Title: ANTI-MICROBIAL GEL FORMULATIONS CONTAINING A SILVER (I) PERIODATE

Abstract: The present invention is silver (I) periodate compounds and their use in preventing or reducing microbial contamination. The invention includes gels, coatings, and articles of manufacture having a surface contacted or coated with a gel comprising an antimicrobial silver (I) compound. Methods of treatment are also disclosed.
ANTI-MICROBIAL GEL FORMULATIONS CONTAINING A SILVER(I) PERIODATE

Field of the Invention

This invention relates to silver iodate compounds, such as silver (I) periodates, and their use in treating, preventing, or reducing microbial contamination. These silver compounds are particularly suited to being formulated into gels or hydrogels without loss of their anti-microbial properties.

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.

The invention also relates to articles produced or formed using the antimicrobial compounds and compositions of the present invention.

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, wound dressing, or an implant.

Background of the Invention

Silver is known for its antimicrobial properties, particularly when incorporated into or onto medical devices. However, it is challenging to coat or incorporate silver onto a surface, whether medical devices or other surfaces (e.g., seeds, plants, metals, etc.). Many products formed using existing silver compounds are poorly soluble, exhibit poor silver release profiles, the silver is inactivated in body fluids, and the antimicrobial activity is designed for planktonic bacteria and shows little or no effect against biofilm. Further, many, if not all, higher oxidation state silver compounds (e.g., oxysilver nitrate and silver (III) periodates) cannot readily be mixed with commercial gel formulations; typically the silver compound does not mix well, or the silver compound reacts with the gel, resulting in loss of its antimicrobial activity and/or loss of gel properties.

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 act like metallic silver in that they do not release silver from the coating and require contact with the coating to provide any antimicrobial action. 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 or fluid.

Another method of coating silver onto a substrate involves deposition or electrodeposition of silver from solution. Drawbacks of previous deposition methods include poor adhesion, low silver pick-up on the substrate, complex manufacturing processes, the need for surface preparation, high labor costs, and the need for additional deposition agents and stabilizing agents.

Some silver coatings release, to varying degrees, silver ions into the solution or tissue surrounding the substrate. However, activation of such coatings often requires conditions that are not suitable for use with some medical implants. These conditions include abrasion of the coating surface, heating to a temperature above 180°C, contact with hydrogen peroxide, and treatment with an electric current.

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 antimicrobial compound can be mixed with monomers of the material prior to polymerization.

There are several disadvantages to this last approach: larger quantities of the antimicrobial material are required to provide effective antimicrobial activity; it is also difficult to produce articles that actually release the antimicrobial ions because most coatings absorb little, if any, water to aid in the diffusion and release of the antimicrobial ions, resulting in articles that provide only a limited antimicrobial effect.

There is also a need for compositions that overcome the solubility, settling, and agglomeration problems of conventional antimicrobial compositions, and exhibit enhanced, sustained release of antimicrobial agents. There is also a need for antimicrobial compositions that may be incorporated into a gel or hydrogel used to make or coat a device, while retaining its antimicrobial effectiveness. There is also a need for antimicrobial compositions that are stable, e.g., thermally stable, light stable, stable in the materials they are included on/with, and are not inactivated in the environment of their intended use.

**Summary of the Invention**

The compositions and methods of the present invention comprise one or more silver iodate compounds and their use as antimicrobial agents. The invention also includes articles of manufacture that include one or more of these compounds as a layer or coating on the article.

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.

The compositions and methods of the present invention are also effective in preventing, treating, and/or eradicating biofilm.

Some of the active agents of the present invention have a small grain size, exhibit polycrystallinity, and have a surface area that, in combination, result in greater antimicrobial activity.

**Detailed Description of the Invention**

The present invention involves silver iodate compounds, such as silver (I) periodates, and their use as antimicrobial agents. Some embodiments of the invention include one or more silver iodate compounds as an active agent(s) imparting an antimicrobial property or properties. The present invention also involves the use of one or more of these active agents to impart an antimicrobial property or properties to a gel or a hydrogel.

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 an oxidized silver ion, e.g. Ag$_5$I$_6$ or Ag$_2$H$_3$I$_6$. The inventors believe that the iodine structure facilitates silver transfer, in a form such as $[\text{Ag}_2 \text{I}_6]^{5+}$, through the biofilm structure or matrix. The inventors also believe that the silver ions, which are present in both the cation ($[\text{Ag}_3 \text{I}_3]^{3+}$) and the anion ($[\text{Ag}_2 \text{I}_6]^{5+}$), combined with the iodate ions, provide multiple antimicrobial methods of action, thus providing improved antimicrobial activity as compared to conventional compounds.

Compounds of the present invention include, but are not limited to, silver (I) iodate; pentasilver hexaoxoidate; Ag$_5$I$_6$; silver orthoperiodate; silver periodate (VII); silver iodate (VII); 5 Ag$_2$O·2$I_2$; Ag$_2$H$_3$I$_6$; Ag$_x$H$_y$I$_z$, where $x + y = 5$; Ag$_9$M$_x$I$_6$, 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, M, 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.

