Name of the Applicant: Shilpa Medicare Limited

Sheet no 1
Total No. of Sheets 3

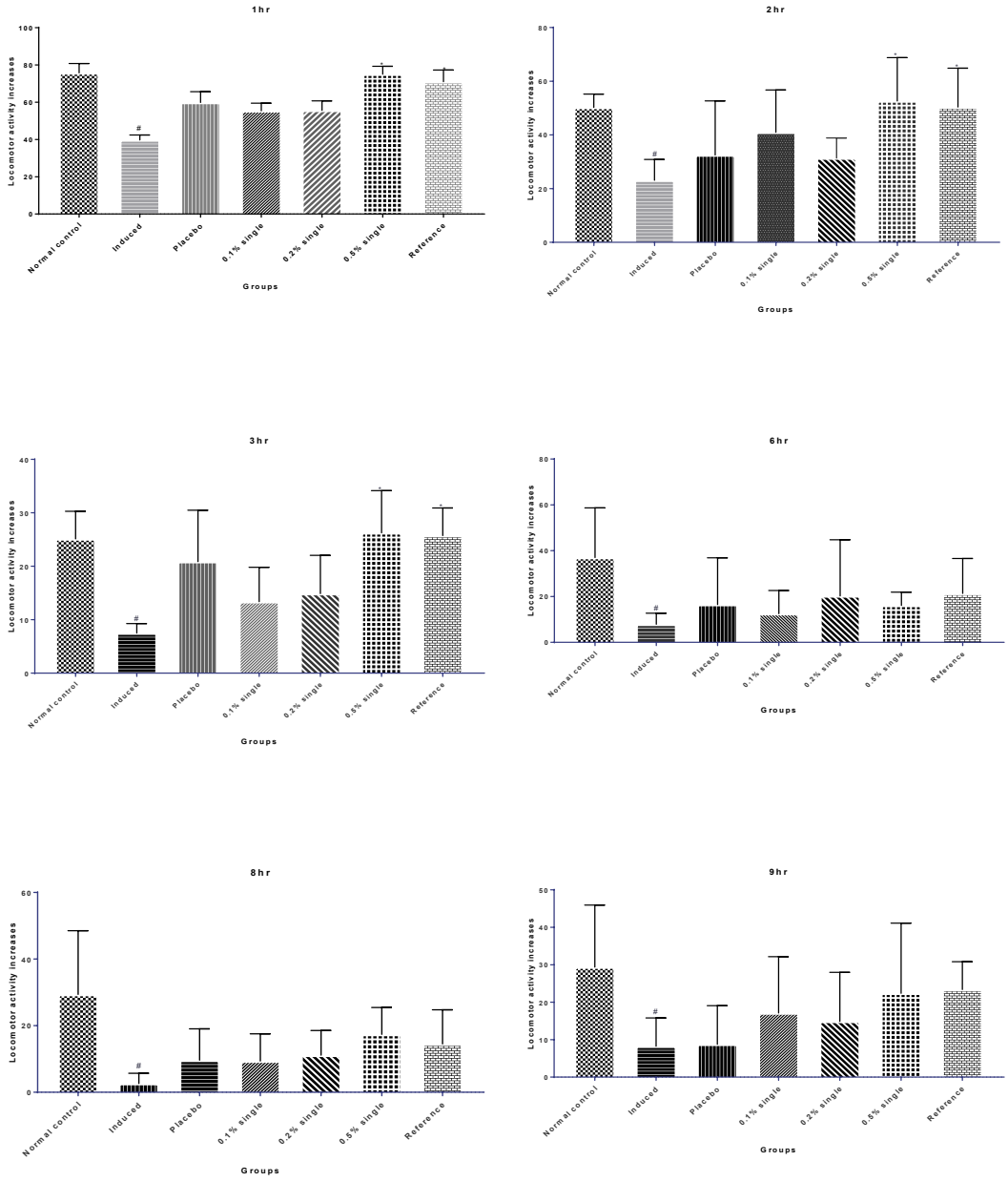

Figure – 1

Viswaprasad Varanasi
Sr. General Manager – IPM
Shilpa Medicare Limited

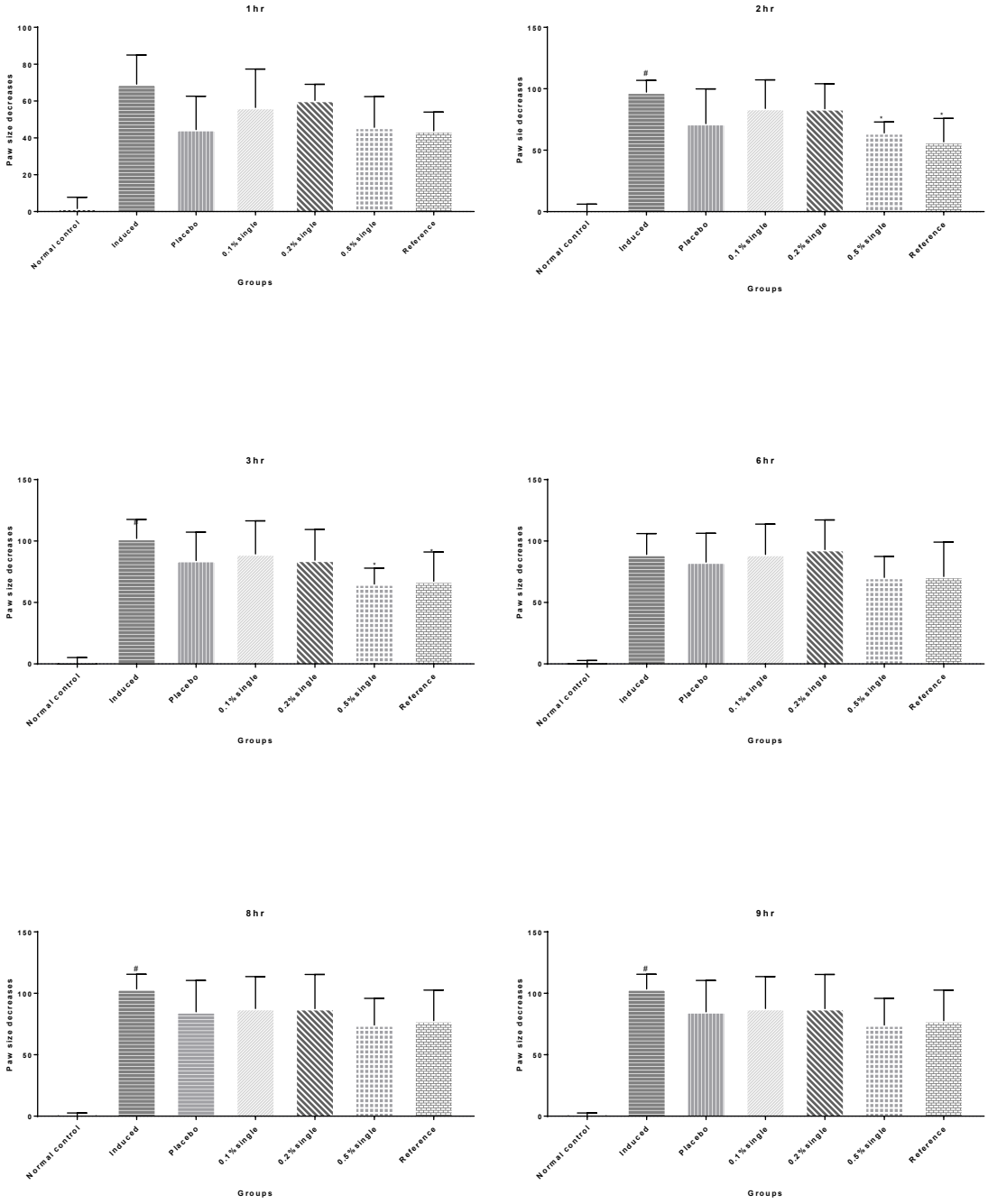

Figure – 2

Viswaprasad Varanasi
Sr. General Manager – IPM
Shilpa Medicare Limited

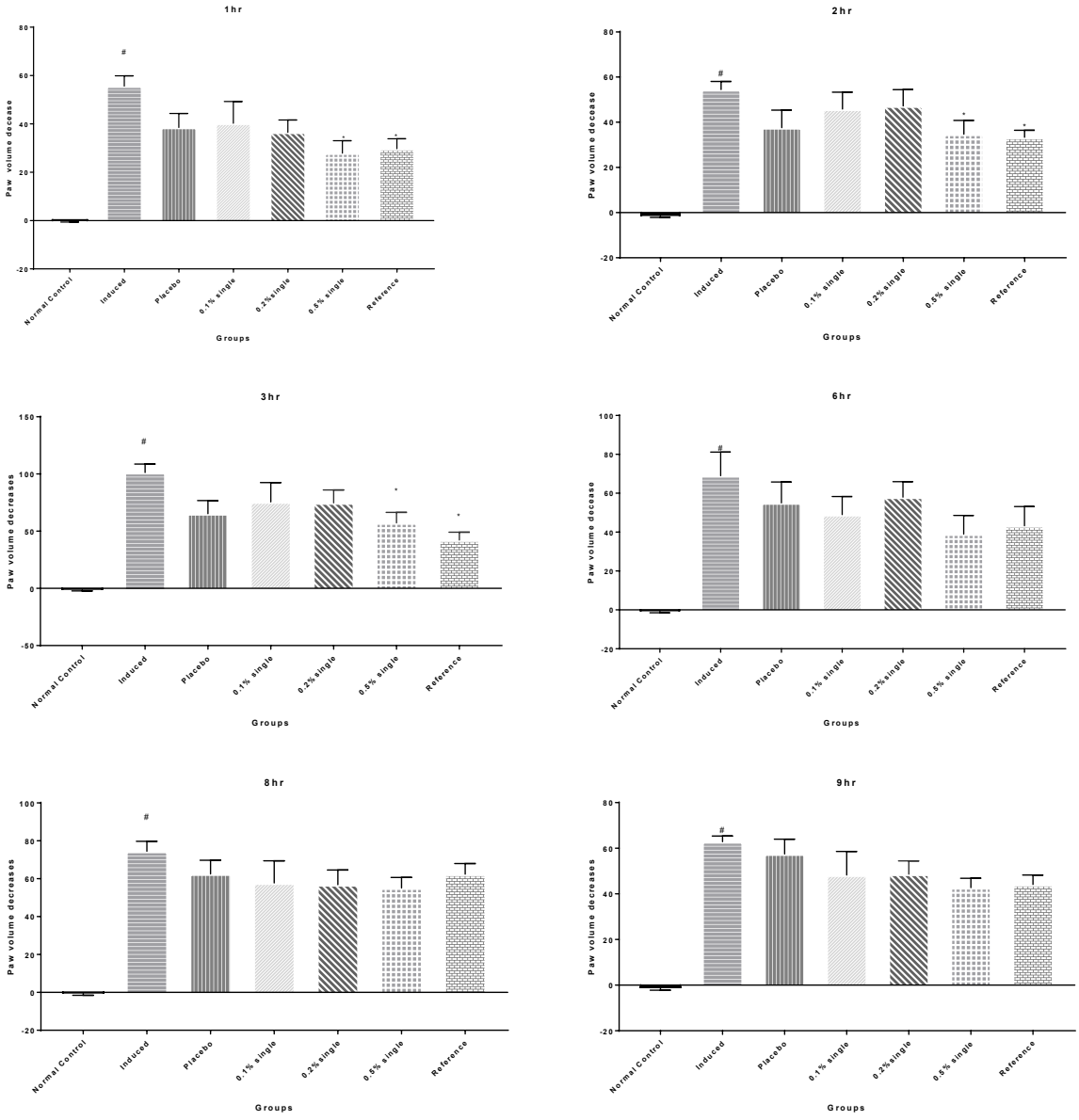

Figure – 3

Viswaprasad Varanasi
Sr. General Manager – IPM
Shilpa Medicare Limited

FORM 2

THE PATENTS ACT,
(39 OF 1970)
THE PATENT RULES, 2003.

COMPLETE SPECIFICATION
(SECTION 10 AND RULE 13)

PALMITOYLETHANOLAMIDE SPRAY COMPOSITIONS

Shilpa Medicare Limited
An Indian Company having its address at
#12-6-214/A1,
Hyderabad Road,
Raichur – 584 135,
Karnataka, India.

The following specification particularly describes the invention and the manner in which it is performed.

[001] FIELD OF THE INVENTION

[002] The present invention relates topical spray compositions of palmitoylethanolamide (Palmidrol), and more particularly compositions comprising palmitoylethanolamide and menthol. Further the present invention also relates to topical spray compositions comprising palmitoylethanolamide and an anti-inflammatory or anti-pain component.

