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(54) Title: STABLE PHARMACEUTICAL COMPOSITIONS OF LORNOXICAM OR SALTS THEREOF

(57) Abstract: The present invention relates to pharmaceutical compositions of lornoxicam for treatment of inflammatory conditions exhibiting greater permeability, and enhanced therapeutic efficacy. The invention also relates to process of preparing such compositions.

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STABLE PHARMACEUTICAL COMPOSITIONS OF LORNOXICAM OR SALTS THEREOF

Field of the Invention

The present invention relates to stable pharmaceutical compositions of lornoxicam or salts thereof comprising nano size droplets of lornoxicam or salts thereof along with other pharmaceutically acceptable excipients. These compositions exhibit excellent permeability, and enhanced therapeutic efficacy. The invention also relates to process for the preparation of such compositions.

Background of the Invention

Lornoxicam (also known as chlortenoxicam) [6-chloro-4-hydroxy-2-methyl-n-2-pyridyl-5H-thieno(2,3-e)-[1,2]-thiazine-2-carboxamide-1,1-dioxide] is a nonsteroidal anti-inflammatory drug (NSAID) that decreases prostaglandin synthesis by inhibiting cyclooxygenase and can be used to treat acute and chronic pain conditions accompanied by inflammatory processes, *e.g.*, post-operative pain, arthritis, rheumatism, injuries to soft parts, etc.

Lornoxicam is available in form of quick release tablets as well as in formulations suitable for intramuscular and intravenous administration. The drug is absorbed rapidly and almost completely from the gastro-intestinal tract and approximately $2/3^{rd}$ of drug is eliminated via the liver and $1/3^{rd}$ of drug via the kidneys as inactive substance. Since no unchanged form is detectable in excreted material, lornoxicam appears to be eliminated predominantly by hepatic biotransformation. The enzyme responsible for the main metabolic pathway, 5′-hydroxylation of lornoxicam, is cytochrome P450 2C9 (CYP2C9) (Eur J Clin Pharmacol 49: 305–308).

Although a major portion of commercial lornoxicam is available in the form of oral medications, the drug causes subacute and chronic oral adverse effects in the gastrointestinal tract, which includes mortality, diarrhoea, prostration, decreased body weight gain and food consumption, faecal occult blood, anaemia, leucocytosis, hypoalbuminaemia, gastrointestinal erosions and ulcerations. Nausea and diarrhea are quite common side effects of oral lornoxicam.

Parenteral route of administration for lornoxicam have also been suggested, however being invasive and thus painful to administer, such formulations are usually less preferred by large patient population.

Since lornoxicam and its salts may scarcely absorbed percutaneously and thereby require higher quantity to be applied topically thus leading to increased frequency of application also. This leads to patient incompliance. Moreover, percutaneous drug delivery is complicated by the fact that the skin behaves as a natural barrier and therefore transport of agents through the skin is, eventually, a complex mechanism.

International (PCT) Publication No. WO 1998/09654 discloses pharmaceutical compositions for parenteral and ophthalmic application containing lornoxicam or pharmaceutically acceptable salts thereof.

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.

International (PCT) Publication No. WO 2008/051186 discloses nanoemulsion compositions having anti-inflammatory activity.

Clinical evidence suggests that topically applied non-steroidal anti-inflammatory drugs 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 topical preparations which does not involve use of such agents as described above to facilitate drug permeation through the skin, and still leads to excellent, permeability, and improved bioavailability resulting in enhanced therpapeutic (pharmacodynamic) 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 pharmaceutical composition comprising nano size droplets of lornoxicam or salts thereof.

D_{90} particle size of droplets of lornoxicam or salts thereof in the compositions of the invention is about 500nm, preferably about 200nm, and more preferably about 100nm or less.

In another general aspect there is provided a pharmaceutical composition comprising nano sized droplets of lornoxicam or salts thereof and methyl salicylate or salts thereof.

In another general aspect there is provided a pharmaceutical composition comprising nano size droplets of lornoxicam or salts thereof, wherein the amount of lornoxicam or salt thereof in the composition ranges from about 0. 01% to about 2.0% w/w of the composition.

In another general aspect there is provided a stable topical pharmaceutical composition comprising nano size droplets of lornoxicam 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 lornoxicam 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 lornoxicam 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.

