

(19) **DANMARK**



Patent- og
Varemærkestyrelsen

(10) **DK/EP 2558132 T3**

(12) Oversættelse af
europæisk patentskrift

-
- (51) Int.Cl.: **A 61 L 15/26 (2006.01)** **A 61 K 33/38 (2006.01)** **A 61 L 15/46 (2006.01)**
A 61 L 26/00 (2006.01)
- (45) Oversættelsen bekendtgjort den: **2021-01-18**
- (80) Dato for Den Europæiske Patentmyndigheds
bekendtgørelse om meddelelse af patentet: **2020-10-14**
- (86) Europæisk ansøgning nr.: **11769176.6**
- (86) Europæisk indleveringsdag: **2011-04-13**
- (87) Den europæiske ansøgnings publiceringsdag: **2013-02-20**
- (86) International ansøgning nr.: **SE2011050452**
- (87) Internationalt publikationsnr.: **WO2011129759**
- (30) Prioritet: **2010-04-14 SE 1050367** **2010-04-14 US 323926 P**
- (84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV
MC MK MT NL NO PL PT RO RS SE SI SK SM TR**
- (73) Patenthaver: **Mölnlycke Health Care AB, P.O. Box 13080, 402 52 Göteborg, Sverige**
- (72) Opfinder: **LÖWENHIELM, Peter, Granitvägen 64, 183 63 Täby, Sverige
HOLMEN, Malin, Sankt Sigfridsgatan 41, 412 66 Göteborg, Sverige
HANSSON, Dennis, Ekereds Höjd 55, , 42456 Gunnilse, Sverige
Bergstrand, Sofia, Anemongatan 10, 434 46 Kungsbacka, Sverige
ARESKOUG, Stefan, Vestagatan 11, 416 48 Göteborg, Sverige**
- (74) Fuldmægtig i Danmark: **Patrade A/S, Ceresbyen 75, 8000 Århus C, Danmark**
- (54) Benævnelse: **ANTIMIKROBIEL GEL**
- (56) Fremdragne publikationer:
EP-A1- 0 425 154
EP-A2- 0 475 807
WO-A1-02/36866
WO-A1-02/062403
WO-A1-2005/102403
WO-A1-2007/105883
WO-A1-2008/057155
KR-B1- 100 859 339

DESCRIPTION

Technical Field

[0001] The present invention pertains to antimicrobial gel-forming compositions, antimicrobial silicone gels, and antimicrobial wound dressings comprising the antimicrobial silicone gels, as well as methods of preparing the above.

Technical Background

[0002] The increasing prevalence of microbial strains exhibiting multidrug resistance as well as the surging pressure on healthcare systems worldwide have resulted in a veritable escalation over recent decades of nosocomial as well as community-acquired infections. Patients undergoing major surgical procedures, implantation of or interaction with medical devices, or patients with severe burns or chronic wounds, are particularly susceptible to microbial, notably bacterial and fungal, infections. Methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, as well as various yeast species of the genus *Candida*, are commonly associated with infected wounds and burns, often resulting in severe and complicated infections, placing additional burden on the healthcare system and on an already distressed patient.

[0003] Hygiene measures applied in healthcare settings, such as isolation of infected patients, improved surface sanitation, and the use of alcohol rubs and gels, undoubtedly mitigate the above problems to a certain extent, but adequate and efficacious wound care is a paramount determinant for preventing initial microbial colonization and subsequent spread of infectious diseases. Conventional wound dressings have long proved insufficient for treating, inter alia, severe burns and chronic wounds, with the implication that various types of antimicrobial dressings have been developed, comprising inter alia conventional antiseptics, antibiotics, antimicrobial peptides, or metallic agents with antimicrobial properties.

[0004] EP1274473, for instance, discloses antimicrobial coatings for wound dressings comprising a bioadsorbable substrate associated with one or more antimicrobial metals that releases said antimicrobial agent upon contact with an alcohol or water-based electrolyte. The bioadsorbable polymer is selected from a group comprising inter alia polyglycolic acid, glycolide, lactic acid, lactide, proteins, or polysaccharides. EP 0 425 154 describes an element, e.g. patch, with adhesive properties, which provides sustained release of an incorporated therapeutic agent, e.g. an antibiotic or antiseptic.

[0005] The inherent antimicrobial properties of certain silver-containing compounds are being explored in various types of wound dressings. WO2002062403, inter alia, teaches a medical dressing comprising a complex of silver and being capable of releasing antimicrobial silver ion activity. More specifically, the silver complex comprises a combination of silver and a Group IV

transition element, preferably zirconium, in order to enable controlled release of the silver ion to a wound bed. KR 100 859 339 discloses a dressing comprising a silicon composition comprising a hydrophilic adsorbent material, and an antimicrobial agent such as silver sulfadiazine. The dressing helps in wound healing.

[0006] US20030036717 describes an elastic compress consisting of an elastomeric matrix highly plasticized with a non-polar oil and containing a dispersed hydrocolloid. The compress additionally comprises at least one antiseptic agent, for instance a silver salt, and at least one surfactant for improving the bioavailability of the antiseptic agent.

[0007] Silicones are commonly utilized in various types of medical devices and in particular in wound dressings, as a result of its favourable intrinsic properties. Unlike many other materials used in wound dressings and medical devices, silicones possess attractive characteristics pertaining to inter alia manufacturing advantages, cohesion, tack, and adhesion, implying that they often constitute the materials of choice for wound dressing applications. WO1993019710 discloses an absorbent wound dressing comprising a layer of hydrophobic silicone gel, a layer of carrier material, and an absorbent body, providing a soft wound dressing having favourable properties relating to adhesive strength, ease of removal, and leakage prevention.

[0008] WO2008057155 discloses silicone gel forming compositions for temporarily adhering a medical device to a biological substrate, such as skin. Said disclosure teaches silicone gel compositions comprising active agents, for instance antibiotics, antiseptics, antifungals, anti-inflammatory agents, hormones, anticancer agents, histamine blockers, beta blockers, vitamins, sedatives, analgesics, proteolytic enzymes, and peptides, which can be bound in the composition. Further, WO2008057155 incidentally teaches including silver and derivatives as active agents that can be bound in the composition, but information about the parameters governing therapeutic efficacy, as well as efficacy validation, is largely absent.

Summary of the Invention

[0009] It is hence an object of the present invention to overcome the above-identified problems and satisfy the existing needs within the art, i. e. to provide for facile and efficient manufacture of antimicrobial silicone-based compositions, gels, and wound dressings, as well as compositions, gels, and wound dressings per se having antimicrobial properties for adequate and efficacious wound treatment, through release of antimicrobial silver-containing compounds, in particular silver salts and/or silver ions. Thus, the present invention pertains to antimicrobial compositions, antimicrobial gels, and antimicrobial dressings, as well as methods for the preparation of said antimicrobial gels and dressings, and said antimicrobial gels and dressings for use as a medicament, more specifically for use in the treatment of burns scars, bacterial infections, viral infections, and/or fungal infections.

[0010] More specifically, the present invention relates to antimicrobial compositions as defined in independent claim 1, as well as antimicrobial gels produced from said antimicrobial

composition through crosslinking the at least one alkenyl- and/or alkynyl-substituted polysiloxane and the at least one polysiloxane comprising silicon-bonded hydrogen atoms (i.e. Si-H moieties). Additionally, the invention pertains to further aspects relating to antimicrobial gels, *inter alia* prepared from compositions in accordance with the present invention, for instance through curing, as well as antimicrobial dressings comprising said antimicrobial gels.

[0011] Moreover, further aspects of the present invention pertain to methods of preparing said antimicrobial gels and dressing, as is defined in independent claims 10 and 11, and comprising *inter alia* the steps of preparation of three mixtures, either simultaneously or sequentially or in any combinations of preparations. Said three mixtures may comprise (i) at least one alkenyl- and/or alkynyl-functional polysiloxane, at least one hydrosilylation catalyst and, optionally, silica particles, (ii) at least one alkenyl- and/or alkynyl-functional polysiloxane, at least one CE and/or at least one CL, and, optionally, silica particles, and (iii) at least one silver salt and at least one siloxane polyether (SPE). Subsequently, at least one silver-release enhancing hydrophilic component is mixed with mixture (i) and/or mixture (ii), followed by optionally heating the obtained mixture(s) to which the silver-release enhancing hydrophilic component was added, in order to melt the silver-release enhancing hydrophilic component. The resulting mixtures are thereafter mixed and, after optional coating of a suitable substrate, cured, thus creating either an antimicrobial gel and/or an antimicrobial dressing, in accordance with the present invention.

[0012] The present invention thus provides antimicrobial compositions, gels, and dressings having substantially improved properties compared to the antimicrobial products for wound treatment constituting the current art. The presence of silver-containing compounds, such as silver salts and/or silver ions, and (optionally silver release-enhancing) hydrophilic components in the compositions, as well as in the gels and dressings, confer antimicrobial properties not only to the products *per se*, but also imply that the silver salts/ions can exert antimicrobial effects in surrounding areas. Further, the silver release can be modulated through the use of various different hydrophilic components that causes the compositions and gels to swell, thereby enhancing the inflow of liquid and the dispersions and distribution of the silver compounds, implying that the antimicrobial products and their intrinsic effects can be adapted to suit specific therapeutic purposes, for instance adjustment of the antimicrobial effects depending on the type and nature of wound/burn/injury to be treated, or depending on the infectious agent in question. Additionally, as an implication of the optimized physical and chemical properties resulting from the presence of various types of additives and excipients, *inter alia* siloxane-containing copolymers, silica particles, and siloxane polymer networks, the patient compliance and comfort, and consequently the antimicrobial efficacy, is optimized.

[0013] The present invention is defined by the appended claims.

Brief Description of the Drawings

[0014]

Figure 1 portrays a flow chart describing the various steps associated with an exemplary manufacturing method for antimicrobial gels and/or dressings.

Figure 2 illustrates a flow chart describing the various steps associated with an exemplary laboratory-scale preparation method for antimicrobial gels and dressings.

Figure 3 illustrates the reduction of *P. aeruginosa* and *S. aureus* after exposure to the antimicrobial gels, and in particular formulation 5N6 disclosed below, of the present invention.

Figure 4 illustrates the reduction of *P. aeruginosa* after exposure to selected antimicrobial gels of the present invention.

Figure 5 illustrates the importance (for enhancing silver release) of the hydrophilic component (silver release is expressed in % of the total added mass of Ag_2SO_4 at 24h and 48h (from various samples in NaNO_3 solution)). The samples denoted 2N1 and 2N2 do not contain any (silver release-enhancing) hydrophilic component, as can be seen from Table 5.

Detailed Description of the Invention

[0015] The present invention pertains inter alia to antimicrobial compositions that inhibit microbial growth, antimicrobial gels, produced inter alia from said compositions, various types of dressings comprising the antimicrobial gels for inhibiting microbial growth, as well as the use of the antimicrobial gels in various types of products for treating wounds and inhibiting microbial growth.

[0016] Where features, embodiments, or aspects of the present invention are described in terms of Markush groups, a person skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group. The person skilled in the art will further recognize that the invention is also thereby described in terms of any combination of individual members or subgroups of members of Markush groups. Additionally, it should be noted that embodiments and features described in connection with one of the aspects and/or embodiments of the present invention also apply mutatis mutandis to all the other aspects and/or embodiments of the invention. For example, the at least one hydrophilic component (which may enhance silver release) described in connection with the antimicrobial compositions may naturally also be included in the antimicrobial gels, the excipients described in connection with the antimicrobial gels may also be comprised in the antimicrobial compositions, the at least one silver salt as well as the concentration of the at least one silver salt described in connection with the antimicrobial compositions naturally also apply to the antimicrobial gels, and the antimicrobial effects described in connection with a certain aspect and/or embodiment relating to a certain antimicrobial gel may also be exerted by other antimicrobial gels, all in accordance with the present invention.

