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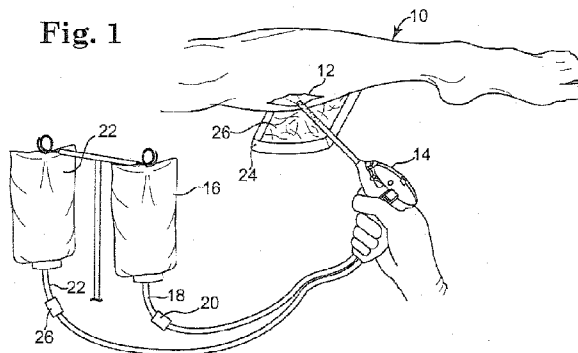
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Fig. 1



(57) Abstract: Chronic wounds may be treated by debriding necrotic and other devitalized tissue from the wound, and applying to the wound an extracellular polymeric substance solvating system comprising a metal ion sequestering agent, surfactant and buffering agent. The solvating system disrupts biofilms which may be present in the wound and aids or enables the resumption of normal healing.

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REPLACEMENT SHEET

**METHOD FOR TREATING CHRONIC WOUNDS WITH AN EXTRACELLULAR
POLYMERIC SUBSTANCE SOLVATING SYSTEM****FIELD OF THE INVENTION**

[0001] This invention relates to chronic wound treatment.

BACKGROUND

[0002] Chronic wounds affect millions of people, and are responsible for significant hospitalization costs and other expenses and inconvenience. Diabetics and people with other circulation impairments are susceptible to diabetic ulcers and venous stasis ulcers. Paralyzed, unconscious or severely debilitated patients are susceptible to decubitus ulcers. Although a variety of chronic wound care treatment therapies have been explored, many wounds can not be adequately treated. In some cases amputation of an affected limb may be the only available remedy.

SUMMARY OF THE INVENTION

[0003] We have found that chronic wounds may be treated by debriding at least some necrotic or other devitalized tissue from the wound, and applying to healthy or healable tissue in the wound an extracellular polymeric substance (EPS) solvating system comprising a metal ion sequestering agent, surfactant and buffering agent. The debriding and application steps desirably are combined by applying the solvating system using a sufficient flow rate or sufficient pressure to debride at least some devitalized tissue from the wound.

[0004] The invention provides in another aspect a method for treating a chronic wound, which method comprises applying to healthy or healable tissue in the wound an EPS solvating system comprising a metal ion sequestering agent, surfactant and buffering agent and having an osmolarity of about 1,000 to about 4,000 milliosmoles (mOsm).

[0005] The invention provides in another aspect an apparatus for treating a chronic wound, comprising a debriding device; a reservoir containing an EPS solvating system comprising a metal ion sequestering agent, surfactant and buffering agent, in fluid communication with an applicator for applying the solvating system to a wound; and an aspirating device which removes at least some debrided necrotic or other devitalized tissue

5 also serves as the debriding device by applying the solvating system at a sufficient flow rate or under sufficient pressure to debride at least some devitalized tissue from the wound.

[0006] The invention provides in another aspect a patient care kit for treating a chronic wound, the kit comprising a tray; syringe; vessel containing an EPS solvating system
10 comprising a metal ion sequestering agent, surfactant and buffering agent; and printed instructions describing the proper use of the kit for treating chronic wounds.

[0006A] The invention provides in yet another aspect chronic wounds, which method comprises debriding at least some necrotic or other devitalized tissue from the wound; and applying to healthy or healable tissue in the wound an extracellular polymeric substance
15 solvating system comprising an aqueous solution of a metal ion sequestering agent, surfactant and buffering agent wherein the solvating system has an osmolarity greater than 900 milliosmoles of solute per litre.

[0006B] The invention provides in another aspect an apparatus for treating a chronic wound, comprising a debriding device; a reservoir containing an extracellular polymeric
20 substance solvating system comprising an aqueous solution of a metal ion sequestering agent, surfactant and buffering agent wherein the solvating system has an osmolarity greater than 900 milliosmoles of solute per litre, in fluid communication with an applicator for applying the solvating system to a wound; and an aspirating device which removes at least some debrided necrotic or other devitalized tissue and excess solvating system from
25 the wound.

[0006C] The invention provides in yet another aspect patient care kit when used in a method for treating chronic wounds, which method includes at least the step of debriding at least some necrotic or other devitalized tissue from a wound, and wherein the kit comprises a tray; syringe; vessel containing an extracellular polymeric substance solvating
30 system comprising an aqueous solution of a metal ion sequestering agent, surfactant and buffering agent wherein the solvating system has an osmolarity greater than 900 milliosmoles of solute per litre; and printed instructions describing the proper use of the kit for treating chronic wounds.

[0006D] product comprising an extracellular polymeric substance solvating system
35 when used for treating a chronic skin wound said treatment including debridement of at least some necrotic or other devitalized tissue from the wound, the solvating system

5 comprising an aqueous solution of at least about 0.01 of metal ion sequestering agent, at least about 0.002 M of surfactant, and buffering agent that maintains the solvating system at an appropriate pH for contacting chronic skin wounds, wherein the solvating system has an osmolarity of greater than 900 milliosmoles of solute per litre, a sufficiently low viscosity to enable delivery to the wound using spray application, and aids in chronic wound biofilm detachment, removal or disruption.

10 [0006E] Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

15 [0006F] Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present disclosure as it existed before the priority date of each claim of this application.

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BRIEF DESCRIPTION OF THE DRAWING

[0007] Fig. 1 is a perspective view of a chronic leg wound being treated with the disclosed solvating system;

[0008] Fig. 2 is a perspective view of an apparatus for treating chronic wounds; and

25 [0009] Fig. 3 is a perspective view of a home care kit for treating chronic wounds.

[0010] Like reference symbols in the various figures of the drawing indicate like elements. The elements in the drawing are not to scale.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

30 [0011] The following detailed description describes certain embodiments and is not to be taken in a limiting sense. All weights, amounts and ratios herein are by weight, unless otherwise specifically noted. The terms shown below have the following meanings:

[0012] The phrase "antimicrobial agent" refers to a substance having the ability to cause greater than a 90% numeric reduction (*viz.*, at least a 1-log order reduction) in a population of one or more aerobic or anaerobic bacteria present in chronic wounds

35

- 5 [0013] The terms “attached” and “adhered” when used in reference to a bacterial biofilm and a surface mean that the biofilm is established on and at least partially coats or covers the surface, and has some resistance to removal from the surface. As the nature of this relationship is complex and poorly understood, no particular mechanism of attachment or adherence is intended by such usage.