[003] BACKGROUND OF THE INVENTION

[004] Palmitoylethanolamide (Palmidrol) is an N-(long-chain-acyl) ethanolamine that is the ethanolamide of palmitic (hexadecenoic) acid that is used as an anti-inflammatory, analgesic, antipyretic, neuroprotective, antihypertensive and anticonvulsant agent. Palmitoylethanolamide acts by blocking the synthesis of prostaglandins by inhibiting cyclooxygenase, which converts arachidonic acid to cyclic endoperoxides, precursors of prostaglandins. Thus, the inhibition of prostaglandin synthesis accounts for their analgesic, antipyretic and platelet-inhibitory actions.

[005] US Patent No. 10,350,179 relates to the combination comprising palmitoylethanolamide and lycopene, wherein palmitoylethanolamide is about 70% of the combination, based on the total weight of the combination, and wherein the percentage amount of lycopene is about 30% of the combination, based on the total weight of the combination which is used for the treatment of inflammatory diseases.

[006] PCT Publication No. WO2016183134A1 relates to the composition comprising palmitoylethanolamide, salicylate, and/or allantoin and one or more solvents for treatment of inflammation and pain.

[007] The prior arts disclose various topical compositions like ointments, lotions, creams, gels, drops, liquids, powders and sprays of palmitoylethanolamide for the treatment of inflammation with various combinations like lycopene, salicylate and/or allantoin. However there exists a need to develop a topical spray composition comprising palmitoylethanolamide for treatment of inflammation for immediate activity.

[008] SUMMARY OF THE INVENTION

[009] The present invention relates to the topical composition comprising (a) palmitoylethanolamide and (b) menthol.

[010] The present invention further relates to the combination comprising palmitoylethanolamide and menthol.

[011] The present invention further relates to the topical spray composition comprising (a) palmitoylethanolamide and (b) menthol.

[012] The present invention specifically relates to the topical spray composition comprising (a) palmitoylethanolamide, (b) menthol and (c) one or more solvents.

[013] The present invention further relates to the topical spray composition comprising

(a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,
(b) about 1% w/v to about 10% w/v menthol and
(c) about 1% w/v to about 99% w/v of one or more solvents.

[014] The present invention relates to the topical spray composition comprising
(a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,
(b) about 1% w/v to about 10% w/v menthol and
(c) about 1% w/v to about 98% w/v of one or more solvents, wherein solvents are selected from group consisting of methanol, ethanol, isopropanol, diethylene glycol monoethyl ether, propylene glycol or combinations thereof.

[015] The present invention further relates to the topical spray composition comprising
(a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,
(b) about 1% w/v to about 10% w/v menthol,
(c) about 5% w/v to about 30% w/v diethylene glycol monoethyl ether,
(d) about 10% w/v to about 70% w/v ethanol, and
(e) isopropyl alcohol.

[016] The present invention further relates to the topical spray composition comprising
(a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,
(b) about 1% w/v to about 10% w/v menthol,
(c) about 5% w/v to about 30% w/v diethylene glycol monoethyl ether,
(d) about 10% w/v to about 70% w/v ethanol,
(e) about 0.1% w/v to about 5% w/v fragrance, preferably lemongrass oil and
(f) isopropyl alcohol.

[017] The present invention relates to the topical spray composition comprising

(a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,

(b) about 1% w/v to about 10% w/v menthol.

(c) about 5% w/v to about 25% w/v diethylene glycol monoethyl ether,

(d) about 20% w/v to about 60% w/v ethanol,

(e) about 0.1% w/v to about 5% w/v fragrance, preferably lemongrass oil and

(f) isopropyl alcohol.

[018] The present invention relates to the topical spray composition comprising

(a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,

(b) about 5% w/v menthol.

(c) about 10% w/v diethylene glycol monoethyl ether,

(d) about 39% w/v ethanol,

(e) about 1% w/v fragrance preferably lemongrass oil and

(f) isopropyl alcohol.

[019] The present invention relates to the topical spray composition comprising (a) palmitoylethanolamide and (b) anti-inflammatory or anti-pain component.

[020] The present invention relates to the topical spray composition comprising (a) palmitoylethanolamide and (b) anti-inflammatory or anti-pain component selected from group consisting of diclofenac, diclofenac diethylamine, ibuprofen, dexibuprofen, piketoprofen, fenoprofen, pelubiprofen, ketoprofen, dexketoprofen, loxoprofen, naproxen, flurbiprofen, celecoxib, etoricoxib,

polmacoxib, imrecoxib, parecoxib, nimesulide, meloxicam, piroxicam, lornoxicam, tenoxicam, indomethacin, felbinac, aceclofenac, etodolac, sulindac, tofacitinib, baricitinib, peficitinib, upadacitinib, filgotinib, peficitinib, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, salicylic acid, methyl salicylate, nabumetone, capsaicin, misoprostol, sulfasalazine, acemetacin, diflunisal, dimethyl sulfoxide, oxaprozin, camphor, lidocaine, ketorolac, menthol and levomenthol.

[021] The present invention further relates to the topical spray composition comprising (a) palmitoylethanolamide and (b) diclofenac diethylamine.

[022] The present invention relates to the topical spray composition comprising (a) palmitoylethanolamide and (b) methyl salicylate.

[023] BRIEF DESCRIPTION OF THE DRAWINGS

[024] Figure – 1 discloses the locomotor activity in carrageenan induced inflammation at different time points of rats in groups of normal control, induced, placebo, spray compositions of example 2, 3 and 4 and reference formulation.

[025] Figure – 2 discloses the evaluation of paw size measurement by Vernier callipers of rats in groups of normal control, induced, placebo, spray compositions of example 2, 3 and 4 and reference formulation.

[026] Figure – 3 discloses the evaluation of paw volume measurement by Plethysmometer of rats in groups of normal control, induced, placebo, spray compositions of example 2, 3 and 4 and reference formulation. normal control, induced, placebo, spray compositions of example 2, 3 and 4 and reference formulation.

[027] DETAILED DESCRIPTION OF THE INVENTION

[028] The present invention provides the topical composition comprising palmitoylethanolamide and the process for preparation thereof.

[029] Palmitoylethanolamide may be used alternatively in non-micronized form, or in micronized form, or in ultra-micronized form. The topical composition as per the present invention is in the form of a topical liquid spray dosage form.