The compounds of the present invention may be used by themselves, may be an ingredient in a composition, or may be a part or element of an article of manufacture (e.g., a wound dressing, a gel, a medical grade metal, or a catheter). The compounds of the present invention may be combined with and/or formulated into a composition. In preferred embodiments of the invention, one or more active agents (e.g. a silver (I) periodate) are an ingredient in a gel or a gel formulation.

Any of the active agents of the present invention may be used to impart antimicrobial properties wherever it is needed, e.g., topically, or to a surface or 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; and plants, including seeds and leaves. The surface may be internal or external;
or the device may be used internally. The active agent(s) and/or formulations of the present
invention may be directly applied to a surface, e.g., directly to a human, animal, or plant
infection or wound (e.g., applied topically to a wound).

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
(2) Cignini, P., Icovi, M., Panero, S., and Pistoia, G. On the possibility of using silver salts
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
(6) International Patent Application No. PCT/CA2011/000941, filed 22 August 2011,
incorporated herein by reference in its entirety.

The present invention also includes methods of coating a surface or a 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 a gel comprising 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, and gels.

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

In some embodiments of the invention, one or more silver (I) periodate compounds are
used to produce an article having improved antimicrobial characteristics. In some of these
embodiments of the invention, the silver (I) periodate compound may be in a coating, gel,
hydrogel, or the like on a surface of the article, or may be incorporated into a material that
forms the article. In some embodiments of the invention, the article comprises titanium or
stainless steel. In some embodiments of the invention, the article is a medical device, such as
a catheter, endoscope, wound dressing, or needle. 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.

For one or more the active agents of the present invention, the small grain size (with a
larger particle size) contribute to enhanced or improved antimicrobial activity. For example,
Ag₈I₀₆ has a grain size of about 15Å (fifteen angstroms), that is, a nano size, 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 solutions or solvents, grains growing together, grains combining into a single larger
grain, and the like.

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, and imparting
improved antimicrobial characteristics to the article or a portion of the article.

In some embodiments of the invention, the composition may be any form that does not
inactivate the silver, including but not limited to a gel, ointment, cream, foam, or ingredient or
layer in a polymer, substrate, or carrier.

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, polymer, or organic material; or a carrier. The preferred forms
are a silver (I) periodate powder, or a coating that includes a silver (I) periodate.

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, plants, and poultry.

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.

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, fungi, yeast, or biofilms.

The silver compositions of the present invention may be used to coat, or may be
incorporated into, any article 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.

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.

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.

Some embodiments of the present invention include providing compositions that provide antimicrobial, antibacterial, antiviral, antifungal, anti-biofilm, or antibiotic activity, or some combination thereof.

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.

As described in more detail below, the methods and compositions of the present invention may be used wherever microorganisms, 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.

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.

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, by syringe (e.g., topical or internal), washing, vacuum, or oral). In some embodiments of the invention, the compositions and methods may include applying the active agent to any portion of an article or an ingredient of an article.

The Examples provide experimental confirmation that the silver (I) periodate compounds of the present invention release silver over time. 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.

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.

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.

The silver compounds may be used in any of the following formats: silver deposition coatings, liquid, suspension, powder, capsule, tablet, coating, incorporation, and similar configurations. In a preferred embodiment of the present invention, active agents are incorporated directly onto or into a material, or may be incorporated 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.

Examples of additional antimicrobial agents which may be included along with the actives described above 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, nitrate, sulphate, and periodate, complexes with carriers, and other forms.

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.

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, Streptococcus spp, Pseudomonads, Xanthomonads, and Curtobacterium species.

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.

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.

The compounds of the present invention and/or their reaction products may be incorporated into any wound dressing, bandage, or wound healing product

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, acetone, acetonitrile, and tetrahydrofuran.

Definitions

The following definitions are used in reference to the invention:

As used herein, active agent describes a silver-containing chemical substance, compound, or complex that exhibits antimicrobial activity, and is Ag(I) combined with a higher oxidation state iodine and coordinated with oxygen atoms. Active agent includes but is not limited to a silver\(^{n+}\) periodate; one or more reaction products of a sodium diperiodoargentate, each of these reaction products containing iodine; one or more reaction products of a potassium diperiodoargentate, each of these reaction products containing iodine; pentasilver hexaoxoiodiate; Ag\(_8\)I\(_{10}\); silver orthoperiodate; silver periodate (VII); silver iodate (VII); 5 Ag\(_2\)O\(_5\); \(\text{Ag}_2\)H\(_2\)I\(_6\); and other combinations of \(\text{Ag}_x\)H\(_y\)I\(_{10}\) where \(x+y=5\); \(\text{Ag}_y\text{M}_x\)I\(_{10}\); 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.

Reaction product, as used herein, refers to any silver containing compound or complex in the silver iodate family, formed by any number of different reaction processes. Exemplary reaction products include but are not limited to pentasilver hexaoxoiodiate; Ag\(_8\)I\(_{10}\); silver orthoperiodate; silver periodate (VII); silver iodate (VII); 5 Ag\(_2\)O\(_5\); \(\text{Ag}_2\)H\(_2\)I\(_6\); and other combinations of \(\text{Ag}_x\)H\(_y\)I\(_{10}\) where \(x+y=5\), \(\text{Ag}_y\text{M}_x\)I\(_{10}\); where the total cationic charge of \(x+y=5\) and \(M\) is one or more cations (including those specified above); and combinations thereof. All of the starting materials form at least one compound or complex that releases silver.

