(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 April 2012 (26.04.2012)

PCT

(10) International Publication Number
WO 2012/053012 A2

(51) International Patent Classification:
A61K 9/06 (2006.01) *A61K 47/10* (2006.01)
A61K 9/107 (2006.01) *A61K 47/44* (2006.01)
A61K 31/704 (2006.01) *A61P 21/02* (2006.01)

(21) International Application Number:
PCT/IN2011/000722

(22) International Filing Date:
19 October 2011 (19.10.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2926/MUM/2010 21 October 2010 (21.10.2010) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2012/053012 A2

(54) Title: TOPICAL PHARMACEUTICAL COMPOSITIONS COMPRISING TFFLOCOLCHICOSIDE

(57) Abstract: The present invention relates to stable pharmaceutical compositions of thiocolchicoside comprising nano size droplets of thiocolchicoside or salts thereof along with other pharmaceutically acceptable excipients. The present invention also relates to stable pharmaceutical compositions of thiocolchicoside comprising nano size droplets of thiocolchicoside or salts thereof, optionally one or more non-steroidal anti-inflammatory agents, along with other pharmaceutically acceptable excipients. These compositions exhibit greater permeability, and improved bioavailability leading to enhanced therapeutic activity. The invention also relates to processes for the preparation of such compositions.

TOPICAL PHARMACEUTICAL COMPOSITIONS COMPRISING THIOCOLCHICOSIDE

Field of the Invention

The present invention relates to stable pharmaceutical compositions of thiocolchicoside comprising nano size droplets of thiocolchicoside or salts thereof along with other pharmaceutically acceptable excipients. The present invention also relates to stable pharmaceutical compositions of thiocolchicoside comprising nano size droplets of thiocolchicoside or salts thereof, optionally one or more NSAIDs, along with other pharmaceutically acceptable excipients. These compositions exhibit greater permeability, and improved bioavailability leading to enhanced therapeutic activity. The invention also relates to processes for the preparation of such compositions.

Background of the Invention

Muscle contracture is a feature characterizing a number of pathologies of the locomotor apparatus, and it is one of the major factors responsible for the persistence of the painful condition related thereto. Muscle contracture also occurs in the inflammatory-rheumatic and degenerative orthopedic pathologies; when affecting an articulation, it causes, in addition to pain, a stiffening which limits the mutual mobility of the joint extremities and therefore the functionality of the part involved.

Arthritis, a musculoskeletal disorder, is the leading cause of disability around the world. It is estimated that millions of people are now affected and expected to increase substantially by 2020.

Pain can be defined as an unpleasant sensation ranging from mild discomfort to agonizing distress, associated with real or potential tissue damage, or a disorder of the nervous system. Pain is a response to impulses from the peripheral nerves in damaged tissue, which pass to nerves in the spinal cord. All animals experience some degree of pain during life, whether through injury or disease. As such, one of the major areas of drug research is the development of analgesics to be used in pain management.

One area in which pain is more frequently experienced than in others is inflammation. Pain associated with inflammation can be caused by pathologic processes in somatic structures or viscera or by prolonged dysfunction of parts the peripheral nervous system. Pain associated with inflammation may be the result of recurrent injuries, trauma, headache, arthritis including osteoarthritis, chronic obstructive pulmonary disease, psoriasis, or other pathologies. Pain associated with

inflammation may be acute or chronic depending on the duration, level and extent of the inflammation.

Irrespective of the type or cause of pain, it is important that early treatment obtained for pain can have profound psychological effects on the patient and acute pain which is poorly managed initially can degenerate into chronic pain which may prove more difficult to treat. However, the difficulty is that pain perception is a complex psychophysical process which can be modified by attitude, attention and suggestion. No other sensation depends as much on cognition and information processing as does pain.

Current treatment of pain usually consists of an oral ingestion of an analgesic such as non-steroidal anti-inflammatory drugs (NSAIDs). Adverse side effects of oral NSAIDs, such as hypersensitivity, gastropathy, renal impairment, liver toxicity and prolonged bleeding merit concern in the very young and elderly. The use of topical analgesic compositions to treat musculoskeletal disorders is an effort to overcome the side effects of oral preparations with the advantage of delivering the analgesic directly to the affected body part.

