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(54) Title: TOPICAL ETORICOXIB FORMULATION

(57) Abstract: The present invention provides pharmaceutical formulations, methods for preparation, and methods of treatment comprising a selective COX-2 inhibitor, a thickening agent, at least one lower alcohol, and water, wherein the formulation comprises about 50% to 80% (w/w) or even 65% to 80% (w/w) of the lower alcohol and water in a ratio of about 2:1 to 8:1. In a preferred aspect, the selective COX-2 inhibitor is etoricoxib. In another preferred aspect, the lower alcohol is ethanol or a mixture of ethanol and isopropanol. Preferably, the formulations enhance permeability and bioavailability of the selective COX-2 inhibitor, and preferably, they are useful for topical treatment of pain or inflammation. In a more preferred embodiment, the method of treatment is directed to pain associated with osteoarthritis.

TOPICAL ETORICOXIB FORMULATION

[0001] This application claims priority to U.S. Provisional Application No. 61/349,712, filed May 28, 2010. The contents of this priority document and all other references disclosed herein are incorporated in their entirety for all purposes.

BACKGROUND OF THE INVENTION

[0002] Osteoarthritis (OA) is a chronic joint disease characterized by progressive degeneration of articular cartilage. Symptoms include joint pain and impaired movement. OA is one of the leading causes of disability worldwide and a major financial burden to health care systems. It is estimated to affect over 15 million adults in the United States alone. *See* Boh, L.E.; Osteoarthritis. In: DiPiro, J.T.; Talbert, R.L.; Yee, G.C. *et al.* editors. *Pharmacotherapy: a pathophysiological approach.* 4th ed. Norwalk (CT): Appleton & Lange, pp. 1441-59 (1999).

[0003] An OA treatment's efficacy is generally assessed by three outcome measures: pain, physical function, and a patient global assessment. *See* Bellamy, N.; Kirwan, J.; Boers, M.; Brooks, P.; Strand, V.; Tugwell, P. *et al.* Recommendations for a core set of outcome measures for future Phase III clinical trials in knee, hip and hand osteoarthritis. Consensus development at OMERACT III., *J Rheumatol*, 24:799-802 (1997). To be suitable for chronic use, a therapy must generally show efficacy on these three variables over a sustained period of time. In the U.S., the Food and Drug Administration (FDA) has required OA therapies to show superiority over placebo over a twelve-week period before approval of a new drug application.

[0004] Oral non-steroidal anti-inflammatory drugs (NSAIDs) are a mainstay in the management of OA. These drugs are thought to exert their analgesic effect by impeding the production of signaling molecules called prostaglandins through inhibition of the cyclooxygenase ("COX") enzyme. The COX enzyme has two isoforms, COX-1 and COX-2. Traditional NSAIDs inhibit both isoforms of the COX enzyme, while the selective COX-2 (coxib) class of NSAIDs preferentially inhibits COX-2.

[0005] NSAIDs have analgesic, anti-inflammatory, and antipyretic effects and are useful in reducing pain and inflammation. They are, however, associated with serious potential side effects including nausea, vomiting, peptic ulcer disease, and gastrointestinal (GI) hemorrhage. Although selective COX-2 inhibitors produce fewer gastrointestinal side

effects, they may increase the risk of thrombotic events (*e.g.*, stroke or heart attack). Because of this potential side effect, most of the selective COX-2 inhibitors have been withdrawn from the U.S. market.

[0006] Topical NSAIDs offer the possibility of achieving local therapeutic benefit while reducing or eliminating the risk of systemic side effects. A topical drug containing a COX-2 selective inhibitor would offer patients an attractive new treatment modality. Such a drug could minimize systemic exposure to the active pharmaceutical ingredient by localizing the drug at the site of action. A topical coxib might have even better GI safety profile than topical formulations containing traditional NSAIDs, making it particularly suitable for patients at risk of GI bleeds.

[0007] Pennsaid Gel™ is a topical formulation comprising diclofenac sodium that overcomes disadvantages of prior art NSAID formulations. U.S. Patent Publication No. 2008/0300311. Pennsaid™ solution has been shown in clinical trials to be effective for treating the pain and symptoms of osteoarthritis, and it has been approved for use in Canada, the U.S., and several European countries.

[0008] A topical drug containing a COX-2 selective inhibitor would offer patients an attractive new treatment modality. Such a drug could minimize systemic exposure to the active pharmaceutical ingredient by localizing the drug at the site of action. At the same time a topical coxib might have even better GI safety profile than topical formulations containing traditional NSAIDs, making it particularly suitable for patients at risk of GI bleeds.

[0009] The dearth of options with robust efficacy data for NSAID treatment of OA partially arise from the difficulty associated with delivering a molecule through the skin in both a sufficient quantity to exert a therapeutic effect and a manner that makes the treatment itself tolerable. It is generally believed that for OA treatments, clinical efficacy requires absorption of the active ingredient and its penetration in sufficient quantities into underlying inflamed tissues including the synovium and synovial fluid of joints. *See* Rosenstein, Topical agents in the treatment of rheumatic disorders, *Rheum. Dis. Clin North Am.*, 25: 899-918 (1999).

[0010] Various factors can affect the absorption rates and penetration depth of topical pharmaceutical preparations, including the nature of the active ingredient, the nature of the vehicle, the pH, and the relative solubility of the active in the vehicle versus the skin (Ostrenga J. *et al.*, Significance of vehicle formulation I: relationship between topical vehicle formulation, skin penetrability, and clinical efficacy, *Journal of Pharmaceutical Sciences*, 60: 1175-1179 (1971)). More specifically, drug attributes such as solubility, size and charge, as

well as vehicle attributes such as the drug dissolution rate, spreadability, adhesion, and ability to alter the membrane permeability can each have significant effects on permeability.

[0011] Seemingly minor variations in formulations can produce significant changes in their performance. For instance, Naito demonstrates significant variability in penetration among topical NSAID formulations simply by changing the gelling agent used in the formulations (Naito *et al.*, Percutaneous absorption of diclofenac sodium ointment, *Int. Jour. of Pharmaceutics*, 24: 115-124 (1985)). Similarly, Ho noted significant variability in penetration by changing the proportions of alcohol, propylene glycol, and water (Ho *et al.*, The influence of cosolvents on the in-vitro percutaneous penetration of diclofenac sodium from a gel system, *J. Pharm. Pharmacol.*, 46:636-642 (1994)). It was noted that the changes affected three distinct variables: (i) the solubility of the drug in the vehicle, (ii) the partition coefficient of the drug between the vehicle and the skin, and (iii) alteration of skin structure.

[0012] Ho *et al.* (*Id.*) also noted that (i) the pH of the vehicle, (ii) the drug solubility, and (iii) the viscosity of a gel matrix can influence penetration from a gel dosage form. The pH value affects the balance between ionized and non-ionized forms of the drug, which have different permeation properties (Obata, *International Journal of Pharmaceutics*, 89: 191-198 (1993)). The viscosity can affect diffusion of the drug through the gel matrix and release of the drug from the vehicle into the skin. The solubility of the drug in the vehicle will affect the partition coefficient of the drug between the formulation and the recipient membrane or tissue (Ho, *Id.*).

[0013] The skin barrier can be compromised by several physical methods, such as iontophoresis, ultrasound, electroporation, heat, and microneedles. Molecular penetration enhancers (MPE™s) are a preferred means for reversibly lowering the skin barrier. At least 400 chemicals have been identified as skin permeability enhancers. General categories of MPE™s include pyrrolidones, fatty acids, fatty acid esters, fatty acid alcohols, sulfoxides, essential oils, terpenes, oxazolidines, surfactants, polyols, azone and derivatives, and epidermal enzymes.

[0014] The mechanisms by which MPE™s reduce the skin barrier function are not well understood (*see* Williams and Barry "Penetration Enhancers" *Advanced Drug Delivery Reviews* 56: 603-618 (2004)), although it has been proposed that the mechanisms can be grouped into three broad categories: lipid disruption, increasing corneocyte permeability, and promoting partitioning of the drug into the tissue.

[0015] The challenge with use of MPE™s is that few seem to induce a significant or therapeutic enhancement of drug transport at tolerable levels. This is because an MPE™'s disruption of the skin barrier can potentially cause skin irritation. With increased disruption, skin irritation is expected to become a greater issue. This is particularly problematic with topical OA treatments where the goal is to have the active penetrate deeply into joint tissue and where the drug must be used on a long-term basis due to the nature of the disease.

[0016] In light of the foregoing, there is a considerable need for the development of topical NSAID formulations suitable for long-term use in the treatment of OA, and especially for topical formulations containing coxibs. The challenge has been to develop an optimal formulation which will deliver the active agent to the underlying tissue in sufficient concentration to treat OA on a long-term basis, while reducing or minimizing the incidence of intolerable skin irritation caused by disrupting the skin barrier and while providing a formulation and dosage that leads to and encourages patient compliance. The present invention is designed to satisfy these and other needs.

BRIEF SUMMARY OF THE INVENTION

[0017] The present invention provides *inter alia* pharmaceutical formulations, methods for preparation, and methods of treatment comprising a selective COX-2 inhibitor, a thickening agent, at least one lower alcohol, and water, wherein the formulation comprises about 50% to 80% (w/w) of the lower alcohol and water in a ratio of about 2:1 to 8:1 (or, alternatively, 65% to 85% (w/w) of the lower alcohol and water in a ratio of about 2:1 to 8:1). In a preferred embodiment, the selective COX-2 inhibitor is etoricoxib. Preferably, the formulations enhance permeability and bioavailability of the selective COX-2 inhibitor, and preferably, they are useful for topical treatment of pain or inflammation. In a more preferred embodiment, the method of treatment is directed to pain associated with OA.

[0018] As such, in one embodiment, the present invention provides a pharmaceutical formulation for topical administration, the formulation consisting of, consisting essentially of, or comprising etoricoxib, a thickening agent, a lower alcohol, and water, wherein the formulation comprises about 50% to 80% (w/w) of the lower alcohol and water in a ratio of about 2:1 to 8:1. Alternatively, the formulation comprises about 65% to 85% (w/w) of the lower alcohol and water in a ratio of about 2:1 to 8:1.

[0019] In a preferred aspect, the formulation comprises about 0.1% to 5% (w/w) of etoricoxib. In a more preferred aspect, the formulation comprises about 1% to 5% (w/w) of a

etoricoxib. Alternatively, and still more preferably, the formulation comprises about 0.5% to 5% (w/w) of a etoricoxib. Yet still more preferably, the formulation comprises about 1% or 2% (w/w) of etoricoxib.

[0020] In another preferred aspect, the formulation further comprises about 1% to 10% (w/w) urea. In more preferred aspects, the formulation comprises about 2.5% to 5% (w/w) urea, about 5% to 7.5% (w/w) urea, or about 5% to 10% (w/w) urea. In a still more preferred aspect, the formulation comprises about 5% (w/w) urea.

[0021] In still yet another preferred aspect, the formulation comprises about 0.1% to 5% (w/w) of the thickening agent. In a more preferred aspect, the formulation comprises about 2% (w/w) of the thickening agent. In a preferred aspect, the thickening agent is hydroxypropyl cellulose.

[0022] In yet another preferred aspect, the lower alcohol is ethanol.

[0023] In still yet another preferred aspect, the lower alcohol is a mixture of ethanol and isopropanol in a ratio of about 4:1 to 12:1; more preferably, 4.5:1 to 12:1; and still more preferably, about 5:1 to 12:1.

[0024] In another aspect, the formulation comprises about 60% to 75% (w/w) lower alcohol. More preferably, the formulation comprises about 65% to 70% (w/w) lower alcohol. Even more preferably, the formulation comprises about 65% to 85% (w/w) lower alcohol.

[0025] In another preferred aspect, the formulation comprises about 55 to 85% (w/w) of a lower alcohol; more preferably, about 55% to 80% (w/w), about 55% to 75% (w/w), or about 65% to 80% (w/w); and still more preferably, 58.5% to 67.5% (w/w).

[0026] In still another preferred aspect, the formulation further comprises 2-(2-ethoxyethoxy)ethanol (Transcutol®). More preferably, the formulation comprises about 5% to 15% (w/w) Transcutol®. Still more preferably, the formulation comprises about 5% or about 10% (w/w) Transcutol®.

[0027] In yet another aspect, the formulation is a low-viscosity gel. Alternatively, the formulation is a high-viscosity gel or a semi-solid formulation. In one preferred aspect, the gel is a pourable gel. In another preferred aspect, the gel is a non-pourable gel.

[0028] In still yet another preferred aspect, the formulation further comprises an alkyl ester. More preferably, the alkyl ester is selected from the group consisting of isopropyl myristate (IPM), diisopropyl adipate, ethyl oleate, ethyl laurate, isopropyl palmitate, diethyl sebacate,

monolaurin, glycerin ricinolate and combinations thereof. Still more preferably, the formulation comprises about 1 to 15% (w/w) of the alkyl ester.

[0029] Alternatively and more preferably, the alkyl ester is isopropyl myristate. Still more preferably, the formulation comprises about 2.5% to 15% (w/w) isopropyl myristate. Yet more preferably, the formulation comprises about 2.5% to 10% (w/w) isopropyl myristate. Yet still more preferably, the formulation comprises about 5% (w/w) isopropyl myristate.

[0030] In another aspect, the stability of the formulation is based on the ratio of the alkyl ester to water. Preferably, the stability of the formulation is based on the ratio of isopropyl myristate (IPM) to water. In a preferred aspect, when the urea:IPM ratio is 1:1 in the absence of Transcutol®, the IPM:water ratio is preferably less than about 1:4.7, and more preferably, less than about 1:3.7. In another preferred aspect, when the urea:IPM ratio is 1:1 in the presence of Transcutol®, the IPM:water ratio is preferably less than about 1:3.1, and more preferably, about 1:2. In still another preferred aspect, when the urea:IPM ratio is 1:2 in the absence of Transcutol®, the IPM:water ratio is preferably less than about 1:4.2 and greater than about 1:1.19 (i.e., between about 1:1.2 and 1:4.2). In yet another preferred aspect, when the urea:IPM ratio is 2:1 in the absence of Transcutol®, the IPM:water ratio is preferably greater than about 1:2.7. In still yet another preferred aspect, when the urea:IPM ratio is 1:1 in presence of Transcutol®, the IPM:water ratio is preferably about 1:3.0.

