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(54) Title: POLYETHYLENE GLYCOL BASED COMPOSITION FOR TOPICAL TREATMENT OF A CLOSED WOUND WITH THERAPEUTIC PHARMACEUTICALS

(57) Abstract: The present invention relates to compositions, methods and kits for improving the appearance or reducing the size of a closed wound or scar. The composition includes a therapeutically effective amount of at least one non- steroidal anti-inflammatory agent, such as a cyclooxygenase inhibitor and/or NF-kB inhibitor in combination with a polyethylene glycol material. The composition also may include one or more of the following: methyl parabenzene, propyl parabenzene, butylated hydroxy toluene, aloe vera, and vitamin E. The composition further may include an anti-irritant, an anti-prurient, an anti-microbial, and/or a deodorant agent. The composition of the present invention may be administered topically or transdermally.

POLYETHYLENE GLYCOL BASED COMPOSITION FOR TOPICAL TREATMENT OF A CLOSED WOUND WITH THERAPEUTIC PHARMACEUTICALS

[0001] The present application claims priority to U.S. Provisional Application Serial No. 60/675,940, filed April 27, 2005.

BACKGROUND OF THE INVENTION

[0002] Although scar formation and remodeling are essential processes in skin wound healing, disorders of excess scar formation, such as hypertrophic scars and keloids, remain a common clinical problem. A hypertrophic scar is an excessive wound scar which is thick and raised, having grown in size beyond that required for normal wound healing. A hypertrophic scar stays essentially within the boundaries of the original injury. A keloid is a raised scar that exceeds the boundaries of the initial injury, and rarely is corrected by surgical intervention.

[0003] The changing patterns of the connective tissue matrix during repair following injury require a delicate balance between synthesis and degradation of collagen and proteoglycans. Under normal circumstances this balance is maintained, while in many diseased states it is altered, leading to an excessive deposition of collagen, to a loss of functional tissue, or to disfigurement. With hypertrophic scars and keloids, the biosynthetic phase continues longer than necessary to repair the wound. In order to maintain nutrient supply in hypertrophic scars and keloids scars, vascular in-growth occurs, resulting in a large, highly vascularized scars which are unsightly and can be disabling.

[0004] Existing therapy for hypertrophic scars and keloids includes surgery, mechanical pressure, steroids, x-ray irradiation and cryotherapy. There are many disadvantages associated with each of these methods. Surgical removal of the scar tissues is often incomplete and can result in further development of hypertrophic scars and keloids at the incision and suture points. Steroid treatments are unpredictable and often result in depigmentation of the skin. X-ray therapy is the only predictable effective treatment to date; however, because of its potential for causing cancer, it is

not generally recommended or accepted. The most common approach to controlling scar formation, and in particular excessive scar formation, is to apply pressure, which appears to be somewhat effective in many instances. However, this treatment has limited application, generally based on the size and location of the scar tissue on the body. Other commonly used treatments are application of Vitamin E and corticosteroids. Each of these agents can interfere with collagen synthesis and promote collagen degradation.

[0005] No formulation for topical application containing salicylic acid and active salicylic acid analogues as an active ingredient and having required safety, stability, and excellent performance has been reported to date for the treatment of closed wounds, including hypertrophic scars and keloids. Thus, there is a need in the art for improved methods of treating patients with closed wounds and patients suffering from various types of scars.

SUMMARY OF THE INVENTION

[0006] The present invention relates to compositions and methods of using those compositions for improving the appearance or reducing the size of a closed wound, which may be a scar. A closed wound may be, for example, a normal scar, a hypertrophic scar, a keloid, a Dupuytren's contracture, a fibrotic scar, a Peyronnie's Disease, an excessive post-operative scar or a reactive scar. A closed wound may be caused by laceration, avulsion, burn, radiation, or chemical facial peel.

[0007] In one example, a composition of the present invention comprises a therapeutically effective amount of a non-steroidal anti-inflammatory agent ("NSAID"), such as a cyclooxygenase inhibitor and/or an NF-kb inhibitor, in combination with a polyethylene glycol ("PEG") material and one or more of methyl parabenzene, propyl parabenzene, butylated hydroxy toluene (BHT), aloe vera, and vitamin E.

[0008] In a further example, a composition of the present invention may comprise: at least one non-steroidal anti-inflammatory agent, wherein the non-steroidal anti-inflammatory agent is present in an amount ranging from approximately 1-5% w/w of the composition; methyl parabenzene, wherein

the methyl parabenzene is present in an amount ranging from approximately 0.001-0.1% w/w of the composition; propyl parabenzene, wherein the propyl parabenzene is present in an amount ranging from approximately 0.001-1% w/w of the composition; and a pharmaceutically acceptable carrier comprising a polyethylene glycol material comprising a first polyethylene glycol having an average molecular weight of 200-600, wherein the first polyethylene glycol is present in an amount ranging from approximately 45-75% w/w of the composition, and a second polyethylene glycol having an average molecular weight of 3350-5000, wherein the second polyethylene glycol is present in an amount ranging from approximately 25-55% w/w of the composition.

[0009] In one example of the invention, the non-steroidal anti-inflammatory agent is sodium salicylate. In another example of the invention, the non-steroidal anti-inflammatory agent is salicylic acid.

[0010] In another example, the composition of the present invention further comprises one or more of the following: butylated hydroxy toluene in an amount ranging from approximately 0.1-2% w/w of the composition; aloe vera in an amount ranging from approximately 0.2-2% w/w of the composition and vitamin E in an amount ranging from approximately 0.001-2% w/w of the composition.

[0011] In a further example, the composition of the present invention may further comprise one of more of the following: an anti-irritant, for example, diphenhydramine, to reduce skin irritation; a deodorant, for example, aluminum zirconium trichlorohydrex, zinc acetate or aluminum hydroxide, to reduce odor formation; an anti-pruritic, for example diphenhydramine, to reduce itching; and/or an anti-microbial agent, for example, aluminum zirconium trichlorohydrex, to reduce surface bacteria.

[0012] The present invention also relates to a method of using a composition of the present invention for improving the appearance or reducing the size of a closed wound. Preferably, a composition of the present invention will both improve the appearance and reduce the size of

a closed wound but a composition still may be within the present invention if it only reduces the size or improves the appearance of a closed wound.

[0013] Yet another example of the invention includes the use, for the manufacture of a medicament for preventing or treating a condition caused by the appearance of a closed wound, such as a hypertrophic or keloid scar, of an effective amount of an NSAID such as an NF-kB inhibitor, or a cyclooxygenase inhibitor in combination with a polyethylene glycol ("PEG") material and one or more of methyl parabenzene, propyl parabenzene, butylated hydroxy toluene (BHT), aloe vera, and vitamin E.

[0014] In another example the invention comprises a kit for use in improving the appearance and/or reducing the size of a closed wound. A kit according to one example of the invention may include at least one NSAID, such as sodium salicylate or salicylic acid in combination with a polyethylene glycol ("PEG") material and one or more of methyl parabenzene, propyl parabenzene, butylated hydroxy toluene (BHT), aloe vera, and vitamin E.

[0015] In a further example, the invention comprises a kit for use in improving the appearance and/or reducing the size of a closed wound wherein the kit consists essentially of: at least one non-steroidal anti-inflammatory agent; methyl parabenzene; propyl parabenzene; butylated hydroxy toluene; and a pharmaceutically acceptable carrier comprising a polyethylene glycol material comprising a first polyethylene glycol having an average molecular weight of 200-600, and a second polyethylene glycol having an average molecular weight of 3350-5000.

DETAILED DESCRIPTION OF THE INVENTION

[0016] It is to be understood that the present invention is not limited to the particular compositions, methodologies or protocols described herein. Further, unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. It is also to be understood that the terminology used herein is for the purpose of

describing particular embodiments only, and is not intended to limit the scope of the present invention, which will be limited only by the claims.

[0017] The present invention relates to methods and compositions for improving the appearance and/or reducing the size of a closed wound or a scar, and for reducing scar irritation. In one embodiment, the present invention provides methods and compositions for the specific inhibition of one distinct pathway in cyclooxygenase regulation, thereby inhibiting the expression of skin irritation and excessive scar symptoms in a closed wound, while leaving balance in other aspects of cyclooxygenase modulation.

[0018] The compositions and methods according to embodiments of the invention can be used on any vertebrate with skin. Examples of such vertebrates include mammals (for example, human, bovine, porcine, canine, feline) and avian.

[0019] The compositions of the present invention show improvement of a scar by reducing scar redness, thickness, tenderness, pain, symptoms of pruritus, firmness, hyperpigmentation and/or hypopigmentation.

[0020] As used herein, the terms "closed wound" or "scar" are both used to refer to a wound or a wound surface that is closed by regrowth of an epithelial barrier. To be more precise, a wound is "closed" after an open wound has been re-epithelialized, typically within 48-72 hours after injury. Some closed wounds eventually result in the formation of a scar. A scar is a closed wound with an unmatching replacement of the original tissue. Scar tissue is typically less elastic than the undamaged tissue and can have surface and contour irregularities. As used herein, the term "affected area of skin" may also be used to refer to either a "closed wound" or a "scar."

[0021] In one embodiment, a closed wound is an area of skin that has pain, tingling, burning, and/or itching. In another embodiment, a closed wound is a scar. In another embodiment, a scar is an area of skin that has pain, tingling, burning, itching, discoloration, surface irregularities, and/or an erratic accumulation of fibrous tissue.

[0022] A closed wound may result from any of a number of types of skin traumas such as laceration, avulsion, burn, surgery, infection, chemical facial peel, and accident. An open wound closes by regrowth of an epithelial barrier, the regrowth replacing some of the normal tissue which had been destroyed by trauma. Sometimes, in the closed wound or scar, excessive and disfiguring deposits of fibrous tissue having an erratic accumulation of collagen occur.

[0023] Normally, wound healing is a continuous process extending over a one-to-two-year period. Conceptually, the wound healing process may be divided into three phases.

[0024] The first phase is an intensely degradative phase called the inflammatory stage. It occurs immediately after injury and provides a means to remove the damaged tissues and foreign matter from the wound as well as regain immunological control over invading skin surface microbes. This phase lasts approximately one week when the wound is immediately closed, for example in a surgical incision. However, the level of the inflammatory response continues at elevated levels in open wounds until the wound surface is closed by regrowth of the epithelial barrier. If wound inflammation is prolonged or more intense, excessive scarring, called hypertrophic scars, usually appear.