[0017] A first aspect of the present invention relates to antimicrobial, silicone gel-forming compositions inhibiting microbial growth, wherein the compositions comprise at least one alkenyl- and/or alkynyl-substituted polysiloxane, at least one polysiloxane comprising silicon-bonded hydrogen atoms, and at least one hydrosilylation catalyst, wherein said composition further comprises at least one silver salt and at least one (optionally silver release-enhancing) hydrophilic component, and wherein said at least one hydrophilic component makes said antimicrobial composition, when cross-linked, swell at least 5% (wt/wt) after 24 hours in Solution A, as measured by the free swell absorption method. In further embodiments as per the present invention, the swelling may be at least 10% (wt/wt) after 24 hours in Solution A, or at least 20% (wt/wt) after 24 hours in Solution A, or at least 20% (wt/wt) after 24 hours in Solution A, or at least 30% (wt/wt) after 24 hours in Solution A, or at least 40% (wt/wt) after 24 hours in Solution A, or at least 50% (wt/wt) after 24 hours in Solution A, or at least 75% (wt/wt) after 24 hours in Solution A, or at least 100% (wt/wt) after 24 hours in Solution A, or at least 150% (wt/wt) after 24 hours in Solution A, or at least 200% (wt/wt) after 24 hours in Solution A, or at least 300% (wt/wt) after 24 hours in Solution A, or at least 400% (wt/wt) after 24 hours in Solution A, or at least 500% (wt/wt) after 24 hours in Solution A, or at least 600% (wt/wt) after 24 hours in Solution A, or at least 700% (wt/wt) after 24 hours in Solution A or at least 800% (wt/wt) after 24 hours in Solution A or any other lower or higher value, and any interval created by the above figures e.g. from 5% (wt/wt) to 800 % (wt/wt) after 24 hours in Solution A.

[0018] Optionally, the swelling may be measured at different time points, for instance at 48 hours or at 72 hours, and also at these time points the swelling may be at least 10% (wt/wt) after 24 hours in Solution A, or at least 20% (wt/wt) after 24 hours in Solution A, or at least 20% (wt/wt) after 24 hours in Solution A, or at least 30% (wt/wt) after 24 hours in Solution A, or at least 40% (wt/wt) after 24 hours in Solution A, or at least 50% (wt/wt) after 24 hours in Solution A, or at least 75% (wt/wt) after 24 hours in Solution A, or at least 100% (wt/wt) after 24 hours in Solution A, or at least 150% (wt/wt) after 24 hours in Solution A, or at least 200% (wt/wt) after 24 hours in Solution A, or at least 300% (wt/wt) after 24 hours in Solution A, or at least 400% (wt/wt) after 24 hours in Solution A, or at least 500% (wt/wt) after 24 hours in Solution A, or at least 600% (wt/wt) after 24 hours in Solution A, or at least 700% (wt/wt) after 24 hours in Solution A or at least 800% (wt/wt) after 24 hours in Solution A or any other lower or higher value, and any interval created by the above figures e.g. from 5% (wt/wt) to 800 % (wt/wt) after 24 hours in Solution A.

[0019] The free swell absorption method employing Solution A is a standard methodology used within the field for assessing swelling capacity. The free swell method is described in more detail below, but briefly the assay encompasses placing a preweighed dressing sample in a quantity of test solution (in this case, Solution A) which is 40 times the mass of the sample. The sample is then allowed to absorb Solution A for a specific time at a specific temperature, after which the sample is weighed again, in order to determine the free swell absorption capacity.

[0020] The silver compounds and/or salts endow the composition with antimicrobial properties,

whereas the release-enhancing hydrophilic component promotes efficient release of the silver salt, thereby enhancing the antimicrobial efficacy of the composition. Without wishing to be bound by any particular theory, it is surmised that the presence of at least one hydrophilic component exhibiting a certain free swell in the antimicrobial composition increases the solubilization, the dispersion, and the inflow of liquid into the composition, thereby increasing the release of silver and increasing the antimicrobial properties of the composition.

[0021] The at least one polysiloxane comprising silicon-bonded hydrogen atoms may, as is well-known within the art, comprise inter alia at least one chain extender (CE) and/or at least one crosslinker (CL). Chain extenders generally comprise polysiloxanes having hydrogen atoms attached to terminal silicon-atoms, whereas crosslinkers normally comprise polysiloxanes having hydrogen-substituted silicon atoms covalently bound only to the internal, non-terminal silicon atoms. Both branched and linear polysiloxanes having various different chemical natures as well as various viscosities may be utilized in accordance with the present invention. The at least one alkenyl- and/or alkynyl-substituted polydiorganosiloxane and the at least one polysiloxane comprising silicon-bonded hydrogen atoms may have hydrogen or various hydrocarbon substituents, such as saturated or unsaturated, branched or linear, C₁-C₂₀, preferably C₁-C₅, hydrocarbon chains, optionally with heteroatoms present. In accordance with the aspects and embodiments of the present invention, said organic substituents may comprise methyl, ethyl, propyl, butyl, vinyl, allyl, and/or aryl, and combinations of these, in any suitable position, for instance as pendant or terminal groups. The term "alkenyl- and/or alkynyl-substituted polysiloxane" is to be understood as comprising polydiorganosiloxanes substituted with groups comprising unsaturated carbon-carbon bonds, i.e. both carbon-carbon double bonds and/or carbon-carbon triple bonds. Thus, the term "alkenyl- and/or alkynyl-substituted polysiloxane" shall be understood as comprising both alkenyl-substituted polysiloxanes as well as alkynyl-substituted polysiloxanes, as well as alkenyl and alkynyl-substituted polysiloxanes. Further, the term "when cross-linked" shall be understood to relate to the cross-link that can be created between alkenyl and/ alkynyl moieties (i.e. unsaturations) of at least one polysiloxane and the Si-H moiety of a second polysiloxane. Additionally, the term "polysiloxane" shall be understood to pertain to all types of polysiloxanes, for instance polydiorganosiloxanes, etc., and within the context of the present invention, these two terms are used interchangeably. Finally, the process feature of "mixing mixture (i) and mixture (ii)" shall be understood to relate to mixing the mixture remaining after the preceding method step (i.e. the mixture that was not mixed with mixture (iii)) with the mixture obtained in the previous step (i.e. with mixture (iii)) combined with either mixture (i) and/or mixture (ii).

[0022] Further in accordance with the aspects and embodiments of the present invention, it is important that moieties capable of crosslinking the at least one alkenyl- and/or alkynyl-substituted polysiloxane and the at least one polysiloxane comprising silicon-bonded hydrogen atoms (i.e. an Si-H moiety), upon reacting said components, are present, in order to mediate formation of silicone gels. Mechanisms within the present invention for reacting, and thereby crosslinking, the at least one alkenyl- and/or alkynyl-substituted polysiloxane and the at least one polysiloxane comprising silicon-bonded hydrogen atoms comprises hydrosilylation, in which a polysiloxane having an Si-H reactive group reacts with a polysiloxane

(polydiorganosiloxane) having an aliphatically unsaturated reactive group, in the presence of a hydrosilylation catalyst, typically Pt and/or Pd. Typical silicone gel forming compositions include alkenyl- and/or alkynyl-functional polyorganosiloxanes (e.g. vinyl functional polyorganosiloxanes), α,ω -hydrogen polyorganosiloxanes, i. e. chain extenders, hydrogen-functional polyorganosiloxanes, i. e. cross-linkers, and a hydrosilylation catalyst (e.g. a platinum complex).

[0023] Further in line with the present invention, the viscosities of the at least one alkenyl- and/or alkynyl-substituted polydiorganosiloxane and the at least one polysiloxane comprising silicon-bonded hydrogen atoms may vary in accordance with the desired properties of the resultant antimicrobial gels and dressings, in accordance with the aspects and the embodiments of the invention. As per an embodiment of the present invention, a mixture of the at least one alkenyl- and/or alkynyl-substituted polydiorganosiloxane and the at least one polysiloxane comprising silicon-bonded hydrogen atoms may have a viscosity at ambient temperature and 1 atmosphere between 500 and 100 000 cSt, preferably between 500 and 20 000 cSt, prior to the addition of any additives and/or excipients, and before cross-linking of the at least one alkenyl- and/or alkynyl-substituted polydiorganosiloxane and the at least one polysiloxane comprising silicon-bonded hydrogen atoms.

[0024] The at least one (optionally silver release-enhancing) hydrophilic component is selected from the group comprising glucose, xylitol, sorbitol, mannitol, cyclodextrins, cellulose, hemicellulose, carboxymethylated cellulose, chitosan, dextran, chitin, amylose, amylopectin, polyethylene glycol, polypropylene glycol, copolymers of polyethylene glycol and polypropylene glycol, polyglycerol, poly(acrylic acid), copolymers of acrylic acid and C₁₀-C₃₀ alkyl acrylate, poly(acrylamide), maleic anhydride polymers and copolymers, carboxy methyl cellulose, methyl cellulose, hydroxymethylpropylcellulose, ethylcellulose, carboxyethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, carboxymethylcellulose, cellulose alkyl sulfonate, polystyrene sulphonates, vinyl acids and vinyl alcohols. The hydrophilic component is present in a concentration that ranges from 3% to 40% (w/w), and more preferably from 4% to 30%.

[0025] Different types of silver salts with antimicrobial properties are within scope of the present invention. The at least one silver salt is selected from the group comprising Ag₂SO₄, Ag₂SO₃, AgNO₃, Ag₂CO₃, Ag₃PO₄, silver zirconium, silver citrate, silver acetate, silver lactate and/or combinations or mixtures thereof. The silver salt concentration ranges from 1% to 30%, and preferably from approximately 2% to 20%. As the silver salt is the primary antimicrobial agent bestowing the composition with its antimicrobial properties, it is conceivable that an increasing silver concentration would correspond to an improved overall antimicrobial effect. However, without wishing to be bound by any particular theory, it is surmised that it may potentially also be essential to provide compositions and gels with optimized combinations of silver release properties and silver salt concentration, as illustrated by the efficacy of the antimicrobial compositions and gels of the present invention. Nevertheless, other aspects and embodiment of the present invention may also contribute the antimicrobial properties.

[0026] In order to further improve the antimicrobial and overall properties of the antimicrobial composition, the present invention relates to compositions that comprise at least one siloxane polyether (SPE). SPEs are block copolymers with segments comprising polysiloxane (for instance PDMS) and additional segments containing at least one type of polyether, for instance polyethyleneglycol (PEG) or polypropylenglycol (PPG). Suitable SPEs may for instance be selected from the group comprising bis-isobutyl PEG/PPG-10/7 dimethicone copolymer (Dow Corning Toray FZ 2233) and Silwet 8500 (from Momenite).