Non-steroidal anti-inflammatory agents (NSAIDs) are useful in relieving pain and tissue swelling, chiefly by inhibiting the biosynthesis of prostaglandins. In small doses, NSAIDs have an analgesic action, but full doses have both analgesic and anti-inflammatory actions, and are effective in reducing pain and swelling. NSAIDs are the first choice for the management of pain.

Muscle relaxant medicaments have are commonly used in management iof pain for their muscle tone or muscle contractures reducing characteristic. Thiocolchicoside is a muscle relaxant with anti-inflammatory and analgesic effects. It acts as a competitive $GABA_A$ receptor antagonist and also inhibits glycine receptors with similar potency and nicotinic acetylcholine receptors to a much lesser extent. It has powerful convulsant activity and should not be used in seizure-prone individuals. It is marketed as injection, oral immediate release tablets or capsules, extended release tablets and conventional topical formulations. Chemically, it is *N*-[(7*S*)-3-(beta-D-glucopyranosyloxy)-1,2-dimethoxy-10-(methylsulfanyl)-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]acetamide

U. S. Patent no. 6,399,093 discloses a method and composition for the treatment of musculoskeletal disorders in mammals by the application of a topical composition comprising a permeation enhancing amount of one or more penetration enhancers, and

one or more bio-affecting agents to provide anti-inflammatory relief and analgesia to the applied body part.

U. S. Patent No. 5,629,021 relates to micellar nanoparticles and methods of their production.

U. S. Patent No. 5,894,019 discloses topical compositions comprising lipid and essentially free of emulsifiers and surfactants.

European Patent No. EP 506197 B1 discloses an aqueous suspension of solid lipid nanoparticles for topical use.

European Patent No. EP 671903 B1 discloses topical compositions in the form of submicron oil spheres.

Clinical evidence suggests that topically applied non-steroidal anti-inflammatory drugs (NSAIDs) are safer than and at least as efficacious as oral NSAIDs in the treatment of rheumatic diseases. Adverse drug reactions after topical administration of NSAID use are rare when compared to the incidence of serious GI events associated with oral NSAIDs. However, formulation may have a dramatic impact on depth of penetration at the site of application, retention of drug molecules within the layers of skin, concentrations achieved in the muscle tissue, synovial fluid and in systemic circulation.

Most of the topical preparations contain vehicles comprising permeation enhancers, solvents, and high amount of surfactants to achieve these goals. But use of these agents is harmful, especially in chronic application, as many of them are irritants.

Therefore, there exists a need to develop such topical preparations which does not involve use of such agents as described above to facilitate drug permeation through the skin, and still leads to greater permeability, and improved bioavailability resulting in enhanced therapeutic activity.

The compositions of the invention overcome all the commonly encountered problems as exemplified above.

Summary of the Invention

In one general aspect there is provided a stable topical pharmaceutical composition comprising nano size droplets of thiocolchicoside or salts thereof.

In another general aspect there is provided a stable topical pharmaceutical composition comprising combination of thiocolchicoside and one or more non-steroidal anti-inflammatory agents or salts thereof, wherein either thiocolchicoside or salts

thereof, or both thiocolchicoside and non-steroidal anti-inflammatory agents or salts thereof are present in the form of nano size droplets.

In another general aspect there is provided a stable topical pharmaceutical composition thiocolchicoside and diclofenac or salts thereof, wherein either thiocolchicoside or salts thereof or both thiocolchicoside and diclofenac or salts thereof are present in the form of nano size droplets.

In another general aspect there is provided a stable topical pharmaceutical composition comprising thiocolchicoside and methyl salicylate or salts thereof, wherein either thiocolchicoside or salts thereof or both thiocolchicoside and methyl salicylate or salts thereof are present in the form of nano size droplets.

In another general aspect there is provided a stable topical pharmaceutical composition comprising nano size droplets of thiocolchicoside, one or more non-steroidal anti-inflammatory agents, and methyl salicylate or salts thereof.