[0025] Inflammation, or an "inflammatory response", is the net result of interconnected physiological events, including increased vascular permeability, fluid accumulation, and the migration of a changing population of inflammatory cells into an inflamed area. The clinical manifestations of inflammation include swelling, increased local temperature, erythema, and pain. The inflammatory response can be triggered by any of a number of causative factors, including certain bacteria, radiation, hypersensitivity to chemical agents, and the like. The inflammatory response is generally believed to be a primary defense mechanism in the body, but, unchecked, can become excessive resulting in functional impairment.

[0026] The second stage of wound healing typically occurs 2-3 days later and typically lasts about 3 weeks. This stage may be referred to as the proliferation and matrix synthesis stage. During this stage fibroblasts from the surrounding tissue invade the wound and proliferate. The fibroblasts in the wound proliferate and actively produce macromolecules, such as collagen and proteoglycans, which are secreted into the extracellular matrix. Fibroblast activity is driven by the chemical signals produced by inflammation. The newly-synthesized collagen fibrils are cross-linked by lysyl oxidase and provide structural integrity to the wound. During this stage, fibroblasts also contract the intact collagen in order to reduce the surface area of the wound.

[0027] In the third and final stage, called the remodeling stage, the previously constructed and randomly organized matrix is remodeled into an organized structure which is highly cross-linked and aligned to maximize mechanical strength. Natural skin wrinkles (relaxed skin tension lines) which align themselves in the direction of mechanical tension and become permanent on the face over time are a common manifestation of this control process.

[0028] The end result of mammalian wound healing is scar formation. Scars are not an exact replacement for undamaged tissue. Skin scars are generally less elastic, creating contour irregularities; color changes and maybe painful if they entrap nerves. Control of dermal scarring is one of the most important objectives in the management of trauma particularly burn trauma. Minimizing dermal scarring and may lead to optimum post-traumatic functional and aesthetic recovery.

[0029] One such scar which can result from an overproduction of collagen and excess deposition of scar tissue is a hypertrophic scar. As used herein, the term "hypertrophic scar" includes a scar characterized by thick, raised scar tissue that stays essentially within the boundaries of the original injury. Hypertrophic scars contain characteristic nodules, and result from a full-thickness injury, such as a surgical incision on skin. These scars can cause problems such as aesthetic deformity and severe limitation of

motion. For example, an excessive post-operative scar can develop as a result of "over-healing" or hypertrophic healing of a post-operative site.

[0030] Hypertrophic scars generally result from an over-production of cells, collagen and proteoglycan [Linares, H. A. et al., Plast. Reconst. Surg., 62:589 (1978); Linares, H. A., Plast. Reconstr. Surg., 818-820 (1983)]. These scars more frequently occur among children and adolescents, suggesting that growth factors may influence the development of this type of scar.

[0031] Hypertrophic scars are especially common in patients who have burns or wounds that are allowed to remain open for more than a few weeks. These scars, by definition, exceed normal wound healing, causing problems that range from aesthetic deformity to severe limitation of motion In these scars, the over-production and compaction of collagen and proteoglycans [Shetlar, M. R. et al., Burns 4:14 (1977)] exceeds the proliferation of cells. These histological observations suggest that the lesions result from loss of the normal control mechanisms which regulate the synthesis of extracellular matrix during wound healing [Shetlar. M. R. et al., Burns 4:14 (1977)].

[0032] Hypertrophic scars are more common on the anterior surfaces of the neck, the shoulder, the chest wall and, in general, the flexor surfaces of the extremities. While some hypertrophic scars will spontaneously resolve within a few years, in many instances, especially in the locations mentioned above, they persist indefinitely. Because these scars are so common, particularly in burns or wounds that heal by secondary intention, their management represents a major unsolved clinical problem.

[0033] Another type of scar in which there is an excess deposition of scar tissue is called a "reactive scar." As the term is used herein, a reactive scar is a normal, healed scar which, through mechanical disruption such as scratching or other irritation, is actively producing a hypertrophic tissue response.

[0034] Excessive scar deposition also occurs in a "fibrotic scar." As the term is used herein, a fibrotic scar is an accumulation of irritated fibrotic

tissue at the site of a healed injury which may or may not have involved an observable wound.

[0035] Another type of scar that can result from an excess deposition of scar tissue is a keloid. As used herein, the term "keloid" includes a scar characterized by thick, raised scar tissue that exceeds the initial boundaries of the trauma and that lacks nodules. In contrast to hypertrophic scars, keloids proliferate beyond the wound edges, can result from superficial injuries, and are rarely treated successfully by surgery. Keloids frequently develop after burns, particularly where the skin is under tension, such as on the breastbone.

[0036] Although appearing similar, keloids and hypertrophic scars differ considerably. The former is genetically based with both autosomal dominant and autosomal recessive modes of transmission reported (Roseborough et al., J. Natl. Med. Assoc. 2004, 96(1), 1-9).The basis for the genetic differences has been shown through several investigations describing the aberrant behavior of keloid fibroblasts. It has also resulted from reports of keloids exhibiting abnormal regulation of apoptosis to abnormally producing collagen, fibronectin, and proteoglycans with atypical responses to metabolic regulators.

[0037] Unlike hypertrophic scars, keloids may occur with only minor insults to the skin. Conversely, hypertrophic scars are usually the result of injury to the deep dermis. They also tend to be more pronounced in wounds with a prolonged inflammatory phase and may develop in areas with increased mechanical tension. Both types of scars may produce considerable cosmetic disfigurement and prompt many patients affected to seek treatment. Although keloids can be successfully treated in a single application, patients may require multiple modes of therapy (Shaffer JJ et al., J. Am. Acad. Dermatol. 2002; 46: 63-67).

[0038] Another type of scar tissue that may be treated by embodiments of the method and compositions of the present invention is Dupuytren's contracture. Dupuytren's contracture arises from unknown causes and is a progressive, scar-like shrinkage and thickening of the flexion contracture of

the cusp-like extended palmar aponeurosis in the palm of the hand, whereby, as the curvature of the fingers increases, especially that of the fourth and fifth fingers, stretching of the fingers becomes ever more restricted. This ailment, which attacks men more frequently than women and can occur in one or both hands, begins with a dimple-like indentation in the palm of the hand and gradually but quite painlessly grows into nodules and fascicles. The flexor tendons of the fingers concerned are not in themselves diseased but their movement is impaired by the scar-fascicles of the palmar aponeurosis. A similar contracture concerning the toes is known.

[0039] Since the illness neither regresses spontaneously nor responds with any degree of long term success to conventional forms of treatment (without surgery) such as massage, heat treatment and the like, it can only be treated surgically, namely, by cutting away the proliferating atrophied tissue. In addition to ordinary risks and unpleasantness associated with any surgical operation, there exists a further risk that scars resulting from the operation can make a later recurrence of the ailment even worse.

[0040] One embodiment of the present invention is based, in part, on the discovery that the size and appearance of a closed wound or a scar can be improved, and the discomfort, itching, pain, and/or other symptoms caused by excessive tissue growth in a closed wound or scar can be alleviated (partially or completely) by the administration of at least one NSAID. For example, compounds that inhibit (partially or completely) cyclooxygenase, (*e.g.*, cyclooxygenase-1, cyclooxygenase-2) directly or indirectly may be used in practicing the present invention. The NSAID compounds of the present invention may inhibit the expression and/or function of cyclooxygenase.

[0041] The compositions of the present invention may directly or indirectly inhibit cyclooxygenase. Thus, according to the present invention, a NSAID compound may act directly on cyclooxygenase or may act indirectly on cyclooxygenase by acting on an upstream or downstream target in the cyclooxygenase pathway. For example, cyclooxygenase can

be inhibited indirectly by inhibiting, *e.g.*, NF-kappa B (NF-k B) or adenosine. Further, one of ordinary skill in the art will appreciate that some compounds of the present invention may inhibit the function of cyclooxygenase both directly and indirectly. Such compounds are more powerful or effective in treating the size and appearance of a closed wound than those compounds that have only one mode of action.

[0042] Cyclooxygenase promotes pain, irritation, overgrowth of scar tissue and other scar symptoms that can lead to excessive scarring, including hypertrophic scars or keloids. Both cyclooxygenase-1 and cyclooxygenase-2 are enzymes that help produce hormones called prostaglandins. There is evidence that prostaglandins made by cyclooxygenase-2 lead to pain, irritation and excessive or abnormal scar growth.

[0043] Thus, in one embodiment of the invention, the compositions and methods described herein to inhibit cyclooxygenase directly are believed to specifically act on cyclooxygenase itself. Examples of compounds that directly inhibit cyclooxygenase include compounds such as salicylic acid; acetylsalicylic acid; aryl, substituted or unsubstituted aralkyl, allyl, and substituted or unsubstituted, linear, branched, or cyclic alkyl esters of salicylic acid; aryl, substituted or unsubstituted aralkyl, allyl, and substituted or unsubstituted, linear, branched, or cyclic alkyl esters of acetylsalicylic acid; ibuprofen; celecoxib; rofecoxib; flufenamic acid; indomethacin; nabumetone; naproxen; pharmaceutically acceptable salts thereof; and blends thereof. Celecoxib is chemically designated as 4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl) benzenesulfonamide, and is a diaryl substituted pyrazole, with a molecular weight of 381.38. Rofecoxib is chemically designated as 4-(4-(methylsulfonyl)phenyl)-3-phenyl-2(5H)-furanone, and has a molecular weight of 314.36.

[0044] Flufenamic acid is chemically designated as (N-(ααα-trifluoro-m-tolyl) anthranilic acid), and has a molecular weight of 281.23.

[0045] Indomethacin is chemically designated as (1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid), and has a molecular weight of 357.8.

[0046] Nabumetone is a naphthylalkanone chemically designated as 4-(6-methoxy-2-naphthalenyl)-2-butanone, and has a molecular weight of 228.3.

[0047] Naproxen is chemically designated as (S)-(+)-6-methoxy-α-methyl-2-naphthaleneacetic acid, and has a molecular weight of 230.27.

[0048] In a preferred embodiment, an ester of acetysalicylic acid such as, methyl acetylsalicylate, ethyl acetylsalicylate, allyl acetylsalicylate, and benzyl acetylsalicylate, is used to inhibit cyclooxygenase.