[030] The present invention further relates to topical spray composition comprising palmitoylethanolamide.

[031] The present inventive palmitoylethanolamide spray dosage form is related to a method of treating pain and/or inflammation which comprises topically administering to a mammal, especially a human, in need thereof a therapeutically effective amount of a topical pharmaceutical composition according to the invention.

[032] As used herein, "human" includes adults and all children, or, for example, in specific cases may refer, for example, to adults of 18 years of age and older; or children 17 years of age and younger; or adults and children aged 12 years and older.

[033] In one aspect, the invention provides a method for relieving chronic pain and associated inflammation in a patient in need thereof. In another aspect, the invention provides a method for relieving acute pain and associated inflammation in a patient in need thereof. Thus, the invention provides a method for the relief of the chronic pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands, or the pain of backache.

[034] The invention also provides a method for treating a mammalian subject in need thereof to provide temporary relief from mild-to-moderate aches and pains of muscles and joints such as associated with conditions selected from one or more of arthritis/mild arthritis, strains, sprains, bruises and simple backache, by administering to the subject a composition according to the invention. Symptoms of mild arthritis include joint pain at rest, joint pain on movement, joint swelling or stiffness (after sleep or long rest).

[035] The invention is also directed to a composition described herein for use in therapy. In particular, this invention provides a composition for use in therapy for the treatment of pain and/or inflammation in a mammalian (e.g., human) subject in need thereof.

[036] In some embodiments, the invention provides a composition for use in therapy for relieving chronic pain and associated inflammation in a patient in need thereof. In another aspect the invention provides a composition for use in therapy for relieving acute pain and associated inflammation.

[037] Thus, the invention provides a composition for use in therapy for relieving the chronic pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands, or the pain of backache, in a patient in need thereof.

[038] The invention also provides a composition for use in therapy for treating a mammalian subject in need thereof to provide temporary relief from mild-to-moderate aches and pains of muscles and joints such as associated with conditions selected from one or more of arthritis, strains, sprains, bruises and simple backache.

[039] In other aspects, the compositions may be topically applied for relief of pain, inflammation, and swelling in post-traumatic inflammation of tendons,

ligaments, muscles and joints (e.g., due to sprains, strains or bruises), localized forms of soft-tissue rheumatism (e.g., tendonitis, epicondylitis, shoulder-hand syndrome and periarthropathy), and the local management of degenerative joint conditions (e.g., osteoarthritis of the peripheral joints and of the vertebral column).

[040] By "acute pain", it is generally meant pain that begins suddenly and is usually sharp in quality. Acute pain may be caused by strains, sprains, and bruises, including blunt, traumatic soft tissue injury and contusions of the limbs, or injury to the joint involving the soft tissue, such as ankle sprain, as well as delayed onset muscle soreness.

[041] Chronic pain persists despite the fact that an injury has healed. Pain signals remain active in the nervous system for weeks, months, or years. Chronic pain may have originated with an initial trauma/injury or infection, or there may be an ongoing cause of pain, or may occur in the absence of past injury or evidence of body damage.

[042] Common chronic pain complaints also include pain from arthritis (osteoarthritis and rheumatoid), and lower back pain (e.g., "simple" backache).

[043] Acute pain may be mild and transient, or may be severe and last for weeks or months. In most cases, acute pain does not last longer than six months and it disappears when the underlying cause of pain has been treated or has healed. Unrelieved acute pain, however, may lead to chronic pain. In general, "acute pain" refers to pain of duration from about 3 to about 6 months from onset; but has also been employed to refer to pain lasting up to about 12 months from onset. Alternatively, the term, "acute pain" has been limited to pain lasting for up to about 30 days from onset, and "chronic pain" to pain lasting six months or greater, with "subacute pain" being pain that lasts up to about six months. Still another definition

of "chronic pain," has no fixed duration, but rather refers to pain that extends beyond the expected period of healing.

[044] The topical compositions of the invention are administered by local application to the skin of the pain-affected area to relieve acute and/or chronic pain conditions.

[045] The topical compositions of the present invention may also be useful in the treatment of and/or in providing relief from the symptoms of actinic keratosis. Thus, the present invention also provides method of treating actinic keratosis.

[046] The topical compositions of the present invention may also be useful in the treatment of juvenile idiopathic arthritis, acute gouty arthritis, gouty arthritis, myalgia, and pain caused by rheumatism. Thus, the present invention also provides method of treating juvenile idiopathic arthritis, acute gouty arthritis, gouty arthritis, myalgia, and pain caused by rheumatism.

[047] The compositions can be prescribed by a medical professional such as a doctor or pharmacist. In one aspect, the compositions may be administered by prescription only (RX). In another aspect, the compositions may be administered without a doctor's prescription by a pharmacist ("behind the counter").

[048] Alternatively, the compositions can provide an effective and safe "over-the-counter" (OTC) regimen for the self-treatment of acute as well as chronic pain by a consumer in need thereof. The term "consumer" as used herein shall refer to a mammalian (e.g., human) subject, preferably an adult human that is age 18 years or older, but also including a child 17 years of age or younger. The OTC regimen can omit the steps of consulting with a physician, obtaining a prescription from the physician, and presenting the prescription to a licensed pharmacy in order to obtain the product. This is a significant advantage in affording consumers' earlier access

to treatment, and thus faster access to pain relief. An OTC treatment regimen addresses a critical need for fast-acting pain relievers in the treatment of the types of injuries most commonly experienced by users of over-the-counter medications, such as strains, sprains, and contusion.

[049] The topical pharmaceutical compositions according to the invention are administered in a manner known per se. Topical administration will generally include any exposed position on the body where it may be advantageous to administer a composition of the invention.

[050] The present invention further provides the topical composition comprising (a) palmitoylethanolamide and (b) menthol.

[051] In one embodiment of the invention the compositions suitable for topical administration are in the form of an ointment, lotion, cream, gel, foam and spray.

[052] In specific embodiment of the invention, the present invention provides the topical spray composition comprising (a) palmitoylethanolamide and (b) menthol.

