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(54) **Titre : FORMULATIONS ET PROCEDES UTILISANT UN DESINFECTANT ANHYDRE**

(54) **Title: ANHYDROUS COMPOSITIONS OF SILVER DIHYDROGEN CITRATE AND CITRIC ACID AS A DISINFECTANT OR FOR ANTIMICROBIAL PROTECTION**

(57) **Abrégé/Abstract:**

Use of dried compositions of silver dihydrogen citrate along with citric acid in antimicrobial amounts directly as disinfectants is described.



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(57) Abstract: Use of dried compositions of silver dihydrogen citrate along with citric acid in antimicrobial amounts directly as disinfectants is described.



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ANHYDROUS COMPOSITIONS OF SILVER DIHYDROGEN CITRATE AND CITRIC ACID AS A DISINFECTANT OR FOR ANTIMICROBIAL PROTECTION

Technical Field

[0001] The invention relates to the use of the anhydrous form of silver dihydrogen citrate (SDC) directly, without reconstitution in aqueous liquid, for antimicrobial protection. More specifically, the invention relates to direct use of SDC in non-aqueous compositions.

Background Art

[0002] The preparation of aqueous solutions of silver dihydrogen citrate (SDC) and citric acid was described in U.S. 6,197,814. In this method, the SDC is generated electrolytically in a solution of 5-25% citric acid. According to the '814 patent, the resulting aqueous disinfectant may optionally be mixed with alcohol and/or a detergent and can be used on exposed or contaminated surfaces to kill bacteria, virus, fungi and other microorganisms. It can also be used to disinfect wounds and to behave as a disinfectant in water systems, such as cooling towers, hot water systems, potable water systems, etc.

[0003] PCT publication WO2005/041861 and U.S. patent 7,732,486 describe preparing an anhydrous form of the SDC/citric acid solution for ease of transport. According to these publications, in order to employ the anhydrous form as a disinfectant, it should be reconstituted to recreate the aqueous systems described in the '814 patent. As noted in the '861 publication and the '486 patent, the anhydrous form is capable of being reconstituted to a fully-active aqueous disinfectant.

[0004] It has now been found that reconstitution of this anhydrous form is unnecessary, and that the anhydrous form itself may be employed in non-aqueous systems as an *in situ* disinfectant and antimicrobial protectant.

Disclosure of the Invention

[0005] In one aspect, the present invention is directed to a method to disinfect a variety of environments, which method comprises employing an anhydrous silver dihydrogen citrate (SDC)/citric acid composition in dry form. For instance, the dry SDC/citric acid may be used as a coating on a surface or as a component of a non-aqueous formulation, such as paint or drywall. The invention is also directed to formulations that comprise an antimicrobial amount of an anhydrous SDC/citric acid composition as part of a non-aqueous formulation.

[0006] Various embodiments of the invention provide a formulation which comprises an antimicrobial amount of an anhydrous composition of SDC and citric acid (citric acid/SDC composition) wherein said citric acid/SDC composition comprises no more than 50% by weight of said formulation, wherein the formulation is a solid formulation or a non-aqueous liquid formulation, and wherein the non-aqueous liquid formulation is a paint, a protective coating system, a caulk, a conforming sealant, a systemic treatment for plant pathogens utilizing time-release methodology, a varnish, a medical device coating, or for use in treating deep internal infections.

[0006a] Various embodiments of the invention provide a non-medical method to provide antimicrobial protection to an environment, which method comprises applying to said environment an antimicrobially effective amount of a formulation as described above, wherein the environment is other than human or animal.

[0006b] Various embodiments of the invention provide a non-medical method to provide antimicrobial protection to a surface, comprising applying to said surface an antimicrobially effective amount of an anhydrous composition of SDC and citric acid without reconstitution of said composition in solvent, wherein the surface is other than that of a human or animal.

[0006c] Various embodiments of the invention provide a method to provide antimicrobial protection to a formulation, which method comprises including in said formulation an antimicrobially effective amount of an anhydrous composition of SDC and citric acid without reconstitution of said composition in solvent.