5 **[0014]** The phrase “bacterial biofilm” means a community of bacteria attached to a surface, with the organisms in the community being contained within an EPS matrix produced by the bacteria.

[0015] The term “biocompatible” when used in reference to a substance means that the substance presents no significant deleterious or untoward effects upon the body.

10 **[0016]** The phrase “chronic wound” means a wound containing exposed devitalized or otherwise compromised tissue which will not heal in a medically acceptable time frame (e.g., within one or two months) through normal healing processes.

[0017] The term “debride” when used in reference to devitalized tissue attached within a chronic wound means to cut away or otherwise excise the tissue so that it is no longer
15 attached. No particular mechanism of debridement is intended by such usage.

[0018] The terms “detaching”, “removing” and “disrupting” when used in reference to a bacterial biofilm attached or adhered to a surface mean that at least a significant amount of the biofilm initially present on the surface no longer is attached or adhered to the surface. No particular mechanism of detachment, removal or disruption is intended by
20 such usage.

[0019] The term “devitalized” when used in reference to wound tissue means tissue that is sufficiently devoid of life so that it will not heal if left untreated.

[0020] The term “osmolality” means the number of osmoles of solute per kilogram of solvent, as measured using a Model 5002 Osmette A™ freezing point depression
25 osmometer (Precision Systems, Inc.).

[0021] The term “osmolarity” means the number of osmoles of solute per liter of solution. Osmolarity may conveniently be calculated from an osmolality measurement.

[0022] The phrase “sequestering agent” means a chemical that will combine with another material, especially a metal ion, to discourage or prevent the material from coming
30 out of solution. The phrase “metal ion sequestering agent” means a sequestering agent that will combine with one or more metal ions such as alkali metals (viz., lithium, sodium, potassium, rubidium, cesium or francium), alkaline earth metals (viz., beryllium, magnesium, calcium, strontium, barium or radium), iron and the like to discourage or prevent the metal ion from coming out of solution.

5 [0023] The term “solvating” means to form a solution or dispersion containing a solvent or other carrier within which a solute is dissolved or suspended.

[0024] The term “wound” means an opening in the skin through which subdermal or deeper tissue (e.g., subcutaneous fat, muscle or other tissue) is exposed.

10 [0025] Referring to **Fig. 1**, a leg **10** with chronic wound **12** (in this instance, a venous stasis ulcer) may be treated using a hydrodebriding device **14** which applies the disclosed EPS solvating system to wound **12** at a sufficient flow rate or under sufficient pressure to debride devitalized tissue. A variety of devices may be used or adapted as need be to provide device **14**, including the Pulsavac™ and Pulsavac Plus™ wound debridement systems (Zimmer, Inc.), the SonicOne™ ultrasonic wound debridement system (Misonix, Inc.), the Versajet™ hydrosurgery system (Smith & Nephew, Inc.), the SpineJet™ hydrosurgery system (HydroCision, Inc.) and the MHS™ hydrodebriding system (Medtronic Xomed, Inc.). Device **14** may include or be connected to a suitable power source (e.g., a rechargeable battery or low voltage transformer) to operate a pump (not shown in **Fig. 1**) within device **14**. The solvating system may be applied from a reservoir such as bag **16** in fluid communication via conduit **18** and valve **20** with device **14**. Sterile saline or other suitable rinsing solution may if desired be supplied from a reservoir such as bag **22** in fluid communication via conduit **24** and valve **26** with device **14**. If desired, other debridement techniques may be employed together with device **14**, including cutting or scraping away devitalized tissue using a scalpel, scissors, swab, plastic stick, tongue depressor or other suitable tool such as the Straightshot™ M4 microdebrider (Medtronic Xomed, Inc.). The debrided devitalized tissue, wound exudates, excess solvating system solution, excess saline or other rinsing solution (if used) and other solid or fluid residues may be collected in pan **24**. Absorbent pad **26** made from a nonwoven or other suitable material may help retain at least the fluid residues in pan **24**. At the conclusion of treatment, a wound dressing (not shown in **Fig. 1**) may if desired be applied to wound **12** to discourage further infection.

30 [0026] **Fig. 2** shows a perspective view of another apparatus **200** for use in the disclosed method. A variety of devices may be used or adapted as need be to provide apparatus **200**, including the V.A.C. Instill™ wound healing system from KCI Licensing (San Antonio, TX), and the Invia™ healing system or the Dominant™ 35c/I suction

35

5 system (both from Medela Healthcare U.S.). Apparatus **200** includes a housing **202** with handle **204**. Touch screen display **206** may be used to control the operation of apparatus **200**. The disclosed solvating system may be supplied from a bag or other suitable reservoir (for example, a bag like bag **16** in **Fig. 1**) to a chronic wound via tubing **208**. The coiled end of tubing **208** may be connected to a suitable dispensing tip (not shown in
10 **Fig. 2**) through which the disclosed solvating system may be delivered into a wound. Shoulder clamp **210** may be used to hold tubing **208** on apparatus **200**. Debrided devitalized tissue, wound exudates, excess solvating system solution, excess saline or other rinsing solution (if used) and other solid or fluid residues may be collected from the wound using a suitable aspirating tip (not shown in **Fig. 2**) connected to the coiled end of
15 tubing **212**. The other end of tubing **212** is attached to a fitting **215** on housing **202** through which the collected solid or fluid residues pass into a pump (not shown in **Fig. 2**) inside housing **202**. Shoulder clamp **214** may be used to hold tubing **212** on apparatus **200**. A removable canister **216** may be used to collect and later dispose of solid and fluid residues passing through the pump. Release button **218** and an associated clamp or other
20 retaining mechanism (not shown in **Fig. 2**) may be used to lock canister **216** in apparatus **200** until such time as removal of canister **216** is desired.

[0027] The apparatus shown in **Fig. 2** does not itself deliver the disclosed solvating system to the wound. Debridement of devitalized tissue could be carried out using any convenient debridement technique including the cutting or scraping techniques mentioned
25 above, or by excising the devitalized tissue using a separately-supplied directed fluid stream such as a pressurized sterile saline stream. The **Fig. 2** apparatus may if desired be altered to permit pressurized delivery of solvating system solution, for example by adding a suitable separate pump, or by modifying the existing pump or associated tubing in apparatus **200** so that sufficient flow rate or sufficient pressure for hydrodebriding and
30 sufficient suction for removal of solid and fluid residues from wounds are available in apparatus **200**. The **Fig. 2** apparatus may also be modified to provide additional measures for discouraging bacterial survival, regrowth or recolonization in the wound, including exposure of the wound to light (e.g., ultraviolet and other wavelengths of light, delivered as non-coherent or as laser radiation), sonication (e.g., ultrasound), gases (e.g., nitrogen or

5 oxygen), heating, cooling, or agents which consume, complex, bind to or replace bacteria or bacterial nutrients such as iron or sugars.