As used herein, antimicrobial includes antibacterial, including planktonic or biofilm forms. A preferred antimicrobial compound or composition is also anti-biofilm. Anti-biofilm agent refers to any element, chemical, biochemical, or the like that is effective against a biofilm. Typical anti-biofilm agents are those that have antimicrobial, antibacterial, anti-fungal or anti-algal properties. Metal and metal compounds, preferably ionic silver-containing species, have been shown generally to have antibacterial and ethylene inhibiting properties, and are preferred.
anti-biofilm agents in accordance with the present invention. In some embodiments of the invention, the anti-biofilm agent is a broad spectrum agent, e.g., having effectiveness or activity against more than one microbial species.

"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 release 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 releases silver ions virtually instantly, but not continuously, in contact with an alcohol, aqueous solution, or electrolyte. The active agents of the present invention are superior to other commercially available silver containing compounds in part because of the slow release of silver.

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, catheters; 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.

Surface, as used herein generally refers to its common dictionary definition, e.g., an outer face, outside, or external boundary of a thing or a portion of a thing. The surface will generally be an external portion, but in some embodiments, the surface may be internal. A surface may also include an outer portion of a device or thing, but the outer portion need not be the farthest outer portion or layer. For example, some medical devices such as catheters are known to include one or more coatings or layers. Any or all of these individual coatings or layers are still considered to be on the surface of the device. Similarly, when applied to a human, animal, or plant, a surface may be the skin or the like, including but not limited to an infection or wound on that surface.

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.

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.

The term "coating" as used herein generally includes coatings that completely cover a surface, or a 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. The preferred coating is a gel or hydrogel (e.g., U.S. patent 5,662,924).

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., rayon or polyester), or cellular (e.g., a plant, a seed, leaves, skin, or hide). Metal substrate includes but is 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 anti-microbial agent.

EXAMPLES

Example 1 - Basic compatibility of AgSIOs with gels

The purpose of this study was to determine whether Ag5I0.6 could be incorporated into various gels without reacting with the gels.

Ag5I0.6 powder was combined with various commercially available hydrogels and then visually examined for stability, along with UV-Vis analysis and x-ray diffraction.

Gels selected: Guardian Laboratories AquaThik™ (Xanthan gum, PEG-180; 3% in water); Lubrajel® RC (Water, glycerin, propylene glycol, polyacrylic acid, sodium polyacrylate, 0.18% methylparaben, 0.02% propylparaben), and Lubrajel® PF (Glycerin, glyceryl acrylate/acrylic acid copolymer); SteriLub™ (unknown composition); BASF Pluronic® F127 + Carbowax 600 (Polyoxyethylene-polyoxypropylene block copolymer ; 18% Pluronic, 15% Carbowax 600); ConvaTec DuoDerm® Hydroactive® Sterile Gel (pectin, sodium carboxy-
methylcellulose); Molnlycke Normlgel® (0.9% NaCl, H₂O, xanthan gum); Smith&Nephew IntraSite Gel (Water >60%, propylene glycol 10-30%, absorbent polymer <10% - crilanomer, a Graft-T starch copolymer) and SoloSite Gel (Water >60%, glycerol 10-30%, absorbent polymer <10%, allantoin <1%, antiseptic/ preservative <1%); carboxymethylcellulose gel (4% in water); Cremophor; and Gelrite (0.4% in water).

For each gel, the samples were mixed in a small glass container with fine Ag₃I₀₆ powder to generate 500 ppm Ag₃I₀₆ in the gels. Each of the above formulations were examined for visual signs of instability, such as dramatic viscosity changes, color changes, release of gas, deposition of precipitate that appears different from the original Ag₃I₀₆, and temperature change during stirring (heat release).

UV-Vis Analysis: Samples were diluted to 1/10th their original concentration. For UV-Vis blanks, control gels (with no Ag₃I₀₆) were prepared as described for each gel, and diluted to 1/10th as well. UV-Vis measurements were performed between 190-500 nm. pHs of the gel formulations were measured with and without the Ag₃I₀₆ added using pH indicator strips.

No viscosity change, gas release, temperature change, or pH change occurred after the addition of Ag₃I₀₆ to the AquaThik™. A color change from clear to translucent purple occurred, but no UV-Vis peaks were observed. XRD results showed that the Ag₃I₀₆ remained 100% pure and thus did not react with the AquaThik™ gel to form a new crystalline compound.

No viscosity change, color change, temperature change, UV-Vis peaks, or pH change was detected after the addition of the Ag₃I₀₆ to the SteriLub™ gel. The Ag₃I₀₆ did not evenly disperse or dissolve; instead it formed small clusters of particles. During mixing, large gas bubbles formed, which were not due a reaction but rather incorporation of air. The XRD results showed that the Ag₃I₀₆ did not react with the gel to form a new crystalline compound (remained 100% pure after mixing).

