-06-2003)
		AU2002357050A1	17 June 2003 (17-06-2003)
		WO03047636A2	12 June 2003 (12-06-2003)
CA 2431126 C	01 August 2002 (01-08-2002)	DE60118602T2	05 April 2007 (05-04-2007)
		ES2261517T3	16 November 2006 (16-11-2006)
		AU2002246277B2	28 September 2006 (28-09-2006)
		DK1343546T3	07 August 2006 (07-08-2006)
		PT1343546T	31 July 2006 (31-07-2006)
		PT1343546E	31 July 2006 (31-07-2006)
		HK1059056A1	02 June 2006 (02-06-2006)
		DE60118602D1	18 May 2006 (18-05-2006)
		AT322298T	15 April 2006 (15-04-2006)
		EP1343546B1	05 April 2006 (15-04-2006)
		NZ526455A	27 May 2005 (27-05-2005)
		JP2004517690A	17 June 2004 (17-06-2004)
		MXPA03005404A	05 May 2004 (05-05-2004)
		EP1343546A2	17 September 2003 (17-09-2003)
		EP1343546A1	17 September 2003 (17-09-2003)
		WO02058756A3	31 October 2002 (31-10-2002
		AU2002246277A1	06 August 2002 (06-08-2002)
		CA2431126A1	01 August 2002 (01-08-2002)
		WO02058756A2	01 August 2002 (01-08-2002)
CA 2639838 A1	30 April 2009 (30-04-2009)	ES2450749T3	25 March 2014 (25-03-2014)
		DK2055327T3	27 January 2014 (27-01-2014)
		EP2055327B1	11 December 2013 (11-12-2013)
		US7820734B2	26 October 2010 (26-10-2010)
		NZ571703A	28 May 2010 (28-05-2010)
		ZA200809326A	24 June 2009 (24-06-2009)
		JP2009131625A	18 June 2009 (18-06-2009)
		AU2008229821A1	14 May 2009 (14-05-2009)
		CN101428156A	13 May 2009 (13-05-2009)
		KR1020090045068A	07 May 2009 (07-05-2009)
		EP2055327A1	06 May 2009 (06-05-2009)
		MX2008013038A	29 April 2009 (29-04-2009)