[0028] Fig. 3 shows a perspective view of a patient care kit 300 (e.g., a home care kit or travel kit) which may be employed in the disclosed method. Kit 300 includes tray 302 which may be lined with absorbent pad 304. Tray 302 may also contain or otherwise be
10 packaged with syringe 306, printed instructions 308 describing the proper use of kit 300 in the home treatment of chronic wounds, and bottle 310 or other suitable vessel containing the disclosed solvating system. Kit 300 may also include one or more manual debriding tools (not shown in Fig. 3) such as a scissors, knife or swab and one or more wound dressings (also not shown in Fig. 3) for application to the wound following treatment.
15 Syringe 306 may for example have a capacity of about 50 to about 75 cc (e.g., about 60 cc), and bottle 310 may for example have a capacity of about 2 to 5 times the capacity of syringe 306. Kit 300 may be sold over-the-counter or by prescription, with prescription sale being preferred in cases where further wound monitoring by a health care professional may be needed once kit 300 and any permitted solvating system refills have been
20 consumed.

[0029] Chronic wounds treatable using the disclosed method wound typically will contain large colonies of one or more aerobic or anaerobic organisms occupying one or more biofilms. For long-term chronic wounds, more anaerobes than aerobes may be present. Representative organisms which may be present in chronic wound biofilms
25 include *Staphylococcus* species (e.g., normal skin flora including *S. epidermidis*, *S. Corynebacterium* and *S. Brevibacterium*, and typical pathogens including *S. aureus*), other normal skin flora including *Propionibacterium acnes*, and other pathogens, for example *Acinetobacter* species including *A. baumannii*, *Bacillus* species including *B. anthracis*, *Brucella* species including *B. melitensis*, *Clostridium* species including *C. tetani*,
30 *Corynebacterium* species including *C. diphtheriae*, *Erysipelothrix* species including *E. rhusiopathiae*, *Escherichia* species including *E. coli*, *Klebsiella* species including *K. pneumoniae* or *K. oxytoca*, *Leptospira* species including *L. interrogans*, *Mycobacteria* species including *M. marinum* or *M. ulcerans*, *Proteus* species including *P. mirabilis*, *P. vulgaris* or *P. penneri*, *Pseudomonas* species including *P. aeruginosa* or *P. maltophilia*,
35 *Stenotrophomonas* species including *S. maltophilila*, Beta-hemolytic *Streptococcus*

5 species including *S. pyogenes* or *S. agalactiae*, *Treponema* species including *T. pallidum*, and *Yersinia* species including *Y. pestis*.

[0030] The wound may exhibit festering or other exudate production, swelling, erythema, pain, localized increased temperature, periwound cellulitis, ascending infection or a change in the appearance of granulation tissue (for example, discoloration, bleeding or
10 friability). The wound may have been caused or aggravated due to a variety of external factors including abrasion, burns, compression, immersion, surgery or trauma. Frequently however the wound may be caused or aggravated and may remain chronic due to a variety of internal factors including a compromised circulatory system (e.g., as in many diabetic patients), a compromised immune system or diseases including impetigo, folliculitis,
15 erysipelas, cellulitis or necrotizing fasciitis. Chronic foot or leg wounds in diabetic patients frequently involve colonies of *S. aureus* and Beta-hemolytic *Streptococcus*, are especially difficult to heal, and are of particular interest for treatment using the disclosed method since doing so may avoid amputation. The wound may be present in other body parts or in other extremities, and may be present not only in humans (including adults,
20 children and the elderly) but also in animals (including livestock, pets, show animals and wild animals).

[0031] The disclosed solvating system may be used to break down bacterial biofilms in chronic wounds and consequently aid in biofilm detachment, removal or disruption. The solvating system preferably is biocompatible with healthy and healable wound tissues,
25 and desirably does not contain ingredients which might potentially harm such tissues or unduly compromise wound healing. The solvating system desirably has a sufficiently low viscosity to enable easy delivery to the wound using for example power spray or other spray application, lavage, misting, mopping, wicking or dripping. The solvating system desirably also may be easily removed from the treatment site by subsequent aspiration,
30 flushing, rinsing, draining or absorption (e.g., using an absorbent pad or other suitable material). While not wishing to be bound by theory, the metal ion sequestering agent may complex, bind or otherwise tie up metal ions which may crosslink, bridge or otherwise assist in binding together the polymer chains in an EPS matrix. The solvating agent may then surround the unbound polymer chains or fragments, breaking down the matrix,
35 solvating the unbound polymer chains or fragments, and bringing them into solution or

- 5 suspension where they can be easily flushed or otherwise removed from the wound site using for example additional amounts of the solvating system or a separate rinsing agent.
- [0032] Solvating systems for use in certain tissue treatments are described in U.S. Patent Application Publication No. US 2007/0264296 A1 and PCT Published Application No. WO 2007/134055 A1. The solvating systems described in these publications have
- 10 particular utility in ear, nose and throat applications such as the treatment of otitis media, cholesteatoma and rhinosinusitis. In general, these solvating systems have insufficient osmolality for the efficacious treatment of chronic wounds, but they may be adapted for use in treating chronic wounds. Ciliated tissue such as that found in the ear, nose and throat is somewhat fragile, and to avoid damaging the cilia it is desirable to use solvating
- 15 systems with low osmolality, e.g., osmolality of about 300 to about 900 mOsm. When treating chronic wounds, it is preferable to use a substantially higher osmolality EPS solvating system, for example one whose osmolality is about 1,000 to about 4,000 mOsm, more preferably about 1,500 to about 2,600 mOsm. Doing so may facilitate wound treatment or wound healing.
- 20 [0033] The metal ion sequestering agent desirably is a mild acid whose acidity is sufficient to sequester one or more metal ions in the EPS matrix, but which is not so acidic so as to harm healthy or healable wound tissue. Metal ions of particular interest (due to their likely involvement in the targeted bacterial biofilms) include sodium, calcium and iron. The metal ion sequestering agent desirably is water-soluble and not unduly toxic.
- 25 Representative acids include but are not limited to carboxylic acids, diacids, or triacids such as formic acid, acetic acid, chloroacetic acid, dichloroacetic acid, oxalic acid, oxamic acid, glycolic acid, lactic acid, pyruvic acid, aspartic acid, fumaric acid, maleic acid, succinic acid, iminodiacetic acid, glutaric acid, 2-ketoglutaric acid, glutamic acid, adipic acid, citric acid, glucuronic acid, mucic acid, nitrilotriacetic acid, salicylic acid,
- 30 ketopimelic acid, benzoic acid, mandelic acid, chloromandelic acid, phenylacetic acid, phthalic acid and boric acid; mineral acids such as hydrochloric acid, orthophosphoric acid and phosphonic acid; and mixtures thereof. Citric acid is a preferred acid. The metal ion sequestering agent may for example be present at a concentration of at least about 0.01 M, at least about 0.05 M or at least about 0.1 M, e.g., about 0.01 to about 1.5 M. Increased
- 35 metal ion sequestering agent amounts may promote faster biofilm breakup.

