

SILICONE GEL-BASED COMPOSITIONS FOR WOUND HEALING AND SCAR REDUCTION

Technical Field

5 The present invention relates to compositions containing various silicone compounds, which are suitable for promoting the healing of skin wounds and for the prevention of scarring.

Background of the Invention

10 Significant skin wounds, such as are caused by injury or surgery, frequently lead to scarring. Scarring in many instances results in a diminished sense of touch, loss of flexibility and loss of range of motion (where scars run across joints). Scarring also results in obvious cosmetic problems, particularly when on the face and hands. Skin wounds are also prone to infection, and even with conventional dressings, infections are fairly common. Burn victims
15 are particularly susceptible to infections, and can be left with severe scarring when the wounds heal. There is a need for methods of treatment of skin injuries that minimize or eliminate scar formation.

 Conventional wound dressings, such as are made from cotton gauze and various polymers, leave much to be desired, especially when a large area of skin must be dressed.
20 The ability of the dressing to remain in place and protect the wound becomes progressively more compromised as the area of the wound increases, while at the same time the removal the dressing without injury to the underlying tissue becomes progressively more difficult. Wound dressings must stretch and flex to accommodate the movement of muscles and joints; this too gets more difficult as the dressing gets larger. In the case of facial dressings, it is
25 desirable to minimize the visual impact of the dressing, and this of course rapidly becomes impossible as the size of the wound increases. Finally, conventional wound dressings require frequent changing, which is particularly costly in a hospital setting where the time value of professional staff, and the costs of disposing of medical waste, are significant. There is a need for improved wound dressings that do not have these disadvantages.

To address these needs, a number of products have been developed and marketed (Reviews: L. Borgognoni, *Wound Repair and Regeneration* (2002), **10**:118-121; D. Leventhal et al., *Arch Facial Plast Surg* (2006), **8**:362-368). Among the more successful are silicone gel sheets ("SGS") and silicone gel ointments, and combinations thereof. The use of these silicone-based polymers and gels has been proven to reduce the appearance of scars when used consistently for sufficiently extended periods of time. (Chan, KY, et al., *Plast Reconstr Surg.* (2005), **116**:1013-1020; Signorini M, Clementonil MT., *Aesthetic Plast Surg.* (2007), **31**:183-187; Chernoff WG, et al., *Aesthetic Plast Surg.* (2007) **31**:495-500; Fonseca Capdevila E, et al., *Piel* (2007) (in press); Sepehrmanesh M., *Kompendium Dermatologie* (2006), **1**:30-32; Murison M, James W., *J Plast Reconstr Aesthet Surg.* (2006), **59**:437-439.)

It is impractical to use sheeting on large areas and near joints, and it cannot be used easily on the face and other areas where the contours or motility of the skin make it difficult to ensure adequate contact and coverage. Taping is often needed to secure the sheeting to the skin. Also, patients may be reluctant to use the sheeting on unclothed areas during the day, making compliance with treatment a concern. Finally, the sheets must be washed frequently to prevent complications such as rashes and infection.

Although the mechanism by which silicone sheets and polymers reduce the appearance of scars is not presently known, it has been hypothesized that the silicone provides a barrier function that somehow promotes the healing process. This may involve increased hydration, pH control, increased temperature, and control of oxygen tension. The presence of unspecified silicone compounds in the healing skin have been proposed to somehow limit scar formation. Commercial products formed from silicone-based polymers and specifically targeting wound healing and the treatment of existing scars are presently available. Specific examples of such commercial products include Neosporin Scar Solutions™ sheets, Cica-Care™ sheets, Mepiform™ scar dressings, and Dermatrix™ silicone gel.

Silicone polymer gel compositions for wound treatment have been described (see for example US Patent No. 5,741,509). Although the silicone-based polymers are effective in reducing the appearance of scars, the known compositions must be applied to the scars for long periods of time in order to achieve noticeable results. In particular, the silicone-based

polymer gels are typically worn on the scars for about 18 hours per day, every day, for several months. Significant discomfort may result from the long periods during which the silicone-based polymers must be worn on the scar. Also, the typical gel is a viscous material that leaves a relatively thick layer on the skin, which is at best imperfectly camouflaged with makeup. Although the layer of silicone can be rendered nearly invisible with suitably sophisticated cosmetic materials and methods, few patients have the time and resources to use these methods or to employ a professional cosmetologist. The resulting impairment of physical appearance can discourage patient compliance with the rigorous and unusually lengthy treatment protocol. There is a need for an effective silicone polymer composition that is more comfortable, less visible, and more easily rendered inconspicuous by ordinary cosmetics.