[053] In embodiments of the invention, the composition comprises from about 0.01% w/v to about 10% w/v palmitoylethanolamide, specifically about 0.05% w/v to about 5% w/v palmitoylethanolamide, and more specifically about 0.1% w/v to about 1% w/v of palmitoylethanolamide and most specifically about 0.1% w/v, 0.15% w/v, 0.2% w/v, 0.25% w/v, 0.3% w/v, 0.35% w/v, 0.4% w/v, 0.45% w/v, 0.5% w/v, 0.55% w/v, 0.6% w/v, 0.65% w/v, 0.7% w/v, 0.75% w/v, 0.8% w/v, 0.85% w/v, 0.9% w/v, 0.95% w/v and 1% w/v of palmitoylethanolamide.

[054] In further embodiments of the invention, the composition comprises from about 0.1% w/v to about 15% w/v menthol, more specifically from about 0.5% w/v to about 10% w/v menthol, most specifically from about 1% w/v to about 5% w/v menthol.

[055] In embodiments of the invention, the present invention provides the topical spray composition comprising (a) palmitoylethanolamide, (b) menthol and (c) one or more solvents.

[056] In embodiments of the invention one or more solvents are selected from group consisting of methanol, ethanol, isopropanol, diethylene glycol monoethyl ether (Transcutol), propylene glycol or combinations thereof.

[057] In embodiments of the invention, diethylene glycol monoethyl ether (Transcutol) shall be used as a penetration enhancer, which facilitate transdermal absorption such as by affecting epithelial tight junctions, and thus are commonly employed in topical formulation which are intended to facilitate drug passage into the dermal layer or beyond. The further penetration enhancer used in the present invention shall be selected from group consisting of DMSO (dimethyl sulfoxide), oleic acid, n-alkanols, 1-alkyl-2-pyrrolidones, N,N-dimethlyalkanamides, and 1,2-alkanediols,

[058] In further embodiment of the invention, the present invention provides the topical spray composition comprising (a) palmitoylethanolamide, (b) menthol and (c) one or more solvents selected from group consisting of methanol, ethanol, isopropanol, diethylene glycol monoethyl ether, propylene glycol or combinations thereof.

[059] In embodiments of the invention the composition comprises from about 1% w/v to about 99.99% w/v of one or more solvents, more specifically of about 5% w/v to about 99% w/v of one or more solvents and most specifically of about 10% w/v to about 99% w/v of one or more solvents.

[060] In embodiments of the invention the present composition comprises of about 10% w/v to about 99% w/v of ethanol (ethyl alcohol). Ethyl alcohol is preferably used in the range of about 15% w/v to about 90% w/v, more preferably of about 20% w/v to about 80% w/v, even more preferably about 25% w/v to about 75% w/v, most preferably about 30% w/v to about 70% w/v and even most preferably about 35% w/v to about 65% w/v.

[061] In embodiments of the invention the present composition comprises of about 2% w/v to about 99% w/v of isopropyl alcohol. Isopropyl alcohol is preferably used in the range of about 5% w/v to about 90% w/v, more preferably of about 10% w/v to about 80% w/v, even more preferably about 15% w/v to about 75% w/v, most preferably about 20% w/v to about 70% w/v and even most preferably about 25% w/v to about 65% w/v.

[062] In further embodiment of the invention, the present invention provides a topical spray composition comprising palmitoylethanolamide and an anti-inflammatory or anti-pain component.

[063] The anti-inflammatory or anti-pain component are selected from group consisting of diclofenac, diclofenac diethylamine, paracetamol, ibuprofen, dexibuprofen, piketoprofen, fenoprofen, pelubiprofen, ketoprofen, dexketoprofen, loxoprofen, naproxen, flurbiprofen, celecoxib, etoricoxib, polmacoxib, imrecoxib, parecoxib, nimesulide, meloxicam, piroxicam, lornoxicam, tenoxicam, indomethacin, felbinac, aceclofenac, etodolac, sulindac, tofacitinib, baricitinib, peficitinib, upadacitinib, filgotinib, peficitinib, mefenamic acid, meclofenamic

acid, flufenamic acid, tolfenamic acid, salicylic acid, acetyl salicylic acid, methyl salicylate, nabumetone, capsaicin, misoprostol, sulfasalazine, acemetacin, diflunisal, camphor, lidocaine, prilocaine, tetracaine, ketorolac, tolmetin, capsaicin, winter green oil, eucalyptus oil, nonivamide, allantoin, zinc oxide, tocopherol acetate, menthol and levomenthol, salts and mixtures thereof.

[064] The anti-inflammatory component or anti-pain component is present in an amount of about 0.1% to about 95%, more preferably of about 0.5% to about 90%, even more preferably of about 1% to about 80% and most preferably of about 2% to about 75% based on the combination with palmitoylethanolamide.

[065] The anti-inflammatory component or anti-pain component is present in an amount of about 0.1% w/v to about 95% w/v, more preferably of about 0.5% w/v to about 90% w/v, even more preferably of about 1% w/v to about 80% w/v and most preferably of about 2% w/v to about 75% w/v of total composition

[066] As used herein, the pharmaceutically acceptable salt of diclofenac comprises any soluble salt of diclofenac with a pharmaceutically acceptable organic or inorganic base. Non-limiting examples of pharmaceutically acceptable inorganic bases are hydroxides, carbonates and hydrogen carbonates of ammonium, calcium, magnesium, sodium and potassium, for instance sodium hydroxide, ammonium hydroxide, calcium hydroxide, magnesium carbonate, sodium hydrogen carbonate and potassium hydrogen carbonate. Non-limiting examples of pharmaceutically acceptable organic bases are arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, N-methylglucamine, glucamine, glucosamine, histidine, N-(2-hydroxyethyl)piperidine, N-(2-hydroxyethyl)pyrrolidine (epolamine salt), isopropylamine, lysine, methylglucamine, morpholine,

piperazine, piperidine, theobromine, triethylamine, trimethylamine, tripropylamine and tromethamine.

[067] In a further embodiment of the invention, diclofenac or its pharmaceutically acceptable salts thereof are present in an amount of about 0.1% to about 95%, more preferably of about 0.5% to about 50%, even more preferably of about 1% to about 25% and most preferably of about 2% to about 15% based on the combination with palmitoylethanolamide.

[068] In a further embodiment of the invention, diclofenac or its pharmaceutically acceptable salts thereof are present in an amount of about 0.1% w/v to about 95% w/v, more preferably of about 0.5% w/v to about 50% w/v, even more preferably of about 1% w/v to about 25% w/v and most preferably of about 2% w/v to about 15% w/v of total composition.