[0031] In a second embodiment, the present invention provides a gel formulation for topical administration, the formulation comprising about 1% to 5% (w/w) etoricoxib (or, alternatively and preferably, about 0.5% to 5% (w/w) etoricoxib), about 2.5% to 10% urea (w/w); about 2% (w/w) thickening agent; about 45% to 63% (w/w) ethanol; about 5% to 10% (w/w) isopropanol; and water. Preferably, the gel formulation further comprises about 5% to 15% (w/w) 2-(2-ethoxyethoxy)ethanol; and more preferably, the gel formulation further comprises about 2.5% to 10% (w/w) isopropyl myristate.

[0032] In a third embodiment, the present invention provides a method for topically treating pain in a subject, the method comprising topically applying a pharmaceutical formulation comprising about 0.1% to 5% (w/w) etoricoxib (or, preferably, about 0.5% to 5% (w/w) etoricoxib), a thickening agent, a lower alcohol, and water; wherein the formulation comprises about 65% to 85% (w/w) (or, alternatively and preferably, about 50% to 80% (w/w)) of the lower alcohol and water in a ratio of about 2:1 to 8:1.

[0033] In a fourth embodiment, the present invention provides a method for topical administration of a gel formulation, the method comprising topically applying a

pharmaceutical formulation to a subject, wherein the formulation comprises about 0.1% to 5% (w/w) etoricoxib (or, preferably, about 0.5% to 5% (w/w) etoricoxib), about 2.5% to 5% urea (w/w), a thickening agent, a lower alcohol, and water. Preferably, the method is for topically treating pain in the subject. More preferably, the formulation comprises about 65% to 85% (w/w) (or, alternatively and preferably, about 50% to 80% (w/w)) of the lower alcohol and water in a ratio of about 2:1 to 8:1 (i.e., the formulation comprises about 50 to 80% (w/w) of the water-alcohol mixture).

[0034] In a preferred aspect, the method comprises topically applying a pharmaceutical formulation comprising about 1% to 5% (w/w) etoricoxib (or, alternatively and preferably, about 0.5% to 5% (w/w) etoricoxib), about 2.5% to 5% urea (w/w), about 2% (w/w) thickening agent, about 45% to 63% (w/w) ethanol, about 5% to 10% (w/w) isopropanol; and water.

[0035] In another preferred aspect, the pain is associated with osteoarthritis.

[0036] In another embodiment, the present invention provides a use of any of the formulations described herein in the manufacture of a medicament for the treatment of osteoarthritis or pain associated therewith.

[0037] These and other objects, aspects, and embodiments will become more apparent when read with the following detailed description and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] **FIG. 1** illustrates etoricoxib permeation through porcine skin from a first series of topical formulations (Table 1) at 4, 21, and 26 hours after application. 10 µl formulations were applied to each donor cell compartment.

[0039] **FIG. 2** illustrates etoricoxib permeation through porcine skin from a second series of topical formulations (Table 2) at 4, 21, and 26 hours after application. 10 µl formulations were applied to each donor cell compartment.

[0040] **FIG. 3** illustrates etoricoxib permeation through human cadaver skin from a third series of topical formulations (Table 3) at 4, 8, 12, 16, and 20 hours after application. 5 µl formulations were applied to each donor cell compartment.

[0041] **FIG. 4** illustrates etoricoxib permeation through porcine skin from a fourth series of topical formulations (Table 4) at 4, 21, and 24 hours after application. 5 µl formulations were applied to each donor cell compartment.

[0042] **FIG. 5** illustrates etoricoxib permeation through human cadaver skin from a fifth series of topical formulations (Table 5) at 4, 8, 12, 16, 20, and 24 hours after application. 5 µl formulations were applied to each donor cell compartment.

[0043] **FIG. 6** illustrates etoricoxib permeation through porcine skin from a sixth series of topical formulations (Table 6) at 4, 21 and 24 hours after application. 10 µl formulations were applied to each donor cell compartment.

[0044] **FIG. 7** illustrates etoricoxib permeation through porcine skin from a seventh series of topical formulations (Table 7) at 4, 21 and 24 hours after application. 10 µl formulations were applied to each donor cell compartment.

[0045] **FIG. 8** illustrates etoricoxib permeation through porcine skin from an eighth series of topical formulations (Table 8) at 4, 21 and 24 hours after application. 10 µl formulations were applied to each donor cell compartment.

[0046] **FIG. 9** illustrates etoricoxib permeation through human cadaver skin from once-daily and twice-daily administration of 1% and 2% etoricoxib formulations (Table 11) at 4, 8, 14, 24, 36, and 48 hours after application. 5 µl formulations were applied to each donor cell compartment.

[0047] **FIG. 10** illustrates the effects of two cumulative days of once- or twice-daily dosing of 1% and 2% etoricoxib formulations across human cadaver skin (Table 12). 5 µl formulations were applied to each donor cell compartment.

[0048] **FIG. 11** illustrates the effects of four dosing regimens, including 1% and 2% etoricoxib formulations (Table 13), across human cadaver skin. 5 µl formulations were applied to each donor cell compartment.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0049] The terms "a," "an," or "the" as used herein not only includes aspects with one member, but also aspects with more than one member. For example, an embodiment including "a thickening agent and a lower alcohol" should be understood to present aspects with at least a second thickening agent, at least a second lower alcohol, or both.

[0050] The term "about" as used herein to modify a numerical value indicates a defined range around that value. If "X" were the value, "about X" would generally indicate a value

from 0.95X to 1.05X. Any reference to "about X" specifically indicates at least the values X, 0.95X, 0.96X, 0.97X, 0.98X, 0.99X, 1.01X, 1.02X, 1.03X, 1.04X, and 1.05X. Thus, "about X" is intended to teach and provide written description support for a claim limitation of, *e.g.*, "0.98X." When the quantity "X" only includes whole-integer values (*e.g.*, "X carbons"), "about X" indicates from (X-1) to (X+1). In this case, "about X" as used herein specifically indicates at least the values X, X-1, and X+1. When "about" is applied to the beginning of a numerical range, it applies to both ends of the range. Thus, "from about 5 to 20%" is equivalent to "from about 5% to about 20%." When "about" is applied to the first value of a set of values, it applies to all values in that set. Thus, "about 7, 9, or 11%" is equivalent to "about 7%, about 9%, or about 11%."

[0051] In formulations comprising an "additional," "further," or "second" component, the second component as used herein is chemically different from the other components or first component. A "third" component is different from the other, first, and second components, and further enumerated or "additional" components are similarly different.

[0052] "Agent" as used herein indicates a compound or mixture of compounds that, when added to a pharmaceutical formulation, tend to produce a particular effect on the formulation's properties. For example, a formulation comprising a thickening agent is likely to be more viscous than an otherwise identical comparative formulation that lacks the thickening agent.

[0053] "Cellulosic thickening agent" as used herein includes a thickening agent that is 1) a natural or synthetic polymeric carbohydrate (*e.g.*, cellulose, pharmaceutically acceptable vegetable gums); 2) a polymeric or oligomeric derivative of a polymeric carbohydrate that is produced by chemical modification (*e.g.*, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose); or 3) mixtures thereof. Representative cellulosic thickening agents include cellulose, hydroxypropyl cellulose ("HPC"), hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose, and the like.

[0054] In general, embodiments described herein that include chiral compounds (*e.g.,* lactic acid) may include embodiments with the racemic form or embodiments enriched in the D- or L- enantiomer thereof (up to and including pure or essentially pure D-lactic acid or L-lactic acid).

[0055] As used herein, the phrase "effective amount" or "effective dose" means an amount sufficient to achieve the desired result and accordingly will depend on the ingredient and its

desired result. Nonetheless, once the desired effect is known, determining the effective amount is within the skill of a person skilled in the art.

[0056] "Enhancement ratio" ("ER") as used herein is the ratio of a test result (*e.g.*, ug/cm^2 accumulated dose of product) from a formulation comprising an active to the corresponding test result from a control composition comprising the same active at the same concentration, but a different vehicle (e.g., the active ingredient in an alcohol-water mixture with no other components).

[0057] In general, the "error bars" on the graphs provided in the figures represent the standard error of the mean value, whereas the top of the solid, shaded, or patterned bar represents a single data value, which is the mean value of the distribution of data values.

[0058] "Finite dosing" as used herein generally includes an application of a limited reservoir of an active agent. The active agent in the reservoir is depleted with time, leading to a tapering off of the absorption rate of the active agent after a maximum absorption rate is reached.

[0059] "Formulation," "pharmaceutical composition," and "composition" as used herein are equivalent terms referring to a composition of matter suitable for pharmaceutical use.

[0060] "Infinite dosing" as used herein generally includes an application of a large reservoir of an active agent. The active agent in the reservoir is not significantly depleted with time, thereby providing protracted, continuous, steady-state absorption of the active.

[0061] "Lower alcohol" as used herein includes straight- or branched-chain alkyl alcohols of 1 to about 6 carbon atoms. Representative lower alcohols include methanol, ethanol, n-propanol, isopropanol (also known as isopropyl alcohol or IPA), n-butanol, t-butanol, n-pentanol, 3-pentanol, 2-methoxyethanol, propylene glycol, and the like.

[0062] "Monohydric alcohol" as used herein includes straight- or branched-chain alkyl alcohols with a single hydroxyl group. Representative monohydric alcohols include methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol, n-pentanol, 3-pentanol, 2-methoxyethanol, 2-(2-ethoxyethoxy)ethanol, olelyl alcohol, and the like.

[0063] The term "or" as used herein should in general be construed non-exclusively. For example, an embodiment of "a formulation comprising A or B" would typically present an aspect with a formulation comprising both A and B. "Or" should, however, be construed to exclude those aspects presented that cannot be combined without contradiction (*e.g.*, a formulation pH that is between 9 and 10 or between 7 and 8).

[0064] "Penetration enhancer", "molecular penetration enhancer" or "MPE™" as used herein includes an agent or a combination of agents that improves the transport of molecules such as a pharmaceutically or cosmetically active agent into or through a physiological barrier such as the skin or nail. A molecular penetration enhancer may be a pure substance or may comprise, consist essentially of, or consist of a mixture of different chemical entities. Various conditions may occur at different sites in the body, either in the skin or below the skin, creating a need to target delivery of compounds. For example, in a treatment for osteoarthritis, delivery of the active agent to the underlying tissue surrounding the joint may be necessary to achieve therapeutic benefit. A molecular penetration enhancer may be used to assist in the delivery of an active agent i) directly into the skin or nail; ii) locally, or regionally, into tissue(s) underlying the skin or nail; or iii) indirectly, via systemic distribution to the site of the disease. If systemic distribution of an active agent (*e.g.*, etoricoxib) would be likely to produce side effects, a molecular penetration enhancer is preferably selected to maximize direct delivery and to minimize systemic distribution. A molecular penetration enhancer may be a pure substance or may comprise, consist essentially of, or consist of a mixture of different chemical entities.

[0065] Generally, when a percentage range is taught, it incorporates all full or partial percentages in between (*i.e.*, within the bounds of the range). For example, a percentage range of 15 to 25% would also teach *inter alia* the specific values of 17.36% and 21%. A percentage range of about 13 to 17% would also teach *inter alia* the specific values of 12.97%, 16%, and 17.1%.

[0066] Where a formulation is not aqueous, the term "pH" as used herein refers to the apparent pH of the formulation as determined by methods standard in the art.

[0067] The term "pH adjusting agent" as used herein refers to a compound added to the compositions of the present application for the purpose of changing the pH of the composition. Examples of such agents include pharmaceutically acceptable acids, pharmaceutically acceptable bases, and pharmaceutically acceptable buffers.

[0068] The term "pharmaceutically acceptable" as used herein means compatible with the treatment of animals, and in particular, humans.

[0069] The term "pharmaceutically acceptable salt" as used herein means a pharmaceutically acceptable acid addition salt or a pharmaceutically acceptable basic addition salt. The formation of a desired compound salt is achieved using standard

techniques. For example, the neutral compound is treated with an acid or base in a suitable solvent and the formed salt is isolated by filtration, extraction, or any other suitable method.

[0070] As it pertains to comparative flux values described herein,a "ratio" iscalculated based on the cumulative amount of active (*e.g.* etoricoxib) delivered through the skin over the period of the experiment (i.e., from 4 to 60 h, and preferably, over 24 h).

[0071] "Selective COX-2 inhibitor" as used herein should in general be construed to mean the selective COX-2 (coxib) class of NSAIDs that preferentially inhibits COX-2, as well as pharmaceutically acceptable derivatives or salts thereof. By extension, the term "etoricoxib" as used herein, includes pharmaceutically acceptable derivatives or salts thereof.

[0072] The term "subject" as used herein includes all members of the animal kingdom, preferably mammals, and most preferably, humans.

[0073] The phrase "substantially free" of X is used herein to include "essentially free" of X. Such embodiments may include trace amounts or *de minimus* amounts of X."

[0074] "Surfactant" as used herein includes a surface-active agent. Surfactants reduce the surface tension of a solvent in which they are dissolved.

[0075] "Thickening agent" as used herein includes an agent or combination of agents that increases the viscosity of a formulation. A thickening agent may be a pure substance, or it may comprise, consist essentially of, or consist of a mixture of different chemical entities. Exemplary thickening agents include carbomer polymers, carbomer derivatives, cellulose polymers, cellulose derivatives, polyvinyl alcohol, poloxamers, polysaccharides, and the like, as well as mixtures thereof. Non-limiting examples of formulations containing a thickening agent include gel and semi-solid formulations.

[0076] "Topical formulation" as used herein includes the administration of a composition (*e.g.*, a formulation containing a pharmaceutically or cosmetically active agent) to the skin, nail, mucosa, or other localized region of the body. Topical application may result in the delivery of an active agent to the skin, a localized region of the body, a localized volume of the body, or the systemic circulation.