The Pluronic® F127 plus Carbowax 600 went through a change in viscosity, color, and a large amount of finely distributed gas bubbles formed in the gel. The initially clear Pluronic® F127 turned white and developed a porous consistency. Ag₃I₀₆ was not visible in the Pluronic® F127 after addition. No temperature change, precipitate formation, or pH change occurred after the addition of the Ag₃I₀₆. A peak at 216 nm was measured by UV-Vis, likely due to dissolved Ag₃I₀₆. A sample was not submitted for XRD because of the undesirable physical changes in the gel after addition of Ag₃I₀₆.

The DuoDerm® did not undergo any change in viscosity, pH or temperature from the addition of Ag₃I₀₆. The gel color changed to a darker brown, and very small quantities of Ag₃I₀₆ were still noticeable in clumps. A peak at 216 nm was measured by UV-Vis, likely due to dissolved Ag₃I₀₆. The XRD data obtained shows that the Ag₃I₀₆ did not react with the DuoDerm® hydrogel to form a new crystalline compound but remained pure.
There was no viscosity change, temperature change, pH change or release of gas from
the carboxymethylcellulose after the addition of Ag$_5$I$_6$. The carboxymethylcellulose turned
from clear to a dark brown color. The Ag$_5$I$_6$ was not visible as clumps, and no new precipitates
were observed to have formed. A UV-Vis peak was measured at 214 nm, likely due to
dissolved Ag$_5$I$_6$. The XRD data showed that the carboxymethylcellulose was not reactive with
the Ag$_5$I$_6$.

There was no viscosity change, temperature change, pH change, release of gas, or
obvious precipitation formation in the Normlgel® after the addition of Ag$_5$I$_6$. The
Normlgel® changed to a translucent brown and no clumps of Ag$_5$I$_6$ were visible in the gel. A
UV-Vis peak was measured at 216 nm, likely due to dissolved Ag$_5$I$_6$ or AgCl. The XRD data
shows that the Normlgel® contained KCl and AgCl, as well as Ag$_5$I$_6$. The Normlgel® blank
contained NaCl and KCl. Thus the AgCl was likely formed by the breakdown of Ag$_5$I$_6$ with
release of Ag$^+$ which then reacted with the NaCl contained in the gel, suggesting that Ag$_5$I$_6$ is
incompatible under these conditions with this gel for long term storage.

The Lubrajel® PF did not have any change in viscosity, temperature, pH or color after
the addition of Ag$_5$I$_6$. No precipitate formed and no gas was released. The Ag$_5$I$_6$ agglomerated, forming larger particles than originally added to the gel. A UV-Vis peak was
measured at 214 nm, likely due to dissolved Ag$_5$I$_6$. The XRD data showed that only Ag$_5$I$_6$ was present in the gel, indicating that the Ag$_5$I$_6$ had not reacted with the Lubrajel® PF
hydrogel.

The Lubrajel® RC did not undergo any change in viscosity, temperature, pH or color
after the addition of Ag$_5$I$_6$. Also, no precipitate formed and no gas was released. The Ag$_5$I$_6$ agglomerated, forming larger particles than what was originally added to the gel. The UV-Vis
data showed peaks or spikes at 230 nm and 284 nm of uncertain identity. The XRD data
showed that the Lubrajel® RC only contained Ag$_5$I$_6$, indicating the Ag$_5$I$_6$ did not react in
Lubrajel® RC.

There was no change in the viscosity, pH, or temperature of the IntraSite gel and no gas
was released after Ag$_5$I$_6$ addition. The color of the IntraSite* became translucent brown and
no Ag$_5$I$_6$ particles were visible in the gel. A UV-Vis peak was detected at 210 nm, suggesting
dissolved Ag$_5$I$_6$. The XRD data showed that only Ag$_5$I$_6$ was present in the gel - no reaction
products.

There was no change in the viscosity, pH, or temperature of the SoloSite gel and no gas
was released after the addition of Ag$_5$I$_6$. The color of the SoloSite became translucent brown
and no Ag$_5$I$_6$ particles were visible in the gel. UV-Vis data showed a peak at 286 nm, the
origin of which was uncertain. The XRD data showed that only Ag$_5$I$_6$ was present in the gel -
no reaction products.

There was no change in viscosity, temperature, pH, UV-Vis signal, or color of the
Cremophor gel after the addition of Ag$_5$I$_6$, nor was there gas release. The Ag$_5$I$_6$ dispersed

within the gel, but particles were still visible. There was no Ag₅L₀₆ detected by the XRD analysis. This could be due to a high level of interference from the Cremophor which hid the Ag₅L₀₆ signal or a reaction of Ag₅L₀₆ with the Cremophor gel. Since no other species of silver were detected, the latter cannot be confirmed.

The Gelrite did not undergo a change in viscosity, pH, or temperature after the addition of Ag₅L₀₆, or release gas. The Ag₅L₀₆ initially formed clumps, but after approximately ten minutes there was no sign of solid Ag₅L₀₆ in the gel. The color became translucent brown as the Ag₅L₀₆ dissolved in the gel. The XRD data showed that the Ag₅L₀₆ did not react with the Gelrite.