In another general aspect there is provided a pharmaceutical composition comprising nano size droplets of lornoxicam or salts thereof in the form suitable for topical administration.

In another general aspect there is provided a stable pharmaceutical composition comprising nano size droplets of lornoxicam or salts thereof, wherein the composition exhibits a significant difference in one or both of the rate and extent of absorption of

lornoxicam or salts thereof as compared to topical formulation containing diclofenac or salts thereof.

In another general aspect there is provided a pharmaceutical composition comprising nano size droplets of lornoxicam or salts thereof and one or more pharmaceutically acceptable excipients comprising oils, lipids, stabilizers, thickening agents and initiators.

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

Embodiments of the 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 composition of the invention exhibits significantly low skin irritation.

In another general aspect there is provided a stable pharmaceutical composition comprising nano size droplets of lornoxicam or salts thereof, wherein the composition exhibits significantly greater percent inhibition of rat paw volume and/or edema as compared to topical formulation containing diclofenac or salts thereof.

Embodiments of the 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 method of improving patient compliance to lornixicam therapy by administering the stable pharmaceutical composition comprising nano size droplets of lornoxicam or salts thereof.

The composition of the invention is safe and effective for dermal application at the dose levels of 0.1, 0.5 and 1.0% w/w.

Embodiments of the 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 pharmaceutical composition comprising nano size droplets of lornoxicam or salts thereof, wherein the composition exhibits a percent inhibition of rat paw edema of at least 10% in 1 hour.

In another general aspect there is provided a stable pharmaceutical composition comprising nano size droplets of lornoxicam or salts thereof, wherein the composition exhibits a percent inhibition of rat paw edema of at least 5% in 5 hours.

Embodiments of the 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 pharmaceutical composition of lornoxicam or salts thereof prepared by a process comprising:

a) combining an oily phase comprising lornoxicam 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 about 500nm or less; and

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

Embodiments of the 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 method of treating prostaglandin associated acute and chronic pain conditions comprising topically applying the

pharmaceutical composition comprising nano size droplets of lornoxicam or salts thereof.

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 surprisingly found that when lornoxicam 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, it leads to highly stable compositions of lornoxicam or salts thereof. Further, such compositions have enhanced permeability characteristics, improved biovailability and greater therapeutic anti-inflammatory effect as compared to topical formulations of diclofenac. Moreover, said such compositions may enhance the curative effect of the medicament, reduce the toxicity and side effects, and avoid the shortcomings of oral and parenteral administration.

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 term "lornoxicam" used throughout the specification refers to not only lornoxicam per se, but also its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs and pharmaceutically acceptable prodrugs thereof. It is also possible to use any salts and free base form of lornoxicam, including polymorphs, hydrates, solvates or amorphous forms.

The pharmaceutical composition comprises nano size droplets of lornoxicam or salts thereof.

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

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

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

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

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

In an embodiment, the pharmaceutical composition is in the form suitable for topical administration.

The amount of lornoxicam in the composition may range from about 0.01% to about 2% by weight of the composition. Preferably, the amount of lornoxicam ranges from about 0.05% to about 1% by weight of the composition.

In a further embodiment, the amount of lornoxicam or salts thereof in the pharmaceutical composition is about 0.1% by weight of the composition.

The pharmaceutical composition remains stable over the storage period. In an embodiment, the composition retains at least 80% potency of lornoxicam or salts thereof after 3 months when stored at 40°C /75% RH.

The composition of the present invention may comprise combination of lornoxicam 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 or salts thereof 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, 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 lornoxicam or its combination with one or more NSAIDs and/or methyl salicylate, and preferably, methyl salicylate.

The amount of methyl salicylate or salt thereof in the composition may range from about 10.0% to about 20.0% w/w (based on 100% total weight of the composition).

The composition of the invention exhibits significantly low and preferably no skin irritation.

The composition of the present invention 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, soybean 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 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 used is in the range of about 0.1% to about 10% w/w of the composition.

In a preferred embodiment, the ratio of stabilizer 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 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.

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 3.5 to about 7.0.

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 composition of the invention may be prepared by a) combining an oily phase comprising lornoxicam 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 or less; and c) mixing other pharmaceutically acceptable excipients to emulsion obtained in step b) and converting it into a suitable finished dosage form.