[0006d] Various embodiments of the invention provide a method to prepare an emulsion or lotion which method comprises providing non-aqueous components of said lotion or emulsion or said lotion or emulsion itself with an antimicrobially effective amount of an anhydrous composition of SDC and citric acid without reconstitution of said composition in solvent.

[0006e] Various embodiments of the invention provide use of a formulation as described above for providing antimicrobial treatment or protection to an environment or surface, including a living surface.

[0006f] Various embodiments of the invention provide use of a formulation as described above in the preparation of a medicament for providing antimicrobial protection to a wound.

[0007] Typically, the mol ratio of citric acid to SDC in the anhydrous compositions is such that there is a molar excess of citric acid over the SDC, of the order of 5, 10, 15, 20 or 25 to 1. All intermediate values are also included.

[0008] This anhydrous composition, then, is employed in the methods and formulations of the present invention.

[0009] In order to avoid confusion, the anhydrous SDC/citric acid itself will be referred to as a "composition" and a solid or non-aqueous liquid formulation in which it has been included will be referred to as a "formulation."

Modes of Carrying Out the Invention

[0010] A method for obtaining anhydrous SDC/citric acid compositions is described in detail in the above-referenced PCT publication WO2005/041861 and U.S. 7,732,486. Briefly, as therein disclosed, an aqueous solution of SDC in the presence of significant amounts of citric acid is prepared generally according to the process set forth in U.S. 6,197,814, *i.e.*, the SDC is generated by applying either DC or AC current across silver electrodes immersed in a citric acid solution containing, for example, citric acid at a concentration of the order of 1-25% generally 5-20% or 5-10% by weight.

[0011] The water is removed from the resulting aqueous disinfectant, preferably by freeze-drying a frozen solution under vacuum effecting sublimation of the water. Other means for removing water from an appropriate SDC/citric acid solution may also be employed, such as vacuum drying, spray drying, or other means of effecting removal of the aqueous solvent so long as the antimicrobial effect of the SDC/citric acid composition is not destroyed.

[0012] The anhydrous composition may be milled into suitable particle sizes for application. Any art-recognized means for disaggregating and fluidizing solids may be employed. Typical particle sizes range from 2-500 μ , but larger or smaller sizes may also be employed. For medical use, for example, the particles may be in the range of 100-1,000 nm.

[0013] “Antimicrobial” includes effective protection against fungi, viruses, bacteria, archaea, and the like. Thus, any infectious agent is included as a “microbial” agent.

[0014] “Non-aqueous formulations” refers to formulations that effectively exclude any water component whatsoever, or that include only 5%-15% water by weight or less. They do not include emulsions, lotions, and the like that have substantial amounts of water but rather either are liquid formulations, wherein no more than 5-15% preferably no more than 1-5% by weight is water, or are solid materials of any type. Emulsions and lotions that contain SDC/citric acid are described in PCT publication WO2006/029213. However, these formulations are prepared directly from the aqueous solutions of SCD/citric acid. The present invention also includes methods of preparing these compositions or similar compositions using the anhydrous composition *per se*.

[0015] In some embodiments, the anhydrous composition or a formulation containing it ultimately comes in contact with an aqueous environment; in other applications, it does not. In each case, however, the anhydrous SDC/citric acid composition is employed without reconstituting it first into an aqueous solution.

[0016] In exemplary, but non-limiting applications, the anhydrous composition is included in various coatings and construction materials, such as paints or other coatings or materials employed to construct solid components such as countertop materials including Formica® and high pressure laminates, drywall, plaster and tile. The use of this material in drywall is especially important to prevent the formation of mold. The anhydrous composition may also directly be used in packaging materials such as paper, cardboard, Styrofoam™, plastics and the like. It may also be used in caulks and sealants as well as in woven and non-woven fabrics including synthetic and natural fabrics.

[0017] Depending on the nature of the application, the weight percentage of the anhydrous composition in the finished product will vary over a wide range from about 0.5% by weight to about 50% by weight, typically 1-2% by weight. The anhydrous composition may be incorporated in the manufacture of the product, for example, by mixing the composition directly into paint or varnish or by including it in a preparation of monomers to be polymerized in the

formation of polymers or in the particulates pressed into fiberboard. The SDC/citric acid anhydrous composition is compatible with a wide variety of materials and skilled artisans will understand how best to incorporate this composition effectively into non-aqueous systems.