[0077] "Topical formulation" as used herein includes a formulation that is suitable for topical application to the skin, a nail, or a mucosa. A topical formulation may, for example, be used to confer a therapeutic or cosmetic benefit to its user. Specific topical formulations can be used for topical, local, regional, or transdermal application of substances.

[0078] "Transdermal" as used herein includes a process that occurs through the skin. The terms "transdermal," "percutaneous," and "transcutaneous" can be used interchangeably. In certain embodiments, "transdermal" may also include epicutaneous.

[0079] "Transdermal application" as used herein includes administration through the skin. Transdermal application can be used for systemic delivery of an active agent; however, it is also useful for delivery of an active agent to tissues underlying the skin with minimal systemic absorption. In certain embodiments, "transdermal application" may also include epicutaneous application.

[0080] "Treatment" as used herein includes any cure, amelioration, or prevention of a disease in a mammal, particularly a human. Treatment may prevent the disease from occurring; inhibit the disease's spread; relieve the disease's symptoms (*e.g.*, fully or partially alleviate pain from osteoarthritis), fully or partially remove the disease's underlying cause, shorten a disease's duration, or do a combination of these things.

[0081] "Treating" or "treatment" as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject's condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (*i.e.*, not worsening) the state of disease, prevention of a disease's transmission or spread, delaying or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable.

[0082] "Treating" and "treatment" as used herein include prophylactic treatment. Treatment methods comprise administering to a subject a therapeutically effective amount of an active agent. The administering step may consist of a single administration or may comprise a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of active agent, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient.

[0083] "Zwitterionic surfactant" as used herein includes a surface-active agent that comprises atoms bearing a formal charge other than zero, but in which the agent has a net charge of zero. Examples include cocoamidopropyl betaine, cocoamphoacetate (*i.e.*, cocoamphoglycinate), cocoamidopropyl hydroxysultaine, dodecyl betaine, phospholipids (*e.g.*, lecithin), alkyl or acyl amphopropionates or sulfobetaines (*i.e.*, sulfonic acid analogs to carboxylic acid betaines), and the like, as well as mixtures and poly(ethylene glycol) derivatives thereof.

[0084] A "charged derivative of a zwitterionic surfactant" or "charged derivative thereof" as used herein indicates a cationic or anionic surfactant that is a salt of a zwitterionic surfactant produced by either protonation or deprotonation (*e.g.*, by reaction of cocoamphodiacetate with sodium hydride or hydroxide to produce disodium cocoamphodiacetate). Examples include sodium cocoamphoacetate, sodium lauroamphoacetate, disodium dicocoamphodicetate, potassium cocoamphodiacetate, dipotassium cocoamphodiacetate, disodium dicocoamphodipropionate, and the like (*e.g.*, metal salts of alkyl or acyl amphopropionates or sulfobetaines), as well as mixtures and poly(ethylene glycol) derivatives thereof.

[0085] The prefix "micro" as used herein can be alternatively abbreviated as "μ" or "u." For example, micrograms are typically abbreviated as μg, but can alternatively be abbreviated as "ug."

[0086] The term "w/w" or "wt/wt" means a percentage expressed in terms of the weight of the ingredient or agent over the total weight of the composition multiplied by 100.

II. Embodiments

A. Active Agent

[0087] In one preferred aspect, the active agent is an anti-inflammatory agent. More preferably, the agent is a non-steroidal anti-inflammatory drug. Preferably, the agent is a coxib. More preferably, the coxib is etoricoxib. In other instances, the active ingredient is a combination or mixture of active agents, such as at least two active agents.

[0088] Non-limiting examples of NSAIDs include acetic acid derivatives such as indomethacin, sulindac, etodolac, and diclofenac; propionic acid derivatives such as ibuprofen, naproxen, fenoprofen, ketoprofen, fluriprofen, and oxaprozin; coxibs such as celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, and etoricoxib; fenamic acid derivatives such as mefenamic acid, meclofenamic acid, flufenamic acid, and tolfenamic

acid; enolic acid derivatives such as piroxicam, meloxicam, tenoxicam, droxicam, and isoxicam; and the compounds' pharmaceutically acceptable salts such as diclofenac sodium, naproxen sodium, and diclofenac potassium. Acetic acid derivatives, coxibs, and their pharmaceutically acceptable salts are preferred.

[0089] Other NSAIDs include aspirin, salicylic acid, diflunisal, etodolac, meclofenamate, nabumetone, salsalate, and their pharmaceutically acceptable salts.

[0090] In a preferred aspect, the present invention provides a pharmaceutical composition comprising, consisting essentially of, or consisting of a selective COX-2 inhibitor. In a preferred aspect, the selective COX-2 inhibitor is selected from the group of celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, valdecoxib, and a combination thereof. More preferably, the selective COX-2 inhibitor is selected from the group of celecoxib, etoricoxib, and rofecoxib. Still more preferably, the selective COX-2 inhibitor is etoricoxib.

[0091] In a preferred aspect, the formulation comprises about 0.05% to 10% (w/w) of a coxib. More preferably, the formulation comprises about 0.1% to 5% (w/w) of a coxib, preferably etoricoxib. Still more preferably, the formulation comprises about 0.5% to 5%, 0.1% to 3%, 1% to 3%, 1% to 5%, 2% to 4%, or 2% to 5% (w/w) of a coxib, preferably etoricoxib. Yet still more preferably, the formulation comprises about 1, 2, 3, 4, or 5% (w/w) of a coxib, preferably etoricoxib. In another preferred aspect, the pharmaceutical composition comprises about 0.1% to 5% (w/w) of etoricoxib, preferably about 1% to 3% (w/w) or about 0.5 to 5% (w/w), and more preferably about 1 or 2% (w/w).

[0092] In one aspect, a formulation enables delivery of a therapeutically effective amount of a selective COX-2 inhibitor. Preferably, a formulation enables delivery of a selective COX-2 inhibitor daily dosage of about 0.01 mg to about 120 mg; more preferably, about 0.1 mg to 60 mg; still more preferably, about 1 mg to about 30 mg; and yet more preferably, about 1 to about 10 mg. Yet still more preferably, the formulation enables delivery of a daily dosage of about 3 mg.

[0093] Preferably, the selective COX-2 inhibitor concentration of the formulation is such that this dosage amount can be provided by application of the composition from one to four times a day, preferably one to two times a day, to a skin area of up to about 2500 cm^2, preferably about 1200 to 1800 cm^2 (*e.g.*, both knees at about 750 cm^2/knee). Alternatively, the composition can be applied to a skin area of about 1 to 50 cm^2, about 50 to 250 cm^2, about 100 to 500 cm^2, about 200 to 800 cm^2, or about 800 to 1200 cm^2.

[0094] In another aspect, the formulation of the present invention provides a total or a systemic dose that is less than 50% of the systemic daily dose of the maximum approved oral dose; preferably, less than 25%; more preferably, less than 10%; and still more preferably, less than 5%, yet provides local or regional delivery levels sufficient for therapeutic benefit or treatment. Preferably, the concentration is such that this dosage amount can be provided by application of the composition from one to four times a day; more preferably, one to two times a day; to a skin area of up to about 2500 cm^2 and preferably about 1200 to 1800 cm^2 (*e.g.*, both knees at about 750 cm^2/knee). Alternatively, the composition can be applied to a skin area of about 1 to 50 cm^2, about 50 to 250 cm^2, about 100 to 500 cm^2, about 200 to 800 cm^2, or about 800 to 1200 cm^2.

[0095] A person skilled in the art will appreciate that the dosage and application area will vary on and can be tailored to the area being treated (*e.g.*, knees, fingers, toes, back, and the like). In one preferred aspect, a single knee is treated and the application area is about 750 cm^2. In another preferred aspect, both knees of an individual are treated and the application area is about 1500 cm^2 (about 750 cm^2 per knee).

[0096] In still another aspect, the pharmaceutical formulation comprising a selective COX-2 inhibitor has a flux value (as determined, e.g., by the Franz cell procedure of Example 10) at least equal to the flux of a known comparative formulation with the same selective COX-2 inhibitor. Preferably, the selective COX-2 inhibitor flux is greater than the flux of the comparative formulation with the same selective COX-2 inhibitor. More preferably, the selective COX-2 inhibitor flux is at least 1.5 times as great as the flux of a comparative formulation with the same selective COX-2 inhibitor. In other words, the ratio of: (i) the selective COX-2 inhibitor flux of the composition to (ii) the flux of a comparative formulation with the same selective COX-2 inhibitor is preferably greater than 1.0, and more preferably at least about 1.5.

[0097] Still more preferably, the formulation has a selective COX-2 inhibitor flux that is at least 2.0 times as great as the flux of a comparative formulation with the same selective COX-2 inhibitor. Yet still more preferably, the formulation has a selective COX-2 inhibitor flux that is at least 4.0 times as great as the flux of a comparative formulation with the same selective COX-2 inhibitor.

[0098] In yet another aspect, the present invention provides a formulation comprising etoricoxib, wherein the formulation provides an etoricoxib flux of at least 0.1 $\mu g/hr/cm^2$ at 24 hours; preferably, at least 0.2 $\mu g/hr/cm^2$ at 24 hours.

[0099] In an alternative aspect, the pharmaceutical formulation comprising etoricoxib provides greater flux (as determined, e.g., by the Franz cell procedure of Example 10) than an analogous comparative formulation comprising a selective COX-2 inhibitor. Preferably, this comparative formulation comprises etoricoxib. More preferably, the flux of etoricoxib is at least 1.5 times as great as the flux of the comparative hydroalcoholic formulation's active agent. In other words, the ratio of: (i) the formulation's etoricoxib flux to (ii) the comparative formulation's coxib flux is preferably greater than 1.0, and more preferably at least about 1.5.

[0100] Still more preferably, the formulation has an etoricoxib flux that is at least 2.0 times as great as the comparative formulation's coxib flux. Yet still more preferably, the formulation has an etoricoxib flux that is at least 4.0 times as great as the comparative formulation's coxib flux.

[0101] Still more preferably, the composition comprising etoricoxib has an enhancement ratio (ER) of at least 2. Yet still more preferably, the composition comprising etoricoxib has an ER of at least 5.0. Yet still more preferably, the composition comprising etoricoxib has an ER that is at least 10.0.

B. Urea

[0102] In another preferred aspect, the formulation further comprises about 0.1% to 25% (w/w) urea. In more preferred aspects, the formulation comprises about 1% to 10% (w/w) urea. Still more preferably, the formulation comprises about 2% to 5%, about 2.5% to 5%, about 3% to 6%, about 5% to 7.5%, about 5% to 10%, or about 7.5% to 10% (w/w) urea. Alternatively, the formulation comprises about 1, 2, 3, 4, 5, 6, 7, or 8% (w/w) urea; more preferably, about 5% (w/w) urea.

C. Thickening Agent

[0103] In still yet another aspect, the formulations herein comprise at least one thickening agent, such as a cellulose polymer, a carbomer, a polyvinyl pyrrolidone, a polyvinyl alcohol, a poloxamer, a xanthan gum, a locus bean gum, a guar gum and mixtures thereof. Preferably, the formulation includes a cellulosic thickening agent. Suitable cellulosic thickening agents include, but are not limited to, hydroxypropyl cellulose (HPC) of various grades, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, hydroxyethyl methyl cellulose, ethyl cellulose, methyl cellulose, carboxymethyl cellulose, dextran, guar gum, pectin, starch, cellulose, and the like. More preferably, the cellulosic thickening agent is HPC.

[0104] In a preferred aspect, the formulation comprises about 0.5% to 5% (w/w) of the thickening agent, such as about 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, or 5% (w/w). More preferably, the formulation comprises from about 0.5% to 1% (w/w) of a thickening agent or about 0.5 to 2% (w/w) of a thickening agent. Still more preferably, the formulation comprises about 2% (w/w) of a thickening agent. Alternatively, the formulation comprises about 1% (w/w) of a thickening agent.

[0105] In preferred embodiments, the formulation has a viscosity of at least 100 centipoise (cP). Preferably, the formulation has a viscosity of at least 500 cP. More preferably, the formulation has a viscosity of at least 1000 cP. Still more preferably, the viscosity is 5000–10,000, 10,000–15,000, 15,000–25,000 or 25,000–50,000 cP. Alternatively, the viscosity is more than 50,000 cP or more than 100,000 cP.

D. Lower Alcohol

[0106] In one preferred aspect, the formulations include a lower alcohol. More preferably, the lower alcohol is a monohydric lower alcohol, and still more preferably, the lower alcohol is selected from a C_1 to C_6 alkanol, such as methanol, ethanol, propanol, isopropanol, butanol, isobutanol, sec-butanol, pentanol, and the like, as well as a mixture thereof. Ethanol is preferred. A combination of ethanol and isopropanol is especially preferred.

[0107] In certain aspects, the formulation includes about 50% to 80% (w/w) of the lower alcohol (preferably, ethanol or a mixture of ethanol and isopropanol). In other aspects, the formulations include about 50, 53, 55, 56, 57, 58, 58.5, 59, 60, 61, 62, 63, 64, 65, 66, 67, 67.5, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, or 79% (w/w) of a lower alcohol. More preferably, the formulation comprises from about 55% to 75% (w/w) of a lower alcohol. Still more preferably, the formulation comprises from about 60 to 75%, about 63 to 75%, about 65 to 75%, about 65 to 70%, about 68 to 75%, or about 70 to 75% (w/w) of a lower alcohol. Alternatively and still more preferably, the formulation comprises from about 50% to 75% (w/w), about 55% to 70%, about 57% to 75%, about 58.5% to 70%, 58.5% to 67.5%, about 60 to 70%, about 65% to 85%, or about 70 to 85% (w/w) of a lower alcohol. Yet still more preferably, the formulation comprises about 56.5, 57, 57.5, 58, 58.5, 59, 59.5, 60, 60.5, 61, 61.5, 62, 62.5, 63, 64.5, 65, 65.5, 66, 66.5, 67, 67.5, 68, 68.5, 69, 69.5, 70, 70.5, or 71% (w/w) of a lower alcohol such as ethanol or a mixture of ethanol and isopropanol. In certain preferred aspects, the lower alcohol is a mixture of ethanol and isopropanol in a ratio of about 4.5:1 to 12:1, and preferably, about 5:1 to 12:1, or even about 4:1 to about 12:1 or 4:1 to 12:1.