Brief description of the invention

The invention provides a topically-applied silicone fluid that dries to a thin film on the skin. The compositions of the invention reduce the formation of overgrown scars (hypertrophic scars and keloids) after surgical incisions or accidental wounds, and reduce the size and improve the appearance of established overgrown scars. The compositions of the invention contain a cyclic siloxane as a base fluid with excellent spreading properties that is compatible with a wide range of other cosmetic ingredients. The compositions of the invention are relatively non-viscous, and are easily spread out into thin, uniform coating. The presence of a cyclic siloxane also imparts a soft silky feel to the skin, and the compositions of the invention are non-greasy and leave no oily residue or buildup.

Brief description of the figures

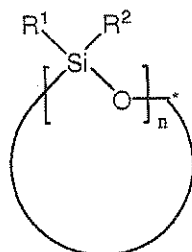
Figure 1: Before (A) and after (B) photographs of a patient treated with a silicone gel composition of the present invention.

Detailed description of the invention

The compositions of the invention comprise a cyclic siloxane, a silicone occlusive fluid, a silicone occlusive gel, and a silicone resin powder. In preferred embodiments, the compositions further comprise an ascorbic acid fatty acid ester or salt thereof.

- 5 The functions of the components are thought to be as follows, but it should be understood that the invention is in no way limited in scope to these particular mechanisms of action: The cyclic siloxane provides fluidity and a smooth and pleasant texture, enabling the convenient application of a thin film over as wide an area as necessary. It may also serve as an emollient. The cyclic siloxane is volatile, and evaporates after application to leave the
- 10 remaining components in the form of a thin occlusive film on the skin. The occlusive fluid and gel components are non-volatile hydrophobic materials that provide a flexible, biocompatible moisture barrier that is adhesive to the skin, emollient, non-irritating and non-toxic. The silicone resin powder is a film-forming agent which confers suitable rheological and tactile properties to the composition, ensuring that the barrier produced upon evaporation
- 15 of the cyclic siloxane has a relatively dry, smooth feel. The three non-volatile silicone components work together to generate a thin film protective barrier that is especially useful in areas of the body that are difficult to cover due to mobility/stretching of the skin, for example, around joints and on the face, as well as parts of the body with irregular shape. The resultant film that forms after evaporation of the cyclic siloxane is flexible, waterproof, yet
- 20 gas permeable. The ascorbate ester is absorbed by the endothelial cells and cleaved *in vivo* to ascorbate, which provides an anti-oxidant function and is believed to promote normal collagen synthesis.

The cyclic siloxanes are of the formula



where $n = 4-6$, and R^1 and R^2 are, in each incidence, independently H or C_1-C_3 alkyl.

Suitable cyclic siloxanes include, but are not limited to, permethylated cyclic siloxanes, which are preferably selected from among the commercially-available materials cyclotetrasiloxane (octamethylcyclotetrasiloxane), cyclopentasiloxane

- 5 (decamethylcyclopentasiloxane), and cyclohexasiloxane (dodecamethylcyclohexasiloxane), and mixtures thereof. In the most preferred embodiments, the cyclic siloxane is cyclopentasiloxane.

The cyclic siloxane constitutes between about 30-80% by weight of the compositions of the invention, preferably between about 45-65%, more preferably between about 55-65%.

- 10 The silicone occlusive fluid is a polyalkylsiloxane having a viscosity between about 50 cSt and 500 cSt, preferably between about 100 to 350 cSt. Suitable polyalkylsiloxanes include, but are not limited to, poly(dimethylsiloxane), poly(methylethylsiloxane), poly(methylphenylsiloxane), and mixtures thereof. Particularly preferred is polydimethylsiloxane having a viscosity of about 200 cSt. The silicone occlusive fluid
- 15 constitutes between about 1-15% by weight of the compositions of the invention, preferably between about 2-10%, and more preferably between about 3-7%.

The silicone occlusive gel is a dispersion of a silicone elastomer in a silicone oil. Particularly suitable elastomers are crosslinked silicone polymers having an average molecular weight in excess of 100,000 (e.g., between about 100,000 and 10,000,000).

- 20 Suitable examples include, but are not limited to, crosslinked siloxanes (e.g., crosslinked dimethicone or dimethicone derivatives), copolymers such as stearyl methyl-dimethyl siloxane copolymer, polysilicone-11 (a crosslinked silicone rubber formed by the reaction of vinyl terminated silicone and (methylhydro dimethyl)polysiloxane in the presence of cyclomethicone), cetearyl dimethicone/vinyl dimethicone crosspolymer (a copolymer of
- 25 cetearyl dimethicone crosslinked with vinyl dimethyl polysiloxane), dimethicone/phenyl vinyl dimethicone crosspolymer (a copolymer of dimethylpolysiloxane crosslinked with phenyl vinyl dimethylsiloxane), and dimethicone/vinyl dimethicone crosspolymer (a copolymer of dimethylpolysiloxane crosslinked with vinyl dimethylsiloxane). Preferred compositions of the invention comprise polysilicone-11.