[0049] In another preferred embodiment, sodium salicylate is used.

[0050] In another embodiment, the compositions and methods described herein inhibit cyclooxygenase indirectly and can work on a compound upstream or downstream of the cyclooxygenase pathway. As this molecular pathway is elucidated, the present invention provides an appropriate intervention in the cascade of reactions which leads to excessive scar growth and related symptoms. In a particular embodiment, the composition which indirectly inhibits upstream of the cyclooxygenase pathway is an inhibitor of NF-kB.

[0051] NF-kB is a signaling molecule that is detected in the body through biotechnology techniques. The results of the work described herein indicate that NF-kB plays a critical role in a biochemical mechanism that promotes irritation in closed wounds and leads to the symptom complex of excessive scar growth, pain and pruritis. NF-kB is a transcription factor, a eukaryotic protein that promotes RNA polymerase to recognize promoters. The structure of NF-kB is that of a heteromeric complex, that is, a molecule made up of sub-units. When the sub-units remain intact, NF-kB resides in the cytoplasm, where it exists in an inactive form, bound to I-kB, an inhibitory protein. A stimulant can trigger release of NF-kB from I-kB, whereupon the NF-kB moves from the cytoplasm to the nucleus, binds to DNA, and regulates transcription of specific genes. NF-

kB binding sites are present on genes which direct the expression of proteins including cytokines and adhesion molecules. NF-kB is believed to activate a number of genes involved in immune and irritation responses.

[0052] When released, NF-kB is believed to signal the induction of cyclooxygenase, which leads to irritation of a closed wound or scar, and excessive growth of the scar. Thus, NF-kB appears to provide the primary mechanism that promotes increased rRNA2, prostaglandinE2, and the symptom complex including excessive scar growth, irritation, pain and pruritis.

[0053] Although the exact mechanisms of pharmacological inhibition of cyclooxygenase and of NF-kB are not fully understood, it appears that one molecular pathway, for example, is the inhibition, by acetylsalicylic acid, of NF-kB's translocation to the nucleus. Another possible mechanism includes inhibition by acetylsalicylic acid of IkB phosphorylation and catabolism. Because phosphorylation and degradation of IkB permit translocation of NF-kB to the nucleus, inhibition of these processes interferes with the movement of NF-kB from the cytoplasm to the nucleus, and ultimately, the activation of genes involved in immune responses and in responses to irritants. In yet another possible mechanism, salicylic acid and other salicylates may cause cells to release small amounts of adenosine, an anti-irritant.

[0054] Thus, in a particular embodiment, the invention includes an indirect inhibitor of cyclooxygenase that is an inhibitor of NF-kB. Examples of inhibitors of NF-kB that can be used according to this embodiment of the invention include the following compounds: salicylic acid; acetylsalicylic acid; aryl, substituted or unsubstituted aralkyl, allyl, and substituted or unsubstituted, linear, branched, or cyclic alkyl esters of salicylic acid; aryl, substituted or unsubstituted aralkyl, allyl, and substituted or unsubstituted, linear, branched, or cyclic alkyl esters of acetylsalicylic acid; nabumetone; sulindac sulfide; sulindac sulfone; sulfasalazine; and pharmaceutically acceptable salts thereof; and blends thereof. In another embodiment, a pro-drug may be used.

[0055] Sulfasalazine is chemically designated as (5-(4-(2-pyridylsulfamoyl-)phenylazo)salicylic acid), and has a molecular weight of 398.40.

[0056] In a preferred embodiment, the NF-kB inhibitor is an ester of acetylsalicylic acid such as methyl acetylsalicylate, ethyl acetylsalicylate, allyl acetylsalicylate, or benzyl acetylsalicylate.

[0057] In another preferred embodiment the NF-kB inhibitor is sodium salicylate.

[0058] By "improving" the appearance of a closed wound or a scar according to an embodiment of the invention is meant alleviating, either partially or completely, symptoms such as pain, tingling, itching, burning, discoloration. Improving the appearance of a closed wound can include reducing the size of a closed wound or scar; reducing surface irregularities of the closed wound or scar; reducing the accumulation of fibrous tissue; and/or partially or completely eliminating the closed wound or the scar.

[0059] In one embodiment of the invention, a composition of the present invention is used to relieve or to prevent a condition of scar irritation. In particular, the compositions and methods of the present invention are useful in cases where scar irritation leads to symptoms including itching, and to a patient's self-inflicted mechanical action of scratching, which can result in further scar irritation, and possible contamination and invasion of the scar with native skin organisms.

[0060] Administration

[0061] To achieve the improvements described herein, the present invention provides for a route of administration of the NSAID, for example the cyclooxygenase inhibitor and/or the NF-kB inhibitor, that is either a topical or transdermal administration, an oral administration, an administration by injection, an administration by inhalation, or that is a combination of two or more of these administration routes.

[0062] While a composition for use in improving the appearance and/or reducing the size of a closed wound or scar may be administered in the form of a raw chemical compound, including a physiologically acceptable

salt of the active ingredient, it is preferred to introduce the active ingredient in a pharmaceutical composition together with a pharmaceutically acceptable carrier and one or more adjuvants, excipients, and/or diluents.

[0063] Therefore, in another embodiment, the present invention also relates to pharmaceutical compositions which include a pharmaceutically acceptable carrier and at least one of the following: a cyclooxygenase inhibitor, an NF-kB inhibitor, an anti-irritant substance, a deodorant agent, aluminum hydroxide, an anti-microbial substance such as aluminum zirconium trichlorohydrex, or other metallic anti-microbial.

[0064] One of ordinary skill in the art will appreciate that any of the compositions of the present invention may be administered with a suitable pharmaceutical carrier, the choice of which depends on the route of administration and the size of the scar. The terms "suitable pharmaceutical carrier" and "pharmaceutically acceptable carrier" and grammatical variations thereof, as they refer to compositions, carriers, diluents and reagents, are used herein interchangeably. As the terms are used herein, "suitable pharmaceutical carrier" and "pharmaceutically acceptable carrier" refer to non-toxic materials that do not interfere with the effectiveness of the biological activity of active ingredients, and represent that the materials are capable of administration to or upon a vertebrate with a minimum of undesirable physiological effects such as nausea, dizziness, gastric upset and the like. The characteristics of the pharmaceutically acceptable carrier will depend on the route of administration.

[0065] The preparation of a pharmacological composition that contains active ingredients dissolved or dispersed therein is well understood in the art and need not be limited based on formulation. Liquid preparations include solutions, suspensions, colloids, hydrogels, PEGs, and emulsions, for example, water, water-propylene glycol mixtures. Such compositions may be prepared as injectables, either as liquid solutions or suspensions, or as topical applications, for example, as salves, lotions, creams. Alternatively, compositions of the present invention can be administered as an aerosol product to spray-on a closed wound.

[0066] Solid forms suitable for dissolving in a hydrogel, a PEG material, or a liquid solution, or for suspending in liquid prior to use, can also be prepared. The preparation can also be emulsified. The active ingredient can be mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient and in amounts suitable for use in the therapeutic methods described herein. Suitable excipients include, for example, water, saline, dextrose, glycerol, ethanol or the like and combinations thereof. In addition, if desired, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like which enhance the effectiveness of the active ingredient. Details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, Pa.).

[0067] At least one NSAID, such as at least one cyclooxygenase inhibitor, or at least one NF-kB inhibitor, or combinations thereof, may be administered topically, orally, by injection, by inhalation, or by any suitable combination of these methods of administration.

[0068] Topical Administration

[0069] For topical or transdermal administration, one embodiment of the invention encompasses placing the cyclooxygenase inhibitor or the NF-kB inhibitor directly on the surface of the scar or closed wound. A composition according to an embodiment of the invention is not intended for use on infected skin or on open wounds. In a particular embodiment, the NSAID is mixed with a pharmaceutically acceptable carrier and then placed directly on the surface of the affected area of skin.

[0070] In another embodiment, a composition for use in improving the appearance and reducing the size of a closed wound or scar is placed in contact with the affected area of skin; the composition may then covered with a thermal insulating material or a PEG material. In each embodiment described herein, the composition placed in contact with the affected area of skin is allowed to remain in place for a period of time sufficient to bring

about an improvement in the appearance and/or a reduction in the size of the closed wound or scar.

[0071] Although there is no minimum time required for duration of use, the duration of use of a composition of the present invention can extend for example, from about 0.5 hour to about 24 hours, or from about 1 hour to about 1 month, or from about 8 hours to about 12 months or from about 24 hours to about 24 months. In one embodiment of the invention, the duration of use typically extends from about 12 hours to about 12 months, for separate time periods. The composition can be used continuously or intermittently for a particular time period and then removed or reapplied. For example, the composition can be used intermittently from about 1 hour to about 72 hours, from about 8 hours to about 48 hours, from about 12 hours to about 24 hours, or from about 18 hours to about 24 hours. The time interval between each use can be from about 1 hour to about 72 hours, from about 8 hours to about 48 hours, from about 12 hours to about 24 hours, or from about 18 hours to about 24 hours. In a particular embodiment, each time period is about 18 hours in a day with a minimum of about 4 hours between time periods.

[0072] In one embodiment, a composition of the present invention comprising at least one NSAID and a PEG material is topically administered. In particular, a layer of the composition is topically applied over the closed wound or scar in a range of about 0.0625"-0.125" in depth of composition and in a range of 1-3 times daily over an interval of time that results in an improvement of the closed wound or scar.

[0073] In a further embodiment, a composition of the present invention comprising at least one NSAID and a PEG material may further comprise conventional adjuvants. Additionally, the composition may further comprise penetration enhancers, buffers, preservatives, emulsifiers, or emollients.

[0074] In one embodiment in which topical administration is used to administer a composition according to an embodiment of the invention, the use of adhesive tape is avoided because adhesives may cause irritation of

a scar and aggravate the scar condition. It is recommended that means such as flexible wraps, elastic garments, netting, ace wraps or spandex sleeves or garments be used to affix a composition according to the invention to the affected area of skin.

[0075] In another embodiment, the invention comprises a cyclooxygenase inhibitor or an NF-kB inhibitor in a thermal insulating material or a PEG material. As used herein, the term "thermal insulating material" includes materials that, when placed in contact with or near to the skin, are capable of retaining sufficient heat to elevate the surface temperature of the affected area of the skin.