[0108] In another aspect, the formulations can include a diol. Suitable diols include, but are not limited to, propylene glycol, butanediol, butynediol, pentanediol, hexanediol, octanediol, neopentyl glycol, 2-methyl-1,3-propanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, dipropylene glycol, dibutylene glycol, propylene glycol, and the like, as well as a mixture thereof. In one aspect, the formulation comprises about 0% to 15% (w/w) of propylene glycol, and preferably, about 0 to 5% (w/w). In certain preferred aspects, the diol is a glycol, such as ethylene glycol, propylene glycol, and a mixture thereof.

E. Water

[0109] In certain aspects, the formulations include water. Preferably, water is present from about 5% to 35% (w/w) such as about 5, 6, 7, 8, 9, 10, 11, 12, 12.5, 13, 14, 15, 16, 16.6, 17, 17.5, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 33, or 35% by weight (w/w). More preferably, the formulation includes from about 5 to 10%, about 10 to 20%, about 10 to 15%, about 15 to 20%, about 20 to 25%, about 25 to 30%, about 30 to 35% (w/w), or about 10 to 35% (w/w) water. Alternatively, the mixture includes about 8, 10, 12, 12.5, 13, 16, 16.6, 17, 18, 19, or 20% (w/w) water. In certain preferred aspects, the ratio of lower alcohol and water is about 2:1 to 8:1. Transcutol®

[0110] In yet another aspect, the formulation further comprises Transcutol®. Preferably, Transcutol®is a solvent. Alternatively and more preferably, the Transcutol®is present from about 5% to 15% (w/w), such as about 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 13, 14, or 15% (w/w). Still more preferably, the formulation includes about 5, 7.5, or 10% (w/w) Transcutol®.

F. Alkyl Ester

[0111] In yet another aspect, the formulation further comprises at least one alkyl ester. Preferably, the alkyl ester is a penetration enhancer. More preferably, the alkyl ester is selected from the group consisting of isopropyl myristate, diisopropyl adipate, ethyl oleate, ethyl laurate, isopropyl palmitate, diethyl sebacate, monolaurin, glycerin ricinolate and combinations thereof. Still more preferably, the formulation comprises from about 1% to about 15% (w/w) alkyl ester.

[0112] Yet still more preferably, the alkyl ester is isopropyl myristate. Preferably, the formulation comprises about 1% to 15% (w/w) isopropyl myristate, such as about 1, 2, 2.5, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 11, 12, 13, 14, or 15% (w/w). Alternatively, the formulation comprises about 2.5% to 10%, about 5% to 10%, about 5% to 15%, or about 10% to 15%

(w/w) isopropyl myristate. Preferably, the formulation comprises about 5, 7.5, or 10% (w/w) isopropyl myristate.

G. Surfactants

[0113] In certain aspects, the formulation may comprise at least one pharmaceutically acceptable surfactant. When present, the surfactant may be a nonionic, cationic, anionic, or zwitterionic surfactant or a charged derivative thereof. The surfactant or derivative may be present at about 1% to 10% (w/w), such as about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10% (w/w).

[0114] In certain other aspects, the formulation is free or substantially free of surfactants, such as polysorbates, zwitterionic surfactants; or molecular penetration enhancers like limonene, lower amino alcohols, hydroxy acids or non-hydroxy acids. Without being bound by theory, minimizing components such as surfactants and penetration enhancers in topical formulations can decrease the chance of skin irritation and other side-effects. This is especially relevant when treating diseases such as osteoarthritis, where long term treatment is required. Thus, in certain aspects, the formulations of the present invention have the added advantage of enhanced penetration of active agents in the absence of additional components, thereby improving patient tolerance of topical formulations. Moreover, in the absence of additional components, certain embodiments of the present invention's topical formulations have good stability and provide properties of higher flux and greater *in vivo* absorption.

1. Nonionic Surfactants

[0115] In one aspect, the composition comprises or may comprise at least one pharmaceutically acceptable nonionic surfactant. Non-limiting examples of nonionic surfactants include polysorbates, such as polysorbate 20 (Tween 20), Tween 40, Tween 60, and Tween 80; poly(oxyethylene) (POE) fatty acid esters, such as Myrj 45, Myrj 49, Myrj 52 and Myrj 59; poly(oxyethylene) alkyl ethers, such as poly(oxyethylene) cetyl ether, poly(oxyethylene) palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, Brij 38, Brij 52, Brij 56 and Brij W1; sucrose esters; partial esters of sorbitol and its anhydrides, such as sorbitan monolaurate; mono or diglycerides and isoceteth-20.

[0116] Other nonionic surfactants include, but are not limited to, cetomacrogol 1000, cetostearyl alcohol, cetyl alcohol, cocoamide diethanolamine, cocoamide monoethanolamine, decyl glucoside, glyceryl laurate, lauryl glucoside, polyoxyethylene ethers of fatty acids such as cetyl alcohol or stearyl alcohol, narrow-range ethoxylates, octyl glucoside, oleyl alcohol,

poloxamers, polyethylene glycol, sorbitan monolaurate, polyoxyethylene sorbitan monolaurate, sorbitan dioleate, sorbitan trilaurate, sorbitan monopalmitate, polyoxyethylene (20) sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, polyoxyethylene (20) sorbitan monostearate, sorbitan monooleate, sorbitan trioleate, polyoxyethylene sorbitan monooleate, stearyl alcohol, sucrose coconut fatty ester mixtures, glycerin monolaurate, and sucrose monolaurate.

[0117] Still other non-ionic surfactants include, but are not limited to, fatty acid diesters, polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products, polyglycerized fatty acids, sterol and sterol derivatives, polyethylene glycol alkyl ethers, sugar esters, polyethylene glycol alkyl phenols, polyoxyethylene- polyoxypropylene block copolymers, sorbitan fatty acid esters and lower alcohol fatty acid esters.

2. Cationic Surfactants

[0118] In another aspect, the composition comprises or may comprise at least one pharmaceutically acceptable cationic surfactant. Non-limiting examples of cationic surfactants include octyl trimethylammonium salts, cetyl trimethyl ammonium salts, stearyl trimethyl ammonium salts, benzyl trimethyl ammonium salts, alkylamines, alkylimidazoles, ethoxylated amines, non-amphoteric quaternary surfactants, esterquats, and mixtures thereof. Quaternary surfactants contain at least one nitrogen atom, which is covalently bonded to four alkyl or aryl groups.

[0119] Cationic surfactants include, but are not limited to, non-amphoteric quaternary ammonium compounds, in particular benzyltrialkyl ammonium chlorides or bromides, *e.g.*, benzyl dimethylstearyl ammonium chloride; alkyl trialkyl ammonium salts, *e.g.*, cetyl trimethyl ammonium chloride or bromide, alkyl dimethylhydroxyethyl ammonium chloride or bromide, dialkyl dimethyl ammonium chloride or bromide, and alkylamide ethyltrimethyl ammonium ether sulfates; alkylpyridinium salts, *e.g.*, lauryl or cetyl pyrimidinium chloride; *N,N'*-dialkylimidazoline derivatives; compounds having cationic character, such as amine oxides, *e.g.*, alkyl dimethylamine oxides or alkylaminoethyl dimethylamine oxides; and the like.

3. Anionic Surfactants

[0120] In yet another aspect, the formulations comprises or may comprise an anionic surfactant, such as an alkyl sulfate, *e.g.*, sodium, ammonium, or triethylammonium (TEA) lauryl sulfate. Other anionic surfactants include acylamino acids (and their salts), such as

acyl glutamates, *e.g.*, sodium acyl glutamate, di-TEA palmitoyl aspartate, and sodium caprylic/capric glutamate; acyl peptides, *e.g.*, palmitoyl-hydrolyzed milk protein, sodium cocoyl-hydrolyzed soya protein and sodium/potassium cocoyl-hydrolyzed collagen; sarcosinates, *e.g.*, myristoyl sarcosin, TEA-lauroyl sarcosinate, sodium lauroyl sarcosinate and sodium cocoyl sarcosinate; taurates, *e.g.*, sodium lauroyl taurate and sodium methylcocoyl taurate; acyl lactylates, lauroyl lactylate, caproyl lactylate; and alaninates; and the like.

[0121] Other anionic surfactants include carboxylic acids and derivatives, such as carboxylic acids, *e.g.*, lauric acid, aluminum stearate, magnesium alkanolate, and zinc undecylenate; ester carboxylic acids, *e.g.*, calcium and sodium stearoyl lactylates, laureth-6 citrate, and sodium PEG-4 lauramide carboxylate; ether carboxylic acids, *e.g.*, sodium laureth-13 carboxylate, and sodium PEG-6 cocoamide carboxylate; and the like.

[0122] Other anionic surfactants include esters of phosphoric acid and salts, *e.g.*, dilaureth-4 phosphate.

[0123] Other anionic surfactants include sulfonic acids and salts, such as acyl isethionate, *e.g.*, sodium ammonium cocoyl isethionate; alkylaryl sulfonates; alkyl sulfonates, *e.g.*, sodium coco monoglyceride sulfate, sodium C_{12-14} olefin-sulfonate, sodium lauryl sulfoacetate and magnesium PEG-3 cocamide sulfate; sulfosuccinates, *e.g.*, dioctyl sodium sulfosuccinate, disodium laureth sulfosuccinate, disodium lauryl sulfosuccinate, disodium undecylenamido-MEA-sulfosuccinate, and PEG-5 lauryl citrate sulfosuccinate; esters of sulfuric acid, such as alkyl ether sulfate, *e.g.*, sodium, ammonium, magnesium, MIPA, TIPA, laureth sulfate, sodium myreth sulfate and sodium C_{12-13} pareth sulfate; and the like.

4. Zwitterionic Surfactants

[0124] In one aspect, the formulation comprises or may comprise a zwitterionic surfactant or a charged derivative thereof. In one aspect, the zwitterionic surfactant or charged derivative thereof is selected from the group of disodium cocoamphodiacetate, sodium cocoamphodiacetate, cocoamidopropyl betaine, and a mixture thereof.

[0125] Other zwitterionic surfactants or charged derivatives thereof include, but are not limited to, amino acids such as β-*N*-alkylaminopropionic acids, aminopropyl alkylglutamide, alkylaminopropionic acid, sodium alkylimidodipropionate, dihydroxyethyl alkyl glycinate, and lauroamphocarboxyglycinate; imino acids such as *N*-alkyl-β-iminodipropionic acids; imidazoline derivatives that are not *N,N'*-dialkylated; quaternary ammonium amino acid

sulfobetaines such as alkyl amidopropyl hydroxysultaines, cocoamidopropyl hydroxysultaine, sodium cocoamphohydroxypropyl sulfonate, or sodium capryloamphohydroxypropyl sulfonate; quaternary ammonium amino acid betaines, *e.g.*, dodecyl betaine; alkyl amidopropyl betaines such as cocoamidopropyl betaine; alkyl dimethyl betaines; phospholipids such as lecithin; acyl dialkyl ethylenediamines, *e.g.*, sodium acyl amphoacetate, disodium acyl amphodipropionate, disodium alkyl amphodiacetate, sodium acyl amphohydroxypropyl sulfonate, disodium acyl amphodiacetate, and sodium acyl amphopropionate; a salt of cocamphodiactetate, such as sodium cocamphodiacetate; and the like.

H. Emollients

[0126] Emollients can optionally be added to the formulations of the invention so that the formulations can maintain or increase the moisture content of the stratum corneum when the formulation is applied (*e.g.*, to the skin of the knee). Emollients may be added to the formulations in addition to the components already described, which may also aid in maintaining or improving the skin condition of the user. The use of emollients in a foamable formulation is discussed in U.S. Patent No. 7,651,990, incorporated herein by reference in its entirety for all purposes.

[0127] In one aspect, added emollients are included in the formulations of the invention at a concentration between about 0.1 and 30% (w/w). In another aspect, the added emollient can be present in the formulation at a concentration between about 0.5% and 10% (w/w). In still another aspect, the emollient concentration can be between about 1% and 5% (w/w).

[0128] Emollients are generally separated into two broad classes based on their function. The first class of emollients functions by forming an occlusive barrier to prevent water evaporation from the stratum corneum. The second class of emollients penetrate into the stratum corneum and physically bind water to prevent evaporation. The first class of emollients is subdivided into compounds which are waxes at room temperature and compounds which are liquid oils. The second class of emollients includes those which are water soluble and are often referred to as humectants.

[0129] Suitable emollients may be selected from any of the classes known in the art. A general list of useful emollients appears, for example, in U.S. Pat. No. 4,478,853 and in EPO patent application 0 522 624A1 as well as in the CTFA Cosmetic Ingredient Handbook published by The Cosmetic, Toiletry, and Fragrance Association, Wash. D.C. (1992) under

the listings "Skin Conditioning agents," "emollients," "humectants," "miscellaneous" and "occlusive" (incorporated herein by reference in its entirety for all purposes).

[0130] In some aspects, emollients may be chosen from the following non-limiting list of general emollients, occlusive emollients, and humectants. Examples of general emollients include short-chain alkyl or aryl esters (C_1–C_7) of long-chain straight- or branched-chain alkyl or alkenyl alcohols or acids (C_8–C_{32}) and their polyethoxylated derivatives; short-chain alkyl or aryl esters (C_1–C_7) of C_4–C_{12} diacids or diols optionally substituted with one or more hydroxyl groups; alkyl or aryl C_1–C_{10} esters of glycerol, pentaerythritol, ethylene glycol, propylene glycol, as well as polyethoxylated derivatives of these with polyethylene glycol; C_{12}–C_{22} alkyl esters or ethers of polypropylene; and C_{12}–C_{22} alkyl esters or ethers of polypropylene/polyethylene glycol copolymer.