5 [0034] The solvating system also includes a surfactant. The surfactant desirably is water-soluble and nontoxic. Exemplary surfactants include anionic surfactants, nonionic surfactants, cationic surfactants and zwitterionic surfactants. Exemplary anionic surfactants include but are not limited to C₆-C₂₄ alkylbenzene sulfonates; C₆-C₂₄ olefin sulfonates; C₆-C₂₄ paraffin sulfonates; cumene sulfonate; xylene sulfonate; C₆-C₂₄ alkyl
 10 naphthalene sulfonates; C₆-C₂₄ alkyl or dialkyl diphenyl ether sulfonates or disulfonates, C₄-C₂₄ mono or dialkyl sulfosuccinates; sulfonated or sulfated fatty acids; C₆-C₂₄ alcohol sulfates (for example C₆-C₁₂ alcohol sulfates); C₆-C₂₄ alcohol ether sulfates having 1 to about 20 ethylene oxide groups; C₄-C₂₄ alkyl, aryl or alkaryl phosphate esters or their alkoxylated analogues having 1 to about 40 ethylene, propylene or butylene oxide units;
 15 and mixtures thereof. For example, the anionic surfactant may be sodium chenodeoxycholate, N-lauroylsarcosine sodium salt, lithium dodecyl sulfate, 1-octanesulfonic acid sodium salt, sodium cholate hydrate, sodium deoxycholate, sodium dodecyl sulfate (also known as sodium lauryl sulfate) or sodium glycodeoxycholate.

[0035] Exemplary cationic surfactants include but are not limited to quaternary amine
 20 compounds having the formula:

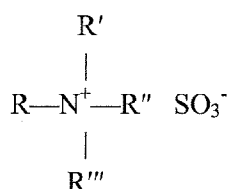


25 where R, R', R'' and R''' are each a C₁-C₂₄ alkyl, aryl or aralkyl group that can optionally contain one or more P, O, S or N heteroatoms, and X is F, Cl, Br, I or an alkyl sulfate. For example, the cationic surfactant may be hexadecylpyridinium chloride monohydrate or hexadecyltrimethylammonium bromide.

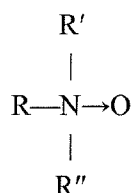
30 [0036] Exemplary nonionic surfactants include but are not limited to C₆-C₂₄ alcohol ethoxylates (for example C₆-C₁₄ alcohol ethoxylates) having 1 to about 20 ethylene oxide groups (for example about 9 to about 20 ethylene oxide groups); C₆-C₂₄ alkylphenol ethoxylates (for example C₈-C₁₀ alkylphenol ethoxylates) having 1 to about 100 ethylene oxide groups (for example about 12 to about 20 ethylene oxide groups); C₆-C₂₄
 35 alkylpolyglycosides (for example C₆-C₂₀ alkylpolyglycosides) having 1 to about 20 glycoside groups (for example about 9 to about 20 glycoside groups); C₆-C₂₄ fatty acid

5 ester ethoxylates, propoxylates or glycerides; C₄-C₂₄ mono or di alkanolamides; and mixtures thereof. For example, the nonionic surfactant may be polyoxyethyleneglycol dodecyl ether, N-decanoyl-N-methylglucamine, digitonin, n-dodecyl B-D-maltoside, octyl B-D-glucopyranoside, octylphenol ethoxylate, polyoxyethylene (8) isooctyl phenyl ether, polyoxyethylene sorbitan monolaurate or polyoxyethylene (20) sorbitan monooleate.

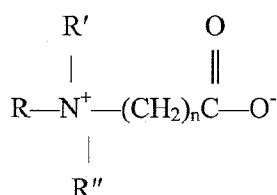
10 [0037] Exemplary zwitterionic surfactants include but are not limited to aminoalkylsulfonate compounds having the formula:



where R, R', R'' and R''' are each a C₁-C₂₄ alkyl, aryl or aralkyl group that can optionally contain one or more P, O, S or N heteroatoms; amine oxide compounds having the formula:



25 where R, R' and R'' are each a C₁-C₂₄ alkyl, aryl or aralkyl group that can optionally contain one or more P, O, S or N heteroatoms; and betaine compounds having the formula:



30 where R, R' and R'' are each a C₁-C₂₄ alkyl, aryl or aralkyl group that can optionally contain one or more P, O, S or N heteroatoms, and n is about 1 to about 10. For example, the zwitterionic surfactant may be 3-[(3-cholamidopropyl) dimethylammonio]-2-hydroxy-1-propane sulfonate, 3-[(3-cholamidopropyl) dimethylammonio]-1-propane sulfonate (sometimes referred to as CHAPS), 3-(decyldimethylammonio) propanesulfonate inner salt (sometimes referred to as caprylyl sulfobetaine), or N-dodecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate.

5 [0038] Preferred surfactants include alkyl sulfates, alkyl sulfonates, aryl sulfonates and zwitterionic surfactants. The desired surfactants may be obtained as pure compounds or in some instances may be obtained by using products such as liquid Castile soap. The surfactant may for example be present at a concentration of at least about 0.002 M, at least about 0.005 M or at least about 0.01 M, e.g., about 0.002 to about 1 M, about 0.005 to
10 about 0.7 M or about 0.01 to about 0.5 M. Expressed on a weight basis, the surfactant preferably is greater than 0.2 wt. % of the solvating system and may for example be about 0.3% to about 30%, about 0.5% to about 25% or about 1% to about 20% of the solvating system. Increased surfactant amounts may promote faster biofilm breakup.

[0039] The solvating system also includes a buffering agent. The buffering agent
15 preferably maintains the solvating system at an appropriate pH for contacting the wound, e.g., at a pH greater than about 4 or greater than about 5. For example, the solvating system may be buffered to have a near-neutral pH, e.g., a pH greater than about 5 and less than about 8.5. Buffering agents may for example be up to about 50% of the solvating system. Exemplary buffering agents include but are not limited to potassium chloride,
20 glycine, potassium hydrogen phthalate, sodium acetate, potassium hydrogen phthalate, barbitone sodium and sodium citrate. When the metal ion sequestering agent is a mild acid, the buffering agent desirably is a salt of that acid.