In another general aspect there is provided a stable topical pharmaceutical composition comprising nano size droplets of thiocolchicoside or salts thereof, wherein the amount of thiocolchicoside or salt thereof in the composition ranges from about 0.05% to about 1.0% w/w of the composition.

In another general aspect there is provided a stable topical pharmaceutical composition comprising nano size droplets of thiocolchicoside or salts thereof, wherein said composition comprises oil in amount ranging from about 5 to about 25% w/w of the composition.

In another general aspect there is provided a stable topical pharmaceutical composition comprising nano size droplets of thiocolchicoside or salts thereof, wherein said composition comprises one or more emulsifier/s in amount ranging from about 0.1 to about 10% w/w of the composition.

In another general aspect there is provided a stable topical pharmaceutical composition comprising nano size droplets of thiocolchicoside or salts thereof, wherein said composition comprises one or more emulsifier/s and oil in the weight ratio ranging from about 0.1:20 to about 0.1:1.

Embodiments of the stable topical pharmaceutical composition may include one or more of the following features. The pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. For example, the pharmaceutically acceptable excipients may include one or more of oils, lipids, stabilizers, emulsifiers,

pH adjusting agents, emollients, humectants, preservatives, stabilizers, antioxidants, chelating agents, initiators, thickening agents, and the like.

In another general aspect there is provided a stable topical pharmaceutical composition comprising nano size droplets of thiocolchicoside or salts thereof, wherein the composition is characterized by enhanced onsite delivery.

In another general aspect there is provided a stable topical pharmaceutical composition comprising nano size droplets of thiocolchicoside and one or more non-steroidal anti-inflammatory agents or salts thereof, wherein the composition is characterized by enhanced onsite delivery, permeability characteristics and/or bioavailability.

In another general aspect there is provided a stable topical pharmaceutical composition comprising nano size droplets of thiocolchicoside and diclofenac or salts thereof, wherein the composition is characterized by enhanced onsite delivery.

In another general aspect there is provided a stable topical pharmaceutical composition comprising nano size droplets of thiocolchicoside or salts thereof, wherein the composition retains at least 80% potency of thiocolchicoside or salts thereof after 3 months at 40°C and 75% relative humidity.

Embodiments of the stable topical pharmaceutical composition may include one or more of the following features. The pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. For example, the pharmaceutically acceptable excipients may include one or more of oils, lipids, stabilizers, emulsifiers, pH adjusting agents, emollients, humectants, preservatives, stabilizers, antioxidants, chelating agents, initiators, thickening agents, and the like.

D_{90} particle size of droplets of thiocolchicoside or salts thereof in the compositions of the invention is less than 500 nm, preferably less than 300nm, more preferably less than 100nm.

In another general aspect there is provided a stable topical pharmaceutical composition of thiocolchicoside or salts thereof prepared by the process comprising:

a) combining an oily phase comprising thiocolchicoside or salts thereof along with other pharmaceutically acceptable excipients with an aqueous phase to form an emulsion;

b) reducing the particle size of emulsion of step a) to a droplet size having D_{90} particle size of less than 500nm; and

c) mixing other pharmaceutically acceptable excipients to the emulsion obtained in step b) and converting it into a suitable finished dosage form.

In another general aspect there is provided a method for management of muscle spasm comprising topical application of the pharmaceutical composition comprising nano size droplets of thiocolchicoside or salts thereof to the patient in need thereof.

Embodiments of the stable topical pharmaceutical composition may include one or more of the following features. The pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. For example, the pharmaceutically acceptable excipients may include one or more of oils, lipids, stabilizers, emulsifiers, pH adjusting agents, emollients, humectants, preservatives, stabilizers, antioxidants, chelating agents, initiators, thickening agents, and the like.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description and claims.

Detailed Description of the Invention

The inventors of the invention have discovered that when thiocolchicoside or salts thereof is formulated into nano size droplets in pharmaceutically acceptable emulgel (emulsion gel) system which includes optimized ratios of oils and/or emulsifiers, the composition exhibits enhanced therapeutic effect and also the composition exhibits excellent storage stability. Further, such compositions have enhanced onsite delivery, enhanced permeability characteristics and/or improved bioavailability.