The SoloSite, IntraSite, carboxymethylcellulose, DuoDerm®, and AquaThik™ appear to incorporate Ag₅L₀₆ well.

The Lubrajel® RC and PF, as well as the Sterilub™, are also but better dissolution/dispersion of the Ag₅L₀₆ within the gel would be valuable.

Example 2 - Antimicrobial activity of Ag^ℓCy-containing gels

The purpose of this study was to measure anti-microbial activity using a relevant microorganism against Ag₅L₀₆ incorporated into two representative hydrogels. This test method describes the physical combination of Ag₅L₀₆ powder into two representative commercially available hydrogels and application of these hydrogels into a dressing material. These coated dressings were then tested in a day-to-day transfer corrected zones of inhibition assay. Each sample set was tested against P. aeruginosa (ATCC 27853).

Samples were prepared as described in Example 1.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>AT-500</td>
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<td>AT-10000</td>
<td>Guardian Lab. AquaThik™ 10000 ppm</td>
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<td>RC-10000</td>
<td>Guardian Lab. Lubrajel® RC 10000 ppm</td>
</tr>
</tbody>
</table>

Rayon/polyester blend dressings were aseptically cut into 1 inch by 1 inch squares. In triplicate, the gels at different concentrations were spread on one side of the dressing to saturate it with gel. The weight of the gel added was determined.
From a fresh streak plate, the study organism was inoculated in broth and incubated overnight, then used full strength.

300 µL of inoculum was pipetted onto three separate locations of large Petri plates and spread.

Dressings were aseptically placed onto the plates.

Plates were incubated overnight. The zones of inhibition were determined by measuring the diameter of the clear zone and the diameter of the test article with calipers in two perpendicular directions. The diameter of the test article was then subtracted from the diameter of the clear zone to yield the corrected zone of inhibition (CZOI).

The above steps were repeated, transferring the samples to fresh lawns of bacteria each day until either no zone was produced or 9 transfers had been performed.

### Amount of Ag₅O₆ added to bandages

<table>
<thead>
<tr>
<th>Sample</th>
<th>Gel Weight (g)</th>
<th>Ag₅O₆ added to bandage (mg)</th>
<th>Average Ag₅O₆/bandage area (mg/cm²)</th>
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<tr>
<td>AT - 500</td>
<td>0.25</td>
<td>0.13</td>
<td>0.02</td>
</tr>
<tr>
<td>AT - 1000</td>
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<td>0.04</td>
</tr>
<tr>
<td>AT - 5000</td>
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</tr>
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<tr>
<td>RC - 10000</td>
<td>0.33</td>
<td>3.30</td>
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</table>

The 500 ppm Aquathik gel had zones of inhibition for 1 day, the 5000 ppm Aquathik gel had zones of inhibition for 4 days, and the 10000 ppm Aquathik gel had zones of inhibition for 6 days. The 500 ppm Lubrajel RC had zones of inhibition for 1 day, the 5000 ppm Lubrajel RC had zones of inhibition for 4 days, and the 10000 ppm Lubrajel RC had zones of inhibition for 4 days.
days. The 10000 ppm Aquathik gel performed the best out of all the gels. It had zones of inhibition that lasted the longest as well as having significantly larger zones than the 10000 ppm Lubrajel RC gel on Days 2, 3, and 4.

Example 3 - $\text{Ag}_3\text{IO}_6$ Solubility in Water and Saline

The purpose of this study was to develop a basic understanding of the solubility (and stability) of $\text{Ag}_3\text{IO}_6$ in pure water and 0.9% (physiological saline), following OECD Method (105) -flask.

The solubility of $\text{Ag}_3\text{IO}_6$ is much lower in saline (0.61±0.05 mg/L) than in ddH$_2$O (24.41±0.87 mg/L). This is likely due to a combination of reaction with the Cl$^-$ and overall ionic strength in the solution reducing the amount of $\text{Ag}_3\text{IO}_6$ dissolvable. The pH in saline (10) was consistently higher than the pH in ddH$_2$O (8). The solids in the presence of saline were a lighter brown than the solids in ddH$_2$O.

While the UV-Vis spectra for the solutions in ddH$_2$O and saline had one peak in common at -206-212 nm, there was a shoulder at -196-200 nm that was only present in the ddH$_2$O sample, possibly indicating some reaction of the $\text{Ag}_3\text{IO}_6$ with the saline. However the spectrum for $\text{Ag}_3\text{IO}_6$ in saline did not match that for AgCl.

The XRD data indicated that in saline, approximately 25% of the solid material collected at the end of the experiment was converted to AgCl, with the remainder as unreacted $\text{Ag}_3\text{IO}_6$. In ddH$_2$O, approximately 99.9% of the solid material remained as $\text{Ag}_3\text{IO}_6$ with 0.1% being converted to Ag metal.

Example 4 - $\text{Ag}_3\text{IO}_6$ Stability in Solvents

The purpose of this study was to determine whether or not $\text{Ag}_3\text{IO}_6$ interacts with methanol, tetrahydrofuran, acetone, and acetonitrile.