[0040] The solvating system also includes water. The water may be distilled, deionized or sterile water. Water may for example be at least 50%, at least 60% or at least
25 75% of the solvating system.

[0041] The solvating system may optionally include various other ingredients, including nonaqueous solvents (e.g., alcohols), antimicrobial agents, therapeutic agents and a variety of adjuvants. Solvating systems which do not contain antimicrobial agents may be preferred for some applications, for example where there may be a risk that an
30 antimicrobial agent might promote the evolution of more resistant bacteria. Solvating systems containing one or more antimicrobial agents, and especially one or more topical antibiotic agents (*viz.*, antibiotics which may be applied to the skin and which in connection with the disclosed method are applied in a chronic wound), may be preferred for other applications. The EPS matrix may allow a biofilm to stick to an underlying
35 tissue surface while protecting the embedded organisms. The bacteria in such a biofilm

5 may be approximately 100 to 1000 times more resistant to the effects of antibiotics than planktonic bacteria. After the biofilm has been broken down into unbound polymers or fragments and solvated or otherwise disrupted by the solvating system, an antimicrobial agent can much more effectively attack the remaining bacteria. Exemplary antimicrobial agents include active oxygen compounds such as hydrogen peroxide, isolated or
10 equilibrium derived or isolated peracids such as chloroperbenzoic acids, peracetic acid, perheptanoic acid, peroctanoic acid, perdecanoic acid, performic acid, percitric acid, perglycolic acid, perlactic acid, perbenzoic acid, and monoester peracids derived from diacids or diesters such as adipic, succinic, glutaric, or malonic acid; amphenicols; ampicillins; ansamycins; beta-lactams such as carbacephems, carbapenems,
15 cephalosporins, cephamycins, monobactams, oxacephems, penicillins and any of their derivatives; carboxylic esters such as p-hydroxy alkyl benzoates and alkyl cinnamates; chitosan salts; cubic-phase lipids; gallium-containing antimicrobial agents such as gallium acetylacetonate, gallium bromide, gallium chloride, gallium fluoride, gallium iodide, gallium maltolate, gallium nitrate, gallium nitride, gallium percolate, gallium phosphide
20 and gallium sulfate; iodo-compounds and other active halogen compounds such as iodine, interhalides, polyhalides, metal hypochlorites, hypochlorous acid, metal hypobromites, hypobromous acid, chloro- and bromo-hydantoins, chlorine dioxide and sodium chlorite; lincosamides; macrolides; nitrofurans; organic peroxides including benzoyl peroxide and alkyl benzoyl peroxides; ozone; phenolic derivatives including o-phenyl phenol, o-benzyl-
25 p-chlorophenol, tert-amyl phenol and C₁-C₆ alkyl hydroxy benzoates; quaternary ammonium compounds such as alkyldimethylbenzyl ammonium chloride and dialkyldimethyl ammonium chloride; quinolines; singlet oxygen generators; sulfonamides; sulfones; sulfonic acids such as dodecylbenzene sulfonic acid; tetracyclines; vancomycin; derivatives thereof and mixtures thereof. Many of these recited agents represent classes
30 containing useful specific materials whose individual utility will be recognized by persons having ordinary skill in the art. For example, exemplary penicillins include but are not limited to amdinocillin, amdinocillin pivoxil, amoxicillin ampicillin, apalcillin, aspoxicillin, axidocillin, azlocillin, acampicillin, bacampicillin, benzylpenicillinic acid, benzylpenicillin sodium, carbenicillin, carindacillin, clometocillin, cloxacillin, cyclacillin,
35 dicloxacillin, epicillin, fenbenicillin, floxacillin, hetacillin, lenampicillin, metampicillin,

5 methicillin sodium, mezlocillin, nafcillin sodium, oxacillin, penamecillin, penethamate
hydriodide, penicillin G benethamine, penicillin G benzathine, penicillin G
benzhydrylamine, penicillin G calcium, penicillin G hydrabamine, penicillin G potassium,
penicillin G. procaine, penicillin N, penicillin O, penicillin V, penicillin V banzathine,
penicillin V hydrabamine, penimepicycline, phenethicillin potassium, piperacillin,
10 pivampicillin propicillin, quinacillin, sulbenicillin, sultamicillin, talampicillin, temocillin,
ticarcillin and mixtures thereof or with other materials (e.g., penicillins combined with
clavulanic aid such as the combination of amoxicillin and clavulanic acid available as
Augmentin™ from GlaxoSmithKline).

[0042] Preferably the antimicrobial agent provides greater than a 99% numeric
15 reduction (*viz.*, at least a 2-log order reduction), greater than a 99.9% numeric reduction
(*viz.*, at least a 3-log order reduction), greater than a 99.99% numeric reduction (*viz.*, at
least a 4-log order reduction) or greater than a 99.999% numeric reduction (*viz.*, at least a
5-log order reduction) in a population of one or more aerobic or anaerobic bacteria present
in chronic wounds.

20 [0043] Exemplary therapeutic agents include any material suitable for use in wound
treatment including analgesics, anti-cholinergics, anti-fungal agents, steroidal or non-
steroidal anti-inflammatory agents, anti-parasitic agents, antiviral agents, biostatic
compositions, chemotherapeutic/antineoplastic agents, cytokines, immunosuppressors,
nucleic acids, peptides, proteins, steroids, vasoconstrictors, vitamins, mixtures thereof, and
25 other therapeutic materials. Bacterially selective peptides may, for example, provide a
more useful or safer therapeutic effect against some pathogens than that provided by broad
spectrum antibiotics.

[0044] Adjuvants which may be included in the solvating system include dyes,
pigments or other colorants (e.g., FD & C Red No. 3, FD & C Red No. 20, FD & C
30 Yellow No. 6, FD & C Blue No.2, D & C Green No. 5, D & C Orange No. 4, D & C Red
No. 8, caramel, titanium dioxide, fruit or vegetable colorants such as beet powder or beta-
carotene, turmeric, paprika and other materials that will be familiar to those skilled in the
art); indicators; antioxidants; antifoam agents; and rheology modifiers including thickeners
and thixotropes.