The composition of the invention results in immediate and sustained action and covers large surface area with less quantity and good spreadability, non-irritant to skin and mucous membranes, reduced frequency of application leading to improved patient compliance and offers cosmetic benefits like non-stickiness, and non- greasy feel.

The embodiments of the present invention relate to a stable pharmaceutical composition comprising nano size droplets of thiocolchicoside or salts thereof.

In a preferred embodiment, the nano size droplets of thiocolchicoside or salts thereof posses a D_{90} particle size of less than about 500nm.

In a preferred embodiment, the nano size droplets of thiocolchicoside or salts thereof posses a D_{90} particle size of less than about 400nm.

In a preferred embodiment, the nano size droplets of thiocolchicoside or salts thereof posses a D_{90} particle size of less than about 300nm.

In a preferred embodiment, the nano size droplets of thiocolchicoside or salts thereof posses a D_{90} particle size of less than about 200nm.

In a preferred embodiment, the nano size droplets of thiocolchicoside or salts thereof posses a D_{90} particle size of less than about 100nm.

In a further embodiment, the composition of the present invention is stable and retains at least 80% potency of thiocolchicoside when stored for at least three months at 40°C and 75% relative humidity.

The composition of the present invention may comprise combination of thiocolchicoside and one or more additional active agents selected from NSAIDs and methyl salicylate. The composition also retains at least 80% potency of additional active agents when stored for at least three months at 40°C and 75% relative humidity.

Suitable NSAIDs which can be used include one or more of aspirin, benoxaprofen, benzofenac, bucloxic acid, butibufen, carprofen, cicloprofen, cinmetacin, clidanac, clopirac, diclofenac, etodolac, fenbufen, fenclofenac, fenclorac, fenoprofen, fentiazac, flunoxaprofen, furaprofen, flurbiprofen, furobufen, furofenac, ibuprofen, ibufenac, indomethacin, indoprofen, isoxepac, ketoprofen, lactorolac, lonazolac, metiazinic, miroprofen, naproxen, oxaprozin, oxepinac, phenacitin, pirprofen, pirazolac, protizinic acid, sulindac, suprofen, tiaprofenic acid, tolmetin, zomepirac, ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alimoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin , zomepirac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflunisal, flufenisal, piroxicam, sudoxicam, isoxicam, celecoxib, veldecoxib and etoricoxib.

The invention further contemplates composition comprising nano size droplets of thiocolchicoside or its combination with one or more NSAIDs and/or methyl salicylate.

In an embodiment, the composition may comprise combination of thiocolchicoside and one or more NSAIDs or salts thereof, wherein either thiocolchicoside, or both thiocolchicoside and NSAID are present in the form of nano size droplets.

In an embodiment, the composition may comprise combination of thiocolchicoside and diclofenac or salts thereof, wherein either thiocolchicoside or both thiocolchicoside and diclofenac are present in the form of nano size droplets.

In an embodiment, the composition may comprise combination of thiocolchicoside and methyl salicylate or salts thereof, wherein either thiocolchicoside or both thiocolchicoside and methyl salicylate are present in the form of nano size droplets.

In another general aspect there is provided a stable topical pharmaceutical composition comprising nano size droplets of thiocolchicoside, one or more NSAIDs, and methyl salicylate or salts thereof.

The amount of thiocolchicoside or salt thereof in the composition may range from about 0.05% to about 1.0% w/w (based on 100% total weight of the composition).

The amount of methyl salicylate or salt thereof in the composition may range from about 8.0% to about 14.0% w/w (based on 100% total weight of the composition).

The amount of diclofenac or salt thereof in the composition may range from about 0.5% to about 3.0% w/w (based on 100% total weight of the composition).

The composition of the present invention further comprises one or more pharmaceutically acceptable excipients selected from, but not limited to lipids, oils, emulsifiers, stabilizers, initiators, pH adjusting agents, emollients, humectants, preservatives, antioxidants and chelating agents.