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 homogenizer 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. Preferred thickening agent is carbomer polymer or derivatives thereof. The amount of the thickening agent that used is in composition may range from about 0.01% to about 10% w/w of the composition.

The pharmaceutical composition of the present invention is provided in the form suitable for topical administration, such as in the form of cream, gel, ointment, lotion, and emulsion. Preferably, the composition is developed in the form of gel.

The invention provides a method of improving patient compliance to lornoxicam therapy by administering a stable pharmaceutical composition of

lornoxicam or salts thereof comprising nano size droplets of lornoxicam or salts thereof.

Further, the invention also provided a method of treating prostaglandin associated acute and chronic pain conditions comprising topically applying the pharmaceutical composition comprising nano size droplets of lornoxicam or salts 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: Lornoxicam Nanogel

Table 1

Sr. No.	Ingredients	%w/w of Composition
1	Lornoxicam	0.010-2.000
2	Absolute Alcohol	5.000
3	Polysorbate 80	3.000
4	Glycerol	5.000
5	Soyabean Oil	9.000
6	Methyl Salicylate	15.000
7	Menthol	5.000
8	Carbopol	1.000
9	Sodium Hydroxide	Q.S
10	Purified Water	Q.S

Procedure: Lornoxicam and absolute alcohol were dissolved in polysorbate 80 along with glycerol. This hydro-alcoholic phase was mixed with soyabean oil. Water was added with stirring to the resulting mixture. The resulting blend was homogenized to reduce the droplet size to D_{90} particle size of about 250 nm using high pressure homogenization to get the nano emulsion. Carbopol was added to water for hydration and kept overnight to ensure complete hydration. pH was adjusted with sodium

hydroxide solution. The aqueous dispersion of carbomer was mixed with methyl salicylate menthol solution and nano emulsion to get nanogel.

Example 2: Stability study on lornoxicam nanogel composition of Example 1

Table 2

Sr. No.	90% to 110% of stated amount of Lornoxicam in the formulation			
	Initial	1 Month	2 Month	3 Month
1	99.8%	97.9% & 99.2%	98.1% & 98.1%	101.5% & 100.6%
2	100.8%	96.1% & 98.3%	99.5% & 100.0%	102.6% & 103.7%

Table 2 provides stability data of lornoxicam nanogel composition of Example 1 when stored at 40°C and 75% relative humidity for three months and indicates that the composition remains stable and retains at least 80% potency of lornoxicam over the storage period.

Example 3: In Vivo Efficacy Study of the Composition of the invention

Anti-inflammatory activity of lornoxicam nano gel was evaluated in two studies conducted using male Wistar rats. In each of the studies, animals were divided into 4 groups, each group comprised of six animals. In each of the study lornoxicam was tested in two different concentrations :(0.05 and 0.1%), first study and (0.5 and 1%) in the second study. In both the studies, one group received diclofenac (1% gel) as reference standard at the left hind paw before the subplanter carrageenan injection. Control group animals received placebo cream only. Paw edema was measured at 0, 3 and 5 hour of carrageenan injection.

Table 3

Treatment Group	% Inhibition of rat paw edema	
	3 hr	5 hr
Vehicle Control	NA	NA
Lornoxicam 0.5%	22.27 ± 2.00	3.82 ± 7.50
Lornoxicam 1%	27.99 ± 2.88	11.92 ± 7.55
Diclofenac 1%	25.52 ± 4.03	5.39 ± 7.09

N=6

The percent inhibition of edema produced by each formulation-treated group was calculated against the respective control group. The results of anti-inflammatory activity were compared using the Dunnett test of 1-way ANOVA.

0.05 and 0.1% of lornoxicam application showed dose dependent decrease in paw edema at 3 hours after carrageenan challenge, whereas 0.5% and 1% lornoxicam application showed significant inhibition of paw swelling which was equivalent to 0.1% lornoxicam. This indicated a saturated anti-inflammatory effect of lornoxicam starting at 0.1% treatment which was equivalent to 1% diclofenac application. Thus, the in vivo efficacy study of composition of the invention demonstrated greater percentage inhibition of paw edema compared to diclofenac formulation.

Example 4: Dermal Dose Toxicity study of the Composition of the invention

Dermal dose toxicity study was carried out to characterize the full range of potential action of the composition of the present invention that is, to determine the dose at which effects occur and a dose which is without such effects.