[0027] Polydimethylsiloxane (PDMS) copolymers, i.e. suitable siloxane-containing polymers in accordance with the present invention, consist of at least two different polymer types, which are arranged in blocks of PDMS and the other polymer, for example polyethylene oxide. When three different polymer components are present in the same polymer, it is termed a terpolymer. Common architectures of copolymers are linear, where the at least two different blocks are arranged in series, or graft copolymers, where for example PEO is grafted along a PDMS backbone, resembling a comb. The relative abundance of the PDMS and the other polymer components will determine properties such as hydrophilicity, which is one of the desirable properties as per the present invention. The co- and terpolymers may also be intramolecularly crosslinked, in which case the polymers form a network (sometimes termed crosspolymer). Said network may be swollen in solvents, for example cyclic siloxanes to form a gel, with advantages relating to for instance ease of processing, in spite of the crosslinked polymer itself having very high viscosity.

[0028] In further embodiments of the present invention, the antimicrobial compositions and gels may comprise particles for facilitating and/or enabling the dispersion of constituents of the composition, primarily certain silver-release enhancing hydrophilic components but potentially also the antimicrobial silver salts. As per an embodiment of the present invention, particles conceivable within the scope of the invention may for instance be silica particles, but other suitable particles are also within the scope of the present invention. The particles may be present in a concentration ranging from 2 to 5%, preferably between 2 to 3%. In accordance with another embodiment of the present invention, the antimicrobial composition may further comprise at least one siloxane-containing copolymer. Said siloxane-containing copolymer may for instance comprise a hydrophilic polymer, such as PEG or PPG, or other polymers known to a person skilled in the art.

[0029] In yet other embodiments of the antimicrobial compositions of the present invention, the at least one alkenyl- and/or alkynyl-substituted polydiorganosiloxane may be covalently crosslinked to the at least one polysiloxane comprising silicon-bonded hydrogen atoms, thereby forming an antimicrobial gel.

[0030] A second aspect of the present invention pertains to antimicrobial gels comprising at least one alkenyl- and/or alkynyl-substituted polysiloxane (polydiorganosiloxanes) covalently bound to at least one polysiloxane comprising silicon-bonded hydrogen atoms, said antimicrobial gel further comprising at least one hydrosilylation catalyst, characterized in that said antimicrobial gel further comprises at least one silver salt, and at least one (optionally

silver release-enhancing) hydrophilic component. Said antimicrobial gels may, inter alia, be produced from the compositions of the present invention, for instance through crosslinking the at least one alkenyl- and/or alkynyl-substituted polysiloxane and the at least one polysiloxane having silicon-bonded hydrogen atoms. The crosslinking may be effected through reacting the at least one alkenyl- and/or alkynyl-substituted polysiloxane and the at least one polysiloxane having silicon-bonded hydrogen atoms, for instance using, in an embodiment of the present invention, curing. Curing may be carried out under a various different conditions depending on the components of the composition, as well as on the desired properties of the resultant gel. In an additional embodiment, the curing may inter alia be carried out at between 40 and 140 degrees Centigrade, preferably between 60 and 130 degrees. In yet another embodiment, the timeframe during which the curing reaction is carried out may also vary depending on the above factors, but the crosslinking curing reaction may for instance be carried out for between 5 seconds and 14 2 hours, preferably between 10 seconds and 30 minutes, and more preferably between 30 seconds and 2 minutes.

[0031] In yet another embodiment as per the present invention, the antimicrobial gel may further comprise one or more excipients, for instance selected from siloxane-containing copolymers, siloxane polymer networks, and silica particles.

[0032] In a further embodiment, the antimicrobial gels of the present invention may comprise numerous different types of silver salts. Said silver salt is selected from the group comprising Ag_2SO_4 , Ag_2SO_3 , AgNO_3 , Ag_2CO_3 , Ag_3PO_4 , silver zirconium, and/or organic silver salts, such as silver citrate, silver acetate, silver lactate and/or combinations or mixtures thereof. In an embodiment of the present invention, the silver salt concentration ranges from 1% to 30% (w/w), and preferably from approximately 2% to 20%.

[0033] The antimicrobial gels of the present invention comprise at least one (silver release-enhancing) hydrophilic component, selected from the group comprising glucose, xylitol, sorbitol, mannitol, cyclodextrins, cellulose, hemicellulose, carboxymethylated cellulose, chitosan, dextran, chitin, amylose, amylopectin, polyethylene glycol, polypropylene glycol, copolymers of polyethylene glycol and polypropylene glycol, polyglycerol, poly(acrylic acid), copolymers of acrylic acid and C_{10} - C_{30} alkyl acrylate, poly(acrylamide), maleic anhydride polymers and copolymers, carboxy methyl cellulose, methyl cellulose, hydroxymethylpropylcellulose, ethylcellulose, carboxyethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, carboxymethylcellulose, cellulose alkyl sulfonate, polystyrene sulphonates, vinyl acids and vinyl alcohols. The (silver release-enhancing) hydrophilic component is present in a concentration that ranges from 3% to 40% (w/w), and more preferably from 4% to 30%.

[0034] The silver-releasing properties of the antimicrobial gels naturally have a significant impact on the overall antimicrobial effects seen when utilizing the gel and other aspects of the present invention in for instance a clinical setting. The amount of silver ions released from the prototypes may be investigated, in accordance with embodiments of the present invention, using a test method based on measurements of silver release from an antimicrobial gel and/or

an antimicrobial wound dressing, using a two-compartment model. A piece of the prototype gel/dressing ($d=20$ mm, area 3.14 cm^2) was placed without release film on the membrane of a cell culture insert (pore size $8.0\text{ }\mu\text{m}$), placed in a 6-well plate containing 4 mL sodium nitrate (NaNO_3 , 0.15 M). The plates were incubated at 35°C and the silver ion concentration was determined in the medium using a silver electrode. When the concentration was to be determined during several days, the samples were placed in fresh NaNO_3 after each measurement. The total silver concentration may also be determined using atomic absorption spectroscopy (AAS), if the medium is not compatible with the silver electrode (e.g. simulated wound fluid (SWF)), as well as other suitable methods.

[0035] As per one embodiment in line with the present invention, the antimicrobial gels may inhibit microbial growth, defined using inter alia the corrected zone of inhibition (CZoi) or the two-compartment test methods, over various time frames. The two-compartment test method involves culturing bacteria in 6-well plates, and, when evaluating the antimicrobial efficacy, placing dressing pieces (20 mm) in co-culture inserts (the porous membrane in the cell culture insert is detached so that the dressing has full contact with the bacterial culture). Bacteria are cultured in chemical simulated wound fluid, cSWF (NaCl $2,922\text{ g}$, NaOHCO_3 $1,68\text{ g}$, KCl $0,149\text{ g}$, $\text{COC12} \times 2\text{H}_2\text{O}$ $0,184\text{ g}$, bovine albumin $16,5\text{ g}$, in 500 ml Super Q water, pH $8,49$). Initial concentration of the test organism is approximately 10^6 CFU/ml prior to adding the test sample. The plates are incubated with agitation (100 rpm) and samples are withdrawn after specified times. The number of viable counts of the test organism is determined with standard surface plate count method and the amount of antimicrobials released is analyzed with relevant methodology, e.g. atomic absorption spectroscopy (AAS) for heavy metals. For release studies, the method can be used only with desired test fluid and no bacteria present.

[0036] The CZoi method involves placing a piece of wound dressing ($d = 20\text{ mm}$) on an agar surface (Muller Hinton agar (MH agar)) in $25\text{ml}/9\text{cm}$ plates that produce an agar depth of 4 mm , which has been seeded with the test microorganism (*Pseudomonas aeruginosa*, ATCC 15442, and *Staphylococcus aureus*, ATCC 6538). Diffusion of antimicrobial agent into the agar results in inhibition of growth, which appears as a clear zone on the agar. The corrected zone of inhibition is determined as the diameter of the whole inhibition zone minus the size of the dressing.

[0037] The CZoi associated with the antimicrobial gels of the present invention may be, inter alia, approximately at least 2 mm at 24 h and approximately at least 2 mm at 48 h . Further in accordance with the invention, the accumulated silver release from the antimicrobial gels may amount to at least $0,3\%$ of the total silver content after 24 h , and at least 0.5% of the total silver content after 48 h . In further embodiments of the present invention, the antimicrobial effects mediated by the antimicrobial gels of the present invention, as evaluated using the two-compartment model, may be in the order of at least one log, preferably at least two logs, and more preferably at least three logs.

[0038] An additional, standard method for evaluating the antimicrobial efficacy of the products

as per the present invention is a modified version of ISO 22196:2007, i.e. a so called antimicrobial contact method. Briefly, the method encompasses covering a 5 x 5 cm sample piece with a thin layer of inoculum, incubating for a specific time period (commonly 24 h) before determining the number of viable test organisms. Test organism viability may be carried out as follows: shake method using neutralization buffer, plating, incubation, and plate count method. The minor deviations from the reference method in this case are that the inoculum used contains agar agar (3g/l) and nutrient broth (5%). The test samples were inoculated with 1ml inoculum containing approximately $1.2 - 3.0 \times 10^6$ CFU/ml.

[0039] Using the above-described, modified ISO method, the antimicrobial products of the present invention caused more than 3 log reductions in *P. aeruginosa* (ATCC 15442) viability.

[0040] The adhesion properties exhibited by the gel of the present invention are naturally highly important both for the actual antimicrobial efficacy and for the patient comfort and compliance. Thus, in accordance with the present invention, the antimicrobial gels may have an adhesion with steel of between 0.1 and 2 N, preferably between 0.1 and 1 N, and most preferably between 0.1 and 0.5 N. The determination of the adhesion is in this instance carried out in accordance with ASTM Internationals' standard D3330/D3330M-04, method F, but other suitable methods and standards may also be utilized. The antimicrobial gel may be combined with or incorporated into a dressing prior to application to a patient, but it also may be for use in applying directly to a patient in need thereof.

[0041] In further embodiments of the present invention, the antimicrobial silicone gels of the present invention can be prepared in the form of layers and/or surface having different thicknesses, morphologies, patterns, functionalities, or the like, using any suitable technique, for instance extruding, calendering, molding, brushing, spraying, casting, coating, and/or application by hand. In yet another embodiment, the silicone gel may be preformed by casting and curing the gel-forming antimicrobial composition on a substrate. In further embodiments as per the invention, the layer and/or surfaces comprising the gel of the present invention may be in any geometric form, for instance dots, circles, networks, continuous configurations, discontinuous configurations, perforated layers and/or surfaces, and the like.

[0042] In accordance with further embodiments of the present invention, the substrate on which the antimicrobial gel is to be applied in order to create a wound dressing comprising the antimicrobial gel may be any surface that will generate the desired properties. The substrate may inter alia be selected from the group comprising inter alia a wound dressing, an ostomy dressing, ostomy baseplate, incision film, surgical drape, a patch, a bandage, a band-aid, a plaster, an adhesive, an adhesive tape, an adhesive plaster, a sticking-plaster, or a court-plaster, and/or any combination thereof. Further, the substrate may also be a component for the manufacture of any one of the above substrates and/or wound dressings, for instance a film, a textile, a foam, a non-woven film, a fiber network, a knitted fabric, or the like. Thus, in additional embodiments, the substrates and/or the wound dressings of the present invention may comprise textiles, films, foams, non-woven films, fiber networks, foams, knitted fabrics, and the like.