[0131] Non-limiting examples of occlusive emollients include cyclic and linear dimethicones; polydialkylsiloxanes; polyarylalkylsiloxanes; long chain (C_8–C_{36}) alkyl and alkenyl esters of long straight- or branched-chain alkyl or alkenyl alcohols or acids; long chain (C_8–C_{36}) alkyl and alkenyl amides of long straight- or branched-chain (C_8–C_{36}) alkyl or alkenyl amines or acids; hydrocarbons including straight and branched chain alkanes and alkenes such as squalene, squalane and mineral oil; jojoba oil; polysiloxane polyalkylene copolymers; short-chain alkyl or aryl esters (C_1–C_{36}) of C_{12}–C_{22} diacids or diols optionally substituted with one or more hydroxyl groups such as diisopropyl dimer dilinoleate; and C_{12}–C_{22} alkyl and alkenyl alcohols; long-chain alkyl or aryl esters (C_8–C_{36}) of C_{12}–C_{22} diacids or diols optionally substituted with one or more hydroxyl groups, such as diisostearyl dimer dilinoleate; lanolin and lanolin derivatives; and beeswax and its derivatives.

[0132] Non-limiting examples of humectant-type emollients include glycerol, polyglycerols (*e.g.*, diglycerol, triglycerol, polyglycerin-3, tetraglycerol, hexaglycerol, decaglycerols), propylene glycol, dipropylene glycol, polypropylene glycol, polyethylene glycol (PEG-2 to PEG-45M, preferably a molecular weight between about 300 and 1,000), sorbitol, polyhydric alcohol ethoxylates (*e.g.*, sorbeth-6, sorbeth-30, glycereth-1 to glycereth-31), methoxy ethers of polyethylene glycol (methoxy-PEG-2 to methoxy-PEG-100) methoxy ethers of polyhydric alcohol ethoxylates (*e.g.*, glycereth-7 methoxide), pantothenol, gluconic acid salts and the like.

[0133] Other humectant-type agents like that could also be employed include: 1,2,6-hexanetriol, acetamide mea, aluminum hydroxide, arginine pea, butoxypropanol, butylene

glycol, dimethyl imidazolidinone, dimethylsilanol hyaluronate, dipotassium glycyrrhizate, erythritol, ethoxy-diglycol, fructose, glucamine, gluconic acid, glucose, glucose glutamate, glucuronic acid, glutamic acid, glycogen, glycyrrhizic acid, heilmoor clay, hexacosyl glycol, histidine, hyaluronic acid, hydrogenated honey, hydrogenated starch, hydrolysate, hydrolyzed collagen, hydrolyzed elastin, hydrolyzed glycosaminoglycans, hydrolyzed keratin, hydrolyzed silk, hydrolyzed soy protein, hydrolyzed wheat protein, hydroxyethyl sorbitol, inositol, inositol hexa-pea, lactamide mea, lactic acid, lactitol, lactose, lysine pea, magnesium pea, maltitol, manganese pea, mannitol, mel (honey extract), menthyl pea, methyl gluceth-10, methyl gluceth-20, pea (pidolic acid), lactamide, polydextrose, polyglucuronic acid, polyglyceryl sorbitol, potassium pea, ppg-20 methyl glucose ether, ppg-38-buteth-37, saccharide isomerate, serica, silk amino acids, sodium carboxymethyl chitin, sodium lactate, sodium mannuronate methylsilanol, sodium pea, sodium pea methylsilanol, sodium polyglutamate, soluble collagen, sorbitol, sucrose, tea-lactate, tea-pea, trehalose, trilactin, urea, xylitol, zea mays, zinc pea, and combinations thereof.

[0134] The addition of one or more emollients may affect the viscosity and stability of the formulations of the present invention. In some embodiments, a single emollient may be added to the formulation. In some embodiments, two or more emollients may be added to the formulation. While any of a variety of emollients may be added to the formulations of the present invention, some embodiments will include wax and oil type emollients either alone or combined with water-soluble emollients. In some embodiments of the invention, emollient systems can be comprised of humectants in addition to occlusive wax and oil emollients in concentrations that achieve a moisturizing effect and which maintains and improves the condition of the skin upon repeated use. Emollients may be non-comedogenic and chosen to avoid skin irritation or sensitization reactions.

I. Other Components

[0135] In one aspect, the formulation additionally comprises an anti-oxidant. Preferred anti-oxidants for use in the present invention include butylated hydroxytoluene, butylated hydroxyanisole, ascorbyl linoleate, ascorbyl dipalmitate, ascorbyl tocopherol maleate, calcium ascorbate, carotenoids, kojic acid and its pharmaceutically acceptable salts, thioglycolic acid and its pharmaceutically acceptable salts (*e.g.*, ammonium), tocopherol, tocopherol acetate, tocophereth-5, tocophereth-12, tocophereth-18, or tocophereth-80. In certain aspects, the anti-oxidant may also be a eutectic agent.

[0136] In another aspect, the formulation is acidic. In certain aspects, the formulation has a pH of below about 7.5, 6.5, 5.5, 4.5, 3.5, or even 2.5. In certain other aspects, the pH of the formulation may range from about 1.5 to 7, about 2 to 7, about 3 to 7, about 4 to 7, or about 5 to 7. In still other aspects, the pH of the formulation may range from about 1.5 to 5.5, about 2.5 to 5.5, about 3.5 to 5.5, or about 4.5 to 5.5. The formulation may include a buffering or pH-adjusting agent to maintain its acidic pH. Preferably, the formulation has a pH value between about 4 and 7, such as 4, 5, 6 or 7 and fractional values between 4 and 7.

[0137] In yet another aspect, the formulation is basic. In certain aspects, the formulation has a pH of above about 7, 8, 9, 10, 11, or 12. In certain other aspects, the pH of the formulation may range from about 7 to 12.5, about 7 to 11.5, about 7 to 10.5, about 7 to 9.5, or about 7 to 8.5. In still other aspects, the pH of the formulation may range from about 9 to 12.5, about 9 to 11.5, about 9 to 10.5, or about 8.5 to 10. The formulation may include a buffering or pH-adjusting agent to maintain its basic pH. Preferably, the formulation has a pH value between about 7 and 10 and fractional values between 7 and 10.

[0138] In still yet another aspect, the formulation is neutral. In certain aspects, the formulation has a pH of about 7. In certain other aspects, the formulation has a pH from about 6 to about 8.5, from about 5.5 to 8, about 6 to 8, about 6.5 to 8.5, or from about 6.5 to 7.5. The formulation may include a buffering or pH-adjusting agent to maintain its neutral pH. Preferably, the formulation has a pH value between about 6 and 8.5 and fractional values between 6 and 8.5.

[0139] In another aspect, the formulation is a cream, lotion, gel, or foam. Preferably, the formulation is a high-viscosity gel. Alternatively, the formulation is a low-viscosity gel. In one embodiment, the gel is a pourable gel. In another embodiment, the gel is a non-pourable gel.

III. Characteristics of Topical Formulations

Viscosity

[0140] In a preferred aspect, the composition is more viscous than water at standard temperature and pressure (STP). Alternatively, the composition has a kinematic viscosity of more than about 1 centistokes (cSt) or a dynamic viscosity of more than about 1 centipoise (cP). In certain aspects, the dynamic viscosity of the composition is at least about 2, 3, 4, 5, 7, 10, 12, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 75, 80, 90, 100, 150, 200, 250, 500, 1000, 2000, 3000, 5000, 10,000 cP at STP. In yet other aspects, the composition is thixotropic (*i.e.*,

it decreases in viscosity upon being stirred or shaken). The composition's viscosity can be adjusted by the addition of a cellulosic thickening agent, such as hydroxypropyl cellulose, or other thickening agents.

Stability

[0141] In still yet another preferred aspect, the composition remains stable for an acceptable time period between preparation and use when stored in a closed container at normal ambient temperature. Preferably, an "acceptable time period" is at least about 30 days, more preferably at least about six months, still more preferably at least about one year, and yet still more preferably at least about two years.

[0142] In an alternative aspect, the present invention provides a formulation that degrades by less than 1% over the course of 6 months at room temperature. More preferably, the rate of degradation is less than 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or less than 0.1 %, and all fractions in between, over the course of six months at room temperature.

[0143] In a preferred aspect, a formulation provides the advantage of favorable stability at six months, as reflected in the lack of any substantial changes in viscosity, the absence of phase separation and crystallization at low temperatures, and a low level of impurities.

[0144] In another aspect, the stability of the formulation is based on the ratio of the alkyl ester to water. More preferably, the stability of the formulation is based on the ratio of isopropyl myristate (IPM) to water. In a more preferred aspect, when the urea:IPM ratio is 1:1 in the absence of Transcutol®, the IPM:water ratio is preferably less than about 1:4.7, and more preferably, less than about 1:3.7. In a more preferred aspect, when the urea:IPM ratio is 1:1 in the presence of Transcutol®, the IPM:water ratio is preferably less than about 1:3.1, and more preferably, about 1:2. In a more preferred aspect, when the urea:IPM ratio is 1:2 in the absence of Transcutol®, the IPM:water ratio is preferably less than about 1:4.2 and greater than about 1:1.19. In a more preferred aspect, when the urea:IPM ratio is 2:1 in the absence of Transcutol®, the IPM:water ratio is preferably greater than about 1:2.7. In an even more preferred aspect, when the urea:IPM ratio is 1:1 in presence of Transcutol®, the IPM:water ratio is preferably about 1:3.0.

Active Penetration and Retention

[0145] In certain other aspects, a composition is designed for high penetration, for high retention in the skin, or for both high penetration and high retention. The optimal composition will have a balance between penetration and retention, enabling an effective

amount of the active ingredient to pass through the skin, but also enabling it to stay in the target area for a sufficient duration to alleviate the patient's pain or other symptoms.

[0146] In another aspect, a composition is designed for topical efficacy with minimal systemic distribution of the coxib via the blood through the body. Without being bound by theory, it is believed that minimization of systemic distribution would decrease the side effects of the composition, especially the side effect of adverse cardiovascular events. The optimal composition will have low systemic bioavailability, but will effectively treat pain or other symptoms associated with the site of application.

[0147] In another preferred aspect, a formulation comprising etoricoxib provides additional advantages in comparison to previously described etoricoxib compositions. Such advantages may include one or more of the following: adhering well to the skin, spreading easily, drying more quickly, and showing greater *in vivo* absorption. In some more preferred aspects, the drying rate results in a residue of at most 50% of the starting amount after 24 hours. In other more preferred aspects, the transdermal selective COX-2 inhibitor (*e.g.*, and still more preferably, etoricoxib) flux as determined by Franz cell procedure at finite dosing or at infinite dosing is at least 1.5 times that of a comparative formulation.

[0148] Due to the properties of higher flux and greater *in vivo* absorption, it is believed that certain embodiments of the present invention's formulations can be administered at lower dosing than previously described etoricoxib formulations. In particular, it is expected that the compositions of the invention can be used at twice-a-day or once-a-day dosing in the treatment of OA. This would represent a significant improvement, as lower dosing is associated with better patient compliance, an important factor in treating chronic conditions.

IV. Methods of Preparation

[0149] In one aspect, the pharmaceutical composition is formulated as a cream, an emulsion, a gel (*e.g.*, a hydrogel, an organogel, or an inorganic or silica gel), a lotion, a lacquer, an ointment, a solution (*e.g.*, a highly viscous solution), or a transdermal patch. The pharmaceutical composition may also be prepared so that it may be applied to the skin as a foam. In a preferred aspect, the composition is a solution. Alternatively, the composition is a transdermal patch.

V. Methods of Treatment

[0150] In a second embodiment, the invention describes a method for treating pain comprising the step of applying a topical formulation to a subject to treat the pain. Preferably, the pain is caused by osteoarthritis.

[0151] In one aspect, the topical formation is a gel or semi-solid formulation.

[0152] In another aspect, the invention provides a gel formulation for topical administration, the formulation comprising a selective COX-2 inhibitor, a thickening agent, at least one lower alcohol, and water, wherein the formulation comprises about 50% to 80% (w/w) of the lower alcohol and water in a ratio of about 2:1 to 8:1. Alternatively, the formulation comprises about 65% to 85% (w/w) of the lower alcohol and water in a ratio of about 2:1 to 8:1.

[0153] In still another aspect, the present invention presents a method for topically treating pain in a subject, the method comprising topically applying a pharmaceutical formulation comprising a selective COX-2 inhibitor, a thickening agent, at least one lower alcohol, and water, wherein the formulation comprises about 50% to 80% (w/w) of the lower alcohol and water in a ratio of about 2:1 to 8:1. Alternatively, the formulation comprises about 65% to 85% (w/w) of the lower alcohol and water in a ratio of about 2:1 to 8:1.

[0154] In yet another aspect, the method comprises topically applying a pharmaceutical formulation comprising a selective COX-2 inhibitor, a thickening agent, at least one lower alcohol, and water, wherein the formulation comprises about 50% to 80% (w/w) of the lower alcohol and water in a ratio of about 2:1 to 8:1. Alternatively, the formulation comprises about 65% to 85% (w/w) of the lower alcohol and water in a ratio of about 2:1 to 8:1.

[0155] In one aspect, the pharmaceutical formulation is applied to the skin of the subject. In another aspect, the pharmaceutical formulation is applied to a joint of the subject. Preferably, the pharmaceutical formulation is applied to the skin covering the joint or near to the joint.

[0156] In another aspect, the active agent is delivered locally to the joint with minimal systemic absorption. In yet another aspect, the active agent is delivered to the tissue surrounding the joint with minimal systemic absorption.

[0157] In still other aspects, the subject is a human. Alternatively, the subject is a non-human mammal.

[0158] In yet still other aspects, the treatment is continued for at least 12 weeks. More preferably, the treatment is continued for at least six months.

[0159] The compositions of the invention may be useful to alleviate acute pain, chronic pain, or both. Compositions of the invention are particularly suited for use in treating OA chronically. They may also be useful for the treatment of other chronic joint diseases characterized by joint pain, degeneration of articular cartilage, impaired movement, and stiffness. Suitable joints include the knee, elbow, hand, wrist and hip. The compositions of the invention may also be useful for the treatment of other pain-associated disorders, including (but not limited to) muscle pain, lower back pain, neck pain, rheumatoid arthritis, fibromyalgia, myofascial pain, gout, sprains, strains, contusions, and neuropathic pain conditions.