[0018] The dried SDC/citric acid composition of the invention is also useful in the context of medical and pharmaceutical applications and can be applied as a dry coating to bandages and medical devices, such as catheters or surgical tools. The dry SDC/citric acid may also be directly applied to wounds, especially wherein deep wounds, internal wounds or subcutaneous infections are a threat. The dry SDC/citric acid can be combined with various other pharmaceuticals in tablets, powders, and the like. Other pharmaceuticals include antibiotics, anti-clotting agents, and effervescent systems.

[0019] Anhydrous SDC/citric acid compositions of the invention are also useful directly in water treatment by integrating them with filter media, and employed in solid form in various contexts such as toilet bowl sanitizers, and are also useful in agriculture for crop-dusting either alone or in combination with other dried materials such as fertilizers and herbicides and pesticides.

[0020] A non-limiting list of such uses is as follows:

Anhydrous SDC combined with an acceptable substrate to provide antimicrobial protection in commercial processes:

Plastics and fiberglass materials (FRP systems)

Woven and nonwoven fabrics: organic and inorganic; filament and monolithic strand

Polymers

Vinyls

Paint: protective coating systems – single and multi-part, *e.g.* to prevent mold in drywall

Latex

Architectural finishes, *i.e.*: Formica[®]/countertop materials and other high pressure laminates

Caulks and conforming sealants

Hardening Foams, thermoformed and catalyzed

Paper/cardboard packaging and attendant coatings

Construction materials: cementitious coatings, drywall and drywall finishing compounds, plaster, tile and tile grouts

Anhydrous SDC for medical and pharmaceutical applications:

Combined with antibiotics as a synergizing/potentiating agent

Combined with anti-clotting agents to provide anti-infective properties

Combined with medical powders to be applied as an anti-infective dusting agent for pre and post surgical procedures or trauma wound application

Combines with co-valent dry chemistry for use as a biological warfare decontaminant

Incorporated into a bandage substrate

Tabletized chemistries: effervescent and non-effervescent systems utilizing other actives and excipients

Gel & semi-solid suppository delivery systems

Medical device coatings

Curative / palliative treatment of subcutaneous and deeper internal infections

Water Treatment:

Dry algacide/bactericide

Combined with water treatment resins

Combined with filter media to mitigate microbial growth

Introduced into fluid handling systems for biofilm mitigation

Aquaculture

Agriculture:

Systemic treatment for plant pathogens utilizing various time-release methodologies

Surface dusting for plant pathogen prevention/mitigation

Soil pH moderator

Dry sanitizer for pre-and post-harvest rinse

Tabletized unit dosing for process equipment

Unit dose ornamental & cut flower preservative

Commercial Mass Market:

Dry formed tablet / pelletized home fruit and vegetable wash

Tabletized unit dose home hard surface sanitizer

Toilet sanitizer

Unit dose carpet and upholstery sanitizer systems

[0021] The following examples are offered to illustrate but not to limit the invention.

Example 1

Preparation of Antimicrobial Drywall

[0022] Antimicrobial drywall is prepared by incorporating silver dihydrogen citrate (SDC) in the gypsum core, in or on the paper covering, or in both the gypsum core and paper covering of drywall. The SDC-containing drywall resists the growth of microbes, in particular fungi, when compared to standard drywall.

[0023] Antimicrobial drywall containing SDC in the gypsum core is prepared by adding solid SDC to a slurry containing gypsum powder, water, paper pulp, starch and/or set controlling agents, in an amount sufficient to exhibit efficacy against microbes. The resultant gypsum slurry is sandwiched between two sheets of craft paper stock, referred to as the front and back paper facings. The paper with the slurry in between is run through a set of rollers to make it flat and smooth, the edges are shaped, and the drywall is cut to the desired size and dried.