[0043] Suitable substrates in accordance with further embodiments of the present invention may comprise polyesters, polyethylenes, polypropylenes, polybutylenes, polymethylpentenes, polyolefins, polyvinyl acetates, polyvinyl chloride derivatives, polyethylene-vinyl acetate (EVA) and its copolymers, polyvinyls, polyvinyl alcohol, polyvinylbutyral, polyvinyl formal, polyacrylonitrile, polyurethanes and polyurethane-ureas, polystyrenes and their copolymers, epoxy and phenolic plastics, polyacrylic and polyacrylates derivatives, cellulose-based films, polyimides, polyamides, silicone elastomers, polyphenyl sulfide, polycarbonates, phenoplastes, fluorinated polymers, polyoxymethylenes, polyphenylene oxides, polysulfones, polysaccharide-based materials, and/or silicones, and/or any combination thereof.

[0044] As per one further aspect, the present invention pertains to an antimicrobial gel wherein said antimicrobial gel is formed by creating at least one covalent bond between at least one an alkenyl and/or alkynyl moiety of a first polysiloxane and at least one Si-H (i.e. a silicon-bonded hydrogen atom) moiety of second polysiloxane, said antimicrobial gel further comprising at least one hydrosilylation catalyst, at least one silver salt, and at least one (silver release-enhancing) hydrophilic component, wherein said at least one hydrophilic component makes said antimicrobial gel swell at least 5% (wt/wt) after 24 hours in Solution A, as measured by the free swell absorption method. Further in accordance with additional embodiments as per the present invention, the swelling may be at least 10% (wt/wt) after 24 hours in Solution A, or at least 20% (wt/wt) after 24 hours in Solution A, or at least 20% (wt/wt) after 24 hours in Solution A, or at least 30% (wt/wt) after 24 hours in Solution A, or at least 40% (wt/wt) after 24 hours in Solution A, or at least 50% (wt/wt) after 24 hours in Solution A, or at least 75% (wt/wt) after 24 hours in Solution A, or at least 100% (wt/wt) after 24 hours in Solution A, or at least 150% (wt/wt) after 24 hours in Solution A, or at least 200% (wt/wt) after 24 hours in Solution A, or at least 300% (wt/wt) after 24 hours in Solution A, or at least 400% (wt/wt) after 24 hours in Solution A, or at least 500% (wt/wt) after 24 hours in Solution A, or at least 600% (wt/wt) after 24 hours in Solution A, or at least 700% (wt/wt) after 24 hours in Solution A or at least 800% (wt/wt) after 24 hours in Solution A or any other lower or higher value, and any interval created by the above figures e.g. from 5% (wt/wt) to 800 % (wt/wt) after 24 hours in Solution A.

[0045] Optionally, the swelling may be measured at different time points, for instance at 48 hours or at 72 hours, and also at these time points the swelling may be at least 10% (wt/wt) after 24 hours in Solution A, or at least 20% (wt/wt) after 24 hours in Solution A, or at least 20% (wt/wt) after 24 hours in Solution A, or at least 30% (wt/wt) after 24 hours in Solution A, or at least 40% (wt/wt) after 24 hours in Solution A, or at least 50% (wt/wt) after 24 hours in Solution A, or at least 75% (wt/wt) after 24 hours in Solution A, or at least 100% (wt/wt) after 24 hours in Solution A, or at least 150% (wt/wt) after 24 hours in Solution A, or at least 200% (wt/wt) after 24 hours in Solution A, or at least 300% (wt/wt) after 24 hours in Solution A, or at least 400% (wt/wt) after 24 hours in Solution A, or at least 500% (wt/wt) after 24 hours in Solution A, or at least 600% (wt/wt) after 24 hours in Solution A, or at least 700% (wt/wt) after 24 hours in Solution A or at least 800% (wt/wt) after 24 hours in Solution A or any other lower or higher value, and any interval created by the above figures e.g. from 5% (wt/wt) to 800 % (wt/wt) after 24 hours in Solution A.

[0046] As abovementioned, the free swell absorption method is utilized to determine the swell properties. The free swell absorption method is carried out approximately as follows.

[0047] A suitable volume of Solution A is prepared. 1 litre is for instance prepared according to the following protocol:

Dissolve 8.298 g of sodium chloride (NaCl) and 0.368 g of calcium chloride dihydrate ($\text{CaCl}_2 \cdot 2 \text{H}_2\text{O}$) in deionised water and fill up to 1 litre in a volumetric flask.

[0048] The first step of the free swell absorption method (which is a standard test method denoted EN 13726-1) involves cutting or punching a test piece of 5 x 5 cm of the product (for instance the antimicrobial gel) to be tested. In case of cavity dressings, use 0.2 gram. Second, condition the test piece at 23 ± 2 °C and (50 ± 2) % RH and subsequently weigh the sample and place it in a Petri dish. Add a quantity of Solution A warmed to 37 ± 1 °C corresponding to 40 times the mass of the sample, ± 0.5 g. Transfer to the oven and allow it to stand for the selected time, e.g. 24h, at 37 ± 1 °C. Then, by using forceps, suspend the sample for 30 s by the corner or by one end as appropriate, carefully blot the sample to remove excess fluid, and then weigh it. Repeat the procedure for another nine samples, in order to obtain statistical significance.

[0049] Finally, express the absorptive capacity as the average mass (g) of solution retained per 100 cm^2 (as presented to the wound), per g of sample or in percentage of the sample weight.

[0050] In one embodiment, the at least one silver-release enhancing hydrophilic component of the antimicrobial gel is selected from a group comprising mono- di- and/or polysaccharides, sugar alcohols, polyols, polyethers, polyesters, polyamides and/or polymers comprising pendant carboxylic acid groups and/or pendant sulphonate groups. The at least one silver salt, that mediated the antimicrobial effect, is selected from the group comprising Ag_2SO_4 , Ag_2SO_3 , AgNO_3 , Ag_2CO_3 , Ag_3PO_4 , silver zirconium, silver citrate, silver acetate, silver lactate and/or combinations or mixtures thereof.

[0051] In additional embodiments, the antimicrobial gel may comprise one or more excipients selected from the group comprising siloxane-containing copolymers, siloxane polymer networks, and silica particles.

[0052] Microbial inhibition may naturally be carried out using numerous different techniques, for instance through corrected zone of inhibition (CZol) tests. The antimicrobial gels as per the present invention may exert an antimicrobial effect, in terms of CZol, of at least 2 mm at 24 h and at least 2 mm at 48 h, and, in yet another embodiment, the accumulated silver release from the antibacterial gel may amount to at least 0.3% of the total silver content after 24 h, or may amount to at least 0.5% of the total silver content after 48 h.

[0053] Further as per the aspects and embodiments of the present invention, the at least one

(optionally silver release-enhancing) hydrophilic component causes the antimicrobial gels and compositions in accordance with the present invention to swell at least 5% (wt/wt) after 24 h in Solution A in accordance with the free swell absorption method, or it may cause the antimicrobial gels and compositions to swell at least 10% after 72 h in Solution A in accordance with the free swell absorption method.

[0054] Thus, another aspect of the present invention pertains to antimicrobial dressings inhibiting microbial growth and comprising the antimicrobial gels of the present invention may be highly useful in various contexts, it may for instance be applied in a professional clinical setting, either by a medical professional or by the patient, or in consumer product setting. The antimicrobial dressing may in accordance with an embodiment of the invention relate to any type of dressing with utility as a substrate for the antimicrobial gel, for instance a wound dressing, an ostomy dressing, ostomy baseplate, incision film, surgical drape, a patch, a bandage, a band-aid, a plaster, an adhesive, an adhesive tape, an adhesive plaster, a sticking-plaster, or a court-plaster, and any combination thereof.

[0055] The antimicrobial gel naturally confers its antimicrobial properties to the antimicrobial dressings of the present invention, but also the dressing as such can be optimized vis-à-vis for instance shape and/or morphology from an antimicrobial efficacy perspective. Thus, the antimicrobial dressings of the present invention may be adjusted to suit specific purposes, both in terms of physical appearance, physical properties, as well as in terms of constituents and chemical properties. The silver-releasing properties of the antimicrobial dressings as such naturally have a significant impact on the overall antimicrobial effects seen when utilizing the dressings in for instance a clinical setting. Hence, further in accordance with the invention, the accumulated silver release from the antimicrobial dressings of the present invention may amount to at least 0.3% of the total silver content after 24 h, and at least 0.5% of the total silver content after 48 h.

[0056] The adhesion properties exhibited by the dressings of the present invention logically depends on the adhesive properties of the antimicrobial gel comprised in the dressing. Again, the adhesion properties are naturally highly important both for the actual antimicrobial efficacy and for the patient comfort and compliance. The antimicrobial dressings of the present invention growth may be highly useful in various contexts, it may for instance be applied in a professional clinical setting, either by a medical professional or by the patient, or in consumer product setting.

[0057] The antimicrobial gels of the present invention may be prepared using a multitude of methods or combinations of method steps, in accordance with yet another aspect of the present invention, inter alia a method comprising an initial step of mixing a first suitable polysiloxane and at least one (silver release-enhancing) hydrophilic component, followed by heating of the obtained mixture until the hydrophilic component is molten. The mixture obtained after the melting step may then be mixed with a silver salt and subsequently with a second suitable polysiloxane. Finally, the mixture is cured in the presence of a catalyst, in an embodiment for instance Pt and/or Pd, and/or any other catalyst suitable for the preparation of

antimicrobial gels. In a further embodiment of the present invention, the curing may inter alia be carried out at between approximately 40 and 140 degrees Centigrade, preferably between 60 and 130 degrees. In yet another embodiment, the timeframe during which the curing reaction is carried out may also vary depending on the above factors, but the crosslinking curing reaction may for instance be carried out for between 5 seconds and 2 hours, preferably between 10 seconds and 30 minutes, and more preferably between 30 seconds and 2 minutes. Naturally, the above steps may be performed simultaneously or sequentially or in any combination of sequential steps. In yet another embodiment of the present invention, the at least one silicone polymer network may be mixed with the mixture comprising the first polysiloxane and the molten release-enhancing hydrophilic component either prior to the addition of the silver salt or after.

[0058] In a further embodiment in accordance with the present invention, methods for preparing the antimicrobial gels may comprise the steps of mixing at least one alkenyl- and/or alkynyl-substituted polysiloxane, at least one catalyst, and silica particles, followed by subsequently adding silver salt paste to the mixture, forming a component A (Figure 1). The silver paste may for instance comprise a polymer network and a suitable silver salt, for instance silver sulfate. A B component may be formed through mixing at least one alkenyl- and/or alkynyl-substituted polysiloxane, at least one CL comprising silicon-bonded hydrogen atoms, and at least one CE comprising silicon-bonded hydrogen atoms. Thereafter, a silver-release enhancing hydrophilic component is mixed with the mixture, optionally after heating and/or melting the silver-release enhancing hydrophilic component. Finally, component A and component B are mixed together prior to coating of a suitable medical substrate, inter alia any type of wound dressing in accordance with the present invention, and the preparation is finalized through curing the mix into an antimicrobial gel. Naturally, the above steps may be performed simultaneously or sequentially or in any combination of sequential steps. The above-described embodiment may be suitable for preparation of antimicrobial gels and wound dressing on a manufacturing scale, as the process steps are optimized vis-à-vis production settings and various important process parameters. Prior to curing the antimicrobial gel, said composition may naturally be applied in any pattern, structure, configuration, and/or morphology to a suitable substrate, e.g. a wound dressing, in order to further optimize the preparation process.