[0076] In one embodiment of the invention, the thermal insulating material when used to cover the affected area, causes an elevation in the surface temperature of the closed wound or scar of from about 0.5°C to about 5°C. In another embodiment, the thermal insulating material, when used to cover the affected area, causes an elevation in the surface temperature of the closed wound or scar of from about 1°C to about 4°C. In a preferred embodiment, the thermal insulating material, when used to cover the affected area, causes an elevation in the surface temperature of the closed wound or scar of from about 2°C to about 3°C.

[0077] In one embodiment, the thermal insulating material may be a sponge. Examples of sponge materials suitable for use as a thermal insulating material in the present invention include collagen and cross-linked collagen. The term "cross-linked," as used herein, refers to covalent bonds formed among polymeric chains and to an interconnected structure wherein cross-links are formed between hydrophobic molecules, between hydrophilic molecules and between hydrophobic molecules and hydrophilic molecules.

[0078] In another embodiment, the thermal insulating material may be a gel, a hydrogel, or a biodegradable hydrogel. Gels and hydrogels generally contain a very high concentration of water, *e.g.*, about 60% to about 98% water and are held together by a variety of cellular groups. The water may

be bound in the form of various hydrates, or unbound, entrapped in cellular pockets formed by the polymer network groups.

[0079] The term "hydrogel" is used herein to mean a polymeric material which can include a cross-linked macromolecular network, which exhibits the ability to swell in water and to retain a significant portion of water within its structure without dissolving.

[0080] A "biodegradable hydrogel," as the term is used herein, is a hydrogel formed from a hydrogel-forming system containing at least one biodegradable component, *i.e.*, a component which is degraded by water and/or by enzymes found in nature.

[0081] There are a number of well-known hydrophilic, polymeric compounds both naturally occurring and synthetic, which form networks, creating a gel in the presence of water. For example, gelatin can be obtained from the hydrolysis of collagen by boiling skin, ligaments, tendons, etc. A mixture of only 2% gelatin in water will form a stiff gel. An example of a gel suitable for use in an embodiment of the invention is Elastogel®, available from Southwest Technologies, Kansas City, Mo.

[0082] A hydrogel may be formed by adding a solute such as gelatin to water at an elevated temperature to dissolve gelatin. The solution is then cooled and the solute(s) (*e.g.*, solid gelatin components) form submicroscopic crystalline particle groups which retain a great deal of water in the interstices (so-called "brush-heap" structure). Methods of making hydrogels suitable for use in the present invention are well-known to those of skill in the art. See, for example, the disclosures of U.S. Pat. No. 4,646,730 to Schonfeld et al.; U.S. Pat. No. 5,013,769 to Murray et al.; U.S. Pat. No. 4,659,700 to Jackson et al.; and U.S. Pat. No. 4,909,244 to Quarfoot et al., the teachings of which are incorporated herein by reference in their entireties. An example of a hydrogel suitable for use in an embodiment of the invention is AVOGEL®, available from Avocet Polymer Technologies, Inc., Plainfield, Il.

[0083] In addition to increasing the surface temperature of the closed wound, the thermal insulating material may also be used to deliver a

therapeutically effective substance to the closed wound. Alternatively, a PEG material may be used to deliver a therapeutically effective substance to the closed wound. As used herein, the terms "therapeutically effective substance" or "therapeutic substance" include:

(i) Compounds and compositions recognized in the official United States Pharmacopoeia, the official Homeopathic Pharmacopoeia of the United States, or the official National Formulary, or any supplement of any of them;

(ii) Compounds and compositions intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and

(iii) Compounds and compositions (other than food) intended to affect the structure or any function of the body of man or other animals.

[0084] Examples of therapeutically effective substances include cyclooxygenase inhibitors; NF-kB inhibitors; substances that relieve skin irritation, such as glyceryl monooleate, diphenhydramine, calamine, and C_3-C_4 diols; deodorant agents such as aluminum zirconium trichlorohydrex and zinc acetate; aluminum hydroxide and anti-microbials; and ibuprofen and other NSAIDs specifically inhibiting prostaglandinE2.

[0085] As used herein, a "PEG material" refers to a polyethylene glycol (PEG) or a blend of at least two PEGs that are of differing molecular weights. Polyethylene glycols are water-soluble, odorless, neutral, lubricating, nonvolatile and nonirritating liquid compositions. Polyethylene glycols are composed of linear polymers formed by the addition reaction of ethylene oxide. The generalized formula for PEG is $H\text{-}(OCH_2CH_2)_n\text{-}OH$ where "n" is the average number of repeating oxyethylene groups. A PEG is typically designated by a number that represents its average molecular weight. For example, a PEG 600 consists of a distribution of polymers of varying molecular weights with an average of 600, which corresponds to an approximate average number of repeating oxyethylene groups ("n").

[0086] It is the repeating ether linkages and terminal hydroxy groups of PEGs that gives rise to the water solubility of PEGs. Polyethylene glycols

also are soluble in organic solvents such as acetone, alcohols, and chlorinated solvents, while they are insoluble in nonpolar solvents such as hydrocarbons.

[0087] Polyethylene glycols are hygroscopic, *i.e.,* they attract and retain moisture from the atmosphere. This property makes PEGs useful as water-soluble ointments and humectants, and as replacements for other hygroscopic materials such as glycerin and propylene glycol in certain applications. Hygroscopicity decreases as the molecular weight of the PEG increases.

[0088] Above their melting/freezing temperatures, PEGs can be considered Newtonian fluids since their viscosities are nearly independent of shear. Kinematic viscosity measurements, therefore, are the most practical way of characterizing PEG viscosity. Viscosities of PEG materials decrease as temperature increases.

[0089] Polyethylene glycols may be liquids or solids at room temperature, depending on the average molecular weight of the PEG. Higher molecular weight PEGs form more rigid solids, while lower molecular weight PEGS tend to be viscous liquids at room temperature. For example, PEGs having average molecular weights from 200-600 are typically clear, viscous liquids at room temperature; PEGs having average molecular weights from 900-1500 are typically soft, opaque white solids at room temperatures; and PEGs having average molecular weights from 3350-8000 typically are hard, opaque white solids at room temperature. Increased molecular weight results in decreased solubility in water and other solvents, decreased hygroscopicity and vapor pressure, and increased melting/freezing range and viscosity. Intermediate physical properties can be achieved by blending PEGs of differing molecular weights. For example, blending two PEGs, for example a 400 MW PEG and a 3350 MW PEG can lead to a composition with the consistency of an ointment or salve, or a composition having a gel tendency.

[0090] Polyethylene glycols make excellent water-soluble ointment bases; they spread easily and evenly over the skin, even if the skin is

moist. The good water solubility of PEGs makes it easy to incorporate aqueous ingredients in the formulation, and they do not become rancid or support microbial growth.

[0091] Additionally, in practicing the present invention, the PEG material may create a waxy gel on the surface of the closed wound or scar that decreases UV light penetration and buffers superoxide radicals. PEG materials preferably limit the area of treatment to an appropriate level of moisture. Further, the structure of the PEG material provides a mechanical barrier for decreased penetration of bacteria and foreign materials. The PEG material also creates an evaporative barrier which augments transdermal delivery of the drugs into the closed wound or scar area. In one embodiment, the PEG material comprises an acidic composition, which is favorable for the skin and for longevity of the PEG material.

[0092] In one embodiment, one or more therapeutically effective substances may be applied to one surface of a thermal insulating material. The thermal insulating material is then applied to the closed wound in a manner such that the therapeutically effective substance is placed in contact with the closed wound.

[0093] In another embodiment, the therapeutically effective substance is dispersed within a hydrogel, a water-insoluble gel, a sponge or a PEG material. The hydrogel, water-insoluble gel, sponge or PEG material within which the therapeutically effective substance is dispersed, is then placed in contact with the affected surface of the skin, and allowed to remain in place for a period of time sufficient to bring about an improvement in the size and appearance of the closed wound.

[0094] As used herein, the term "dispersed" includes ionic, covalent, hydrophilic, or hydrophobic interactions between the therapeutically effective substance and the hydrogel, water-insoluble gel, sponge, or PEG material.

[0095] For example, a therapeutically effective substance containing a cationic moiety can be immobilized on a hydrogel polymer chain. As will be

recognized by those skilled in the art, this cationic site may serve as a noncovalent, ionic binding site for anionic substances, such as certain NSAIDs.

[0096] In another example, a hydrogel or sponge can be chosen which covalently bonds to the therapeutic substance used according to one embodiment. For example, through hydrophilic interactions with water in the hydrogel, any water soluble drug will dissolve in the hydrogel. A hydrophobic interaction between a non-water soluble therapeutic substance and a hydrogel can occur when the hydrogel selected includes a hydrophobic entity which is receptive to further interaction with a therapeutic substance having a hydrophobic moiety.

[0097] One skilled in the art will know, or will be able to ascertain with no more than routine experimentation, what hydrogels or PEG materials are suitable for dispersing a particular therapeutic substance.

[0098] A therapeutic substance which covalently bonds to the hydrogel, sponge or PEG material can form a drug delivery substance with controlled or sustained release. If a biodegradable hydrogel or sponge is used, delivery of the therapeutic substance to the closed wound or scar is also related to the rate of degradation of the hydrogel or sponge. The degradation rate of the hydrogel or sponge is usually slower than the diffusion rate of the therapeutic substance. As is well-known to those of skill in the art, by choosing a particular concentration of each therapeutic substance used in a particular embodiment, and a particular hydrogel or sponge, one can control the rate of degradation or the rate of diffusion, and thus, the rate of delivery of the therapeutic substance.

[0099] The hydrogel, other thermal insulating material, or PEG material containing the therapeutically effective substance can remain in contact with the surface of the affected area of skin for about between 0.5 to about one hour per day, from about one hour to about 8 hours per day, from about 12 hours to about 15 hours per day, from about 12 hours to about 18 hours per day, from about 18 hours to about 24 hours per day, or over a number of days, for a sufficient number of days to bring about an

improvement in the size and appearance of the closed wound or scar. The hydrogel, other thermal insulating material, or PEG material can be removed periodically in order to cleanse the scar surface and to apply a fresh sample of therapeutically effective substance and hydrogel, other thermal insulating material, or PEG material.