2-3 mm of $\text{Ag}_3\text{IO}_6$ 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.

$\text{Ag}_3\text{IO}_6$ 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). In terms of the solubility of $\text{Ag}_3\text{IO}_6$ in different organic solvents, methanol>THF>acetone>acetonitrile.
Example 5 Storage Stability

Even at 90°C, at 14 and 28 days, grain growth occurred (from 14A to 62A) but no compositional change was observed (the material remained 100% AgsI0e).

Since stability at 54°C for 28 days suggests a shelf life of >2 years at room temperature, this data demonstrates very good storage stability of AgsI0e. The AgsI0e had a relatively high water content as-made (137370 ppm), indicating that even relatively "wet" product as dried using the current drying technique has very good storage stability.

With DSC and TGA analysis, AgsI0e is stable past 400°C, indicating that it can be put through the thermal processing required to generate some medical devices without decomposition, although the grain size may increase.

Example 6 - A cα=10e Photostability

The purpose of this study was to assess the photostability of AgsI0e in accordance with the FDA's 1997 recommendations regarding the photostability testing of new products.

AgSIOe was ground, spread thinly on watch glasses, protected from foreign objects, and, along with aluminum foil covered controls, the watch glasses were placed face up under cool-light metal halide lamps such that the samples were receiving at least 700 fc, and the lux exposure was measured regularly until greater than 1.3 million lux hours exposure had occurred. The samples were then submitted for XRD.

After greater than 1.3 million lux hours exposure, the material was still 100% AgsI0e. AgsI0e has very good photostability and does not need to be stored protected from light.

Example 7

The purpose of this study was to evaluate the clarity, weight vs. time under potentially drying conditions, and dispensing properties of various hydrogels after the incorporation of AgsI0e. AgsI0e is a black solid that is thought to be slightly soluble in water, stable at high temperatures and to have properties that allow for compatibility with metals, dressings, and gels.

For each sample preparation described below, the samples were mixed in a small glass container (e.g. beaker or flask). A small magnetic stir bar was placed in the glass container, which was sealed with parafilm and stirred on a magnetic stirrer. Once the sample appeared well-mixed, it was transferred to a scintillation vial. Samples were protected from light using aluminum foil. The AgsI0e did not dissolve in all of these gels, in which case, samples were taken from a well stirred dispersion.

If the powder gels without AgsI0e were too thin for testing, the gels were re-made in a higher concentration to have a similar viscosity as the pre-made/commercial gels. The amount of powder and water used was recorded.
AquaThik™: 3% AquaThik™ was made by combining 0.3g AquaThik™ with 10 mL ddH2O. 3% AquaThik™ with 500 ppm Ag5I06 was made by combining 0.3g AquaThik™ with 5 mg Ag5I06 and then adding 10 mL ddH2O. 3% AquaThik™ with 10000 ppm Ag5I06 was made by combining 0.3g AquaThik™ with 100 mg Ag5I06 and then adding 10 mL ddH2O.

SteriLub™: SteriLub™ with 500 ppm Ag5I06 was made by combining 5 mg Ag5I06 with 10 g SteriLub™. SteriLub™ with 10000 ppm Ag5I06 was made by combining 100 mg Ag5I06 with 10 g SteriLub™.

DuoDERM®: DuoDERM® with 500 ppm Ag5I06 was made by adding 5 mg Ag5I06 to 10g DuoDERM®. DuoDERM® with 10000 ppm Ag5I06 was made by adding 100 mg Ag5I06 to 10g DuoDERM®.

Carboxymethylcellulose (CMC): A 4% CMC gel was made by combining 0.4g CMC with 10 mL ddH2O. A 4% CMC gel with 500 ppm Ag5I06 was made by combining 0.4g CMC with 5 mg Ag5I06, then adding 10 mL ddH2O. A 4% CMC gel with 10000 ppm Ag5I06 was made by combining 0.4g CMC with 100 mg Ag5I06, then adding 10 mL ddH2O.

Lubrajel® PF: Lubrajel®PF with 500 ppm Ag5I06 was made by adding 5 mg Ag5I06 to 10 g Lubrajel® PF. Lubrajel®PF with 10000 ppm Ag5I06 was made by adding 100 mg Ag5I06 to 10 g Lubrajel® PF.

Lubrajel® RC: Lubrajel® RC with 500 ppm Ag5I06 was made by adding 5 mg Ag5I06 to 10 g Lubrajel® RC. Lubrajel® RC with 10000 ppm Ag5I06 was made by adding 100 mg Ag5I06 to 10 g Lubrajel® RC.

IntraSite Gel: IntraSite with 500 ppm Ag5I06 was made by adding 5 mg Ag5I06 to 10 g IntraSite. IntraSite with 10000 ppm Ag5I06 was made by adding 100 mg Ag5I06 to 10 g IntraSite.

SoloSite Gel: SoloSite with 500 ppm Ag5I06 was made by adding 5 mg Ag5I06 to 10 g SoloSite. SoloSite with 10000 ppm Ag5I06 was made by adding 100 mg Ag5I06 to 10 g SoloSite.