[0059] In additional embodiments of the present invention, methods for preparing antimicrobial products, such as antimicrobial gels and/or dressings, may comprise initial preparation of three mixtures, either simultaneously or sequentially or in any combination. Said three mixtures may comprise (i) at least one alkenyl- and/or alkynyl-functional polysiloxane, at least one hydrosilylation catalyst and, optionally, silica particles, (ii) at least one alkenyl- and/or alkynyl-functional polysiloxane, at least one CE and/or at least one CL, and, optionally, silica particles, and (iii) at least one silver salt and at least one SPE. Subsequently, at least one silver-release enhancing hydrophilic component is mixed with mixture (i) and/or mixture (ii), followed by optionally heating the obtained mixture(s) to which the silver-release enhancing hydrophilic component was added, in order to melt the silver-release enhancing hydrophilic component. The resulting mixtures are thereafter mixed and, after optional coating of a suitable substrate,

cured, thus creating either an antimicrobial gel and/or an antimicrobial dressing, in accordance with the present invention.

[0060] In further embodiments in accordance with the present invention, the method for preparing the antimicrobial gels may comprise mixing at least one alkenyl- and/or alkynyl-substituted polysiloxane, at least one catalyst, and silica particles, in order to form a component A. A component B may be formed through mixing at least one alkenyl- and/or alkynyl-substituted polysiloxane, at least one CL comprising silicon-bonded hydrogen atoms, and at least one CE comprising silicon-bonded hydrogen atoms. Further, a silver salt paste may be prepared through mixing a polymer network with a suitable silver salt, for instance silver sulfate. Subsequently, component A is mixed with a release-enhancing hydrophilic component, and heated if necessary, prior to addition and mixing of the silver paste, and finally addition and mixing of component B, followed by optional coating of a substrate and curing, in order to form a antimicrobial gel and/or wound dressing in accordance with the present invention.

[0061] In another embodiment of the present invention pertaining to the preparation of an antimicrobial gel, and an antimicrobial substrate, a first component is prepared, comprising inter alia an alkenyl- and/or alkynyl-substituted polydiorganosiloxane, a silver salt, silica particles, a catalyst, and an inhibitor. Subsequently, said first component is mixed in a speedmixer until the silica particles have been thoroughly dispersed, wherein after a second component, comprising an alkenyl- and/or alkynyl-substituted polydiorganosiloxane, chain extenders, and crosslinkers, is added, followed by speedmixing and subsequent application on a suitable substrate. Finally, the substrate and the antimicrobial gel is cured, for instance for approximately 10 minutes at 120 degrees, resulting in a product with antimicrobial properties. As per other embodiments and aspects of the present invention, antimicrobial gels may be prepared using numerous additional constituents, in order to achieve certain effects pertaining to inter alia increased silver release, optimized tack, viscosity, mechanical strength, and/or patient comfort and compliance.

[0062] The antimicrobial dressings of the present invention may be prepared using a multitude of methods or combinations of method steps, inter alia a method comprising, as per an embodiment, an initial step of mixing a first suitable polysiloxane and at least one hydrophilic component, followed by heating of the obtained mixture until the at least one (optionally silver release-enhancing) hydrophilic component is molten. The mixture obtained after the melting step may then be mixed with a silver salt and subsequently with a second suitable polysiloxane. Thereafter, the mixture may be applied to a substrate, in various suitable patterns, morphologies, and thicknesses, followed by curing of the substrate and the applied mixture in the presence of a suitable catalyst, for instance, in an embodiment, Pt and/or Pd, and/or any other suitable catalyst. In a further embodiment, the curing may inter alia be carried out at between 40 and 140 degrees Centigrade, preferably between 60 and 130 degrees. In yet another embodiment, the timeframe during which the curing reaction is carried out may also vary depending on the above factors, but the crosslinking curing reaction may for instance be carried out for between 5 seconds and 2 hours, preferably between 10 seconds and 30

minutes, and more preferably between 30 seconds and 2 minutes.

[0063] Naturally, the above steps may be performed simultaneously or sequentially or in any combination of sequential steps, for instance may the mixture, as per an embodiment, be applied to the substrate prior to the mixing with the second polysiloxane. In a further embodiment, the substrate utilized for the preparation of antimicrobial dressings may be any type of dressing with utility as a substrate for the antimicrobial gel, for instance wound dressing, an ostomy dressing, ostomy baseplate, incision film, surgical drape, a pad, a patch, a bandage, a band-aid, a plaster, an adhesive, an adhesive tape, an adhesive plaster, a sticking-plaster, or a court-plaster. According to another embodiment, the at least one silicone polymer network may again be mixed with the mixture comprising the first polysiloxane and the molten release-enhancing hydrophilic component either prior to the addition of the silver salt or after.

[0064] In yet another embodiment, antimicrobial dressings are prepared through initially heating at least one silver-release enhancing component, at least one alkenyl- and/or alkynyl-substituted polydiorganosiloxane, at least one hydrosilylation catalyst, and, optionally, silica particles, followed by mixing of said components, in order to obtain an emulsion. Subsequently, the emulsion is mixed with a silver paste comprising at least one silver salt and a polysiloxane - polyether copolymer network. Finally, the silver-containing emulsion is blended with a mix of at least one alkenyl- and/or alkynyl-substituted polydiorganosiloxane and at least one crosslinker polysiloxane comprising silicone-bonded hydrogen, followed by application to a suitable substrate, and curing.

[0065] In an additional embodiment in accordance with the present invention, antimicrobial dressings are prepared mixing at least one silver-release enhancing hydrophilic component, for instance particles of a suitable sugar alcohol, at least one alkenyl- and/or alkynyl-substituted polydiorganosiloxane, and at least one hydrosilylation catalyst, in order to form a suspension. The suspension is subsequently mixed with a silver paste comprising at least one silver salt and a polysiloxane - polyether copolymer network. Finally, the silver-containing emulsion is blended with a mix of at least one alkenyl- and/or alkynyl-substituted polydiorganosiloxane and at least one crosslinker polysiloxane comprising silicone-bonded hydrogen, followed by application to a suitable substrate, and curing.

[0066] Further as per the present invention, antimicrobial dressings can be prepared through mixing at least one alkenyl- and/or alkynyl-substituted polydiorganosiloxane and at least one hydrosilylation catalyst to form a component A. Subsequently, at least one alkenyl- and/or alkynyl-substituted polydiorganosiloxane is mixed with a polysiloxane comprising silicon-bonded hydrogen atoms to form a component B, followed by continuous mixing of components A and B by joining two streams comprising component A and component B, respectively. A suitable silver salt and additional excipients, for instance a silver-release enhancing hydrophilic component, is subsequently added, inter alia in the form of a powder. Finally, the obtained mixture is applied to a substrate and cured, in order to generate an antimicrobial dressing as per the present invention.

[0067] An additional aspect in accordance with the present invention relates to use of the antimicrobial gel in a product for treating wounds, burns, cuts, bruises, and the like, in various settings and for various purposes.

Examples

[0068] The following materials were used in the preparation of the antimicrobial compositions and gel. Vinyl 1000 A dimethylvinyl siloxy-terminated polydimethylsiloxane, having a viscosity of 1000 mPa.s containing 0,18-0,26 wt % vinyl, the chain extender trimethylsiloxy-terminated methylhydrogen polydimethylsiloxane, having a viscosity of 25-35 m Pa.s containing 25-30 mol % MeHSiO, and the crosslinker trimethylsiloxy-terminated methylhydrogen polydimethylsiloxane having a viscosity of 25-35 m Pa.s containing 25-30 mol % as MeHSiO were obtained from ABCR GmbH & Co. KG (AB109358, AB109366, and AB109380 respectively). Platinum catalyst, Cat 511, was obtained from Hanse Chemie, silica, H15, was obtained from Wacker Chemie, mannitol was obtained from Sigma Aldrich, Polyethyleneglycol 3000 S was obtained from Clariant (referred to as PEG 3000 below), Pluriol 6005 and Pluriol 8005 were obtained from BASF (referred to as PEG 6000 and PEG 8000, respectively), silver sulfate (Ag_2SO_4) was obtained from Alpha Aesar (stock number 11417), and Velvesil plus and Velvesil 125 were obtained from Momentive.

Example 1: Silicone gel compositions

[0069] Silicone gel compositions were prepared by mixing together the components in the amounts listed below. First, a silicone gel formulation was prepared, which was utilized together with the antimicrobial and release-enhancing additives.

[0070] The silicone gel was prepared in a two-component system in order to separate the catalyst and the crosslinker/chain extender prior to the curing process.

[0071] Component A may, inter alia, comprise the following components:

1. 1. Vinyl terminated PDMS (Vin 1000) and Silica (HDK, H15) were mixed in a jar and blended for 5 minutes with a Speedmixer.
2. 2. The catalyst was added and the mixture was blended for 2 min in the Speedmixer

[0072] Component B may, inter alia, comprise the following components:

1. The polymers, including Vin 1000, CL, and CE, were mixed in a jar and blended 2 min in the Speedmixer.

Table 1.

Component A			Component B		
Vin 1000	Silica HDK H15	Catalyst 511	Vin 1000	CL AB 109380	CE AB 109366
0,479	0,02	0,001	0,197	0,003	0,3
(47,9 g)	(2 g)	(0,1 g)	(19,7 g)	(0,3 g)	(30 g)

[0073] Based on the above outlined base formulation, two antimicrobial formulations were prepared.

Example 2: Silicone formulation with silver sulfate and PEG

[0074] A formulation was prepared using a method comprising the following steps:

- 1) Adding a silicone component A (3,75 g), in accordance with example 1, in ajar with PEG 8000 (3 g).
- 2) heating at 80 °C until the PEG is molten. The phases are subsequently mixed in a Speedmixer until an emulsion is formed (a timeframe of approximately 2 min).
- 3) preparing a paste of Ag_2SO_4 (3 g) and Velvesil plus (1,5 g) by mixing the silver powder and the Velvesil in a jar, and blending with the Speedmixer.
- 4) adding the silver paste to component A and mix
- 5) adding inhibitor (0,015 g) to silicone B and mix
- 6) add silicone component B (3,75 g)

Table 2.

PEG 8000	Velvesil Plus	Ag_2SO_4	Silicone A	Silicone B	Inhibitor
0,2	0,1	0,2	0,25	0,25	0,001
(3 g)	(1,5 g)	(3 g)	(3,75 g)	(3,75 g)	(0,015 g)

[0075] The above outlined steps may naturally, where applicable, be performed simultaneously or sequentially or in any combination of sequential steps.

Example 3: Silicone formulation with silver sulfate and mannitol

[0076] A formulation was prepared using a method comprising the following steps:

- 1) putting the silicone component A (3 g), in accordance with example 1, in a jar with mannitol (4,5 g).
- 2) mixing the phases in a Speedmixer until a suspension is formed (approximately 2 min).
- 3) preparing a paste of Ag_2SO_4 (3 g) and Velvesil plus (1,5 g) by mixing the silver powder and Velvesil in a jar and blending with the Speedmixer.

- 4) adding the silver paste to component A and mix
- 5) adding inhibitor (0,015 g) to silicone B and mix
- 6) adding the silicone component B (3,75 g)

Table 3.

Mannitol	Velvesil Plus	Ag ₂ SO ₄	Silicone A	Silicone B	Inhibitor
0,3	0,1	0,2	0,2	0,2	0,001
(4,5 g)	(1,5 g)	(3 g)	(3 g)	(3 g)	(0,015 g)

[0077] The formulations were coated on a film substrate comprising polyurethane. Test pieces with a diameter of 20 mm were punched and subjected to antimicrobial testing according to the CZol method and the two-compartment test method.