- 5 **[0045]** The wound may be debrided to detach devitalized tissue using manual debriding tools such as those described above. Preferably the wound is debrided using a directed stream of the disclosed solvating system or other suitable fluid. The flow rate or pressure desirably are high enough to promote rapid and sufficiently complete debriding, and low enough to avoid undue pain or injury to healthy or healable wound tissue. At least part and preferably all of the devitalized wound tissue is debrided.
- 10 **[0046]** The solvating system desirably is applied to at least an extent sufficient to cover healthy or healable tissue in the wound. In some instances it will be desirable to apply the solvating system within and not merely atop exposed tissue within the wound. Sufficient solvating system should be applied to the wound and to a targeted biofilm contained therein so that the biofilm and its organisms are wholly or partially disrupted, solvated or removed, either during treatment or at some subsequent time. Doing so may involve chemical dilution or mechanical disruption, and may be accompanied by breakdown of the biofilm EPS matrix through calcium ion sequestering by the metal ion sequestering agent, and by solvation of the resulting breakdown fragments (e.g.,
- 15 mannuronic and guluronic acids) into aqueous solution so as to facilitate their removal using aspiration, lavage or other removal techniques. High flow rates (for example, more than 7 and less than 20 cm³/sec) or high delivery pressures (for example, about 30 to about 500 KPa or about 60 to about 350 KPa, as measured at the pump outlet when the desired application tip is attached) may assist in wound debridement and biofilm disruption. It may be desirable to apply sufficient solvating system into the wound to displace any pus or other wound exudates which may be present, allowing excess solvating system to overflow from the wound until the color of the excess solvating system no longer changes. The solvating system may be left in place until it can drain away or is otherwise eliminated or resorbed, or the solvating system may be allowed to stand for a suitable time
- 20 (e.g., a few minutes, a few hours or longer) and then may be rinsed away using sterile saline or another suitable liquid. Application of the solvating system and removal of dislodged or disrupted biofilm and bacteria may also be repeated as desired for more thorough removal of the offending organisms.
- 25 **[0047]** The solvating system may desirably be used as a part of a multi-step treatment regimen which disrupts the bacterial biofilm and discourages its return. For example, a
- 30

5 series of steps that may be broadly classified as Cleansing/Disrupting, Killing, Protecting/Coating, Aerating, and Healing may be carried out. The Cleansing/Disrupting step may be carried out by applying the solvating system to a chronic wound as described above. The Killing step may be carried out by applying a suitable antimicrobial agent to the wound site. This may for example be accomplished by including an antimicrobial
10 agent in the solvating system or by separately applying such an agent intra operatively or post operatively (e.g., topically, orally or systemically). The Killing step may employ additional measures to discourage bacterial survival, regrowth or recolonization in the wound, e.g., as discussed above in connection with the **Fig. 2** apparatus. The Protecting/Coating step may be carried out by coating at least part of the treated wound
15 with a protective sealant layer. The sealant may provide a variety of benefits such as discouraging or preventing recolonization of the wound with bacteria and new biofilm-forming colonies; reducing inflammation; improving wound healing or allowing for the recovery of the body's natural innate immune response. The sealant may include one or more antimicrobial agents to further attack any bacterial biofilm, biofilm fragments or
20 bacteria remaining following the Cleansing/Disrupting step described above, and to discourage its or their return. A preferred sealant may be based on the sealant disclosed in U.S. Patent Publication No. US 2007/0264310 A1, filed April 24, 2007. The Aerating step may be carried out by applying a wound dressing with a suitable opening or openings (e.g., slits or pores) and leaving it or them open for a period of time sufficient to allow
25 aeration of the treated wound. The Healing step may be carried out by allowing the cleansed, protected and optionally sealed wound to undergo a return to a normal state, e.g., through one or more normal healing mechanisms such as an inflammatory response, fibroblast proliferation and wound remodeling.

[0048] The invention is further described in the following Example, in which all parts
30 and percentages are by weight unless otherwise indicated.

Example

[0049] **Biofilm formation.** *Pseudomonas aeruginosa* PAO1 (ATCC number: BAA-47), *Enterococcus faecalis* V583 (ATCC number: 700802), and *Staphylococcus aureus*
35 Mu50 (ATCC number: 700699) grown on agar plates made from tryptic soy broth (TSB,

5 Sigma Chemical Co., St. Louis, MO, USA) were inoculated into TSB broth and grown at 37 °C in a shaker for 16 hr. An aliquot was diluted in TSB broth to a series of dilutions for each individual bacteria type. The diluted bacteria were plated out to count colony forming units (CFU). They were further diluted to 1×10^6 cfu ml⁻¹ and mixed equally as inoculums. Bolton broth (Oxoid Ltd, Basingstock, Hampshire, England) with 50% Bovine
 10 plasma (Biomeda, Foster City, CA, USA) was used for biofilm formation media. Glass 16×150 mm test tubes with caps were autoclaved, and 7 ml biofilm formation media aseptically dispensed in each tube. The normalized cultures of the three bacteria were mixed and 10 µl portions of the combined and normalized 1×10^6 CFU ml⁻¹ culture were inoculated into glass tubes by ejecting the pipette tips into the tubes. The pipette tip acts
 15 as a surface for biofilm formation. The tubes were then grown at 37° C in a shaker for 24 hours at 140 rpm.

[0050] **Solvating system preparation.** A solvating system (referred to below as “CAZS”) was prepared at four osmolarity levels by combining deionized water, caprylyl sulfobetaine zwitterionic surfactant ($\text{CH}_3(\text{CH}_2)_9\text{N}^+(\text{CH}_3)_2\text{CH}_2\text{CH}_2\text{CH}_2\text{SO}_3^-$, CAS 15163-
 20 36-7), citric acid (CAS 77-92-9) and sufficient sodium citrate (CAS 6132-04-3) to buffer the system to pH 5.5, using the amounts shown below in Table 1:

Table 1

Ingredient	Osmolarity, mOsm		
	830	1,586	3,628
Caprylyl Sulfobetaine (g/L)	5.08	5.15	5.35
Citric Acid (g/L)	5.78	12.5	25
Sodium Citrate (g/L)	55.13	120.5	240.5
pH	5.5	5.5	5.5

[0051] **Incubation with formed biofilms.** In a series of runs the formed biofilms
 25 were washed and then incubated with the three CAZS solutions, then associated with a 30 µg/ml solution of Gentamicin sulfate (MP Biomedicals, Illkirch, France) in distilled water, or with a 20 ppm solution of 2,4,4'-trichloro-2-hydroxydiphenyl ether (Triclosan, KIC Chemicals, New Paltz, NY, USA) dissolved in propylene glycol (ScienceLab, Houston, TX, USA). The resulting mixtures were stirred at 37° C and 140 rpm for 1, 2, 3 and 4
 30 hours. Biofilm formation was subjectively observed and the biofilms were collected. A set