[069] In other embodiments of the inventions, diclofenac diethylamine is present in an amount of about 0.1% w/v to about 95% w/v, more preferably of about 0.5% w/v to about 50% w/v, even more preferably of about 1% w/v to about 25% w/v and most preferably of about 2% w/v to about 15% w/v of total composition.

[070] In one embodiment of the invention, the present invention provides the topical spray composition comprising

(a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,
(b) about 1% w/v to about 10% w/v menthol and
(c) about 1% w/v to about 99% w/v of one or more solvents.

[071] In another embodiment of the invention, the present invention provides the topical spray composition comprising

(a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,

(b) about 1% w/v to about 10% w/v menthol and

(c) about 1% w/v to about 99% w/v of one or more solvents.

[072] In further embodiment of the invention, the present invention provides the topical spray composition comprising

(a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,

(b) about 1% w/v to about 10% w/v menthol,

(c) about 5% w/v to about 15% w/v diethylene glycol monoethyl ether,

(d) about 20% w/v to about 70% w/v ethanol and

(e) isopropyl alcohol.

[073] The present invention further relates to the topical spray composition comprising

(a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,

(b) about 1% w/v to about 10% w/v menthol,

(c) about 5% w/v to about 30% w/v diethylene glycol monoethyl ether,

(d) about 10% w/v to about 70% w/v ethanol, and

(e) isopropyl alcohol.

[074] The present invention further relates to the topical spray composition comprising

(a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,

(b) about 1% w/v to about 10% w/v menthol,

(c) about 5% w/v to about 30% w/v diethylene glycol monoethyl ether,

(d) about 10% w/v to about 70% w/v ethanol,

(e) about 0.1% w/v to about 5% w/v fragrance, preferably lemongrass oil and

(f) isopropyl alcohol.

[075] The present invention relates to the topical spray composition comprising

(a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,

(b) about 1% w/v to about 10% w/v menthol.

(c) about 5% w/v to about 25% w/v diethylene glycol monoethyl ether,

(d) about 20% w/v to about 60% w/v ethanol,

(e) about 0.1% w/v to about 5% w/v fragrance, preferably lemongrass oil and

(f) isopropyl alcohol.

[076] The present invention relates to the topical spray composition consisting of

(a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,

(b) about 5% w/v menthol.

(c) about 10% w/v diethylene glycol monoethyl ether,

(d) about 39% w/v ethanol,

(e) about 1% w/v fragrance, preferably lemongrass oil and

(f) isopropyl alcohol.

[077] In embodiments of the invention, the present topical spray further comprises excipients selected from group consisting of preservatives, antioxidants and fragrance agents.

[078] In embodiments of the invention, the present topical spray compositions shall comprise one or more preservatives. The preservatives used in the present invention are selected from group consisting of sorbic acid, benzoic acid, methyl paraben, propyl paraben, glycerin or any combinations thereof.

[079] In embodiments of the invention, the present topical spray compositions shall comprise one or more antioxidants. Antioxidants used in the present invention are selected from group consisting of natural vitamins (vitamin A, C and E), butylated hydroxy toluene and butylate hydroxy anisole or any combinations thereof.

[080] In embodiments of the invention, the present topical spray compositions shall comprise one or more fragrance or flavouring agents. In some embodiments, the one or more fragrance agents are selected from the group consisting of aloe fragrance, anise fragrance, apple fragrance, banana fragrance, berry fragrance, black currant fragrance, camphor fragrance, cherry fragrance, cherry cream fragrance, cinnamon fragrance, citrus fragrance, citrus cream fragrance, eucalyptus fragrance, fresh rain fragrance, grape fragrance, grapefruit fragrance, honey fragrance, lemon fragrance, lime fragrance, lemon cream fragrance, mixed berry fragrance, orange fragrance, pear fragrance, peach fragrance, peppermint fragrance, peppermint cream fragrance, raspberry fragrance, strawberry fragrance, strawberry cream fragrance, tangerine fragrance, vanilla fragrance, or any combination thereof. Preferably lemongrass fragrance is used as the fragrance. Fragrance used in the present composition is of about 0.1% w/v to about 5% w/v of the composition.

[081] The present invention further provides the spray composition for the methods of reducing or alleviating pain, reducing or alleviating inflammation in a subject.

[082] In some embodiments, the method is a method of reducing or alleviating pain in a subject in need thereof, comprising administering to the subject an effective amount of a composition provided herein. In some embodiments, the

method is a method of reducing pain. In some embodiments, the method is a method of alleviating pain. In some embodiments, the method comprises topical administration of a composition provided herein.

[083] The following examples are provided to illustrate the present invention. It is understood, however, that the invention is not limited to the specific conditions or details described in the examples below. The examples should not be construed as limiting the invention as the examples merely provide specific methodology useful in the understanding and practice of the invention and its various aspects. While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modification to the disclosed embodiments can occur to those who are skilled in the art.

[084] EXAMPLE 1:

[085] Topical Spray Composition of Palmitoylethanolamide

S. No	Ingredient	% w/v
1)	Palmitoylethanolamide	0.5%
2)	Menthol	2%
3)	Diethylene glycol monoethyl ether	10%
4)	Ethyl Alcohol	50%
5)	Lemongrass oil (fragrance)	1%
6)	Isopropyl Alcohol	q.s to 100%

[086] Process for Preparation

1) Mix ethyl alcohol and isopropyl alcohol.
2) Mix diethylene glycol monoethyl ether in above solvent mixture.
3) Dissolve palmitoylethanolamide and menthol in above solvent mixture.
4) Mix fragrance in above mixture and make up to 100% with isopropyl alcohol.
5) Fill into container fitted with spray pump.

[087] EXAMPLE 2:

[088] Topical Spray Composition of Palmitoylethanolamide

S. No	Ingredient	% w/v
1)	Palmitoylethanolamide	0.1%
2)	Menthol	5%
3)	Diethylene glycol monoethyl ether	10%
4)	Ethyl Alcohol	39.1%
5)	Lemongrass oil (fragrance)	1%
6)	Isopropyl Alcohol	q.s to 100%

[089] Process for Preparation

1) Ethyl alcohol and isopropyl alcohol was mixed.
2) Palmitoylethanolamide was added to above solution under mixing and stirring was continued till complete dissolution of palmitoylethanolamide.
3) Diethylene glycol monoethyl ether was added to the above solution under stirring.
4) Menthol and Lemongrass Oil was added to the above solution and mixed and the volume was made up to 100% with isopropyl alcohol to get a clear solution.
5) The above solution is filled into a container fitted with a spray pump.