The silicone oil dispersant may be any silicone liquid capable of dispersing the elastomer. Preferably it is a non-volatile silicone fluid. Suitable examples include, but are not limited to, dimethicone, phenyl trimethicone, phenyl dimethicone, dimethicone copolyol, and alkyl dimethicone copolyol. Preferably, the occlusive gel is a dispersion of polysilicone-
 5 11 in phenyltrimethicone. The occlusive gel comprises between about 10-60% by weight of the compositions of the invention, preferably between about 20-50%, and more preferably between about 30-40%. The silicone elastomer, in conjunction with the silicone occlusive fluid, provide favorable elasticity to the final film formed on the scar. This is especially beneficial at joints and on the face where the skin is particularly mobile.

10 The silicone resin powder may be one of the many film-forming silicone resins known in the cosmetic arts. Silsesquioxanes, approximately represented by the average formula $(R_3SiO_{3/2})_x$, are particularly suitable. Silsesquioxanes, typically prepared by partial hydrolysis of alkoxy- and halo-alkylsilane precursors, are structurally ill-defined, insoluble cross-linked materials, comprised of a combination of R_3SiO- , $-OSiR_2O-$, and $RSi(O-)_3$
 15 monomer units. The R groups are generally methyl groups, but may be replaced in part by lower alkyl, vinyl, and phenyl groups in order to modify the physical properties of the polymer. Polymethylsilsesquioxanes ($R = CH_3$) having a particle size of 4-8 μm are preferred for use in the present invention. The silicone resin powder comprises between about 1-10% by weight of the compositions of the invention, preferably between about 1-5%, and more
 20 preferably between about 2-3%. In addition to the rheological and tactile properties imparted by the addition of the silicone resin powder, the silsesquioxanes are capable of dispersing additional materials in cosmetic compositions, such as pigments.

Ascorbic acid fatty acid esters are ascorbic acid acylated with single or multiple fatty acid groups, wherein the fatty acids typically have 8 to 24 carbon atoms, and their salts. A
 25 variety of tetra(C_8 - C_{24} acyl)ascorbic acids, and salts thereof, are commercially available. The more oxidation-resistant saturated fatty acid esters of ascorbic acid are preferred, including, but not limited to, ascorbyl laurate, ascorbyl myristate, ascorbyl palmitate, ascorbyl isopalmitate, ascorbyl stearate, and ascorbyl behenate, and their salts, e.g., magnesium ascorbyl stearate. Ascorbic acid tetraisopalmitate is particularly preferred. The esters may be
 30 prepared using hydrogenated natural oils or fats, or fractions thereof, and accordingly may contain small amounts of various mixed esters in addition to that corresponding to the

nominal identity of the material. Ascorbyl stearate prepared from canola oil, for example, commonly contains about 4% palmitate residues. The ascorbate ester is an optional component, but is preferably present in the compositions of the invention. The amount of ascorbate ester can be between about 0.1 and 2% by weight of the composition, in some
5 embodiments between about 0.2 and 1%, and in still other embodiments, between about 0.3 and 0.7%. As an optional ingredient, the ascorbate ester can also be present in any amount between about 0 and 0.1 % by weight, in addition to up to about 2% by weight. Therefore, the ascorbic acid ester or salt thereof can present in between about 0.01 and 2% by weight, for example. One skilled in the art will recognize the beneficial antioxidant effects of vitamin
10 C, especially as it relates to wound healing. See for example, Lund, C.C.; Crandon, J.H. "Ascorbic Acid and Human Wound Healing," *Annals of Surgery*, 1941, 776-790.

Examples

1. Preparation of exemplary composition (Example 1):

15 A mixture of cyclopentasiloxane (585 g), phenyltrimethicone dispersion of polysilicone-11 (Gransil™ PM-Gel) (350 g) and polydimethylsiloxane 200cSt (40g) is stirred and heated slowly to 50°C. While the heating is in progress, polymethylsilsequioxane powder, 4-8 µm (Tospearl™ 2000B) (25 g) is added, followed by ascorbyl tetraisopalmitate (0.5 g). The mixture is stirred at 50°C until homogenous, then cooled to room temperature.

20

2. In vivo testing (rabbit ear model):

Using a dermal biopsy punch and a dissecting microscope, 7-mm wounds were made on the ventral surface of each ear of four 3-kg New Zealand White rabbits (6 wounds on each ear). The wounds involved complete removal of the epithelium, dermis, and perichondrium.

25 The wounds were covered with a polyurethane film until healing was complete (17 days).

The wounds on one ear were then treated once daily for 18 days by topically application of the silicone gel composition of Example 1. The six wounds on the other ear served as untreated controls. The animals were sacrificed on day 36 of the experiment.