Suitable lipids which can be used include one or more of hydrocarbons, fatty alcohols, fatty acids, glycerides or esters of fatty acids with C_1-C_{36} alkanols. Hydrocarbons may include paraffin or petroleum jelly. Fatty alcohols may include decanol, dodecanol, tetradecanol, hexadecanol or octadecanol. Fatty acids may include C_6-C_{24} alkanoic acids such as hexanoic acid, octanoic acid, decanoic acid, dodecanoic acid, tetradecanoic acid, hexadecanoic acid, octadecanoic acid, unsaturated fatty acids such as oleic acid and linoleic acid. Glycerides may include olive oil, castor oil, sesame oil, caprylic/capric acid triglyceride or glycerol mono-, di- and tri-esters with palmitic and/or stearic acid. Esters of fatty acids may include C_1-C_{36} alkanols such as beeswax, carnauba wax, cetyl palmitate, lanolin, isopropyl myristate, isopropyl stearate, oleic acid decyl ester, ethyl oleate and C_6-C_{12} alkanoic acid esters and the like.

Suitable oils may include one or more of almond oil, apricot seed oil, borage oil, canola oil, coconut oil, corn oil, cotton seed oil, fish oil, jojoba bean oil, lard oil, linseed oil, boiled macadamia nut oil, mineral oil, olive oil, peanut oil, safflower oil,

sesame oil, soyabean oil, squalane, sunflower seed oil, tricaprylin (1,2,3 trioctanoyl glycerol) and wheat germ oil and the like. The preferred quantity of oil used is in the range of about 5 to about 25% w/w, and more preferably in the range of about 5% to about 20% w/w of the composition.

Suitable emulsifiers may include one or more of ionic polysorbate surfactant, Tween® 20, Tween® 40, Tween® 60, Tween® 80, Nonylphenol Polyethylene Glycol Ethers, (alkylphenol-hydroxypolyoxyethylene), Poly(oxy-1,2-ethanediyl), alpha-(4-nonylphenol)-omega-hydroxy-, branched (i.e. Tergitol® NP-40 Surfactant), Nonylphenol Polyethylene Glycol Ether mixtures (i.e. Tergitol® NP-70 (70% AQ) Surfactant), polymers or copolymers of acryilic acid (commercially available as Carbopol®), phenoxypolyethoxyethanols and polymers thereof such as Triton®, Poloxamer®, Spans®, Tyloxapol®, different grades of Brij, sodium dodecyl sulfate and the like. The preferred quantity of the emulsifiers used is in the range of about 0.1% to about 10% w/w of the composition.

In a preferred embodiment, the ratio of emulsifier or surfactant to oil in the pharmaceutical composition of the present invention ranges from about 0.1:20 to about 0.1:1, preferably about 0.1:10 to about 0.1:1.

Suitable pH adjusting agents which can be used include one or more of organic or inorganic acids and bases including sodium hydroxide, potassium hydroxide, ammonium hydroxide, phosphate buffers, citric acid, acetic acid, fumaric acid, hydrochloric acid, malic acid, nitric acid, phosphoric acid, propionic acid, sulfuric acid, tartaric acid and the like. In an embodiment, the pH of the composition of the invention may range from about 4.5 to about 7.0, and preferably from 5.0 to about 6.5.

Suitable emollients which can be used include one or more of caprylic/capric triglyerides, castor oil, ceteareth-20, ceteareth-30, cetearyl alcohol, ceteth 20, cetostearyl alcohol, cetyl alcohol, cetyl stearyl alcohol, cocoa butter, diisopropyl adipate, glycerin, glyceryl monooleate, glyceryl monostearate, glyceryl stearate, isopropyl myristate, isopropyl palmitate, lanolin, lanolin alcohol, hydrogenated lanolin, liquid paraffins, linoleic acid, mineral oil, oleic acid, white petrolatum, polyethylene glycol, polyoxyethylene glycol fatty alcohol ethers, polyoxypropylene 15-stearyl ether, propylene glycol stearate, squalane, steareth-2 or -100, stearic acid, stearyl alcohol, urea and the like.

Suitable preservatives which can be used include one or more of phenoxyethanol, parabens (such as methylparaben and propylparaben), propylene glycols, sorbates, urea derivatives (such as diazolindinyl urea), and the like.