[0160] In certain other aspects, the treatment may be administered once a day. Preferably, the treatment may be administered twice a day. Alternatively, the treatment may be administered three times a day. Alternatively, the treatment may be administered four times a day. More preferably, the treatment is administered one to two times a day.

[0161] Formulations of the present invention may, if desired, be presented in a bottle, jar, or other container-closure system approved by the Food and Drug Administration or other regulatory body, which may provide one or more dosages containing the active ingredient. The package or dispenser may also be accompanied by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, the notice indicating approval by the agency. In certain aspects, the present invention includes a kit containing, consisting essentially of, or comprising a coxib formulation as taught herein, a container closure system comprising the formulation, and a notice describing a method of use for the formulation.

[0162] Formulations of the present invention are useful and effective when applied topically to treat a pain. The amount of the active agent present in the formulation will be the amount that is therapeutically effective, *i.e.*, an amount that will result in the effective treatment of the pain (preferably, a pain from osteoarthritis) when applied. The formulation may be applied directly to the skin or applied in an absorbent pad.

[0163] The therapeutically effective amount will vary depending on the subject and the severity of the affliction and can be determined routinely by one of ordinary skill in the art. In some embodiments, the formulation is a liquid or semisolid, such as a cream, ointment,

lotion, lacquer, or gel (preferably, a gel) having a solvent in which the active agent or its pharmaceutically acceptable salt is dissolved.

[0164] The formulation can be any of the inventive formulations disclosed in the claims or specification of this application.

VI. EXAMPLES

[0165] In these experiments, 5–10 µl of each homogeneous formulation was applied to each donor cell compartment. Formulations applied to each donor cell compartment were those described as physically stable (Y) or physically unstable (N). Comparisons were mainly performed using human cadaver skin, but in some cases, porcine skin was used (*i.e.*, Figures 1, 2, 4, and 6–8).

[0166] According to one embodiment of the invention, the compositions were prepared by first weighing etoricoxib and urea into a container and mixing the ingredients for ~ 2–3 min. Then, a portion of the ethanol and water was added to the mixture. Next, the following ingredients, if included, were added: isopropyl myristate, isopropanol and Transcutol®. The mixture was then topped up with the remaining ethanol and water. While vortexing, the cellulose thickener (e.g., HY121 or HY117) was slowly added to the mixture, followed by vortexing for ~ 30 min or until a clear and homogenous system formed.

Example 1: Etoricoxib Formulations I

[0167] In the first set of formulations tested, urea and Transcutol® were important for maintaining physical stability (Table 1). Trials were performed on porcine skin (Figure 1) using the general procedure described in Example 10 with a finite dosing regimen of 10 µl/cell. Concentrations of urea at 5% provided best physical stability for the formulation (e.g. F1 vs. F2, F3, F4). The proportion of isopropanol to ethanol was also important for physical stability. For this series, the best physical stability and permeation were observed when the amount of ethanol and isopropanol was 67.5% (e.g., F10 vs. F11).

[0168] The formulation with 10% Transcutol®/10% isopropanol provided better permeation enhancement than the 5%/5% formulation (F8–F14). The 5%/5% formulation also proved to be physically unstable (F13). A 5%/10% formulation was stable, but provided lower delivery of etoricoxib (F14).

[0169] Reducing the proportion of isopropyl myristate in this set of formulations did seem to decrease permeation (F5, F6, F7).

[0170] Table 1: Formulation Optimization Study: Constant Ethanol Concentration

	Formulations														
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**Ctrl**
ETO	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Ethanol	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	48
Water	18.5	21	23.5	13.5	21	23.5	13.5	28.5	23.5	18.5	8.5	23.5	18.5	13.5	50
IPA	10	10	10	10	10	10	10	0	5	0	10	0	5	10	0
Urea	5	2.5	0	10	5	5	5	5	5	5	5	5	5	5	0
Transcutol®	0	0	0	0	0	0	0	0	0	10	10	5	5	5	0
IPM	5	5	5	5	2.5	0	10	5	5	5	5	5	5	5	0
HPC HY117	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0
24 hr Cuml (ug/cm^2)[a]	46.6	n/a	n/a	42.6	55.2	42.8	47.9	n/a	n/a	n/a	37.2	n/a	n/a	27.2	15.9
SEM[b]	3.6	n/a	n/a	3.1	7.6	5.1	11.4	n/a	n/a	n/a	4.9	n/a	n/a	10.2	2.8
ER[c] over Control	2.9	n/a	n/a	2.7	3.5	2.7	3.0	n/a	n/a	n/a	2.3	n/a	n/a	1.7	1.0
Physical Stability·*	Y	N	N	N	Y	Y	Y	N	N	N	Y	N	N	Y	Y

[a]24-hour accumulated amount of etoricoxib (ETO) (Fig. 1)
[b]standard error of the mean (Fig. 1)
[c]enhancement ratio over control (Fig. 1)
*Y=physically stable formulation based on visual inspection; N= physically unstable formulation based on visual inspection
Ctrl=Control

Example 2: Etoricoxib Formulations II

[0171] Table 2: Formulation Optimization: Constant Ethanol and Water Concentration

	Formulations														
	Ctrl	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**	**F21**	**F22**	**F23**	**F24**	**F25**	**F26**	**F27**	**F28**
ETO	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Ethanol	48	57.5	57.5	57.5	57.5	57.5	5.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5
Water	50	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5	18.5
IPA		10	10	10	10	10	10	10	0	5	0	10	0	5	10
Urea		5	25	0	10	5	5	5	5	5	5	5	5	5	5
Transcutol®		0	0	0	0	0	0	0	0	0	10	10	5	5	5
IPM		5	5	5	5	2.5	2.5	10	5	5	5	5	5	5	5
HPC HY117		2	2	2	2	2	2	2	2	2	2	2	2	2	2
24 hr Cum1 (ul/cm^2)[a]	8.2	41.1	27.5	29.9	n/a	34.3	28.9	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
SEM[b]	2.5	6.9	2.9	3.0	n/a	2.1	2.0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
ER[c] over Control	1.0	5.0	3.4	3.6	n/a	4.2	3.5	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Physical Stability *	Y	Y	Y	Y	N	Y	Y	N	N	N	N	N	N	N	N

[a]24-hour accumulated amount of etoricoxib (ETO) (Fig. 2)
[b]standard error of the mean (Fig. 2)
[c]enhancement ratio over control (Fig. 2)
*Y=physically stable formulation based on visual inspection; N=physically unstable formulation based on visual inspection
Ctrl=Control

[0172] In the second set of formulations tested, a formulation with 5% urea was most effective (F15). As in Example 1, trials were performed on porcine skin (Figure 2) using the general procedure described in Example 10 with a finite dosing regimen of 5 µl/cell. Isopropyl myristate seemed to increase permeation. For this series of formulations, best results were observed from formulations containing at least 67.5% lower alcohol and from an ethanol/isopropanol ratio higher than 5:1 but less than 12:1.

[0173] Non-homogeneous formulations were observed with 10% isopropyl myristate and with 0–5% isopropanol. Transcutol® did not appear to be compatible with isopropanol (IPA) when the water amount was held constant at 18.5%.

Example 3: Etoricoxib Formulations III

[0174] Table 3: Further Formulations

Ingredients	**F31**	**F32**	**F33**	**F34**	**Ctrl**
Percentage in	**wt/wt%**	**wt/wt%**	**wt/wt%**	**wt/wt%**	**wt/wt%**
Etoricoxib	2	2	2	2	2
Ethanol	57.5	57.5	60	62.5	48
Water	18.5	8.5	18.5	18.5	50
Isopropanol	10	10	10	10	0
Urea	5	5	2.5	0	0
Hydroxypropyl cellulose HY117	2	2	2	2	0
Transcutol®	0	10	0	0	0
Isopropyl myristate	5	5	5	5	0

[0175] In the third set of formulations tested, reduction of the urea level reduced permeation (Figure 3). Transcutol® in the formulation may increase permeation, especially at early hours.

Example 4: Etoricoxib Formulations IV

[0176] Table 4: Further Formulations 2

Ingredients	F41	F42	F43	F44	F45	F46	Ctrl
Percentage in	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%
Etoricoxib	2	2	2	2	2	2	2
Ethanol	51	48.5	46	51	51	46	48
Isopropyl alcohol	10	10	10	10	10	10	0
Isopropyl myristate	5	5	5	5	5	5	0
Urea	5	7.5	10	2.5	0	5	0
Transcutol®	10	10	10	10	10	15	0
Water	15	15	15	17.5	20	15	50
Hydroxy-propyl cellulose HY117	2	2	2	2	2	2	0

[0177] In the fourth set of formulations tested, a formulation with 5% urea produced the best permeation (Figure 4). Transcutol® may have slightly increased permeation.

Example 5: Etoricoxib Formulations V

[0178] Table 5: Further Formulations 3

Ingredients	F51	F52	F53	F54	F55	Ctrl
Percentage in	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%
Etoricoxib	0.5	1	2	3	5	2
Ethanol	52.5	52	51	50	48	48
Isopropanol	10	10	10	10	10	0
Isopropyl myristate	5	5	5	5	5	0
Urea	5	5	5	5	5	0
Transcutol®	10	10	10	10	10	0
Water	15	15	15	15	15	50
Hydroxy-propyl cellulose HY117	2	2	2	2	2	0

[0179] In the fifth set of formulations, the formulation with 1% active agent had the highest permeation (Figure 5). In one aspect of the invention, these formulations are preferred.

Example 6: Etoricoxib Formulations VI

[0180] Table 6: Further Formulations 4

Ingredients	Ctrl	F61	F62	F63	F64	F65	F66	F67	F68	F69	F70
Percentage in	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%
Etoricoxib	2	1	1	1	1	1	1	1	1	1	1
EtOH	48	52	52	52	52	52	52	56	55	51	50
IPA		10	10	10	10	10	10	10	10	10	10
IPM		5								5	5
Urea		5	5	5	5	5	5	5	5	5	5
Transcutol®		10	10	10	10	10	10	10	10	10	10
Water	50	15	15	15	15	15	15	15	15	15	15
HPCHY117		2	2	2	2	2	2	2	2	2	2
Diisopropyl adipate			5								
Ethyl oleate				5							
Ethyl laurate					5						
Isopropyl palmitate						5					
Diethyl sebacate							5				
Monolaurin								1		1	
Glycerin ricinoleate									2		2

[0181] In the sixth set of formulations, isopropyl myristate (IPM) was substituted with one or more other alkyl esters (Figure 6). Initially, homogeneous formulations could not be obtained with ethyl oleate and isopropyl palmitate (F63 and F65, respectively). However, by increasing the ethanol level, homogeneous formulations were possible, albeit with lower permeation than for IPM.

[0182] Although ethyl laurate behaves similar to IPM, permeation behavior of IPM was more reliable. Monolaurin, as hydroxy ester alone gave similar behavior to IPM at 1 % level, whereas glycerin ricinoleate did not improve the delivery over IPM.

Example 7: Etoricoxib Formulations VII

Ingredients	Ctrl	F61	F62	F63	F64	F65	F66	F67	F68	F69	F70
Percentage in	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%
Etoricoxib	2	1	1	1	1	1	1	1	1	1	1
EtOH	48	52	52	52	52	52	52	56	55	51	50
IPA		10	10	10	10	10	10	10	10	10	10
IPM		5								5	5
Urea		5	5	5	5	5	5	5	5	5	5
Transcutol®		10	10	10	10	10	10	10	10	10	10
Water	50	15	15	15	15	15	15	15	15	15	15
HPCHY117		2	2	2	2	2	2	2	2	2	2
Diisopropyl adipate			5								
Ethyl oleate				5							
Ethyl laurate					5						
Isopropyl palmitate						5					
Diethyl sebacate							5				
Monolaurin								1		1	
Glycerin ricinoleate									2		2

[0183] Table 7: Further Formulations 5

Ingredients	Ctrl	F71	F72	F73	F74	F75	F76	F77	F78	F79
Percentage in	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%
Etoricoxib	2	1	1	1	1	1	1	1	1	1
EtOH	48	52	52	56	51	50	51	50	51	53
IPA		10	10	10	10	10	10	10	10	10
IPM		5			5	5				
Urea		5	5	5	5	5	5	5	5	5
Transcutol ®		10	10	10	10	10	10	10	10	10
Water	50	15	15	15	15	15	15	15	15	15
HPCHY117		2	2	2	2	2	2	2	2	2
Ethyl laurate			5				5	5	5	3
Monolaurin				1	1		1			1
Glycerin ricinoleate						2		2	1	

[0184] In the seventh set of formulations, ester/hydroxyester combinations achieved the same or reduced permeation compared to IPM (Figure7).

Example 8: Etoricoxib Formulations VIII

[0185] Table 8: Further Formulations 6

Ingredients	Ctrl	F81	F82	F83	F84	F85	F86	F87	F88	F89	F90
Percentage in	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%	wt/wt%
Etoricoxib	2	1	1	1	1	1	1	1	1	1	1
EtOH	48	52	52	52	52	57	57	56	55	51	50
IPA		10	10	10	10	10	10	10	10	10	10
IPM		5								5	
Urea		5	5	5	5	5	5	5	5	5	5
Transcutol ®		10	10	10	10	10	10	10	10	10	10
Water	50	15	15	15	15	10	10	15	15	15	15
HPC HY117		2	2	2	2	2	2	2	2	2	2
Diisopropyl adipate			5								
Ethyl oleate						5					5
Ethyl laurate				5							
Isopropyl palmitate							5				
Diethyl sebacate					5						
Monolaurin								1			
Glycerin ricinoleate									2	2	2

[0186] In the eighth set of formulations, diesters (*e.g.*, diisopropyl adipate, diethyl sebacate) showed the same or reduced permeation compared to IPM (Figure 8).

[0187] Although IPM containing formulations give the best reliable performance, the results in Examples 6-8 suggest that IPM may be replaced with other suitable alkyl esters or combinations thereof.