[00100] In one embodiment, at least one cyclooxygenase inhibitor, and/or at least one NF-kB inhibitor, or combinations thereof, are administered topically with a suitable pharmaceutical carrier, including one or more substances that relieve skin irritation. In a particular embodiment of the invention wherein the method of administration is topical, the substance that relieves skin irritation includes at least one of the following substances: glyceryl monooleate, diphenhydramine, calamine, and a C_3-C_4 diol.

[00101] In one embodiment, a closed wound, such as a scar, is contacted with a hydrogel or PEG material comprising at least one a cyclooxygenase inhibitor, for example, ibuprofen, indomethacin, sodium salicylate, or at least one NF-kB inhibitor, for example, acetyl salicylic acid, sulfasalazine, or combinations thereof, and a deodorant agent to reduce surface bacteria and odor formation.

[00102] In one embodiment, a closed wound is treated by contacting the closed wound with a hydrogel or a PEG material comprising an effective amount of salicylic or derivatives/analogues thereof in a pharmaceutically acceptable carrier. The hydrogel preferably elevates the surface temperature of the affected area of skin. The hydrogel or PEG material is allowed to remain in contact with the affected area of skin for a period of time sufficient to result in an improvement in the closed wound.

[00103] Examples of suitable patterns of use according to an embodiment of the invention include, among others: use of various hydrogel or PEG material combinations in sequence; use of various hydrogel or PEG material combinations simultaneously; use of various hydrogel or PEG material combinations in systemic-topical co-administration, such as oral administration simultaneously with topical

administration; use of combinations of active ingredients mixed by a pharmacist according to a prescription; and use of combinations of separate active ingredients available in kit form, mixed by the patient and self-administered according to physician instructions or directions provided with the kit.

[00104] Examples of various hydrogel or PEG combinations (*i.e.*, hydrogel or PEG material combined with one or more active ingredients) that may be used according to an embodiment of the invention are provided in the Table below. Many other combinations are possible, and the examples are not to be construed as limiting the scope of the invention.

[00105] Key for Table:

AL - aluminum zirconium trichlorohydrex
ASA - acetylsalicylic acid
NX - naproxen
D - diphenhydramine
NM - Nabumetone
C - calamine
NaSal – sodium salicylate
Zn - zinc acetate

Check mark - indicates use of ingredient

Hydrogel/ PEG/ other insulating materials	**Antipruritic**		**Inhibitors of Cyclooxygenase**			**Inhibitors of NF-kB**			**Antibacterials**	
	C	D	ASA	NM	NX	NM	ASA	NaSal	AL	Zn
1			√				√			√
2		√	√				√			
3		√	√				√			√
4		√	√				√		√	
5	√		√				√			
6		√		√		√			√	
7		√		√		√				√
8					√				√	
9					√		√		√	
10		√			√			√	√	

[00106] Oral and Parenteral Administration

[00107] In addition to compositions suitable for topical or transdermal administration to the affected area of skin, in another embodiment of the invention, compositions may be those suitable for oral or parenteral (including intramuscular, sub-cutaneous and intravenous) administration, or those in a form suitable for administration by inhalation. The therapeutically effective substance of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use; or in the form of sterile injectable solutions for parenteral (including sub-cutaneous) use.

[00108] In one embodiment of the invention, aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents, as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

[00109] Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like. Solid form preparations include, among others, powders, tablets, pills, capsules, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary

binding capacity in suitable proportions and compacted in the shape and size desired.

[00110] According to an embodiment of the invention, powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa buffer, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly lozenges are included. Tablets, powders, capsules, pills and lozenges can be used as solid forms suitable for oral administration.

[00111] According to an embodiment of the invention, liquid preparations include solutions, suspensions, and emulsions, for example, sterile water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated with PEG in aqueous solution. Other suitable pharmaceutical carriers for parenteral administration include, for example, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. An embodiment of a therapeutically effective substance according to the present invention may thus be formulated for parenteral administration (by injection, for example, by bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, *e.g.* sterile, pyrogen-free water, before use.

[00112] Administration by Inhalation

[00113] According to an embodiment of the invention, administration may also be made to the respiratory tract by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dosage of the therapeutic substance may be controlled by provision of a metered valve. In compositions intended for administration to the respiratory tract, including intranasal compositions, compounds used in an embodiment will generally have a small particle size, for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

[00114] Therapeutically Effective Amount and Dosage

[00115] As used herein, the terms "therapeutically effective amount" and "therapeutically effective dose" refer to the amount of an active agent, for example, a therapeutically effective substance, such as a cyclooxygenase inhibitor, an NF-kB inhibitor, or an anti-irritant, required to be administered in order to induce a desired result in the patient. That result may be alleviation or amelioration (complete or partial) of the symptoms or condition of irritation, pain, tingling, redness or other discoloration of a closed wound, an improvement in the appearance or reduction in the size of the closed wound, or any other desired improvement in the affected area of skin.

[00116] As used herein, the term "therapeutically effective amount" may also refer to the quantity of active agent or therapeutically effective substance, the administration of which results in improvement in the size, appearance, or condition of a closed wound, where little or no improvement would occur in the absence of the active agent. Typically, the active agent is administered for a sufficient period of time to achieve the desired therapeutic effect.

[00117] Therapeutic efficacy may be determined as described herein and by using standard pharmacological procedures in experimental animals.

[00118] The active ingredient of an embodiment of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous) use, or in the form of aerosol formulations for inhalation therapy. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Merck Publishing Co., Easton, Pa.).

[00119] When desired, compositions adapted to give sustained release of the active ingredient may be employed.

[00120] The dose administered is adjusted to the size and severity of the closed wound or affected area of skin, the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired. The exact dosage should of course be determined by the practitioner.

[00121] The active ingredient can be administered in one or several doses per day. In one embodiment, it is presently contemplated that, for therapeutic treatments, at least one composition of the present invention, such as a cyclooxygenase inhibitor or an anti-irritant, can be administered in an amount comprising from about 1 microgram to about 3000 micrograms, from about 10 micrograms to about 2000 micrograms, from

about 20 micrograms to about 1000 micrograms, or from about 40 micrograms to about 400 micrograms per square centimeter of treated tissue.

[00122] In another embodiment, for therapeutic treatments, at least one NF-kB inhibitor is administered in an amount comprising from about 1 microgram to about 2000 micrograms, from about 10 micrograms to about 1000 micrograms, or from about 40 micrograms to about 400 micrograms per square centimeter of treated tissue. The amount of composition of the present invention can be administered by any suitable method of administration, including, but not limited to, topical application, subcutaneous or parenteral administration, oral administration, administration by inhalation, and by combinations of these methods.

[00123] In one embodiment, the amount of composition of the present invention can be included in an amount from about 1 percent by weight to about 75 percent by weight, from about 5 percent to about 50 percent by weight, or from about 10 percent to about 40 percent by weight, in a thermal insulating material or a PEG material. In a particular embodiment, the composition of the present invention is included in an amount of about 40 percent by weight in a thermal insulating material or PEG material.

[00124] In another embodiment of the present invention, the PEG material of the present invention comprises a first PEG of 200-600 MW blended with a second PEG of 3350-5000 MW as a pharmaceutical carrier and anti-bacterial adhesion agent. For example, the first PEG may have a molecular weight of 400 and may form approximately 45-75% of the pharmaceutical carrier while the second PEG may have a molecular weight of 3350 and may form approximately 25-55% of the pharmaceutical carrier. Specifically, the PEG of 400 MW may form approximately 55-65% of the pharmaceutical carrier while the PEG of 3350 may form approximately 35-45%. More specifically, the PEG of 400 MW may form approximately 60% of the pharmaceutical carrier while the PEG of 3350 MW forms approximately 40%. In one example, the PEG material of the present invention comprises a PEG of 400 MW forms approximately 68%

of the pharmaceutical carrier, the PEG of 3350 MW forms approximately 29%.

[00125] In a further embodiment, the PEG material of the present invention further comprises methyl parabenzene, propyl parabenzene, aloe vera, vitamin E, and salicylic acid. For example, methyl parabenzene may form approximately 0.001-1% of the composition, propyl parabenzene may form approximately 0.001-1%, aloe vera may form from approximately 0.001-2%, vitamin E may form from approximately 0.001-2% and an NSAID, such as salicylic acid, or a derivative thereof, may form from about 1-5% of the composition.

[00126] In a further example, a PEG material of the present invention comprises: a first PEG having a molecular weight of 200-600, wherein the first PEG forms approximately 45-75% of the composition; a second PEG having a molecular weight of 3350-500, wherein the second PEG forms approximately 25-55% of the composition; methyl parabenzene, wherein the methyl parabenzene forms approximately 0.2% of the composition; propyl parabenzene, wherein the propyl parabenzene forms approximately 0.1% of the composition; aloe vera, wherein the aloe vera comprises approximately 0.001% of the composition; vitamin E, wherein the vitamin E forms approximately 0.001% of the composition; and at least one NSAID, such as salicylic acid, wherein the at least one NSAID forms approximately 2% of the composition.

[00127] The composition can be administered topically to deliver an amount comprising from about between about 1 microgram to about 3000 micrograms, from about 10 micrograms to about 2000 micrograms, from about 20 micrograms to about 1000 micrograms, or from about 40 micrograms to about 400 micrograms, for example, of NF-kB inhibitor or cyclooxygenase inhibitor, per square centimeter of treated tissue.

[00128] For example, in one embodiment, a closed wound is treated by contacting the closed wound with a hydrogel or a PEG material comprising an NSAID, such as acetylsalicylic acid, present in an amount up to about 40 percent of the weight of the hydrogel or PEG material; the amount of

NSAID that is administered comprises from about 1 microgram to about 2000 micrograms, or from about 40 micrograms to about 400 micrograms of NSAID per square centimeter of treated tissue. Wherein the closed wound is treated using a hydrogel according to the present invention, the surface temperature of the closed wound is elevated by the hydrogel from about 0.5°C to about 5°C.

[00129] In another embodiment, a closed wound is treated by contacting the closed wound with a thermal insulating material or a PEG material including an effective amount of at least one anti-irritant compound in a suitable pharmaceutical carrier. Examples of an anti-irritant compound or substance that relieves skin irritation that can be used according to this embodiment of the invention include: glyceryl monooleate, diphenhydramine, calamine, and a C_3-C_4 diol. The amount of anti-irritant compound used in this embodiment comprises from about 1 microgram to about 2000 micrograms, or from about 40 micrograms to about 400 micrograms of anti-irritant compound per square centimeter of treated tissue. The thermal insulating material elevates the surface temperature of the closed wound. The thermal insulating material or the PEG material is allowed to remain in contact with the affected area of skin.