5 of tubes with biofilms were placed in an oven at 80° C for 48 hours to obtain a dry weight. The biomass dry weight was measured as the total weight minus the empty tube weight measured before use. Tests were performed in triplicate for each treatment group. A separate set of tubes in triplicate was used for DNA extraction and quantitative PCR analysis to determine relative bacterial levels in the treated biofilms. The results for the
 10 830 and 1,586 mOsm CAZS solutions are shown below in Table 2:

Table 2

Sample	Dry Weight, mg	Relative Bacterial Levels		
		<i>P. aeruginosa</i>	<i>E. faecalis</i>	<i>S. aureus</i>
Control	126	46.8	29.7	23.5
20 mg/ml Gentamicin	78	0.2	50.3	49.6
20 mg/ml Gentamicin + 200 µl 830 mOsm CAZS	68.5	0.2	49.7	50.1
20 mg/ml Gentamicin + 200 µl 1,586 mOsm CAZS	68	0.1	62.2	37.8
20 ppm Triclosan	88	60.0	39.9	0.13
20 ppm Triclosan + 200 µl 830 mOsm CAZS	28.5	53.0	47.0	0.1
20 ppm Triclosan + 200 µl 1,586 mOsm CAZS	15	69.1	30.9	0.1
200 µl 830 mOsm CAZS	115.5	45.0	32.7	22.4
200 µl 1,586 mOsm CAZS	87	51.1	35.1	13.8

[0052] The results in Table 2 show that the biofilm dry weight was reduced using all
 15 treatments. Biofilm dry weight was also reduced using the CAZS solution alone, and

5 further reduced when used in combination with Triclosan. CAZS solution also appeared to exhibit a selective inhibitory effect on *S. aureus*.

[0053] Although specific embodiments have been illustrated and described herein for purposes of description of the preferred embodiments, it will be appreciated by those of
10 ordinary skill in the art that a wide variety of alternate or equivalent implementations calculated to achieve the same purposes may be substituted for the specific embodiments shown and described without departing from the scope of the present invention. This application is intended to cover any adaptations or variations of the preferred embodiments discussed herein. Therefore, it is manifestly intended that this invention be
15 limited only by the claims and the equivalents thereof.

We claim:

1. A method for treating chronic wounds, which method comprises:
debriding at least some necrotic or other devitalized tissue from the wound; and
5 applying to healthy or healable tissue in the wound an extracellular polymeric substance solvating system comprising an aqueous solution of a metal ion sequestering agent, surfactant and buffering agent wherein the solvating system has an osmolarity greater than 900 milliosmoles of solute per litre.
- 10 2. An apparatus when used for treating a chronic wound, comprising a debriding device;
a reservoir containing an extracellular polymeric substance solvating system comprising an aqueous solution of a metal ion sequestering agent, surfactant and buffering agent wherein the solvating system has an osmolarity greater than
15 900 milliosmoles of solute per litre, in fluid communication with an applicator for applying the solvating system to a wound; and
an aspirating device which removes at least some debrided necrotic or other devitalized tissue and excess solvating system from the wound.
- 20 3. A patient care kit when used in a method for treating chronic wounds, which method includes at least the step of debriding at least some necrotic or other devitalized tissue from a wound, and wherein the kit comprises a tray; syringe; vessel containing an extracellular polymeric substance solvating system comprising an aqueous solution of a metal ion sequestering agent, surfactant
25 and buffering agent wherein the solvating system has an osmolarity greater than 900 milliosmoles of solute per litre; and printed instructions describing the proper use of the kit for treating chronic wounds.
- 30 4. A product comprising an extracellular polymeric substance solvating system when used for treating a chronic skin wound said treatment including debridement of at least some necrotic or other devitalized tissue from the

- wound, the solvating system comprising an aqueous solution of at least about 0.01 of metal ion sequestering agent, at least about 0.002 M of surfactant, and buffering agent that maintains the solvating system at an appropriate pH for contacting chronic skin wounds, wherein the solvating system has an osmolarity of greater than 900 milliosmoles of solute per litre, a sufficiently low viscosity to enable delivery to the wound using spray application, and aids in chronic wound biofilm detachment, removal or disruption.
- 5
5. A method according to claim 1, apparatus according to claim 2, kit according to claim 3 or product according to claim 4 wherein the metal ion sequestering agent comprises a mild acid having an acidity which is sufficient to sequester one or more metal ions in a bacterial biofilm but which is not so acidic so as to harm healthy or healable tissue in the wound.
- 10
6. A method according to claim 1, apparatus according to claim 2, kit according to claim 3 or product according to claim 4 wherein the metal ion sequestering agent comprises a sequestering agent for sodium, calcium or iron.
- 15
7. A method according to claim 1, apparatus according to claim 2, kit according to claim 3 or product according to claim 4 wherein the metal ion sequestering agent comprises a carboxylic acid, diacid, triacid or mixture thereof.
- 20
8. A method according to claim 1, apparatus according to claim 2, kit according to claim 3 or product according to claim 4 wherein the metal ion sequestering agent comprises citric acid.
- 25
9. A method according claim 1, apparatus according to claim 2, kit according to claim 3 or product according to claim 4 wherein the metal ion sequestering agent is present at a concentration of about 0.01 to about 1.5 M, the surfactant is about 0.3% to about 30% of the solvating system, and the solvating system comprises sufficient buffering agent so that the solvating system has a pH
- 30

greater than about 4.

10. A method according to claim 1, apparatus according to claim 2, kit according to claim 3 or product according to claim 4 wherein the solvating system further comprises an antimicrobial agent.
11. A method, apparatus, kit or product according to claim 10 wherein the antimicrobial agent comprises a peptide.
12. A method, apparatus, kit or product according to claim 10 wherein the antimicrobial agent comprises gallium acetoacetate, gallium bromide, gallium chloride, gallium fluoride, gallium iodide, gallium maltolate, gallium nitrate, gallium nitride, gallium percolate, gallium phosphide, gallium sulphate or mixture thereof.
13. A method according to any one of claims 1 and 5 to 12 comprising treating a foot or leg wound in a diabetic patient.
14. A method according to any one of claims 1 and 5 to 12 comprising treating the wound to disrupt a bacterial biofilm and discourage its return.
15. A method according to claim 1, apparatus according to claim 2, kit according to claim 3 or product according to claim 4, wherein the solvating system has an osmolarity of about 1,000 to about 4,000 mOsm.
16. A method, apparatus, kit or product according to claim 15 wherein the solvating system has an osmolarity of about 1,500 to about 2,600 mOsm.
17. A method or apparatus according to any one of claims 1, 2 and 5 to 16 wherein the solvating system applicator also serves as a debriding device by applying the solvating system at a sufficient flow rate or under sufficient pressure to

debride at least some devitalized tissue from the wound.