Example 9: Etoricoxib Formulations IX

[0188] Table 9 sets forth a preferred aspect of the formulation (F91).

[0189] Table 9. Composition of a Preferred Aspect of the Formulation

Ingredients	F91 wt/wt%
Etoricoxib	2.0
Ethanol	48.5
Isopropanol	10.0
Isopropyl Myristate	5.0
Urea	5.0
HPC; HY 117	2.0
Transcutol ®	10.0
Water	15.0

[+]as an excipient in the Lidoderm patch
*molecular penetration enhancer

Example 10: General Procedure for Skin Permeation Measurement

[0190] The permeation of etoricoxib through human cadaver or porcine skin from each of the present compositions was measured using Franz diffusion cells ("FDC"s). Some measurements were taken with an alternative system that gives equivalent results to measurement with Franz diffusion cells.

[0191] Franz cells with a 3 ml receptor well volume were used in conjunction with split thickness cadaver skin (0.015''-0.018'', AlloSource) or Dermatomed porcine skin. The donor well had an area of about 0.55 cm^2. Receptor wells were filled with isotonic phosphate buffered saline (PBS) with a pH of 5.5 and doped with 0.01% sodium azide. The flanges of the Franz cells were coated with vacuum grease to ensure a complete seal and were clamped together with uniform pressure using a pinch clamp (SS #18 VWR 80073-350). After Franz cells were assembled, the skin was allowed to pre-hydrate for 45 minutes with PBS. The PBS was then removed and an appropriate amount of formulation was added to the skin. Dosing level was 5-10 µl per cell (~9-18 µl/cm^2) except as otherwise indicated herein. Receptor wells of the Franz cells were maintained at 37°C (temperature on the surface of the skin is about 32°C) in a stirring dry block with continual agitation via a stir bar. Samples were drawn from the receptor wells at varying time points. Measurements were made in five- or six-fold replicates. The concentration of etoricoxib in the samples was analyzed using high-performance liquid chromatography.

Example 11: The Effect of Increasing Etoricoxib Concentration on Delivery

[0192] A prototype formulation chassis containing a specific penetration enhancer combination of isopropyl myristate, urea and Transcutol® was used in this study to explore the optimal dosing regimen for etoricoxib.

[0193] To maximize the transdermal delivery of etoricoxib (ETO), the ETO concentration in the formulation chassis was increased from 0.5% to 5%. The amount of ETO delivery over 24 hours was quantified and compared (Table 10, Figure 5).

[0194] Table 10: The Effect of Increasing Etoricoxib Concentration on the Delivery of Etoricoxib Across Intact Human Skin in Vitro

	Formulations/ Concentration (% w/w)					
Ingredients/Lot #	**F101=F51**	**F102=F52**	**F103=F53**	**F104=F54**	**F105=F55**	**Ctrl**
Etoricoxib	0.5	1.0	2.0	3.0	5.0	2.0
Ethanol	52.5	52.0	51.0	50.0	48.0	48.0
Isopropyl alcohol	10.0	10.0	10.0	10.0	10.0	
Isopropyl myristate	5.0	5.0	5.0	5.0	5.0	
Urea	5.0	5.0	5.0	5.0	5.0	
Transcutol ®	10.0	10.0	10.0	10.0	10.0	
HPC, HY117	2.0	2.0	2.0	2.0	2.0	
Water	15.0	15.0	15.0	15.0	15.0	50.0
24 hr Cuml (ug/cm^2)[a]	2.42	4.33	3.41	3.65	2.62	0.16
SEM[b]	0.48	0.66	0.46	0.79	0.46	0.11
ER[c] over Control	15.14	27.16	21.36	22.90	16.41	1

[a]24-hour cumulative amount of etoricoxib
[b]standard error of the mean
[c]enhancement ratio over control

[0195] The results showed that for a single-dose regimen, a progressive increase in the cumulative ETO delivery was observed by increasing the ETO concentrations from 0.5% to 1%. The maximal cumulative ETO delivery across intact human skin was observed at 1% ETO concentration. For the particular formulations tested, there was no further increase of ETO delivery at higher ETO concentrations, i.e. 2%, 3% or 5%. The low ETO delivery observed with 5% formulation may be caused by the precipitation of ETO after the formulation was applied to the skin.

[0196] In this study, the ETO delivery from the control formulation was below the average values. The maximal ETO delivered from the 1% formulation over 24 hours was $4.33\mu g/cm^2$, approximately 20% of the maximal target dose.

Example 12: Once- and Twice-Daily Application of 1% or 2% Etoricoxib Formulations

[0197] In this study, once-daily and twice-daily dosing regimens were evaluated with both 1% and 2% etoricoxib formulations. For twice-daily application, the respective formulation was applied at time 0 and at 8 hours on Day 1; the control formulation was applied only once

at time 0. The amount of etoricoxib delivered across intact human skin was followed over 24 hours and 48 hours and compared among the various dosing regimens (Table 11; Figure 9).

[0198] Table 11: Effects of Once- and Twice-Daily Dosing (Time 0 and 8 h) Frequencies for 1% and 2% Etoricoxib Formulations' Transdermal Delivery Across Intact Human Skin

Ingredients	Formulations/ Concentration (% w/w)				
	F111	**F112**	**F113**	**F114**	**Ctrl**
Etoricoxib	1.0	1.0	2.0	2.0	2.0
Ethanol	52.0	52.0	51.0	51.0	48.0
Isopropyl alcohol	10.0	10.0	10.0	10.0	
Isopropyl Myristate	5.0	5.0	5.0	5.0	
Urea	5.0	5.0	5.0	5.0	
Transcutol®	10.0	10.0	10.0	10.0	
HPC, HY117	2.0	2.0	2.0	2.0	
Water	15.0	15.0	15.0	15.0	50.0
[a] 24 hr Cuml (ug/cm^2) (avg±sem)	6.56±0.89	10.34±2.26	6.32±1.04	10.59±2.58	0.55±0.14
[a] 48 hr Cuml (ug/cm^2) (avg±sem)	11.03±1.24	17.29±3.24	11.01±1.60	15.44±3.30	0.68±0.19
ER[c] over Control at 48 hours	16.33	25.60	16.30	22.86	1

[a]24-hour or 48-hr cumulative amount of etoricoxib
[b]standard error of the mean
[c]enhancement ratio over control

[0199] The results showed that twice-daily application of either 1% or the 2% formulations increases etoricoxib delivery over the once daily application. However, there was no apparent difference in the etoricoxib delivery found between once-daily application of either 1% or 2% formulations, consistent with the conclusion from the previous concentration effect study. There was also no apparent difference in the etoricoxib delivery found between the twice-daily application of either 1% or 2% formulations.

Example 13: Once- and Twice-Daily Application of 1% or 2% Etoricoxib Formulations

[0200] This study continued to explore the comparison between once-daily and twice-daily dosing regimens of 1% and 2% formulation where dosing occurred for two consecutive days (specifically at time 0, 9, 21, and 29 hours).

[0201] Table 12: The Effect of Two Consecutive Days of Once- or Twice-Daily Dosing (Time 0, 9, 21 and 29 hours) at 1% and 2% Etoricoxib Concentrations on the Transdermal Delivery Across Intact Human Skin

Ingredients	Formulations/ Concentration (% w/w)				
	F121	F122	F123	F124	Ctrl
Etoricoxib	1.0	1.0	2.0	2.0	2.0
Ethanol	52.0	52.0	51.0	51.0	48.0
Isopropyl alcohol	10.0	10.0	10.0	10.0	0
Isopropyl Myristate	5.0	5.0	5.0	5.0	0
Urea	5.0	5.0	5.0	5.0	0
Transcutol®	10.0	10.0	10.0	10.0	0
HPC, HY117	2.0	2.0	2.0	2.0	0
Water	15.0	15.0	15.0	15.0	50.0
[a]24 hr Cuml (ug/cm2) (avg±sem)	4.39±0.48	7.33±0.91	4.59±1.04	4.49±0.55	0.52±0.06
[a]48 hr Cuml (ug/cm2) (avg±sem)	8.44±1.00	16.96±2.02	8.16±2.02	8.16±2.00	1.00±0.10
ER[c] over Control at 48 hours	16.33	25.60	16.30	22.86	1
Residual Skin ETO Level at the End of the Delivery Study	2.25±0.30	4.81±0.38	3.01±0.46	20.17±14.70	0.68±0.09

[a]24-hour or 48-hour cumulative amount of etoricoxib (ETO)
[b]standard error of the mean
[c]enhancement ratio over control

[0202] Based on the cumulative etoricoxib delivery during the first 24 hours of the study (Table 12, Figure 10), twice-daily application of 1% etoricoxib formulation was effective in increasing the amount of etoricoxib delivered across skin over the once-daily dosing regimen. However, there was no difference in the etoricoxib delivery between once-daily to twice-daily application of the 2% formulation.

[0203] Based on the cumulative etoricoxib delivered during the first 24 hours and the entire 48-hour study (Table 12, Figure 10), 1% formulation applied twice daily was the most effective dosing regimen in delivering etoricoxib transdermally. Interestingly, the residual etoricoxib levels was the highest at the end of the 48 hours study in skin treated with twice daily applications of the 2% formulation, indicating that there appears to be no direct correlation between the skin level and the amount of etoricoxib delivered across skin.

Example 14: Once- and Twice-Daily Application of 1% or 2% Etoricoxib Formulations

[0204] In the studies discussed above, there apparently was a continuous etoricoxib delivery in the second 24 hours with the single-dosing regimen, and increasing dosing frequency to twice-daily application further increased the etoricoxib delivery. However, the increase in etoricoxib delivery from QD dosing to BID was not a doubling. In fact, a lesser degree of increase with BID dosing regimen was observed with the 2% formulation than the 1% formulation. Without intending to be bound by theory, the etoricoxib may be at saturation in the skin reservoir following the administration of the 1% formulation. Possibly, the residual etoricoxib in the skin from Day 1 dosing contributes to the continuous etoricoxib delivery following consecutive dosing over multiple days.

[0205] In this preliminary study, etoricoxib deliveries from four different dosing regimens (two treatment regimens each for the 1% and 2% formulations) were evaluated. The four dosing regimens were the following:

1. Application of the vehicle formulation (i.e., no active) on Time 0 followed by 1% formulation on Time 21, and 29 hours; treatment 1
2. Application of the 1% formulation on Time 0 followed by 1% formulation at Time 21 and 29 hours; treatment 2
3. Application of the vehicle formulation (i.e., no active) on Time 0 followed by 2% formulation at Time 21 and 29 hours; treatment 1
4. Application of the 2% formulation on Time 0 followed by 2% formulation at Time 21 and 29 hour; treatment 2.

[0206] Without being bound by theory, if the cumulative etoricoxib delivered over the second 24 hours was equivalent between treatment 1 and treatment 2 for the 1% etoricoxib formulation, it would suggest that placebo application on Day 1 was effective in altering the skin barrier functions so that even without etoricoxib applied on Day 1, enhanced ETO delivery can still be observed following Day two dosing. Alternatively, if the total etoricoxib delivered over the second 24 hours from treatment 1 was less than that reported with treatment 2; it would suggest that the residual etoricoxib in the skin plays an important role in subsequent etoricoxib delivery. A similar rationale applies to the comparison between treatments 1 and 2 for the 2% etoricoxib formulation.

[0207] The compositions of formulations used in the study are listed in Table 13. The cumulative etoricoxib delivered across intact human skin at the end of the 24 hours and 48 hours studies are summarized in Table 14 (Figure 11). The etoricoxib delivered during the

second 24 hours of the study was calculated manually by subtracting the amount delivered during the first 24 hours from cumulative amount over the entire 48 hours.

[0208] Table 13: Formulation Compositions for Example 14

Ingredients	Formulations/ Concentration (% w/w)				
	F131	**F132**	**F133**	**F134**	**Ctrl**
Etoricoxib	1.0	1.0	2.0	2.0	2.0
Ethanol	52.0	52.0	51.0	51.0	48.0
Isopropyl alcohol	10.0	10.0	10.0	10.0	
Isopropyl Myristate	5.0	5.0	5.0	5.0	
Urea	5.0	5.0	5.0	5.0	
Transcutol®	10.0	10.0	10.0	10.0	
HPC, HY117	2.0	2.0	2.0	2.0	
Water	15.0	15.0	15.0	15.0	50.0

[0209] Table 14: Amount of Etoricoxib (ETO) Delivered Across Intact Human Skin over 24-hour and 48-hour Periods: A Mechanistic Study of a Sample Formulation

Treatment Regimen	**Amount of ETO Accumulated over the 24-Hour Period in the Receiver Phase (µg/cm^2)**	**Amount of ETO Accumulated over the 48-hour in the Receiver Phase (µg/cm^2)**	**Calculated Amount of ETO Accumulated during the Second 24 Hours of the Study (µg/cm^2)**
Time 0: placebo gel Time 21 and 29: 1% ETO Formulation	3.84±0.75	21.18±2.81	17.34
Time 0: 1% ETO Formulation Time 21 and 29: 1% ETO Formulation	2.49±0.73	18.29±2.31	15.8
Time 0: placebo gel Time 21 and 29: 2% ETO Formulation	17.27±1.06	32.34±2.94	15.07
Time 0: 2% ETO Formulation Time 21 and 29: 2 % ETO Formulation	19.12±4.36	25.11±5.15	5.99
Time 0: Control Formulation Dosed once only	0.23±0.07	0.36±0.08	0.13

Conclusions

[0210] A technical target was to deliver 2 μg to 20 μg etoricoxib/cm^2 over 24 hours at steady-state from a topical dosage form across intact human skin. Using a single-dose regimen, a 1% etoricoxib formulation provided good results (Table 15).

Table 15: Etoricoxib (ETO) Delivered Across Intact Human Skin: Single Dosing Regimen

	Technical Target	ETO Delivery from the 1% ETO F102 Formulation
24 hr Cuml (ug/cm^2) [a](avg±sem)	2-20 μg	4.33±0.66
Enhancement Ratio*		27.16

sem = standard error of the mean; *ER calculated against control comprising 2% etoricoxib, 48% ethanol and 50% water.