5 Scar tissue was harvested, bisected at the highest point of the scar, and processed for histological analysis using hematoxylin and eosin staining. An observer blinded to the treatment quantified scar elevation by measuring the “scar elevation index” under 100X magnification. The scar elevation index was calculated as the area of the scar dermis (S) divided by the normal area of dermis (N), the latter being based on the height of the dermis in adjacent, unwounded skin (R. Reid et al., *J Plast Reconstr Aesthet Surg.* (2006), **60**:64-72).

10 The mean scar elevation index in the control animals (N = 20) was 1.68, and the mean scar elevation index in the treated animals (N=19) was 1.40 (p = 0.007 vs. control, independent samples t-test).

3. Clinical results.

15 Application daily for two months to a large surgical facial scar resulted in substantial reduction in the amount and visibility of scar tissue (Fig. 1).

What is claimed is:

1. A composition comprising:
a cyclic siloxane;
a silicone occlusive fluid;
5 a silicone occlusive gel, and
a silicone resin powder.
2. The composition of claim 1, further comprising an ascorbic acid ester or salt thereof.
3. The composition of claim 1, wherein the cyclic siloxane constitutes 30-80%
10 by weight of the composition.
4. The composition of claim 3, wherein the cyclic siloxane constitutes 45-65% by weight of the composition.
5. The composition of claim 4, wherein the cyclic siloxane constitutes 55-65% by weight of the composition.
- 15 6. The composition of claim 1, wherein the silicone occlusive fluid is a polyalkylsiloxane having a viscosity between 50 cSt and 500 cSt.
7. The composition of claim 6, wherein the viscosity is between 100 cSt and 350 cSt.
8. The composition of claim 6, wherein the polyalkylsiloxane is chosen from
20 poly(dimethyldiloxane), poly(methylethylsiloxane), poly(methylphenylsiloxane), and mixtures thereof.
9. The composition of claim 8, wherein the polyalkylsiloxane is polydimethylsiloxane and the viscosity is 200 cSt.
10. The composition of claim 1, wherein the silicone occlusive fluid constitutes 1-
25 15% by weight of the composition.

11. The composition of claim 10, wherein the silicone occlusive fluid constitutes 2-15% by weight of the composition.

12. The composition of claim 11, wherein the silicone occlusive fluid constitutes 3-7% by weight of the composition.

5 13. The composition of claim 1, wherein the silicone occlusive gel is a dispersion of a silicone elastomer in a silicone oil.

14. The composition of claim 13, wherein the silicone elastomer is a crosslinked silicone polymer having an average molecular weight between about 100,000 and 10,000,000.

10 15. The composition of claim 14, wherein the crosslinked silicone polymer is chosen from crosslinked dimethicone, stearyl methyl-dimethyl siloxane copolymer, polysilicone-11, cetearyl dimethicone/vinyl dimethicone crosspolymer, dimethicone/phenyl vinyl dimethicone crosspolymer, and dimethicone/vinyl dimethicone crosspolymer.

15 16. The composition of claim 15, wherein the crosslinked silicone polymer is polysilicone-11.

17. The composition of claim 13, wherein the silicone oil is chosen from phenyl trimethicone, phenyl dimethicone, dimethicone copolyol, and alkyl dimethicone copolyol.

18. The composition of claim 17, wherein the silicone oil is phenyl trimethicone.

20 19. The composition of claim 1, wherein the silicone resin powder is a silsesquioxane.

20. The composition of claim 1, wherein the silicone resin powder comprises 1-10% by weight of the composition.

21. The composition of claim 20, wherein the silicone resin powder comprises 1-5% by weight of the composition.

25 22. The composition of claim 21, wherein the silicone powder comprises 2-3% by weight of the composition.

23. The composition of claim 19, wherein the silsesquioxane is polymethylsilsesquioxane.

24. The composition of claim 2, wherein the ascorbic acid ester or salt thereof comprises a fatty acid ester having 8 to 24 carbon atoms.

5 25. The composition of claim 2, wherein the ascorbic acid ester or salt thereof is chosen from ascorbyl laurate, ascorbyl myristate, ascorbyl palmitate, ascorbyl isopalmitate, ascorbyl stearate, ascorbic acid tetraisopalmitate, and ascorbyl behenate, and salts thereof.

26. The composition of claim 2, wherein the ascorbic acid ester or salt thereof comprises between 0.1 and 2% by weight of the composition.

10 27. The composition of claim 26, wherein the ascorbic acid ester or salt thereof comprises between 0.2 and 1% by weight of the composition.

28. The composition of claim 27, wherein the ascorbic acid ester or salt thereof comprises between 0.3 and 0.7% by weight of the composition.

15 29. The use of the composition of claim 1 in the manufacture of a medicament for the treatment of wounds to reduce scarring.

30. The use of claim 29, wherein the composition of claim 1 further comprises an ascorbic acid ester or salt thereof.