5

18. A method or apparatus according to claim 17 wherein the applicator applies the solvating system at a flow rate more than 7 and less than 20 cm³/sec.
19. A method or apparatus according to claim 17 wherein the applicator applies the solvating system at a delivery pressure of about 30 to about 500 kPa.

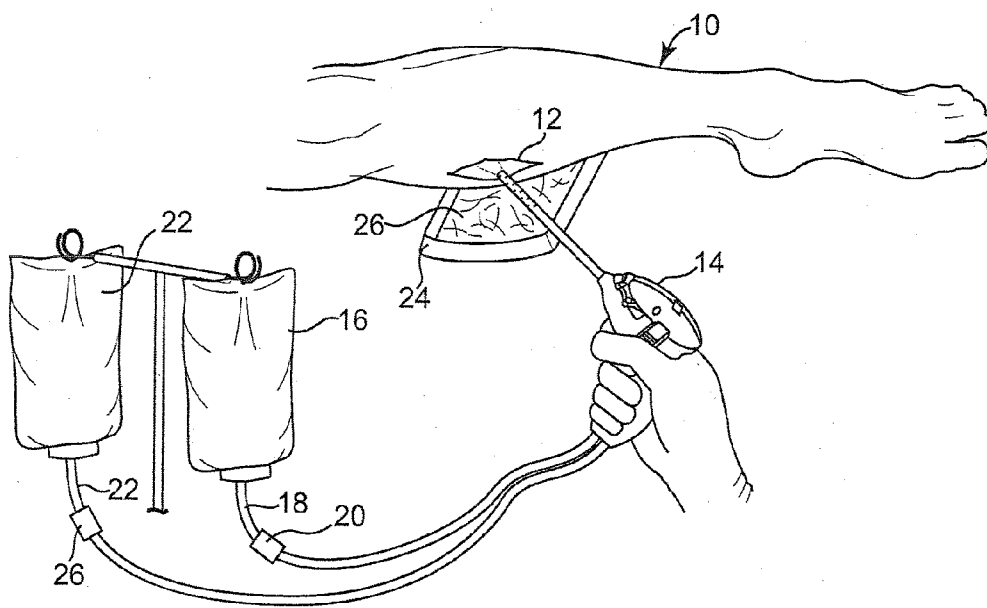


Fig. 1

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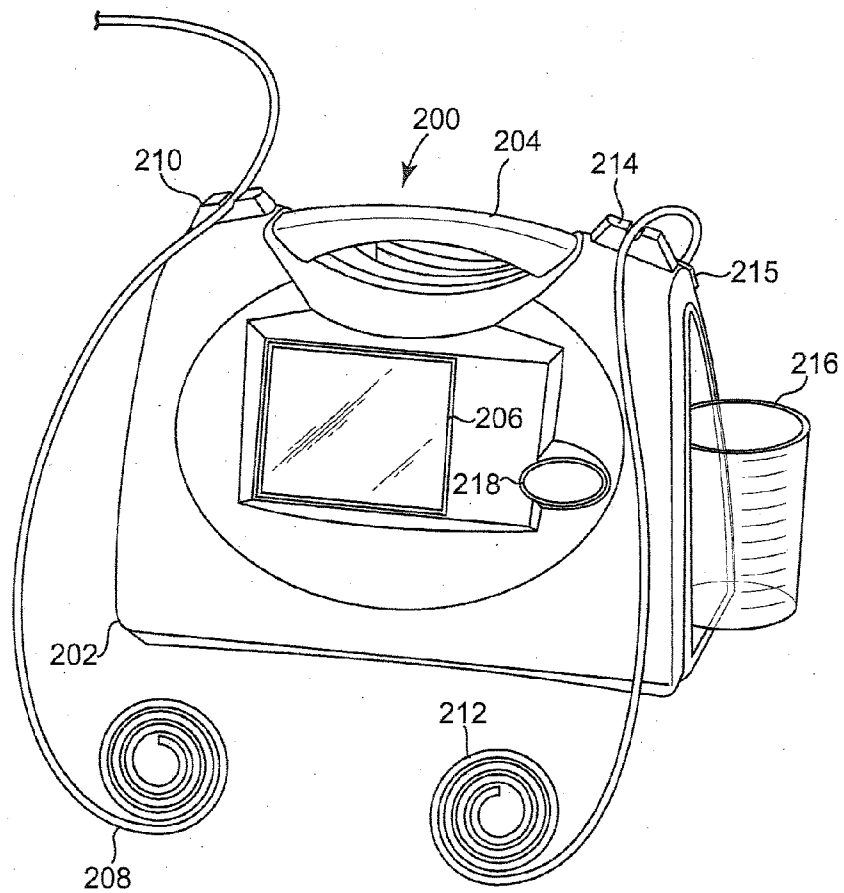


Fig. 2

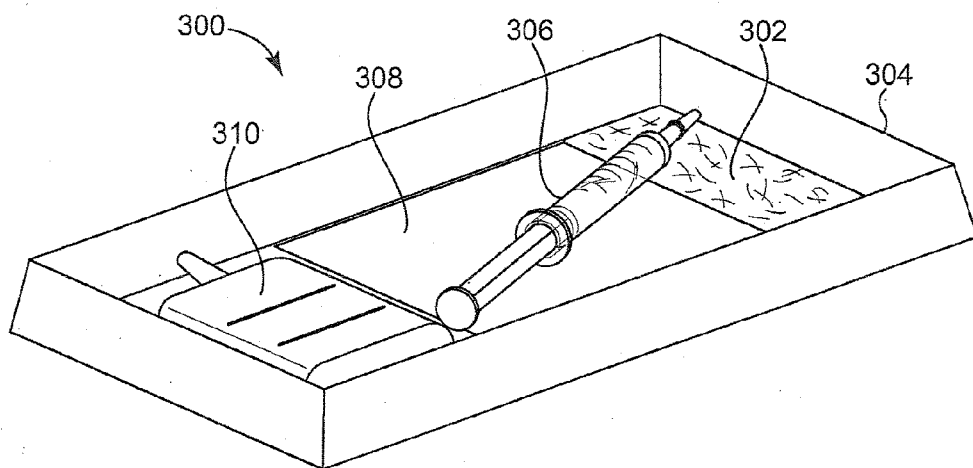


Fig. 3