Suitable antioxidants which can be used include one or more of ascorbic acid, alpha-tocopherol (vitamin-E), butylated hydroxyanisole, butylated hydroxytoluene, glutathione, sodium metabisulphite and the like.

Suitable humectants which can be used include one or more of propylene glycol, glycerin, butylene glycol, sorbitol, triacetin and the like.

Suitable chelating agents which can be used include one or more of disodium EDTA, edetate trisodium, edetate tetrasodium, diethyleneamine pentaacetate and the like. The amount of chelating agent may range from about 0.05% to about 0.5% w/w of the total weight of the composition.

Suitable stabilizers may include one or more of ionic polysorbate surfactant, Tween® 20, Tween® 40, Tween® 60, Tween® 80, Nonylphenol Polyethylene Glycol Ethers, (alkylphenol-hydroxypolyoxyethylene), Poly(oxy-1,2-ethanediyl), alpha-(4-nonylphenol)-omega-hydroxy-, branched (i.e. Tergitol® NP-40 Surfactant), Nonylphenol Polyethylene Glycol Ether mixtures (i.e. Tergitol® NP-70 (70% AQ) Surfactant), phenoxypolyethoxyethanols and polymers thereof such as Triton®, Poloxamer®, Spans®, Tyloxapol®, different grades of Brij, sodium dodecyl sulfate and the like. The preferred quantity of the stabilizer or surfactant used is in the range of 1 to 10% w/w of the composition.

Suitable initiators may include one or more of alcohols like C_1-C_{12} alcohols, diols and triols, glycerol, methanol, ethanol, propanol, octanol, and the like. The amount of initiator may range from about 3.0% to about 7.0% w/w of the total weight of the composition.

The composition of the invention may be prepared by a) combining an oily phase comprising thiocolchicoside or salts thereof along with other pharmaceutically acceptable excipients with an aqueous phase to form an emulsion; b) reducing the particle size of emulsion of step a) to a droplet size having D_{90} particle size of 500nm; and c) mixing other pharmaceutically acceptable excipients to emulsion obtained in step b) and converting it into a suitable finished dosage form.

In an embodiment, the process of preparing stable pharmaceutical composition comprising nano size droplets of thiocolchicoside or salts thereof comprising:

a) preparing a hydroalcoholic phase of thiocolchicoside or salts thereof with one or more alcohol, surfactant and thickening agent.

b) mixing the above hydroalcoholic phase was mixed with one or more oil and water.

c) homogenizing the blend of step (b) to reduce the droplet size to D_{90} particle size of less than 500 nm to form a nano emulsion; and

optionally adding the aqueous dispersion of thickening agent to the above nano emulsion to get the nanogel.

The nano size droplets may be produced with reciprocating syringe instrumentation, continuous flow instrumentation, high speed mixing or high pressure homogenization. However, it will appreciated to the person skilled in the art any known method of reducing the size of droplet may be adopted to serve the purpose of the present invention.

Small droplets of the nano emulsion may be formed by passing the emulsion through a homogeniser under different pressures ranging from 3,500-21,500 psi. The emulsion may be passed between 4-5 times under the same conditions to get a final D_{90} droplet size of about 500 nm. The nano droplets formed may be filtered through 0.2 to 0.4 micron filter.

The gel base may be used in the present invention to form a gel matrix for the preparation of nanogel from nanoemulsion. The gel base comprises of one or more of thickening agents.

Suitable thickening agents may include one or more of cellulose polymer, a carbomer polymer, a carbomer derivative, a cellulose derivative, polyvinyl alcohol, poloxamers, polysaccharides and the like.

Suitable dosage form of the invention may include cream, gel, ointment, lotion, and emulsion.

In a preferred embodiment, the composition of the invention is in the form of gel.

The present invention further provides a method for management of muscle spasm comprising topical application of the pharmaceutical composition comprising nano size droplets of thiocolchicoside or salts thereof to the patient in need thereof.