[0024] Antimicrobial drywall containing SDC in the paper covering is prepared by spraying one or both of the front and back paper facings with a solution of SDC in an appropriate solvent prior to drying the cut drywall. Alternatively, SDC is applied as a coating on one or both sides of the paper covering before the paper is contacted with the gypsum slurry.

Example 2

Preparation of Antimicrobial Paper

[0025] A slurry of paper forming fibers prepared according to a wet-laid process is mixed with an aluminum silicate or titanium dioxide filler in a quantity of about 1%-10% parts per weight of fiber. The mixture is stirred constantly with the addition of starch paste as a sizing compound. An interfiber binding agent is prepared by adding solid SDC to latex polyacrylamide or polyvinyl acetate, as a melt or as a solution in a compatible solvent, and mixing to incorporate the SDC within the polymeric matrix. The binding agent mixture is added to the pulp material and mixed, and the mixture is poured onto a wire screen, dewatered, pressed and calendared to obtain a smooth finish.

Example 3

Preparation of Antimicrobial Grout

[0026] Silver dihydrogen citrate (SDC) is admixed with a standard dry grout compound in an amount sufficient to exhibit efficacy against microbes.

[0027] The dry admixture is mixed with water according to packaging instructions and cast into 1-2 inch diameter rounds for testing. The SDC-containing samples resist *Aspergillus niger* (household black mold) relative to control samples lacking SDC when exposed to simulated household shower conditions.

Example 4

Preparation of Antimicrobial High Pressure Laminate

[0028] SDC is admixed into a conventional melamine formulation, including ceramic reinforcement materials and pigments, in an amount sufficient to exhibit efficacy against microbes. The melamine mixture is spread onto craft paper and dried. The SDC-containing melamine layers are pressed together using conventional heating and pressing equipment to produce a high-pressure laminate material.

[0029] The SDC-containing laminate material resists the growth of microbes, including bacteria and fungi, relative to traditional laminates.

Example 5

Preparation of Antimicrobial Coated Catheters

[0030] An antimicrobial coating composition is prepared by admixing finely ground silver dihydrogen citrate (SDC) with a hexane dispersion of room temperature vulcanized (RTV) silicone resin. The surface of the catheter to be coated is cleaned, and the article is dip-coated by immersing in the SDC-containing mixture for several minutes. The catheter is dipped into the solution 1 to 3 times, until the desired thickness of the coating is achieved. The article is allowed to dry between coatings and then further dried at elevated temperature.

[0031] The treated catheter resists the growth of undesirable microbes relative to an untreated control when incubated at 37°C for 24 to 48 hours with inoculum cultures of test bacteria, such as *E. coli* (e.g., clinical isolate from UTI).

Claims

1. A formulation which comprises an antimicrobial amount of an anhydrous composition of silver dihydrogen citrate (SDC) and citric acid (citric acid/SDC composition); wherein said formulation comprises no more than 50% by weight of the citric acid/SDC composition; wherein the formulation is a solid formulation or a non-aqueous liquid formulation; and wherein said non-aqueous liquid formulation is a paint, a protective coating system, a caulk, a conforming sealant, a systemic treatment for plant pathogens utilizing time-release methodology, a varnish, a medical device coating, or is for use in treating deep internal infections.
2. The formulation of claim 1, wherein the formulation is a paint.
3. The formulation of claim 2, wherein the paint is a latex paint.
4. The formulation of claim 1, wherein the formulation is a varnish.
5. The formulation of claim 1, wherein the formulation is a solid formulation, and wherein the solid formulation is: plastic, fiberglass material, woven or nonwoven fabric, a polymer, vinyl, countertop material, high pressure laminate, paper/cardboard packaging, construction material, a cementitious coating, drywall, a drywall finishing compound, plaster, tile, tile grout, a combination with an anti-clotting agent to provide an anti-infective property, a combination with a medical powder for use as an anti-infective dusting agent in pre and post surgical procedures or trauma wound application, a combination with co-valent dry chemistry for use as a biological warfare decontaminant, a bandage substrate, a tabletized chemistry, a suppository delivery system, a dry algaecide/bactericide, a combination with a water treatment resin, a combination with a filter medium to mitigate microbial growth, a surface dusting for plant pathogen prevention/mitigation, a soil pH moderator, a dry sanitizer for pre- and post-harvest rinse, a tabletized unit dosing for process equipment, a unit dose for use as an ornamental and cut flower preservative, tablet formulated for fruit and vegetable wash, a

tableted unit dose home hard surface sanitizer, a pelletized toilet sanitizer, a unit dose carpet sanitizer, or a unit dose upholstery sanitizer.