Example 4: Silicone formulation with silver sulfate and CMC

[0078] A formulation was prepared using a method comprising the following steps:

- 1) putting the silicone component A (5,92 g), in accordance with example 1, in a jar with CMC Akucell AF 2781W (1,5 g).
- 2) mixing the phases in a Speedmixer until a suspension is formed (approximately 2 min).
- 3) to component A adding Ag₂SO₄ (1,5 g) and Velvesil plus (0,15 g) to the mixture and blending with the Speedmixer (approximately 2 minutes).
- 4) adding the silicone component B (5,92 g) to the mixture and mix in the speedmixer (approximately 2 minutes).

Table 4.

CMC	Velvesil Plus	Ag ₂ SO ₄	Silicone A	Silicone B
0,10	0,01	0,10	0,395	0,395
(1,5 g)	(0,15 g)	(1,5g)	(5,92 g)	(5,92 g)

[0079] The formulations were coated on a film substrate comprising polyurethane. Test pieces with a diameter of 20 mm were punched and subjected to antimicrobial testing according to the CZol method and the two-compartment test method.

Example 5: Addition of silver sulfate and CMC with the addition of silicone polyether

[0080]

1. 1) To 80 g of component A of silicone gel (Dow Corning 7-9900) 10 g of silver sulfate and 10 g of CMC (Akucell 2781) was added and blended in a speed mixer for 2 min
2. 2) To this mixture 0,2 g of silicone polyether (Dow Corning FZ 2233) was added and

- blended in the speed mixer for 2 min
3. 3) To this mixture 80 g of component B (Dow corning 7-9900) was added and blended in the mixer.
4. 4) The sample was left to cure at room temperature.

[0081] The sample cured to a gel.

Example 6: addition of silver sulfate and CMC with the addition of silicone polyether crosspolymer

[0082]

1. 1) To 80 g of component A of silicone gel (Dow Corning 7-9900) 10 g of silver sulfate and 10 g of CMC (Akucell 2781) was added and blended in a speed mixer for 2 min
2. 2) To this mixture 1 g of silicone polyether crosspolymer (Momentive, Velvesil plus) was added and blended in the speed mixer for 2 min
3. 3) To this mixture 80 g of component B (Dow corning 7-9900) was added and blended in the mixer.
4. 4) The sample was left to cure at room temperature.

[0083] The sample cured to a gel.

Example 7: Silver release and antimicrobial effects

[0084] The antimicrobial effects of the antimicrobial gels were evaluated for a number of differently formulated gels, as summarized in Table 5 below. Essentially no antimicrobial activity was detected when omitting the at least one (optionally silver release-enhancing) hydrophilic component (cf. samples 2N1 and 2N2 in Table 5 below). Additionally, hydrophilic components that do not at all enhance the swelling of the antimicrobial products as per the present invention analogously cause essentially no antimicrobial effects. Thus, it is clear that the swelling effects mediated by the hydrophilic components as per the present invention result in enhanced antimicrobial efficacy.

Table 5.

ID	2N1*	2N2*	3N1	3N6	3N8	5N6	7N4*	9N4	9N5	9N8
Ag ₂ SO ₄	0,1	0,1	0,05	0,2	0,2	0,2	0,2	0,1	0,1	0,2
PEG 3000			0,1	0,1	0,25					
PEG 6000							0,2			

ID	2N1*	2N2*	3N1	3N6	3N8	5N6	7N4*	9N4	9N5	9N8
PEG 8000						0,2				
Velvesil plus		0,1	0,1	0,1	0,1	0,1		0,1	0,1	0,1
Velvesil							0,1			
125										
Mannitol								0,3		0,3
Sorbitol									0,3	
PDMS	0,9	0,8	0,75	0,6	0,55	0,5	0,5	0,5	0,5	0,4
Test results										
CZol 24 h (mm)	<1	<1	<1	3	5	6	3,5	4	5	6
Total Ag Release 24 h (%)	0	0	0,7	0,3	16	17	0,03	5	10	34
Total Ag Release 48 h (%)	0	0	0,8	0,8	27	34	0,07	7,5	12	54
* means reference example										

[0085] The antimicrobial gels prepared in accordance with the present invention displayed desirable properties both in terms of silver release over time and in terms of antimicrobial effects, with the antimicrobial efficacy being based on measurements of corrected zone of inhibition (CZol) (Table 4), on the reduction of the number of colony-forming units (CFU) of *Pseudomonas aeruginosa* only (Figure 4) and *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Figure 3), and on the modified ISO antimicrobial contact method. Briefly regarding the data presented in Figures 3 and 4, wound dressings comprising composition 5N6 were tested against two common infectious agents, i. e. *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The samples were inoculated with 10^6 bacteria and subjected to substrates coated with antimicrobial compositions of the invention. Comparisons of the sample and the control show the antimicrobial effect as log reductions over time, with the antimicrobial gels as per the present invention being able to reduce the number of colony forming units (CFUs) of *Staphylococcus aureus* from 10^6 to at least 10^5 in 24 h, or preferably from 10^6 to at least 10^4 in 24 h, or most preferably from 10^6 to at least 10^3 in 24 h.

[0086] Figure 4 displays data resulting from two-compartment model tests on *P. aeruginosa*, based on antimicrobial gels in accordance with the present invention, comprising excipients such as PEG and mannitol. Substantial antimicrobial effects can be seen with both gels, with at least four logs reduction in CFU/ml over time frames as long as one week

Example 8: Swelling properties

[0087] The swelling properties of various antimicrobial gels and cross-linked compositions in accordance with the present invention were analyzed using the free swell absorption method. As can be seen from Table 6, the (optionally silver release-enhancing) hydrophilic components of the present invention mediate substantial swelling, leading to improved silver release and/or enhanced antimicrobial efficacy.

Table 6.

No	Sample Description	Swelling			
		% 6h	% 24h	% 48h	% 72h
1	MAG11-B: 5% Pemulen TR-2	31%	39%	71%	85%
2	MAG11-D: 10% Pemulen TR-2	64%	60%	73%	72%
3	MAG11-G: 10% CMC 3281	114%	125%	143%	135%
4	MAG 11-H: 20% CMC 3281	279%	326%	353%	360%
5	MAG11-I: 10% Mannitol	53%	62%	69%	67%
6	MAG11-J: 20% Mannitol	55%	66%	69%	61%
7	MAG11-K: 10% pestle Mannitol	38%	66%	74%	86%

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

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- [WO2008057155A](#) [0008] [0008]

PATENTKRAV

1. En antimikrobiel sammensætning omfattende:
 - mindst en alkenyl- og/eller alkynylsubstitueret polysiloxan,
 - mindst en polysiloxan omfattende siliciumbundne hydrogenatomer,
 - 5 - mindst en hydrosilyleringskatalysator
 - mindst et sølvsalt i en koncentration mellem 1% og 30% (masse/masse), der er udvalgt blandt gruppen omfattende Ag_2SO_4 , Ag_2SO_3 ; AgNO_3 , Ag_2CO_3 , Ag_3PO_4 , sølvzirkoniumsølvsalt, sølvcitrat, sølvacetat, søvlactat og/eller kombinationer eller blandinger deraf,
 - 10 - mindst en hydrofil komponent, der gør nævnte antimikrobielle sammensætning, når den er tværbundet, svulmer mindst 5% (vægt/vægt) efter 24 timer i en deioniseret vandopløsning indeholdende 8,298 g/L natriumchlorid og 0,368 g/L calciumchloriddihydrat, målt ved fri svulme-absorption fremgangsmåde, hvor koncentrationen af den mindst ene hydrofile komponent er mellem 3% og 40% (vægt/vægt) og
 - 15 - mindst en siloxanpolyether (SPE), der er til stede i en koncentration på mellem 0,1% og 30% (vægt/vægt),

hvor den mindst ene hydrofile komponent er udvalgt blandt gruppen omfattende glucose, xylitol, sorbitol, mannitol, cyclodextriner, cellulose, hemicellulose, carboxymetyleret cellulose, chitosan, dextran, chitin, amylose, amylopectin, polyethylenglycol, polypropylenglycol, copolymerer af polyethylen og polypropylenglycol, polyglycerol, poly (acrylsyre), copolymerer af acrylsyre og C_{10} - C_{30} alkylacrylat, poly(acrylamid), maleinsyreanhydridpolymerer og copolymerer, carboxymethylcellulose, methylcellulose, hydroxymethylpropylcellulose, ethylcellulose, carboxyethylcellulose, hydroxypropylcellose alkylsulfonat, polystyrensulfonater, vinylsyrer og vinylalkoholer.

- 25
- 2. Antimikrobiel sammensætning ifølge krav 1, der yderligere omfatter mellem 1% og 5% (vægt/vægt) silicapartikler.
- 30
- 3. En antimikrobiel gel fremstillet ud fra sammensætningen ifølge et hvilket som helst af kravene 1 til 2, hvor gelen fremstilles ved tværbinding af mindst en alkenyl- og/eller alkynylsubstitueret polysiloxan og den mindst ene polysiloxan omfattende siliciumbundne hydrogenatomer.

4. Antimikrobiel gel ifølge krav 3, hvor tværbinding af polysiloxanerne udføres ved hjælp af hærkning.
- 5 5. Antimikrobiel gel ifølge et hvilket som helst af kravene 3 til 4, yderligere omfattende et eller flere excipienser udvalgt blandt gruppen omfattende siloxanholdige copolymerer og silicapartikler.
- 10 6. Antimikrobiel gel ifølge et hvilket som helst af kravene 3 til 5, hvor inhiberingen af mikrobiel vækst forårsaget af den antimikrobielle gel, defineret som korrigeret inhiberingszone (CZol), er mindst 2 mm efter 24 timer.
- 15 7. Antimikrobiel gel ifølge et hvilket som helst af kravene 3 til 6, hvor en cirkulær prøve af nævnte antimikrobielle gel vurderet ved anvendelse af to-kammer test fremgangsmåde med en diameter på ca. 20 mm og en belægningsvægt på ca. 500 g/m². når den udsættes for 4 ml bakterier indeholdende kemisk simuleret sårveske ved en temperatur på 37 °C, er i stand til at reducere antallet af kolonidannende enheder (CF Us) af *Staphylococcus aureus* fra 10⁶ til mindst 10⁵ på 24 timer.
- 20 8. Antimikrobiel gel ifølge et hvilket som helst af kravene 3 til 7, hvor nævnte gel har en adhæsion med stål på mellem 0,1 og 2 N målt ved ASTM International standard D3330/D3330M-04, metode F.
- 25 9. En antimikrobiel forbindelse udvalgt blandt gruppen omfattende en sårforbinding, en stomiforbinding, stomibundplade, snitfilm, kirurgisk afdækning, en klap, en bandage, et plaster, et gips, et klæbemiddel, et klæbemiddelbånd, et klæbemiddel gips, et klæbende gips og et hæfteplaster og en hvilken som helst kombination deraf omfattende den antimikrobielle gel ifølge et hvilket som helst af kravene 3 til 8, hvor den antimikrobielle gel påføres på et substrat.
- 30 10. Fremgangsmåde til fremstilling af en antimikrobiel gel ifølge et hvilket som helst af kravene 3 til 8, omfattende følgende trin:
- (a) fremstilling af de tre blandinger (i), (ii) og (iii), enten samtidigt eller sekventielt eller i en hvilken som helst kombination af (i), (ii) og (iii), omfattende:

(i) mindst en alkenyl- og/eller alkynylfunktionel polysiloxan, mindst en hydrosilyleringskatalysator og eventuelt silicapartikler;

(ii) mindst en alkenyl- og/eller alkynylfunktionel polysiloxan, mindst et CE omfattende siliciumbundne hydrogenatomer og/eller mindst en CL omfattende siliciumbundne hydrogenatomer og eventuelt silicapartikler;

(iii) mindst et sølvsalt og mindst en siloxanpolyether (SPE);

(b) blanding af mindst en hydrofil komponent med blanding (i) og/eller blanding (ii) efterfulgt af eventuelt opvarmning af blanding(er), hvortil den mindst ene hydrofile komponent blev tilsat, for at smelte den mindst ene hydrofile komponent;

(c) blanding af blanding (iii) med blanding (i) og/eller blanding (ii)

(d) blanding af blanding (i) og blanding (ii); og

(e) hærkning af blandingen opnået i trin (d), hvorved nævnte antimikrobielle gel opnås,

hvor nævnte sammensætning yderligere omfatter mindst et sølvsalt i en koncentration mellem 1% og 30% (vægt/vægt), og koncentrationen af den mindst ene hydrofile komponent er mellem 3% og 40% (vægt/vægt).