The invention is further illustrated by the following examples which are provided to be exemplary of the invention and do not limit the scope of the invention. While the present invention has been described in terms of its specific embodiments,

certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1: Thiocolchicoside and Methyl salicylate Nanogel

Table 1

Ingredients	% w/w
Thiocolchicoside	0.05- 1
Absolute Alcohol	3 – 7
Polysorbate 80	1 – 5
Glycerine	3 – 7
Refined Soyabean Oil	7 – 12
Methyl Salicylate	8 – 14
Menthol	3 - 7
Carbopol 974P	0.1 - 1
Sodium Hydroxide	Q.S
Purified Water	Q.S

Procedure: Thiocolchicoside, alcohol were dissolved with tween 80, glycerol, soyabean oil, Water was. The resulting blend was homogenized to reduce the droplet size to D90 particle size of about 250 nm by high pressure homogenization to get the nano emulsion. Methyl Salicylate menthol solution was added to the aqueous dispersion of Carbopol 974P followed by addition of sodium hydroxide solution to adjust the desired pH. This aqueous dispersion of Carbopol 974P was then mixed with nano-emulsion to form a nanogel.

Example 2: Thiocolchicoside and Methyl salicylate Nanogel

Table 2

Ingredients	% w/w
Diclofenac sodium	1
Thiocolchicoside	0.25
Absolute Alcohol	5
Tween 80	3
Glycerine	5
Refined Soyabean Oil	9
Methyl Salicylate	15

Menthol	5
Carbopol 974P	1
Sodium Hydroxide	Q.S
Purified Water	Q.S

Procedure: Diclofenac sodium was added to absolute alcohol and Tween 80, followed by addition of glycerin and refined soyabean oil to prepared diclofenac sodium mixture. Separately, thiocolchicoside was dissolved in water and the resulting solution was then added to diclofenac sodium mixture to form an emulsion. The resulting emulsion was homogenized by high pressure homogenization to get the nano-emulsion. A solution of methyl Salicylate and menthol was added to the aqueous dispersion of Carbopol 974P. This aqueous dispersion of Carbopol 974P was then mixed with nano-emulsion to form a nanogel. Sodium hydroxide solution was added to the nano emulsion to adjust the desired pH.

Example 3: Stability study on Nanogel composition of Example 1

Table 3

Drug	% Drug in the formulation			
	Initial	1 Month	2 Month	3 Month
Thiocolchicoside	98.1	97.8	95.1	97.0
Methyl salicylate	102.0	103.0	103.0	95.4

Table 3 provides stability data of nanogel composition of Example 1 when stored at 40°C and 75% relative humidity for three months and indicates that said compositions remains stable and retains at least 80% potency of thiocolchicoside and methyl salicylate over the storage period.

Example 4: Stability study on Nanogel composition of Example 2

Table 4

Drug	% Drug in the formulation			
	Initial	1 Month	2 Month	3 Month
Thiocolchicoside	96.6	99.2	100.3	98.1
Diclofenac	100.2	100.7	96.6	96.7
Methyl salicylate	100.6	100.1	100.5	96.6

Table 4 provides stability data of nanogel composition of Example 2 when stored at 40°C and 75% relative humidity for three months and indicates that said compositions remains stable and retains at least 80% potency of thiocolchicoside, diclofenac and methyl salicylate over the storage period.

While the invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the invention.

We claim:

1. A stable topical pharmaceutical composition comprising nano size droplets of thiocolchicoside or salts thereof.

2. The stable topical pharmaceutical composition as claimed in claim 1, wherein the nano size droplets of thiocolchicoside or salts thereof have a particle size (D_{90}) of about 500nm or less.

3. The stable topical pharmaceutical composition as claimed in claim 1, wherein the nano size droplets of thiocolchicoside or salts thereof have a particle size (D_{90}) of about 300nm or less.

4. The stable topical pharmaceutical composition as claimed in claim 1, wherein the nano size droplets of thiocolchicoside or salts thereof have a particle size (D_{90}) of about 100nm or less.

5. The stable topical pharmaceutical composition as claimed in claim 1, wherein the composition comprises about 0.05% to about 1.0% w/w of thiocolchicoside or salts thereof of the total weight of the composition.

6. The stable topical pharmaceutical composition as claimed in claim 1, wherein the composition further comprises one or more non-steroidal anti-inflammatory agents and/or methyl salicylate or salts thereof.