Gelrite: 0.4% Gelrite was made by adding 0.04g Gelrite powder to 10 mL ddH2O. 0.4% Gelrite with 500 ppm Ag5I06 was made by combining 0.04 g gelrite powder with 5 mg Ag5I06 and then...
adding it to 10 mL ddH₂O. 0.4% Gelrite with 10000 ppm Ag₅I₀₆ was made by combining 0.04 g Gelrite powder with 100 mg Ag₅I₀₆ and then adding it to 10 mL ddH₂O.

In most gels, addition of Ag₅I₀₆ at increasing concentrations caused the gels to become an opaque brown. For two of the gels, opacity was not achieved due to particles of Ag₅I₀₆ clumping in the gel rather than a uniform dispersion or dissolution of the Ag₅I₀₆.

The dispensing behavior of the CMC, Lubrajel PF, Lubrajel RC, and Gelrite gels were affected by the addition of Ag₅I₀₆ while the other gels tested were not. Based on the results of the dispensing behavior tests, the CMC gel increased in viscosity, and the Lubrajel RC, Lubrajel PF, and Gelrite gels decreased in viscosity after the addition of Ag₅I₀₆, thus no clear overall pattern was observed, but in select gels, the viscosity was impacted.

For the majority of the gels, adding Ag₅I₀₆ had no impact on the % weight loss over time due to water loss at a set temperature and humidity. In the CMC gel only, adding 10000 ppm Ag₅I₀₆ reduced water loss.

Example 8

The gels of examples 1 and 7 were tested against additional species.

Commercial gels (without Ag₅I₀₆) None of the commercial gels performed well against *P. aeruginosa, S. aureus, S. epidermidis* or *C. albicans*. Overall, the three commercial gels did not have a significant antimicrobial effect on the *P. aeruginosa*. The SilvaSorb, Silver-Sept, and Elta Silver gel did not have any antimicrobial effect on *S. aureus*. The Silver-Sept, SilvaSorb, and Elta Silvergel gels did not have any antimicrobial effect on *S. epidermidis*. All 3 commercial gels tested did not produce an antimicrobial effect against *C. albicans*.

Ag₅I₀₆ Gels:

Based on zone size and longevity, the 50000 ppm Aquathik, 50000 ppm Lubrajel RC, and 50000 ppm Lubrajel PF gels had the greatest overall longevity and zone size against *P. aeruginosa*. All three gels had zones of inhibition lasting 7 days. The 50000 ppm carboxymethylcellulose gel also performed well against *P. aeruginosa*, but only had zones of inhibition lasting 6 days. The 10000 ppm Ag₅I₀₆ gels only had zones of inhibition lasting 3 days, which shows that the higher gel concentration is required to produce long lasting zones of inhibition.

For *S. aureus*, the 10000 ppm Ag₅I₀₆ gels lasted a minimum of 2 days (Intrasite) and a maximum of 5 days (carboxymethylcellulose). There were four 50000 ppm gels that had zones lasting the entire 10 days. These included the Aquathik, Lubrajel RC, Lubrajel PF, and carboxymethylcellulose gels. These gels had good longevity and zone size against *S. aureus*. 

- 18 -
For S. epidermidis, only the 50000 ppm carboxymethylcellulose gel had zones of inhibition lasting 10 days. All other gels had zones lasting 7 days or less. The 10000 ppm Ag₅I₀₆ gels had zones of inhibition lasting between 2 and 3 days.

For C. albicans, all of the Ag₅I₀₆ gels had zones of inhibition on Day 1, but on Day 2 a less dense lawn of bacteria grew within the visible zone. Based on this, the Ag₅I₀₆ gels were deemed to not have produced any zones of inhibition on Day 2. The Ag₅I₀₆ gels were more effective against C. albicans than the commercial gels in producing an antimicrobial effect, but did not achieve the desired longevity of -10 days. Therefore, the Ag₅I₀₆ gels were not effective against C. albicans.
CLAIMS:

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

2. The article of claim 1 wherein the gel is a gel selected from the group consisting of Xanthan gum and PEG-180; water, glycerin, propylene glycol, polyacrylic acid, sodium polyacrylate, methylparaben, and propylparaben; glycerin, and glyceryl acrylate/acrylic acid copolymer); polyoxyethylene-polyoxypropylene block copolymer, pluronic, and carbowax 600); pectin, and sodium carboxy-methylcellulose; NaCl, water, and xanthan gum); water, propylene glycol, absorbent polymer, crilanomer, and a Graft-T starch copolymer; water, glycerol, absorbent polymer, allantoin, and antiseptic/preservative; and carboxymethylcellulose gel.

3. The article of claim 1 wherein the gel is a hydrogel.

4. The article of claim 1 wherein the silver (I) periodate is one or more compounds selected from the group consisting of silver (I) iodate; pentasilver hexaoxoiodate; Ag5I06; silver orthoperiodate; silver periodate (VII); silver iodate (VII); 5 Ag20-I207; Ag2H3I06; AgxHyl06, where x + y = 5; AgxMyI06, where the total cationic charge of x + y = 5 and M is a cation; and combinations thereof.