[00130] The amount of cyclooxygenase inhibitor, NF-kB inhibitor, anti-irritant, or combination thereof that is administered, and the dosing regimen used, will, of course, be dependent on the particular drug selected, the route or routes of administration employed, the age and general condition of the subject being treated, the severity of the subject's condition, and the judgment of the prescribing physician. Generally, the daily dosage when administered topically or by injection will be determined by, among other factors, the dosage which may be given by some other mode of administration, such as oral. Alternatively, a large initial loading dose can be used to achieve effective levels of the agent, and can be followed by smaller doses to maintain those levels.

[00131] In another embodiment, the invention comprises a kit, or packaged assembly, in the form of a consumer package or prescription

package which provides the necessary ingredients described herein together with directions on how to combine the ingredients to make a hydrogel for use in treatment of a closed wound (*e.g.*, to treat a condition of scar irritation, or to reduce hypertrophic scarring). In one embodiment, a kit may include ingredients that can be co-administered with a hydrogel or PEG material by mixing one or more ingredients with the hydrogel or PEG material for topical application, or for another mode of administration such as oral.

[00132] In one embodiment, a kit for improving the appearance and/or reducing the size of a closed wound can include a composition of the present invention, such as a cyclooxygenase inhibitor, and/or an NF-kB inhibitor, or an anti-irritant and a hydrogel or a PEG material. Such a kit may further include a sterile solution (*e.g.*, saline, water) for mixing with the composition of the present invention. The composition can be applied to the closed wound and covered with the hydrogel or PEG material. In another embodiment, a kit may include a hydrogel or PEG material that includes a composition of the present invention such as a cyclooxygenase inhibitor or an NF-kB inhibitor.

[00133] In another embodiment, a kit may include a hydrogel or a PEG material and a composition comprising up to about 35 percent of each of the following: salicylic acid or a derivative thereof; acetylsalicylic acid or a derivative thereof; a compound selected from aluminum hydroxide, aluminum zirconium trichlorohydrex, and other metallic anti-microbials; a compound selected from diphenhydramine and other anti-pruritic agents; a compound selected from ibuprofen and other NSAIDs specifically inhibiting prostaglandin E2; and a compound selected from NSAIDs specifically inhibiting cyclooxygenase .

[00134] In a particular embodiment, a kit can include a hydrogel or a PEG material and a composition comprising about 2 percent to about 5 percent of salicylic acid or a derivative thereof; about 2 percent to about 5 percent of acetylsalicylic acid or a derivative thereof; about 2 percent to about 5 percent of a compound such as aluminum hydroxide, aluminum

zirconium trichlorohydrex, and other metallic anti-microbials; about 2 percent to about 5 percent of a compound such as diphenhydramine and other anti-pruritic agents; about 2 percent to about 5 percent of a compound such as ibuprofen and other NSAIDs specifically inhibiting prostaglandin E2; and about 2 percent to about 5 percent of a compound such as a NSAIDs specifically inhibiting cyclooxygenase , and mixtures thereof.

[00135] In a further embodiment, the kit comprises a PEG material comprising a PEG of 400 MW combined with a PEG of 3350 MW as a pharmaceutically acceptable carrier. For example, the PEG of 400 MW may form approximately 45-75% of the pharmaceutical carrier while the PEG of 3350 MW may form approximately 25-55% of the pharmaceutical carrier. The PEG material included in the kit of the present invention may further comprise methyl parabenzene, propyl parabenzene, aloe vera, vitamin E, and an NSAID, such as salicylic acid or a derivative thereof. For example, methyl parabenzene may form approximately 0.001-1% of the composition, propyl parabenzene may form approximately 0.001-1%, aloe vera may form from approximately 0.001-2%, vitamin E may form from approximately 0.001-2% and an NSAID, such as salicylic acid, or a derivative/analogue thereof, may form from about 1-5% of the composition.

[00136] In another embodiment the kit may include, in addition to active ingredients and other materials for topical administration, a cyclooxygenase inhibitor and/or an anti-irritant such as diphenhydramine for oral administration.

[00137] In one embodiment, a kit may include a hydrogel composition including up to 20% by weight PEG with up to 95% by weight sterile water. Because PEG is most efficiently sterilized when in powder form, the preparation of the hydrogel by the consumer or patient increases the quality of available gels and reduces the cost of the scar control therapy by leaving the addition of water to the PEG powder until immediately prior to use.

[00138] In addition, a kit-based preparation of a hydrogel or a PEG material which includes, in one embodiment, an anti-pruritic ingredient and/or a cyclooxygenase inhibitor and/or an NF-kB inhibitor, and/or a topical antimicrobial, permits a consumer or patient access to a therapy individually tailored or designed to the size and severity of the irritated scar condition. The components can be prescribed by a treating clinician or can be self-selected based on the patient's current assessment of the scar condition.

[00139] A closed wound control kit according to an embodiment can include devices such as "control top" panties or other garments for use with scars of the lower abdominal skin, stretch bandages (*e.g.* elastic-type sports wraps or ace wraps), and gloves to keep the hydrogel or the PEG material affixed to the affected area of skin.

[00140] Materials in a kit may also include: protective gloves for user to wear during hydrogel or PEG material preparation; miniature timer to allow user to time the hydrogel or PEG material preparation; miniature spatula to smooth or stir hydrogel or PEG material ingredients; hydrogel or PEG material "tray" or "mold" of depth not to exceed 0.5 cm, and length and width varying depending on the amount of hydrogel or PEG material to be prepared by user; a ruler either in paper, plastic, or tape form, to allow user to measure affected skin to be treated and to choose correctly the size and amount of hydrogel or PEG material to be prepared.

[00141] An example of a method according to one embodiment of using a kit may include reading directions prior to kit use; using included ruler to measure affected area of skin; comparing scar size to hydrogel or PEG material preparation table for ingredients and recipe or to prescription or clinician recommendation; using spatula to mix recommended amount of water with hydrogel or PEG material ingredients in amount specific to scar size; placing hydrogel or PEG material mixture in mold or tray and timing; adding active ingredients according to prescription or as recommended by clinician or by personal preference; applying resulting hydrogel or PEG material to affected area of skin and securing the hydrogel or PEG material

to the skin. A method according to an embodiment may also include co-administering other compositions depending on prescription, as recommended by clinician, or according to personal preference.

[00142] A kit according to an embodiment may include ingredients or components for one treatment or may include ingredients or components for multiple treatments. A kit according to an embodiment may include a combination of medications and devices tailored to a patient's irritated scar condition.

[00143] It is intended that the foregoing detailed description be regarded as illustrative rather than limiting. The present invention is further illustrated by the following experimental investigations and examples, which should not be construed as limiting. The contents of all references, patents and published applications cited throughout this patent are hereby incorporated by reference herein.

[00144] EXAMPLE 1: Manufacture of PEG Material Incorporating Salicylic Acid

[00145] In one example, a composition of the present invention comprises a PEG material incorporating salicylic acid. This composition of the present invention can be made by combining approximately 718 pounds of a PEG material having a molecular weight of 400 (*e.g.* Carbowax® available from The Dow Chemical Company®) ("PEG400") with approximately 308 pounds of a PEG material having a molecular weight of 3350 (*e.g.* Carbowax® available from The Dow Chemical Company®) ("PEG3350") in a large stainless steel kettle. Preferably, the kettle has been cleaned and sanitized prior to combining the PEG materials. The combined PEG materials are heated until the temperature of the PEG materials reaches approximately 65°C. The combined PEG materials are mixed under heated conditions until they are completely in liquid form.

[00146] Once the combined PEG materials are liquid, the liquid PEG is maintained at a temperature of approximately 65°C. Methyl parabenzene, propyl parabenzene, aloe vera powder, vitamin E, and salicylic acid are then added to the kettle containing the liquid PEG mixture. The mixture is

then cooled to approximately 40°C. PEG materials incorporating salicylic acid can be formed into a shape for use in the present invention at a temperature of approximately 31-35°C.

[00147] In this example, PEG 400 forms approximately 45-75% w/w of the composition; PEG 3350 forms approximately 25-55% w/w of the composition; salicylic acid forms approximately 1-5% w/w of the composition, aloe vera forms approximately 0.2-2% w/w of the composition; Vitamin E forms approximately 0.2-2% w/w of the composition, methyl-parabenzene forms approximately 0.001-0.1%; and propyl-parabenzene forms approximately 0.001-0.1% w/w of the composition.

[00148] EXAMPLE 2: Manufacture of PEG Material Incorporating Sodium Salicylate

[00149] In another example, a composition of the present invention may comprise a PEG material in combination with sodium salicylate. In particular, a PEG material can be made by combining approximately 718 pounds of a PEG400 material (*e.g.* Carbowax® available from The Dow Chemical Company®) with approximately 308 pounds of a PEG3350 material (*e.g.* Carbowax® available from The Dow Chemical Company®) in a large stainless steel kettle. Preferably, the kettle has been cleaned and sanitized prior to combining the PEG materials. The combined PEG materials are heated until the temperature of the PEG materials reaches 65°C. The combined PEG materials are mixed under heated conditions until they are completely in liquid form.

[00150] Once the combined PEG materials are liquid, the liquid PEG is maintained at approximately 65°C. Methyl parabenzene, propyl parabenzene, aloe vera powder, vitamin E, BHT, and sodium salicylate are then added to the mixture. The mixture is then cooled to approximately 40°C. PEG materials incorporating sodium salicylate can be formed into a shape for use in the present invention at a temperature of approximately 31-35°C.

[00151] In this example, PEG 400 forms approximately 45-75% w/w of the composition; PEG 3350 forms approximately 25-55% w/w of the composition; sodium salicylate forms approximately 1-5% w/w of the composition; methyl parabenzene forms approximately 0.001-0.1% w/w of the composition; propyl parabenzene forms approximately 0.001-1% w/w of the composition; aloe vera forms approximately 0.2-2% w/w of the composition; Vitamin E forms approximately 0.2-2% w/w of the composition; and BHT forms approximately 0.1- 2% w/w of the composition.