11. Fremgangsmåde til fremstilling af en antimikrobiel forbindelse ifølge krav 9, omfattende følgende trin:

(a) fremstilling af de tre blandinger (i), (ii) og (iii), enten samtidigt eller sekventielt eller i en hvilken som helst kombination af (i), (ii) og (iii), omfattende:

(i) mindst en alkenyl- og/eller alkynylfunktionel polysiloxan, mindst en hydrosilyleringskatalysator og eventuelt silicapartikler;

(ii) mindst en alkenyl- og/eller alkynylfunktionel polysiloxan, mindst et CE omfattende siliciumbundne hydrogenatomer og/eller mindst en CL omfattende siliciumbundne hydrogenatomer og eventuelt silicapartikler;

(iii) mindst et sølvsalt og mindst en siloxanpolyether (SPE);

(b) blanding af mindst en hydrofil komponent med blanding (i) og/eller blanding (ii) efterfulgt af eventuelt opvarmning af blanding(er), hvortil den mindst ene hydrofile komponent blev tilsat, for at smelte den hydrofile komponent;

(c) blanding af blanding (iii) med blanding (i) og/eller blanding (ii);

(d) blanding af blanding (i) og blanding (ii);

(e) belægning af et substrat med blandingen opnået i trin (d); og

(f) hærkning af den blanding, der er belagt på substratet fra trin (e), hvorved den antimikrobielle forbindelse opnås,

hvor nævnte sammensætning yderligere omfatter mindst et sølvsalt i en koncentration mellem 1% og 30% (vægt/vægt), og koncentrationen af den mindst ene hydrofile komponent er mellem 3% og 40% (vægt/vægt).

12. Fremgangsmåde ifølge krav 11, hvor substratet er udvalgt blandt gruppen omfattende en sårforbinding, en stomiforbindelse, en stomibundplade, en snitfilm, en kirurgisk afdækning, en klap, en bandage, et plaster, et gips, et klæbemiddel, et klæbemiddelbånd, et klæbemiddel gips, et klæbende gips og et hæfteplaster og en hvilken som helst kombination deraf, eller hvor substratet er en komponent til fremstilling af et hvilket som helst af de ovennævnte substrater, udvalgt blandt gruppen omfattende en film, et tekstil, et skum, en ikke-vævet film, et fibernetværk og et strikket stof.

13. Antimikrobiel gel ifølge et hvilket som helst af kravene 3 til 8 eller den antimikrobielle forbindelse ifølge krav 9 til anvendelse som et medikament.

14. Antimikrobiel gel ifølge et hvilket som helst af kravene 3 til 8 eller den antimikrobielle forbindelse ifølge krav 9 til anvendelse til behandling af brandsår, ar, bakterielle infektioner, virusinfektioner og/eller svampeinfektioner.

DRAWINGS

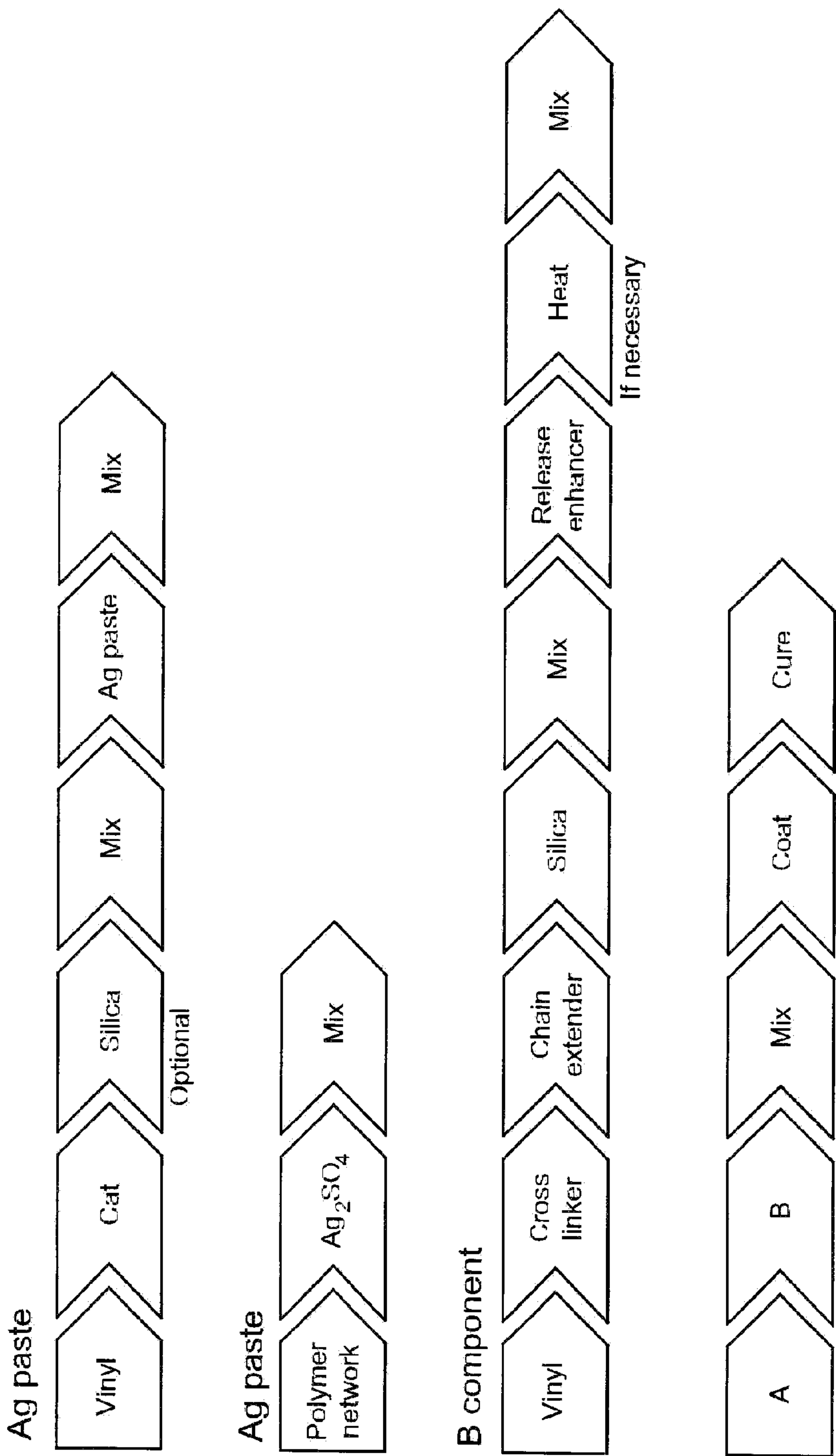
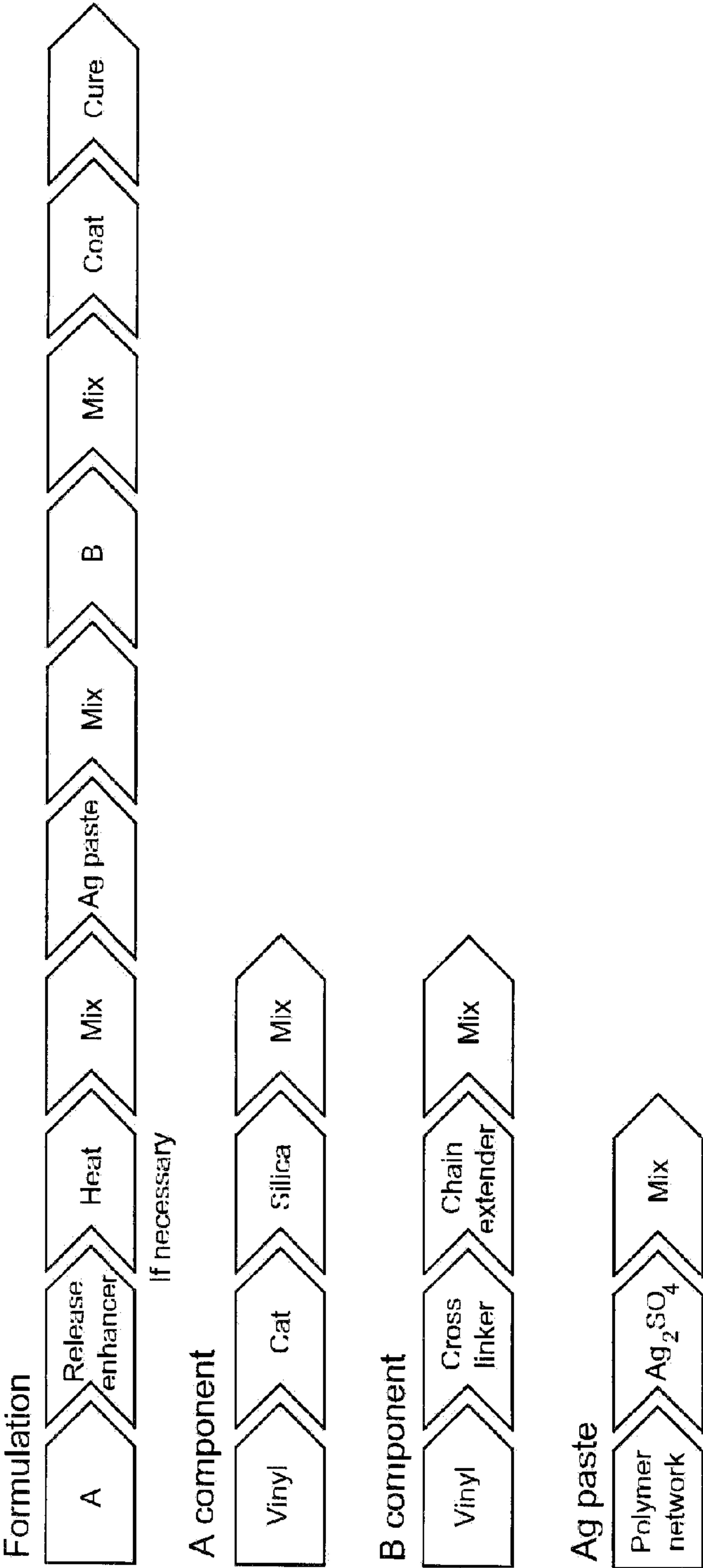