7. The stable topical pharmaceutical composition as claimed in claim 6, wherein the composition comprises about 8.0% to about 14.0% w/w of methyl salicylate or salts thereof of the total weight of the composition.

8. The stable topical pharmaceutical composition as claimed in claim 6, wherein the non-steroidal anti-inflammatory agent is diclofenac or salts thereof.

9. The stable topical pharmaceutical composition as claimed in claim 1, wherein the composition further comprises nano size droplets of one or more non-steroidal anti-inflammatory agents or salts thereof.

10. The stable topical pharmaceutical composition as claimed in claim 1, wherein the composition further comprises nano size droplets of diclofenac or salts thereof.

11. The stable topical pharmaceutical composition as claimed in claim 1, wherein the composition further comprises nano size droplets of methyl salicylate or salts thereof.

12. The stable topical pharmaceutical composition as claimed in claim 1, wherein the composition further comprises nano size droplets of diclofenac and methyl salicylate or salts thereof.

13. The stable topical pharmaceutical composition as claimed in claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients comprising lipids, oils, emulsifiers, initiators, pH adjusting agents, thickening agents, emollients, humectants, preservatives, antioxidants, and chelating agents.

14. The stable topical pharmaceutical composition as claimed in claim 13, wherein the emulsifiers comprise about 0.1% to about 10% w/w of the total weight of the composition.

15. The stable topical pharmaceutical composition as claimed in claim 13, wherein the oil comprises about 5% to about 25% w/w of the total weight of the composition.

16. The stable topical pharmaceutical composition as claimed in claim 13, wherein the emulsifiers and oil are present in the composition in a weight ratio of from about 0.1:20 to about 0.1:1.

17. The stable topical pharmaceutical composition as claimed in claim 1, wherein the composition retains at least 80% potency of thiocolchicoside or a salt thereof after storage for 3 months at 40°C and 75% relative humidity.

18. The stable topical pharmaceutical composition as claimed in claim 1, wherein the composition is characterized by enhanced onsite delivery, permeability characteristics and/or bioavailability.

19. The stable topical pharmaceutical composition as claimed in claim 1, wherein the composition is in the form of a cream, an ointment, a gel, lotion, liniment, paste or an emulsion.

20. The stable topical pharmaceutical composition as claimed in claim 1, wherein the composition is in the form of a gel.

21. A topical gel comprising-

(a) nano sized droplets comprising about 0.05% to about 1.0% w/w of thiocolchicoside;

(b) optionally, nano sized droplets comprising about 0.5% to about 3.0% w/w of diclofenac or salts thereof;

(c) optionally, nano sized droplets comprising about 8.0% to about 14.0% w/w of methyl salicylate or salts thereof;

(d) about 3.0% to about 7.0% w/w of alcohol;

(e) about 0.1% to about 10.0% w/w of emulsifiers;

(f) about 5% to about 25% w/w of oil and/or lipids;

(g) about 0.05% to about 0.5% w/w of chelating agents;

(h) one or more pH adjusting agents; and

(i) water.

22. A process for the preparation of a stable topical pharmaceutical composition comprising thiocolchicoside or a salt thereof, and one or more pharmaceutically acceptable excipients comprising one or more of lipids, oils, emulsifiers, initiators, pH adjusting agents, thickening agents, emollients, humectants, preservatives, and chelating agents, the process comprising:

a) combining an oily phase comprising one or more thiocolchicosides or salts thereof along with other pharmaceutically acceptable excipients with an aqueous phase to form an emulsion;

b) reducing the particle size of emulsion of step a) to a droplet size having a particle size (D_{90}) of about 500nm or less; and

c) mixing the other pharmaceutically acceptable excipients to the emulsion obtained in step b) and converting it into a suitable finished dosage form.

23. A method for management of muscle spasm, the method comprising administering a stable topical pharmaceutical composition comprising nano size droplets of thiocolchicoside or salts thereof.

24. The stable topical pharmaceutical composition as claimed in claim 23, wherein the composition further comprises nano size droplets of diclofenac and/or methyl salicylate or salts thereof.