[00152] **EXAMPLE 3: Manufacture of PEG Material**

[00153] In another example, a composition of the present invention comprises a PEG material composed of a PEG400 with BHT dissolved in the PEG 400. Specifically, BHT is obtained from Spectrum Chemical & Laboratory Products, Inc., (Gardena, California 90248-2027). As supplied by Spectrum Chemical and Laboratory Products, Inc., BHT is granular and therefore, is powdered. Powdered BHT is dissolved in PEG 400 by dropping the powdered BHT through a clean and dried glass funnel into a reaction flask (outside bath temperature 65 ^{0}C) containing PEG 400 (*e.g.* Carbowax® available from The Dow Chemical Company®). PEG 400 with BHT dissolved in it is mixed with PEG 3350 (*e.g.* Carbowax® available from The Dow Chemical Company®) in a large stainless steel kettle. The kettle is cleaned and sanitized prior to combining the PEG materials. The combined PEG materials are heated until the temperature of the PEG materials reaches approximately 65°C. The combined PEG materials are mixed at approximately 65°C until they are completely in liquid form.

[00154] Once the combined PEG materials are liquid, the liquid PEG is maintained at approximately 65°C and sodium salicylate followed by methyl parabenzene, and propyl parabenzene are added. The mixture is then cooled to approximately 40°C. PEG materials are formed into a shape for use in the present invention at a temperature of approximately 31-35°C.

[00155] In this example, PEG 400 forms approximately 45-75% w/w of the composition; PEG 3350 forms approximately 25-55% w/w of the composition; sodium salicylate forms approximately 1-5% w/w of the composition; methyl parabenzene forms approximately 0.001-0.1% w/w of

the composition; propyl parabenzene forms approximately 0.001-1% w/w of the composition; and BHT forms approximately 0.1- 2% w/w of the composition.

[00156] EXAMPLE 4: Formulation of a PEG Material

[00157] In a further example, a composition of the present invention comprises a PEG material composed of a PEG400 with BHT dissolved in the PEG 400. Specifically, BHT is obtained from Spectrum Chemical & Laboratory Products, Inc., (Gardena, California 90248-2027). As supplied by Spectrum Chemical and Laboratory Products, Inc., BHT is granular and therefore, is powdered.

[00158] A mechanical stirrer is fitted into a thoroughly clean and dried glass conical flask (2000 ml capacity) in a water bath maintained at 65-70 ^{0}C. Throughout the experiment, the mouth of the flask is covered with a parafilm except while pouring / dropping chemicals. Powdered BHT is dropped through a clean and dried glass funnel into the 2000 ml reaction flask (outside bath temperature 65 ^{0}C) containing approximately PEG 400 (*e.g.* Carbowax® available from The Dow Chemical Company®).

[00159] Approximately 60 % (w/w) PEG 400 containing the dissolved BHT is mixed with approximately 37% (w/w) PEG 3350 (e.g. Carbowax® available from The Dow Chemical Company®) in a large stainless steel kettle. Preferably, the kettle has been clean and sanitized prior to combining the PEG materials. The combined PEG materials are heated until the temperature reaches approximately 65°C. The combined PEG materials are mixed until they are completely in liquid form.

[00160] Once the combined PEG materials are liquid, the liquid PEG is maintained at 65°C and sodium salicylate followed by methyl parabenzene, propyl parabenzene are added. Then the mixture is cooled to approximately 40°C. PEG materials are formed into a shape for use.

[00161] The formulation for the PEG material described in this example is set forth below in Table I:

Table 1: Exemplary PEG Formulation

Ingredients	Percentage (w/w of the total composition)
PEG 400	61.39 %
PEG 3350	36.11%
Sodium Salicylate	2 %
BHT	0.2%
Methyl Parabenzene (Methyl 4-hydroxy Benzoate)	0.2%
Propyl Parabenzene (Propyl 4-hydroxy Benzoate)	0.1%

[00162] EXAMPLE 5: Microbial Contamination Testing of PEG Material with BHT Dissolved in PEG400

[00163] Northview Labs in Northbrook, Illinois conducted a standard microbial contamination study according to guideline 5064-0M02. Individual containers each containing a 20 gram sample of a PEG material incorporating the formulation of Example 4 were inoculated with a microorganism suspension to achieve sample inoculum levels of $1x\ 10^5$ to 1×10^6 CFU per gram. Specifically, the PEG material was comprised of the formulation set forth above in Table I.

[00164] Each container was inoculated with a microorganism suspension to achieve sample inoculum levels of $1x\ 10^5$ to 1×10^6 CFU per gram. The microorganism suspension consisted of *P. aeruginosa, E. coli, S. aureus, C. albicans, and A. niger.* As determined by the plate count validation procedure, plate count results just after inoculation showed the bacterial count was less than 10 CFU/g. Both mold and yeast counts were also less than 10 CFU/g.

[00165] The inoculated sample containers were stored at 20-25°C. The population of the challenge organisms was determined by pour plate method at day 14 and day 28 after inoculation. The plate counts were performed at a 1:10 dilution using D/E neutralizing broth as the diluent and tryptic soy and Sabouraud dextrose agars. There was a 2 log reduction of bacterial organisms at day 14 with no increase at day 28. Fungal organisms also demonstrated no increase from the initial inoculum during the 28 day test period.

[00166] EXAMPLE 6: Primary Irritation Test

[00167] The formulation for the PEG material described in Example 4 was evaluated for skin irritation in accordance with the guidelines of the International Organization for Standardization (ISO). Specifically, the procedure outlined in test ISO10993:Biological Evaluation of Medical Devices, Pt 10:Test for Irritation and Sensitization was followed by NAMSA (Northwood, Oh). Per the ISO10993 protocol, the control article was four ply gauze cut into 25 mm x 25 mm sections, moistened with 0.5 ml of saline per section and backed with polyethylene plastic. The test article was a PEG material comprising the formulation of Example 4.

[00168] Two 0.5 gm portions of the test article and two 25 mm x 25 mm sections of the control article were topically applied to the skin of each of three rabbits and left in place for 24 hours. Sites of application of the test and control articles were graded for erythema and edema at 1, 24, 48, and 72 hours after removal of the single sample application. . Primary irritation index of the test was calculated following completion for each animal. The erythema and edema scores obtained at 24, 48 and 72 hour intervals were added together and divided by the total number of observations. This calculation was conducted separately for the test control article for each animal. The score of the control was subtracted from the score of the test article to obtain the primary irritation score. Under the conditions of this study, no erythema and no edema were observed on the skin of the rabbits. The primary irritation index for the test was calculated to be 0.0 thus response of the formulation was categorized as negligible. A mean score of 0.0 to 0.4 is considered negligible, 0.5-1.9 is considered slight, 2.0 to 4.9 is considered moderate and 5.0 to 8.0 is considered severe.

[00169] EXAMPLE 7: Stability Study

[00170] Stability of the PEG formulation discussed in Example 4 was studied by validated HPLC assay. In particular, the stability of sodium salicylate in a cream formulation comprised of the PEG formulation of Example 4 and the chemical stability of sodium salicylate was established

in squeeze tubes held at environmental conditions of 40°C and 75% relative humidity.

[00171] About 0.5 g of a cream formulation comprised of the PEG formulation of Example 4 was fortified with approximately 65 mg sodium salicylate (approximately 12%) and mixed very well. The fortified sample and a non-fortified sample were stored at 50°C and approximately 85% relative humidity for eight days. A second fortified cream sample was freshly prepared on the day of analysis for comparison.

[00172] For analysis by HPLC, each of the three samples, in its entirety, was dissolved in 20 mL of acetonitrile to form solutions with nominal concentrations of about 3.0 mg/mL for the fortified samples and about 0.5 mg/mL for the non-fortified sample (a 2% formulation). Ten-microliter injections of these solutions were analyzed by HPLC.

[00173] Results from the HPLC analysis of the three samples indicate one degradation product was formed in the fortified samples. However, the degradation product was only a minor impurity, representing approximately a 0.05% breakdown of sodium salicylate in the sample.

[00174] At typical levels of approximately 2% active ingredient (*e.g.* sodium salicylate) in the formulation, *i.e.* the non-fortified test samples, no degradation product is observed. This is likely because any degradation product that might be present would be present in too small an amount to be detected.

[00175] Therefore, this example demonstrates that the formulations of the present invention, for example a formulation comprised of 45-75% w/w PEG400, 25-55% w/w PEG3350, 1-5% w/w sodium salicylate, 0.001-0.1% w/w methyl parabenzene, 0.001-1% w/w propyl parabenzene, and 0.1-2% w/w BHT have excellent stability, as exemplified by the formulation of example 4 examined in this example. Thus, formulations of the present invention are not prone to degradation of the sodium salicylate ingredient.

[00176] **EXAMPLE 8: Storage Stability**

[00177] Six tubes of cream comprised of 45-75% w/w PEG400, 25-55% w/w PEG3350, 1-5% w/w sodium salicylate, 0.001-0.1% w/w methyl

parabenzene, 0.001-1% w/w propyl parabenzene, and 0.1-2% w/w BHT were place in storage at conditions of 40°C and 75% relative humidity (%RH). One tube of cream was analyzed to serve as time zero analysis. Three tubes of cream were removed for analysis after 31 days of storage at the controlled conditions. The remaining two tubes of cream were analyzed at 120 days. All samples were analyzed for appearance and sodium salicylate content.

[00178] HPLC Injections of the cream stability sample preparations were made and evaluated as to the concentration of sodium salicylate present in the cream formulation. Quantification was made by comparison of peak areas in the sample chromatogram to those in chromatograms of external standard solutions, which were never subjected to stress conditions of 40°C and 75% relative humidity.

[00179] Appearances of the cream stability samples were determined by squeezing the tube containing the cream to obtain a bead of the material on a piece of weighing paper. The material was then carefully observed under a bright light source and the characteristics of the appearance recorded.

[00180] The pH values of the cream stability samples were determined by using a calibrated Sentron pH meter. The seals were removed from the tubes and a small amount of cream was place on the microsensor of the meter. The pH values of the formulations were recorded directly from the instrument output. At time zero days, the average pH of three samples was 8.06 with a standard deviation of 0.11. After 31 days, the average pH of two samples was 7.96 with a standard deviation of 0.10. After 120 days, the average pH of three samples was 8.0 with a standard deviation of 0.24.