6. The formulation of claim 5, wherein the solid formulation is a solid polymer.
7. The formulation of claim 5, wherein the solid formulation is a paper product.
8. The formulation of claim 5, wherein the solid formulation is in the form of a tablet.
9. The formulation of claim 5, wherein the solid formulation is construction material.
10. The formulation of claim 9, wherein the construction material is drywall.
11. The formulation of any one of claims 1 to 10, wherein said anhydrous citric acid/SDC composition is in the form of microparticles.
12. The formulation of claim 11, wherein the microparticles have average diameters of 2 μm to 500 μm .
13. The formulation of any one of claims 1 to 12, wherein the citric acid in said anhydrous citric acid/SDC composition is in molar excess of the SDC.
14. The formulation of claim 13, wherein the citric acid is in at least 5 fold molar excess of the SDC.
15. The formulation of any one of claims 1 to 14, wherein the percentage by weight of said anhydrous citric acid/SDC composition in the formulation is 0.5% to 2% by weight.

16. A method to provide antimicrobial protection, which method comprises applying to an environment that does not comprise a human or animal, an antimicrobially effective amount of a formulation as defined in any one of claims 1 to 15.

17. A method to provide antimicrobial protection to a surface, which method comprises applying to said surface an antimicrobially effective amount of an anhydrous composition of silver dihydrogen citrate (SDC) and citric acid (anhydrous citric acid/SDC composition) without reconstitution of said composition in solvent, wherein said surface is not that of a human or animal.

18. The method of claim 17, wherein the surface is a plant surface, carpeting, a bandage, or upholstery.

19. The method of claim 18, wherein the surface is that of an ornamental flower or a cut flower.

20. The method of claim 17, 18 or 19, wherein the citric acid in said anhydrous citric acid/SDC composition is in molar excess of the SDC.

21. A method to provide antimicrobial protection to a formulation, which method comprises including in said formulation an antimicrobially effective amount of an anhydrous composition of silver dihydrogen citrate (SDC) and citric acid (anhydrous citric acid/SDC composition) without reconstitution of said composition in solvent.

22. The method of claim 21, wherein said formulation is: plastic, fiberglass material, woven or nonwoven fabric, a polymer, vinyl, a paint, a latex, an architectural finish, a caulk, a conforming sealant, a hardening foam, paper/cardboard packaging, a coating for packaging, a cementitious coating, drywall, a drywall finishing compound, plaster, tile, or tile grout.

23. The method of claim 21 or 22, wherein the citric acid in said anhydrous citric acid/SDC composition or formulation is in molar excess of the SDC.

24. The method of any one of claims 17 to 23, wherein said anhydrous citric acid/SDC composition is in the form of microparticles.

25. The method of claim 24, wherein the microparticles have average diameters of 2 μm to 500 μm .

26. A method to prepare an emulsion or lotion which method comprises providing nonaqueous components of said lotion or emulsion or said lotion or emulsion itself with an antimicrobially effective amount of an anhydrous composition of silver dihydrogen citrate (SDC) and citric acid without reconstitution of said composition in solvent.

27. Use of a formulation as defined in any one of claims 1 to 15 for providing antimicrobial treatment or protection to an environment.

28. The use of claim 27, wherein the environment is a surface.

29. The use of claim 28, wherein the surface is a plant surface, carpeting, a wound, a bandage, or upholstery.

30. The use of claim 29, wherein the plant surface is that of an ornamental flower or a cut flower.

31. The use of claim 27, wherein the environment is a wound.

32. Use of a formulation as defined in any one of claims 1 to 15 in preparation of a medicament for providing antimicrobial treatment or protection to a wound.