5. The article of manufacture of claim 4 wherein the cation is selected from the group consisting of K, Na, Mg, Ca, Au, Pt, Cu, Zn, and Fe; or combinations thereof.

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

7. A method of making a surface antimicrobial, comprising forming or coating the surface with a gel comprising one or more silver (I) periodates.

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; Ag5I06; silver orthoperiodate; silver periodate (VII); silver iodate (VII); 5 Ag20-I207; Ag2H3I06; AgxHyl06, where x + y = 5; AgxMyI06, 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 wound healing material or composition, a medical instrument, a medical device, a metallic article, human or animal skin, a plant, a seed, or a portion thereof.

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

11. The method of claim 10 wherein the silver (I) periodate is one or more compounds selected from the group consisting of silver (I) iodate; pentasilver hexaoxiodate; Ag5I06; silver orthoperiodate; silver periodate (VII); silver iodate (VII); 5 Ag20-I207; Ag2H3I06; AgxHyl06, where x + y = 5; AgxMyl06, where the total cationic charge of x + y = 5 and M is a cation; and combinations thereof.

12. The method of claim 10 wherein the substrate is a wound dressing, a wound healing material or composition, a medical instrument, a medical device, a metallic article, human or animal skin, a plant, a seed, or a portion thereof.

13. An antimicrobial wound dressing or wound healing composition comprising an antimicrobial gel coating containing one or more silver (I) periodates.

14. The wound dressing of claim 13 wherein the silver (I) periodate is one or more compounds selected from the group consisting of silver (I) iodate; pentasilver hexaoxiodate; Ag5I06; silver orthoperiodate; silver periodate (VII); silver iodate (VII); 5 Ag20-I207; Ag2H3I06; AgxHyl06, where x + y = 5; AgxMyl06, where the total cationic charge of x + y = 5 and M is a cation; and combinations thereof.

15. The wound dressing of claim 13 wherein one or more silver (I) periodates are coated onto a wound dressing material.

16. A gel formulation comprising a two-phase colloidal system consisting of a solid and a liquid, wherein said system further comprises at least one silver (I) periodate.

17. The gel formulation of claim 16 wherein the silver (I) periodate is one or more compounds selected from the group consisting of silver (I) iodate; pentasilver hexaoxiodate; Ag5I06; silver orthoperiodate; silver periodate (VII); silver iodate (VII); 5 Ag20-I207; Ag2H3I06; AgxHyl06, where x + y = 5; AgxMyl06, where the total cationic charge of x + y = 5 and M is a cation; and combinations thereof.
18. The gel formulation of claim 16 wherein the gel is a gel selected from the group consisting of xanthan gum and PEG-180; water, glycerin, propylene glycol, polyacrylic acid, sodium polyacrylate, methylparaben, and propylparaben; glycerin, and glyceryl acrylate/acrylic acid copolymer; polyoxyethylene-polyoxypropylene block copolymer, pluronic, and carbowax 600; pectin, and sodium carboxy-methylcellulose; NaCl, water, and xanthan gum); water, propylene glycol, absorbent polymer, crilanomer, and a Graft-T starch copolymer; water, glycerol, absorbent polymer, allantoin, and antiseptic/ preservative; and carboxymethylcellulose gel.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC: A61L 15/46 (2006.01), A01N 59/16 (2006.01), A61K 33/38 (2006.01), A61L 2/16 (2006.01), A61P 31/02 (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61L 15/46 (2006.01), A01N 59/16 (2006.01), A61K 33/38 (2006.01), A61L 2/16 (2006.01), A61P 31/02 (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, Scopus, Epoque (epodoc, clxte and txtusl databases)

keywords: silver iodate, silver periodate, pentasilver hexaoxiodate, silver orthoiodate, wound, gel, hydrogel, medical, antibacterial, antimicrobial, plaruric, carboxy, carboxymethylcellulose

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category*</th>
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<td>WO 2006/034249 A2 (Karandikar et al), 30 March 2006 (30-03-2006) abstract page 5, line 20 page 13, lines 15-16 page 16, line 5 page 18, lines 23-25 page 19, lines 1-3</td>
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

Date of the actual completion of the international search 11 October 2013 (11-10-2013)
Date of mailing of the international search report 25 October 2013 (25-10-2013)

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 Pierre Tessier (819) 934-0073

Form PCT/ISA/210 (second sheet) (July 2009) Page 3 of 5
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INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim Nos.: 9 and 12
   because they relate to subject matter not required to be searched by this Authority, namely:
   Claims 9 and 12 are directed to a method of treatment of the human or animal body by surgery or therapy, and are not required to be searched, nor is a written opinion required by this Authority. Specific reference is made to those instances of claims 9 and 12 wherein human or animal skin is made antimicrobial through use of the gels. Regardless, this Authority has established a written opinion based on the alleged effect or purpose/use of the product defined in claims 9 and 12.

2. [ ] Claim Nos.: 
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim Nos.: 
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.: 

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.: 

   **Remark on Protest** [ ] The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.
   [ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
   [ ] No protest accompanied the payment of additional search fees.
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