[00181] Appearances of the cream stability samples were determined by squeezing the tube containing the cream to obtain a bead of the material on a piece of weighing paper. The material was then carefully observed under a bright light source and the characteristics of the appearance recorded.

[00182] No changes in the appearance of the cream formulations of example 4 were found after 120 days at 120 days at 40°C and 75% RH. The appearance of all samples examined, at time zero (one sample), one month (three samples) and three months (three samples), were described as follows: white, opaque paste with no visible particulates and a sheen on the surface of the cream.

[00183] These data (Quantitative HPLC, pH and Appearance) suggest that sodium salicylate is stable in the cream formulation of example 4 at 40°C and 75% RH over a 120-day period.

[00184] EXAMPLE 9: PEG400 Material Incorporating BHT at Room Temperature

[00185] In another example, a formulation of the present invention may comprise a PEG400 material incorporating BHT. This formulation may be made by combining approximately 718 pounds of a PEG400 material (*e.g.* Carbowax® available from The Dow Chemical Company®) with Vitamin E acetate, Sodium Salicylate, BHT, Methyl Parabenzene (Methyl 4- hydroxy Benzoate) and Propyl Parabenzene (Propyl 4- hydroxy Benzoate) in a in a large stainless steel kettle at room temperature. Preferably, the kettle has been cleaned and sanitized prior to combining the materials. The materials are thoroughly mixed.

[00186] In this example, PEG 400 forms approximately 45-75% w/w of the composition; sodium salicylate forms approximately 1-5% w/w of the composition; methyl parabenzene forms approximately 0.001-0.1% w/w of the composition; propyl parabenzene forms approximately 0.001-1% w/w of the composition; Vitamin E acetate forms approximately 0.2-2% w/w of the composition; and BHT forms approximately 0.1- 2% w/w of the composition.

[00187] EXAMPLE 10: Anti-Microbial Preservative Effectiveness Testing of PEG Material

[00188] Northview Labs in Northbrook, Illinois conducted an anti-microbial preservative effectiveness study per the standardized protocol, USP51, set forth by the US Pharmacopeia. Per the USP51 protocol, individual containers each containing a 20 gram sample of a PEG material comprised of 584 g of PEG400, 391 g PEG3350, 2 g BHT, 20 g sodium salicylate, 2 g methyl

parabenzene, and 1 g propyl parabenzene were inoculated with aerobic microorganisms to achieve sample inoculum levels of 1x 10^5 to 1 x 10^6 CFU per gram.

[00189] Each container was inoculated with a microorganism to achieve sample inoculum levels of 1x 10^5 to 1 x 10^6 CFU per gram. The microorganism inoculated consisted of *P. aeruginosa, E. coli, S. aureus, C. albicans, and A. niger.* As determined by the plate count validation procedure, plate count results just after inoculation showed the bacterial count was less than 10 CFU/g. Both mold and yeast counts were also less than 10 CFU/g.

[00190] The inoculated sample containers were stored at 20-25°C. The population of the challenge organisms was determined by pour plate method at day 14 and day 28 after inoculation. The plate counts were performed at a 1:10 dilution using D/E neutralizing broth as the diluent and tryptic soy and Sabouraud dextrose agars. There was a 2 log reduction of bacterial organisms at day 14 with no increase at day 28. Fungal organisms also demonstrated no increase from the initial inoculum during the 28 day test period.

[00191] While this invention has been particularly shown and described, for example, by reference to the above examples, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

[00192] It is therefore intended that the foregoing detailed description be regarded as illustrative rather than limiting, and that it be understood that it is the following claims, including all equivalents, that are intended to define the spirit and scope of this invention.

CLAIMS

1. A composition for improving the appearance or reducing the size of a closed wound comprising:

(a) at least one non-steroidal anti-inflammatory agent, wherein the at least one non-steroidal anti-inflammatory agent comprises approximately 1-5% w/w of the composition;

(b) methyl parabenzene comprising approximately 0.001-1% w/w of the composition;

(c) propyl parabenzene comprising approximately 0.001-1 % of the composition; and

(d) a pharmaceutically acceptable carrier comprising a polyethylene glycol material, wherein the polyethylene glycol material comprises a blend of a first polyethylene glycol having an average molecular weight of 200-600 and a second polyethylene glycol having an average molecular weight of 3350-5000, wherein the first polyethylene glycol comprises approximately 45-75% w/w of the composition and wherein the second polyethylene glycol comprises approximately 25-55% w/w of the composition.

2. The composition of claim 1, further comprising butylated hydroxy toluene in an amount of approximately 0.1-2% w/w of the composition.

3. The composition of claim 1 or 2, further comprising vitamin E in an amount of approximately 0.001-2% w/w of the composition.

4. The composition of claim 1, 2, or 3 further comprising aloe vera in an amount of approximately 0.001-2% w/w of the composition.

5. The composition of claim 1, 2, 3, or 4, wherein the first polyethylene glycol has an average molecular weight of 400 and comprises approximately 50-70% w/w of the composition and wherein the second polyethylene glycol has an average molecular weight of 3350 and comprises approximately 30-45% w/w of the composition.

6. The composition of claim 5, wherein the at least one non-steroidal anti-inflammatory agent is a cyclooxygenase inhibitor, an NF-kB inhibitor, a cyclooxygenase and NF-kB inhibitor, or some combination thereof.

7. The composition of claim 6, wherein the at least one non-steroidal anti-inflammatory agent is dispersed within the polyethylene glycol material, and wherein the at least one non-steroidal anti-inflammatory agent is selected from the group consisting of: acetylsalicylic acid, sodium salicylate, aryl, substituted or unsubstituted aralkyl, allyl, and substituted or unsubstituted, linear, branched, or cyclic alkyl esters of acetylsalicylic acid; ibuprofen; celecoxib; rofecoxib; flufenamic acid; indomethacin; nabumetone; naproxen; salicylic acid; salts of salicylic acid; aryl, substituted or unsubstituted aralkyl, allyl, and substituted or unsubstituted, linear, branched, or cylic alkyl esters of salicylic acid; sulindac sulfide; sulindac sulfone; sulfasalazine; and pharmaceutically acceptable salts and blends thereof.

8. The composition of claim 6, wherein the closed wound is a scar selected from the group consisting of: a normal scar; a hypertrophic scar; a keloid scar; a Dupuytren's contracture; a Peyronnie's Disease; a reactive scar; an excessive post-operative scar; or a fibrotic scar.

9. The composition of claim 6, wherein the closed wound is selected from a group consisting of: a wound caused by laceration; a wound caused by avulsion; a wound caused by burn; a wound caused by radiation; and a wound caused by chemical facial peel.

10. The composition of claim 1, 2, 3, or 4, further comprising an anti-irritant.

11. The composition of claim 10, wherein the anti-irritant is selected from the group consisting of glycerol monooleate, diphenhydramine, calamine and C3-C4 diol.

12. The composition of claim 1, 2, 3, or 4, further comprising a deodorant agent.

13. The composition of claim 12, wherein the deodorant agent is selected from the group consisting of aluminum zirconium trichlorohydrex and zinc acetate.

14. A composition for improving the appearance or reducing the size of a closed wound comprising:

(a) at least one non-steroidal anti-inflammatory agent, wherein the at least one non-steroidal anti-inflammatory agent comprises approximately 1-5% w/w of the composition;

(b) methyl parabenzene comprising approximately 0.001-1% w/w of the composition;

(c) propyl parabenzene comprising approximately 0.001-1 % of the composition; and

(d) a pharmaceutically acceptable carrier comprising a polyethylene glycol material, wherein the polyethylene glycol material comprises a blend of a first polyethylene glycol having an average molecular weight of 200-600 and a second polyethylene glycol having an average molecular weight of 3350-5000, wherein the first polyethylene glycol comprises approximately 45-75% w/w of the composition and wherein the second polyethylene glycol comprises approximately 25-55% w/w of the composition

wherein the polyethylene glycol material provides a mechanical barrier for decreased penetration of bacteria and foreign material.

15. A composition for improving the appearance or reducing the size of a closed wound comprising:

(a) at least one non-steroidal anti-inflammatory agent, wherein the at least one non-steroidal anti-inflammatory agent comprises approximately 1-5% w/w of the composition;

(b) methyl parabenzene comprising approximately 0.001-1% w/w of the composition;

(c) propyl parabenzene comprising approximately 0.001-1 % of the composition; and

(d) a pharmaceutically acceptable carrier comprising a polyethylene glycol material, wherein the polyethylene glycol material comprises a blend of a first polyethylene glycol having an average molecular weight of 200-600 and a second polyethylene glycol having an average molecular weight of 3350-5000, wherein the first polyethylene glycol comprises approximately 45-75% w/w of the composition and wherein the second polyethylene glycol comprises approximately 25-55% w/w of the composition

wherein the polyethylene glycol material enhances transdermal penetration of active ingredients.

16. The composition of claim1, wherein the at least one non-steroidal anti-inflammatory agent is salicylic acid and further wherein the salicylic acid is present in an amount ranging from approximately 1-5% w/w of the composition.

17. The composition of claim 1, wherein the at least one non-steroidal anti-inflammatory agent is sodium salicylate and further wherein the salicylic acid is present in an amount ranging from approximately 1-5% w/w of the composition.

18. A method of improving the appearance or reducing the size of a closed wound comprising administering the composition of claim 1, 2, 3, 4, 14, 15, 16, or 17.

19. The method of claim 18, wherein the composition is topically administered to a closed wound.

20. The method of claim 18, wherein the closed wound is a scar selected from the group consisting of: a normal scar; a hypertrophic scar; a

keloid scar; a Dupuytren's contracture; a Peyronnie's Disease; a reactive scar; an excessive post-operative scar; and a fibrotic scar.

21. The method of claim 18, wherein the closed wound is selected from a group consisting of a wound caused by laceration; a wound caused by avulsion; a wound caused by burn; a wound caused by radiation; and a wound caused by chemical facial peel.

22. A kit comprising the composition of claim 1, 2, 3, 4, 6, 9, 11, 14, 15, 16, or 17.

23. Use of a hydrogel or a gel in combination with a composition of claim 1, 2, 3, 4, 6, 9, 11, 14, 15, 16, or 17 to improve the appearance or reduce the size of a closed wound on the patient's skin.