[090] EXAMPLE 3:

[091] Topical Spray Composition of Palmitoylethanolamide

S. No	Ingredient	% w/v
1)	Palmitoylethanolamide	0.2%
2)	Menthol	5%
3)	Diethylene glycol monoethyl ether	10%
4)	Ethyl Alcohol	39.1%

5)	Lemongrass oil (fragrance)	1%
6)	Isopropyl Alcohol	q.s to 100%

[092] The process for the preparation of example 3 is similar to the process as disclosed in example 2.

[093] **EXAMPLE 4:**

[094] **Topical Spray Composition of Palmitoylethanolamide**

S. No	**Ingredient**	**% w/v**
1	Palmitoylethanolamide	0.5%
2	Menthol	5%
3	Diethylene glycol monoethyl ether	10%
4	Ethyl Alcohol	39.1%
5	Lemongrass oil (fragrance)	1%
6	Isopropyl Alcohol	q.s to 100%

[095] The process for the preparation of example 4 is similar to the process as disclosed in example 2.

[096] **EXAMPLE 5:**

[097] **Anti-inflammatory activity of compositions of example 2, 3 and 4 on carrageenan induced paw edema in wistar rats.**

[098] Wistar Rats (*Rattus norvegicus*) were divided into seven treatment groups, each group consisting of 8 rats.

[099] Acute inflammatory pain was induced by injecting 0.1 mL of 1% carrageenan into the plantar surface of the right hind paw of all treatment group rats.

[100] Group of animals were divided as depicted in Table -1, with group description and the route of administration of respective composition.

Table – 1

Group	Group Description	Route of Administration
1	Sterile Water (Normal Control)	Topical
2	Placebo	Topical
3	Carrageenan Control (Induced)	*
4	Palmitoylethanolamide Spray 0.1% (0.1% single) (Example 2)	Topical
5	Palmitoylethanolamide 0.2% (0.2% single) (Example 3)	Topical
6	Palmitoylethanolamide 0.5% (0.5% single) (Example 4)	Topical
7	Volini® Spray (Reference)	Topical

[101] Group 2, group 4, group 5, group 6 and group 7 rats were sprayed with Placebo, palmitoylethanolamide spray 0.1% (Example 2), palmitoylethanolamide spray 0.1% (Example 3), palmitoylethanolamide 0.5% (Example 4) and Reference (Volini® Spray) approximately 4 to 5 cm distance from the active site (inflammation paw) and the spray pin was held for 3 to 4 seconds. Group 4, group 5 and group 6 was sprayed with palmitoylethanolamide spray immediately after carrageenan induction.

[102] Normal control group (group 1) was administered with 0.1mL of normal saline. Group 3 is the induced Carrageenan Control.

[103] Locomotor activity scores, hind paw size measurement and paw volume measurement was measured by actophotometer, digital calliper and Plethysmometer respectively. The results of locomotor activity, paw size and

paw volume are depicted in Table – 2 (figure – 1), Table – 3 (figure – 2) and Table – 4 (figure – 3).

Table – 2: Evaluation of locomotor activity in carrageenan induced inflammation

Locomotor activity increases: percentage change mean values						
Groups	**Time**					
	1hr	**2hr**	**3hr**	**6hr**	**8hr**	**9hr**
Normal control (Group 1)	75.75± 14.24	50.25± 4.95	25.13± 5.17	37.00± 21.70	29.38± 19.14	29.38± 16.55
Placebo (Group 2)	59.88± 16.40	32.50± 7.75	20.88± 1.77	16.50± 20.38	9.63± 3.07	8.75± 7.55
Induced (Group 3)	39.75± 7.57	23.13± 20.16	7.50± 9.61	7.88± 4.85	2.63± 9.43	8.25± 10.33
0.1% single (Group 4)	55.38± 11.58	41.00± 15.76	13.38± 6.44	12.50± 10.13	9.38± 8.16	17.13± 15.04
0.2% single (Group 5)	55.63± 14.48	31.38± 7.50	14.88± 7.16	20.25± 24.52	11.13± 7.43	14.88± 13.11
0.5% single (Group 6)	75.00± 12.09	52.63± 16.17	26.25± 7.91	16.13± 5.79	17.38± 8.09	22.38± 18.74
Reference (Group 7)	71.00± 17.82	50.38± 14.48	25.75± 5.15	21.38± 15.20	14.50± 10.25	23.38± 7.44

Values are expressed in Mean ± SD.

Table – 3: Evaluation of Paw size measurement by using Vernier callipers

Paw size is decease: percentage change mean values						
Groups	**Time**					
	1hr	**2hr**	**3hr**	**6hr**	**8hr**	**9hr**
Normal control (Group 1)	1.63± 6.14	0.75± 5.34	0.13± 5.06	0.63± 1.92	0.38± 2.20	0.38± 2.33

Placebo (Group 2)	44.50± 18.09	71.63± 28.24	84.13± 23.08	82.88± 23.43	85.00± 25.50	84.88± 24.18
Induced (Group 3)	56.25± 21.55	95.50± 9.12	100.63± 14.94	89.13± 16.92	95.75± 18.05	103.63± 21.08
0.1% single (Group 4)	56.50± 20.83	84.00± 23.23	89.50± 26.97	89.13± 24.69	87.63± 25.98	87.63± 24.37
0.2% single (Group 5)	60.38± 8.68	84.00± 18.87	88.38± 19.89	93.13± 24.03	87.50± 27.82	74.25± 18.31
0.5% single (Group 6)	51.00± 21.49	62.88± 8.95	65.00± 12.92	70.38± 17.07	74.25± 21.63	80.50± 8.91
Reference (Group 7)	50.63± 15.23	58.75± 18.38	67.38± 23.69	75.00± 28.08	77.75± 24.83	77.63± 21.91

Values are expressed in Mean ± SD.