FIG. 1



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FIG. 2

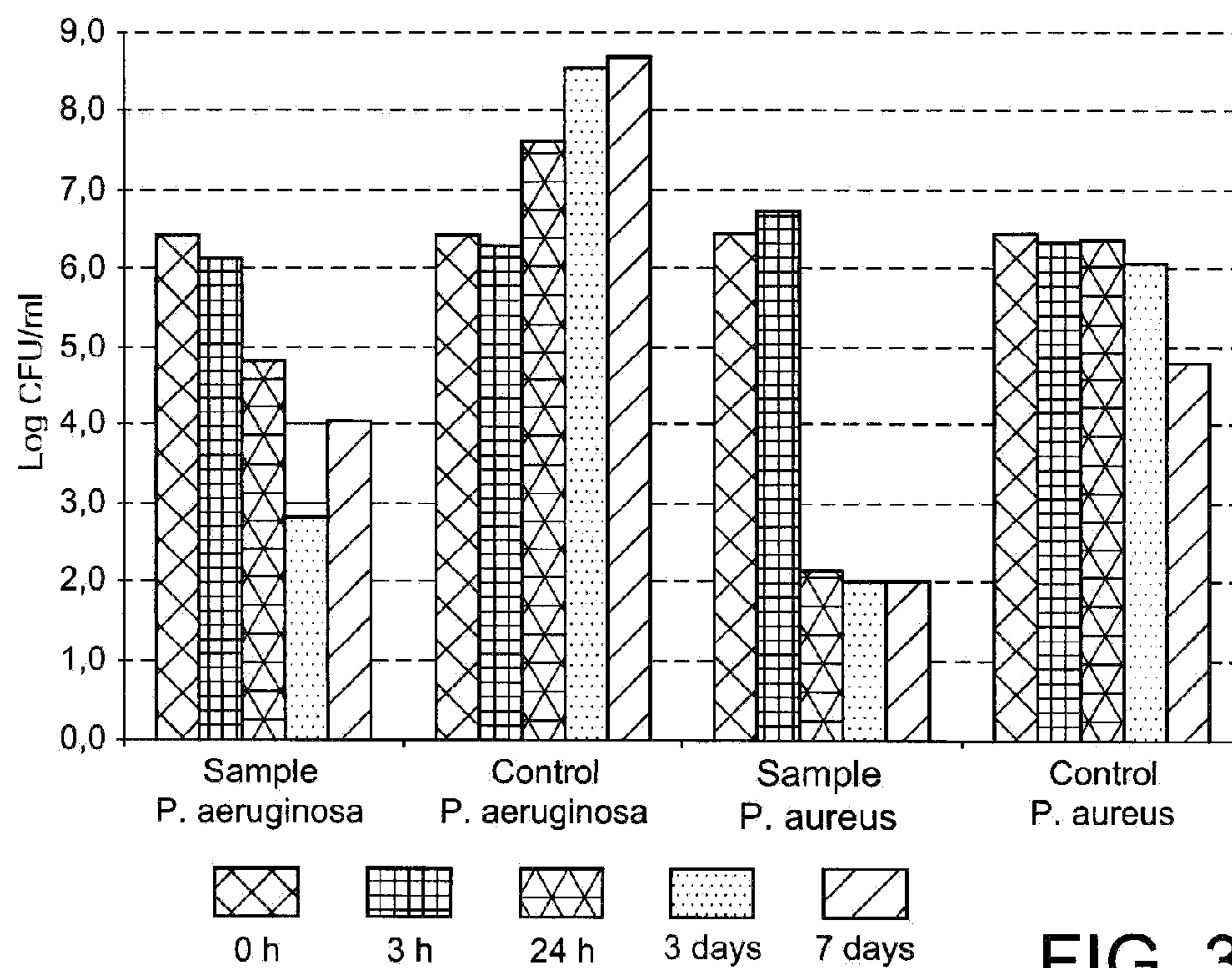


FIG. 3

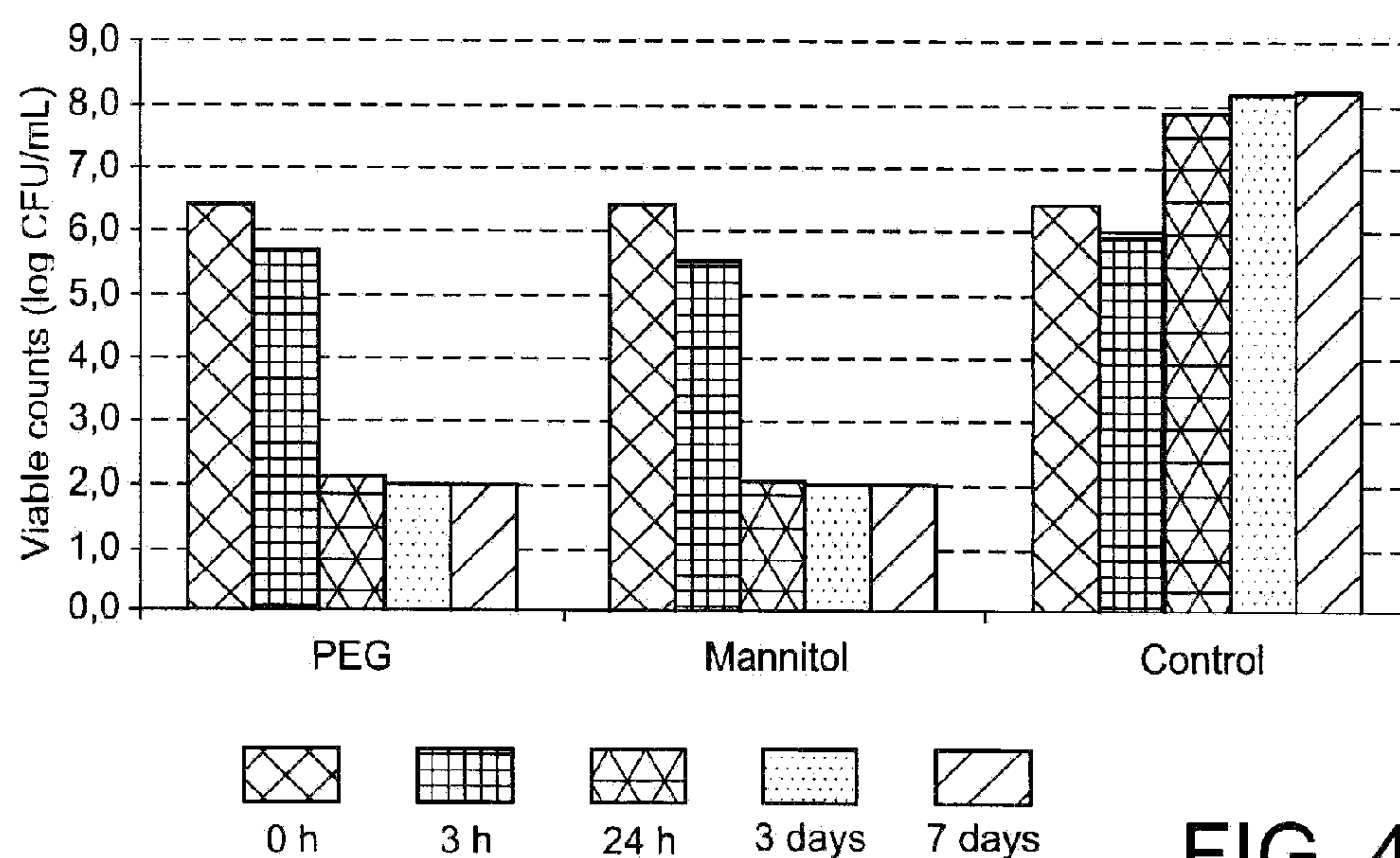
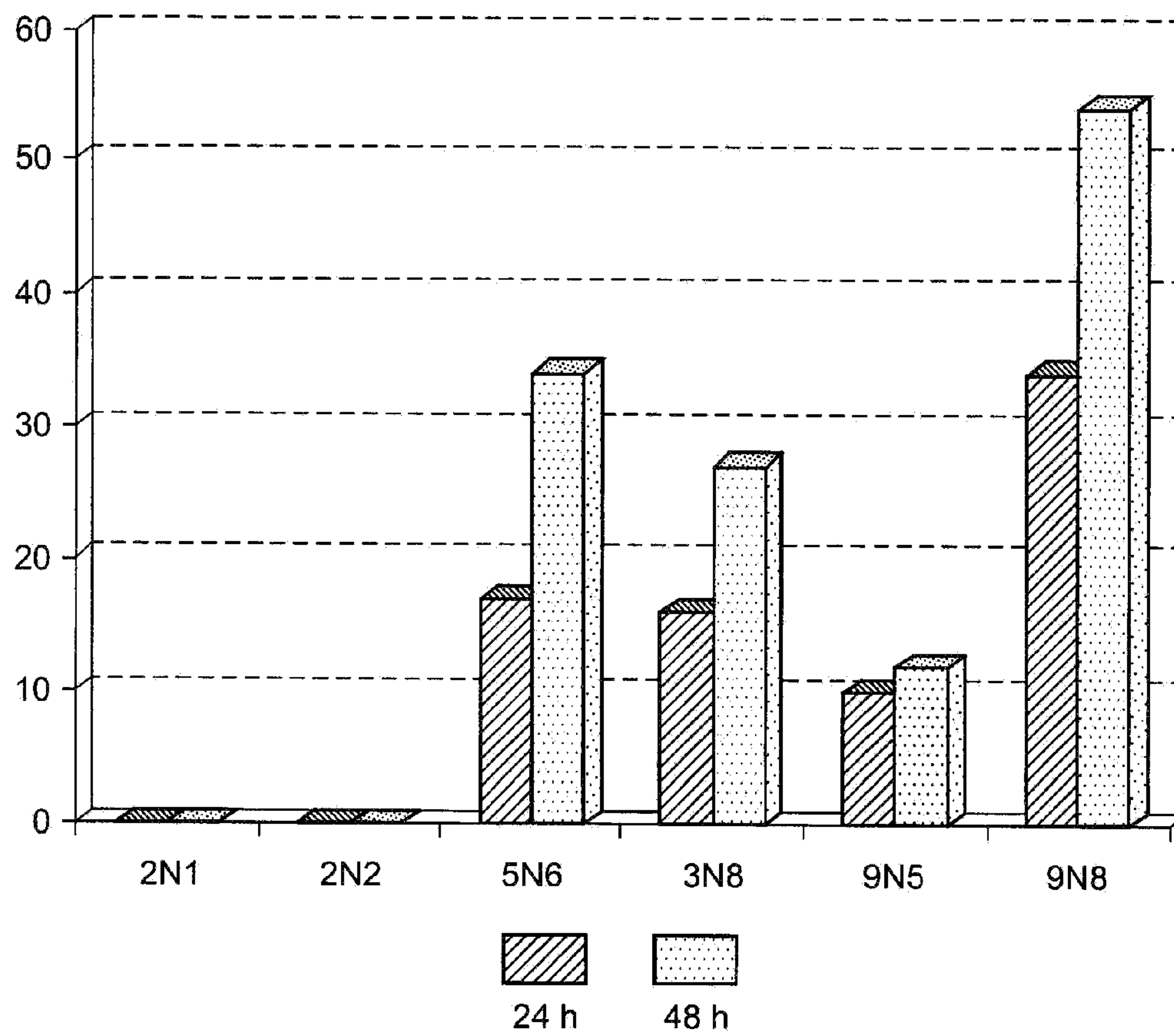


FIG. 4

**FIG. 5**

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