The composition of the present invention was applied by dermal route to rats at three different concentrations for a minimum period of 28 days. Recovery groups were maintained to determine the persistence or reversibility or delayed toxic effects at high concentration along with a vehicle control group for 14 days treatment free period. To check the effects of placebo, additional untreated control group was maintained.

The results of the study showed that single daily dermal application of the composition of the present invention for four weeks at the dose levels of 0.1, 0.5 and 1.0% did not affect the survival of Wistar rats. No adverse changes were noticed during detailed clinical observations, biochemical estimations and organ weights in this study.

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 pharmaceutical composition comprising nano size droplets of lornoxicam or salts thereof.

2. The pharmaceutical composition as claimed in claim1, wherein the nano size droplets of lornoxicam or salt thereof have a D_{90} particle size of about 500nm or less.

3. The pharmaceutical composition as claimed in claim1, wherein the nano size droplets of lornoxicam or salt thereof have a D_{90} particle size of about 300nm or less.

4. The pharmaceutical composition as claimed in claim1, wherein the nano size droplets of lornoxicam or salt thereof have a D_{90} particle size of about 100nm or less.

5. The pharmaceutical composition as claimed in claim1, wherein the composition comprises about 0.01% to about 2.0% w/w of lornoxicam or salt thereof by total weight of the composition.

6. The pharmaceutical composition as claimed in claim1, wherein the composition further comprises methyl salicylate or salts thereof.

7. The pharmaceutical composition as claimed in claim6, wherein the composition comprises about 10.0% to about 20.0% w/w of methyl salicylate or salt thereof by total weight of the composition.

8. The pharmaceutical composition as claimed in claim1, 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.

9. The pharmaceutical composition as claimed in claim8, wherein the emulsifiers comprise about 0.1% to about 10% w/w of the total weight of the composition.

10. The pharmaceutical composition as claimed in claim8, wherein the oil comprises about 5% to about 25% w/w of the total weight of the composition.

11. The pharmaceutical composition as claimed in claim8, 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.

12. The pharmaceutical composition as claimed in claim1, wherein the composition retains at least 80% potency of lornoxicam or salt thereof after storage for 3 months at 40°C and 75% relative humidity.

13. The pharmaceutical composition as claimed in claim1, wherein the composition is in the form of cream, ointment, gel, lotion, liniment, paste or emulsion.

14. The pharmaceutical composition as claimed in claim1, wherein the composition is in the form of gel.

15. The pharmaceutical composition as claimed in claim1, wherein the composition exhibits a percent inhibition in rat paw edema of at least 10% in 1 hour or at least 5% in 5 hours.

16. A topical gel comprising-

(a) nano sized droplets comprising about 0.01% to about 2.0% w/w of lornoxicam or salt thereof;

(b) optionally, about 10.0% to about 20.0% w/w of methyl salicylate or salt thereof;

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

(d) about 0.1% to about 10.0% w/w of stabilizer;

(e) about 5% to about 25% w/w of oil/lipid;

(f) about 0.1% to about 10.0% w/w of thickening agent;

(g) one or more pH adjusting agents; and

(h) water.

17. A process for the preparation of a pharmaceutical composition comprising lornoxicam or salts 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 lornoxicam 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 about 500nm or less; and

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

18. A method of treating prostaglandin associated acute and chronic pain conditions comprising topically applying a pharmaceutical composition comprising nano size droplets of lornoxicam or salts thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2012/000143

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/06 A61K9/107 A61K47/10 A61K47/14 A61K47/26
A61K47/32 A61K9/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93/18752 A1 (PHARMOS CORP [US]) 30 September 1993 (1993-09-30) examples 25,27,30	1-18
Y	US 2007/036831 A1 (BAKER JAMES R [US]) 15 February 2007 (2007-02-15) paragraph [0034]; claim 5; examples	1-18
Y	WO 2010/116382 A2 (CADILA HEALTHCARE LTD [IN]; ROY SUNILENDU BHUSHAN [IN]; SHEIKH SHAFIQ) 14 October 2010 (2010-10-14) page 2, paragraph 2; example 1; table 1	1-18
Y	US 2006/241175 A1 (SCHWARZ JOSEPH [CA] ET AL) 26 October 2006 (2006-10-26) paragraphs [0007], [0019]; examples 5,14,15	1-18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 2012	05/09/2012

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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