Table – 4: Evaluation of paw volume by using Plethysmometer

Paw volume: percentage change mean values						
Groups	**Time**					
	1hr	**2hr**	**3hr**	**6hr**	**8hr**	**9hr**
Normal control (Group 1)	-0.13± 1.36	-1.50± 1.77	-1.25± 2.87	-0.75± 2.12	-0.63± 2.62	-1.38± 2.39
Placebo (Group 2)	55.63± 12.07	37.63± 21.91	65.25± 32.51	55.00± 30.51	62.50± 20.55	57.50± 18.26
Induced (Group 3)	38.50± 16.41	54.50± 10.07	101.25± 21.00	69.00± 34.37	74.50± 14.79	62.88± 7.04
0.1% single (Group 4)	40.25± 25.44	45.88± 20.99	75.63± 47.71	49.00± 26.39	57.75± 33.09	48.25± 29.29
0.2% single (Group 5)	36.50± 14.51	47.25± 20.37	74.75± 31.90	58.00± 22.46	56.88± 21.76	48.63± 16.46
0.5% single (Group 6)	27.88± 14.55	34.75± 17.18	57.25± 25.87	39.00± 27.06	55.13± 15.66	42.75± 11.49
Reference (Group 7)	29.75± 11.54	33.38± 8.63	42.25± 19.45	43.25± 27.96	62.38± 15.95	44.13± 11.64

Values are expressed in Mean ± SD.

[104] Rats treated with palmitoylethanolamide spray compositions of group 4, group 5, and group 6 has significant locomotor activity as compared to, induced group. Palmitoylethanolamide compositions of example 2, 3 and 4 shows significant analgesic activity in dose dependent manner between 0.1% and 0.5%.

[105] Rats treated with palmitoylethanolamide spray compositions of group 4, group 5 and group 6 has significant lesser paw size and paw volume as compared to induced group. Palmitoylethanolamide compositions of example 2, 3 and 4 shows significant anti-inflammatory activity in dose dependent manner between 0.1% and 0.5%.

[106] EXAMPLE 6:

[107] Topical Spray Composition of Palmitoylethanolamide and diclofenac diethylamine.

S. No	Ingredient	% w/v
1)	Palmitoylethanolamide	0.5%
2)	Diclofenac diethylamine	4.64%
3)	Menthol	5%
4)	Diethylene glycol monoethyl ether	20%
5)	Ethyl Alcohol	10%
6)	Isopropyl Alcohol	q.s to 100%

[108] Process for Preparation

1) Ethyl alcohol and isopropyl alcohol was mixed.
2) Palmitoylethanolamide was added to above solution under mixing and stirring was continued till complete dissolution of palmitoylethanolamide.
3) Diclofenac diethylamine was added to above step 2 and stirred till complete dissolution of diclofenac diethylamine.

4) Diethylene glycol monoethyl ether was added to the above solution under stirring.
5) Menthol was added to the above solution and mixed and the volume was made up to 100% with isopropyl alcohol to get a clear solution.
6) The above solution is filled into a container fitted with a spray pump.

[109] EXAMPLE 7:

[110] Topical Spray Composition of Palmitoylethanolamide and Methyl salicylate.

S. No	Ingredient	% w/v
1)	Palmitoylethanolamide	0.5
2)	Methyl salicylate	30
3)	Menthol	50
4)	Diethylene glycol monoethyl ether	10
5)	Ethyl Alcohol	10
6)	Isopropyl Alcohol	q.s to 100%

[111] Process for Preparation

1) Ethyl alcohol and isopropyl alcohol was mixed.
2) Palmitoylethanolamide was added to above solution under mixing and stirring was continued till complete dissolution of palmitoylethanolamide.
3) Methyl salicylate was added to above step 2 and stirred till complete dissolution of diclofenac diethylamine.
4) Diethylene glycol monoethyl ether was added to the above solution under stirring.
5) Menthol was added to the above solution and mixed and the volume was made up to 100% with isopropyl alcohol to get a clear solution.
6) The above solution is filled into a container fitted with a spray pump.

[112] We Claim

1. A topical spray composition comprising palmitoylethanolamide.

2. The topical spray composition as claimed in claim 1, wherein the composition comprises about 0.1% w/v to about 1% w/v palmitoylethanolamide.

3. The topical spray composition as claimed in claim 1, wherein the composition comprises one or more solvents or combinations thereof.

4. The topical spray composition as claimed in claim 1, wherein the composition comprises about 1% w/v to about 10% w/v menthol.

5. The topical spray composition as claimed in claim 1, wherein the composition comprises of about 1% w/v to about 99% w/v of one or more solvents.

6. The topical spray composition as claimed in claim 1, wherein the composition comprises a solvent selected from group consisting of methanol, ethanol, isopropanol, diethylene glycol monoethyl ether, propylene glycol or combinations thereof.

7. The topical spray composition as claimed in claim 6, wherein the composition comprises of about 5% w/v to about 25% w/v diethylene glycol monoethyl ether.

8. The topical spray composition as claimed in claim 6, wherein the composition comprises of about 20% w/v to about 60% w/v ethanol.

9. A topical spray composition comprising
   (a) about 0.1% w/v to about 1% w/v palmitoylethanolamide,

(b) about 1% w/v to about 10% w/v menthol,

(c) about 5% w/v to about 25% w/v diethylene glycol monoethyl ether,

(d) about 25% w/v to about 60% w/v ethanol and

(e) isopropyl alcohol.

10. A topical spray composition comprising

(a) palmitoylethanolamide and

(b) anti-inflammatory or anti-pain component selected from group consisting of diclofenac, diclofenac diethylamine, ibuprofen, dexibuprofen, piketoprofen, fenoprofen, pelubiprofen, ketoprofen, dexketoprofen, loxoprofen, naproxen, flurbiprofen, celecoxib, etoricoxib, polmacoxib, imrecoxib, parecoxib, nimesulide, meloxicam, piroxicam, lornoxicam, tenoxicam, indomethacin, felbinac, aceclofenac, etodolac, sulindac, tofacitinib, baricitinib, peficitinib, upadacitinib, filgotinib, peficitinib, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, salicylic acid, methyl salicylate, nabumetone, capsaicin, misoprostol, sulfasalazine, acemetacin, diflunisal, dimethyl sulfoxide, oxaprozin, camphor, lidocaine, ketorolac, menthol and levomenthol.

Dated this 26th day of August 2022.

Viswap

Mr. Viswaprasad Varanasi
Sr. General Manager – GIPM
Shilpa Medicare Limited.

[113] ABSTRACT

[114] PALMITOYLETHANOLAMIDE SPRAY COMPOSITIONS

[115] The present invention provides a topical spray composition comprising palmitoylethanolamide and menthol and the process for preparation thereof. The topical spray composition comprising palmitoylethanolamide as per the present invention are used for the treatment of pain and inflammation.