[0211] Increasing the dosing frequency increased the overall ETO delivery across intact skin in a 48-hour study. Based on results from two consecutive days of twice-daily applications, the amount of ETO delivered was evaluated and compared (Table 16).

[0212] Table 16: Etoricoxib (ETO) Delivered Across Intact Human Skin: Twice-Daily Dosing Regimen

	Technical ETO Delivery Target	ETO Delivery from the 1% ETO F112 Formulation
24 hr Cuml (ug/cm^2) [a](avg±sem)	2-20 μg	10.34±2.26
Enhancement Ratio*		18.8
48 hr Cuml (ug/cm^2) [a](avg±sem)		17.29±3.24
Enhancement Ratio*		25.6

sem = standard error of the mean; *ER calculated against control comprising 2% etoricoxib, 48% ethanol and 50% water.

Example 15: Stability of Etoricoxib Formulations

[0213] Table 17A: Urea:Transcutol®:IPM:Water Ratio Effect (F1–F14)

Urea:Transcutol®:IPM:Water Ratio					Stability	IPM:Water Ratio
Formulation	Urea	Transcutol®	IPM	Water		
F1	1	0	1	3.7	OK	1:3.7
F2	1	0	2	8.4	Not OK	1:4.2
F3	0	0	1	4.7	Not OK	1:4.7
F4	2	0	1	2.7	Not OK	1:2.7
F5	2	0	1	8.4	OK	1:8.4
F6	1	0	0	4.7	OK	NA
F7	1	0		2.7	OK	1:1.4
F8	1	0	1	5.7	Not OK	1:5.7
F9	1	0	1	4.7	Not OK	1:4.7
F10	1	2	1	3.7	Not OK	1:3.7
F11	1	2	1	1.7	OK	1:1.7
F12	1	1	1	4.7	Not OK	1:4.7
F13	1	1	1	3.7	Not OK	1:3.7
F14	1	1	1	2.7	OK	1:2.7

[0214] Table values were calculated by first comparing the ratio of urea to IPM and then comparing the ratio of IPM to water both in the presence and absence of Transcutol®.

[0215] When the urea:IPM ratio is 1:1 in the absence of Transcutol®, the IPM:water ratio preferably is less than 1:4.7, and more preferably 1:3.7 and below (Table 17A). When the urea:IPM ratio is 1:1 in the presence of Transcutol®, the IPM:water ratio preferably is less than 1:3.7, and more preferably, less than 1:2.7.When the urea:IPM ratio is 2:1 in absence of Transcutol®, the IPM:water ratio is preferably greater than 1:2.7.When the the urea:IPM ratio is 1:2 in the absence of Transcutol®, the IPM:water ratio is preferably less than 1:4.2.

[0216] Table 17B: Urea:Transcutol®:IPM:Water Ratio Effect (F15–F28)

Urea: Transcutol®:IPM:Water Ratio					Stability	IPM:Water Ratio
Formulation	Urea	Transcutol®	IPM	Water		
F15	1	0	1	3.7	OK	1:3.7
F16	1	0	2	7.4	OK	1:3.7
F17	0	0	1	3.7	OK	1:3.7
F18	1	0	2	3.7	Not OK	1:3.7
F19	2	0	1	7.4	OK	1:7.4
F20	1	0	0	3.7	OK	NA
F21	1	0	2	3.7	Not OK	1:1.9
F22	1	0	1	3.7	Not OK	1:3.7
F23	1	0	1	3.7	Not OK	1:3.7
F24	1	2	1	3.7	Not OK	1:3.7
F25	1	2	1	3.1	Not OK	1:3.1
F26	1	1	1	3.7	Not OK	1:3.7
F27	1	1	1	3.7	Not OK	1:3.7
F28	1	1	1	3.7	Not OK	1:3.7

[0217] When the urea:IPM ratio is 1:1 in the absence of Transcutol®, the IPM:water ratio is preferably less than 1:4.7, and more preferably 1:3.7 and below. When the urea:IPM ratio is 1:1 in the presence of Transcutol®, the IPM:water ratio is preferably less than 1:3.1, and more preferably 1:2.7. When the urea:IPM ratio is 1:2 in the absence of Transcutol®, the IPM:water ratio is preferably less than 1:4.2 and greater than 1:1.19. When the urea:IPM ratio is 2:1 in the absence of Transcutol®, the IPM:water ratio is preferably greater than 1:2.7.

Conclusion

[0218] When the urea:IPM ratio is 1:1 in the absence of Transcutol®, the IPM:water ratio is preferably less than 1:4.7, and more preferably 1:3.7 and below.When the urea:IPM ratio is 1:1 in the presence of Transcutol®, the IPM:water ratio is preferably less than 1:3.1, and more preferably 1:2. When the urea:IPM ratio is 1:2 in the absence of Transcutol®, the IPM:water ratio is preferably less than 1:4.2 and greater than 1:1.19. When the urea:IPM ratio is 2:1 in the absence of Transcutol®, the IPM:water ratio is preferably greater than 1:2.7.

[0219] For at least these aspects of the formulations, a desirable ratio of urea:IPM is 1:1 in presence of Transcutol®, and a preferable IPM:water ratio is 1:3.0

Table 17C: Urea:Transcutol:IPM:Water Ratio Effect (F101-F105)

Urea:Transcutol®:IPM:Water Ratio					Stability	IPM:Water Ratio
Formulation	Urea	Transcutol	IPM	Water		
F101	1	2	1	3	OK	1:3
F102	1	2	1	3	OK	1:3
F103	1	2	1	3	OK	1:3
F104	1	2	1	3	OK	1:3
F105	1	2	1	3	OK	1:3

[0220] For this series of formulations, when the urea:IPM ratio is 1:1 in the presence of Transcutol®, the IPM:water ratio is preferably 1:3.

[0221] It is understood that the examples and embodiments described herein are for illustrative purposes only. Various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

1. A gel formulation for topical administration, the gel formulation comprising:

about 0.1% to 5% (w/w) etoricoxib;

a thickening agent;

at least one lower alcohol; and

water, wherein the formulation comprises about 50% to 80% (w/w) of said lower alcohol and water in a ratio of about 2:1 to 8:1.

2. The pharmaceutical formulation of claim **1**, wherein the formulation comprises about 0.5% to 5% (w/w) etoricoxib.

3. The pharmaceutical formulation of claim **2**, wherein the formulation comprises about 1% (w/w) etoricoxib.

4. The pharmaceutical formulation of claim **2**, wherein the formulation comprises about 2% (w/w) etoricoxib.

5. The pharmaceutical formulation of claim **1**, wherein the formulation further comprises about 1% to 10% (w/w) urea.

6. The pharmaceutical formulation of claim **5**, wherein the formulation comprises about 2.5% to 5% (w/w) urea.

7. The pharmaceutical formulation of claim **6**, wherein the formulation comprises about 5% (w/w) urea.

8. The pharmaceutical formulation of claim **5**, wherein the formulation comprises about 5% to 7.5% (w/w) urea.

9. The pharmaceutical formulation of claim **1**, wherein the formulation comprises about 0.1% to 5% (w/w) of the thickening agent.

10. The pharmaceutical formulation of claim **9**, wherein the formulation comprises about 2% (w/w) of the thickening agent.

11. The pharmaceutical formulation of claim **9**, wherein the thickening agent is hydroxypropyl cellulose.

12. The pharmaceutical formulation of claim **1**, wherein the at least one lower alcohol is ethanol.

13. The pharmaceutical formulation of any one of claims **1**–**12**, wherein the at least one lower alcohol is a mixture of ethanol and isopropanol in a ratio of about 4:1 to 12:1.

14. The pharmaceutical formulation of claims **13**, wherein the at least one lower alcohol is a mixture of ethanol and isopropanol in a ratio of about 4.5:1 to 12:1.

15. The pharmaceutical formulation of claims **14**, wherein the at least one lower alcohol is a mixture of ethanol and isopropanol in a ratio of about 5:1 to 12:1.

16. The pharmaceutical formulation of claim **13**, wherein the formulation comprises about 55% to 80% lower alcohol.

17. The pharmaceutical formulation of claim **16**, wherein the formulation comprises about 65% to 80% lower alcohol.

18. The pharmaceutical formulation of claim **17**, wherein the formulation comprises about 65% to 70% lower alcohol.

19. The pharmaceutical formulation of claim **18**, wherein the formulation comprises about 58.5% to 67.5% lower alcohol.

20. The pharmaceutical formulation of claim **1**, wherein the formulation further comprises 2-(2-ethoxyethoxy)ethanol.

21. The pharmaceutical formulation of claim **20**, wherein the formulation comprises about 5% to 15% (w/w) 2-(2-ethoxyethoxy)ethanol.

22. The pharmaceutical formulation of claim **21**, wherein the formulation comprises about 5% 2-(2-ethoxyethoxy)ethanol.

23. The pharmaceutical formulation of claim **21**, wherein the formulation comprises about 10% 2-(2-ethoxyethoxy)ethanol.

24. The pharmaceutical formulation of claim **1**, wherein the formulation is a low-viscosity gel.

25. The pharmaceutical formulation of claim **1**, wherein the formulation is a high-viscosity gel or a semi-solid formulation.

26. The pharmaceutical formulation of claim **25**, wherein the formulation is a pourable gel.

27. The pharmaceutical formulation of claim **25**, wherein the formulation is a non-pourable gel.

28. The pharmaceutical formulation of claim **1**, wherein the formulation further comprises an alkyl ester selected from the group consisting of isopropyl myristate, diisopropyl adipate, ethyl oleate, ethyl laurate, isopropyl palmitate, diethyl sebacate, monolaurin, glycerin ricinolate, and combinations thereof.

29. The pharmaceutical formulation of claim **28**, wherein the stability of the formulation is based on its ratio of the alkyl ester to water.

30. The pharmaceutical formulation of claim **1**, wherein the formulation further comprises isopropyl myristate.

31. The pharmaceutical formulation of claim **30**, wherein the formulation comprises about 1% to 15% (w/w) isopropyl myristate.

32. The pharmaceutical formulation of claim **31**, wherein the formulation comprises about 2.5% to 10% (w/w) isopropyl myristate.

33. The pharmaceutical formulation of claim **32**, wherein the formulation comprises about 5% (w/w) isopropyl myristate.

34. A gel formulation for topical administration, the formulation comprising:

about 0.5% to 5% (w/w) etoricoxib;
about 2.5% to 10% urea;
about 2% thickening agent;
about 45% to 63% ethanol;
about 5% to 10% isopropanol; and
water.

35. The gel formulation of claim **34**, wherein the formulation comprises about 1% to 5% (w/w) etoricoxib.

36. A method for topically treating pain in a subject, the method comprising:

topically applying a pharmaceutical formulation comprising:

about 0.1% to 5% (w/w) etoricoxib;

a thickening agent;

at least one lower alcohol; and

water, wherein the formulation comprises about 50% to 80% (w/w) of said lower alcohol and water in a ratio of about 2:1 to 8:1.

37. The method of claim **36**, wherein the pharmaceutical formulation comprises about 0.5% to 5% (w/w) etoricoxib.

38. The method of claim **37**, the method comprising:

topically applying a pharmaceutical formulation comprising:

about 0.5% to 5% (w/w) etoricoxib;

about 2.5% to 5% urea;

about 2% thickening agent;

about 45% to 63% ethanol;

about 5% to 10% isopropanol; and

water.

39. The method of claim **38**, wherein the formulation comprises about 1% to 5% (w/w) etoricoxib.

40. The method of any of claims **36**– **38**, wherein the pain is associated with osteoarthritis.

41. Use of any of the formulations of claims **1**–**34** in the manufacture of a medicament for the treatment of osteoarthritis or pain associated with osteoarthritis.

42. The formulation of claim **34** further comprising about 5% to 15% (w/w) 2-(2-ethoxyethoxy)ethanol.

43. The formulation of claim **42** further comprising about 2.5% to 10% (w/w) isopropyl myristate.

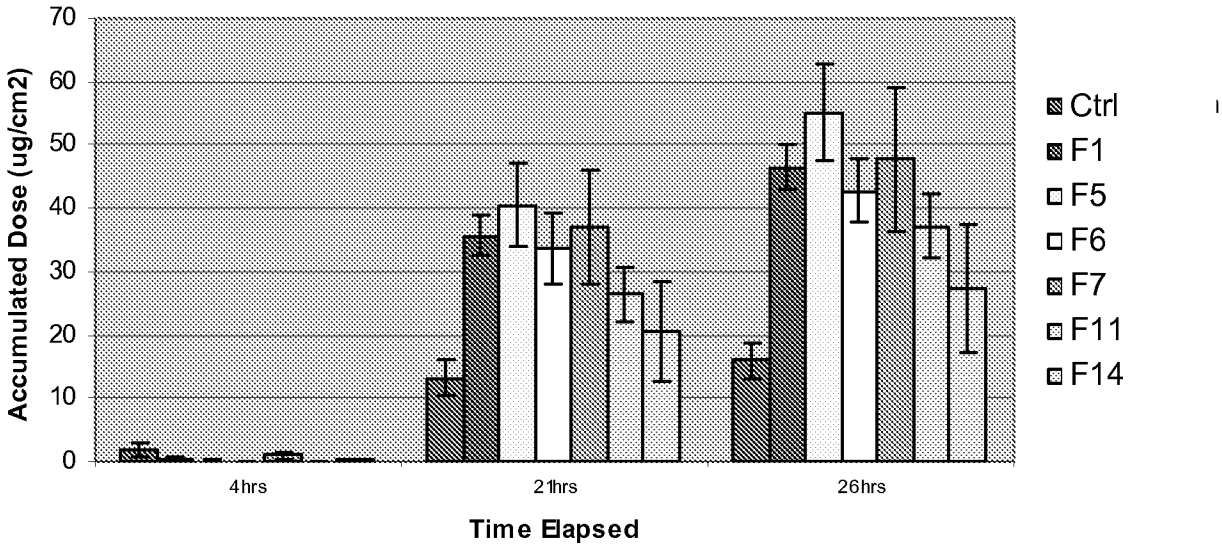
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FIG. 1

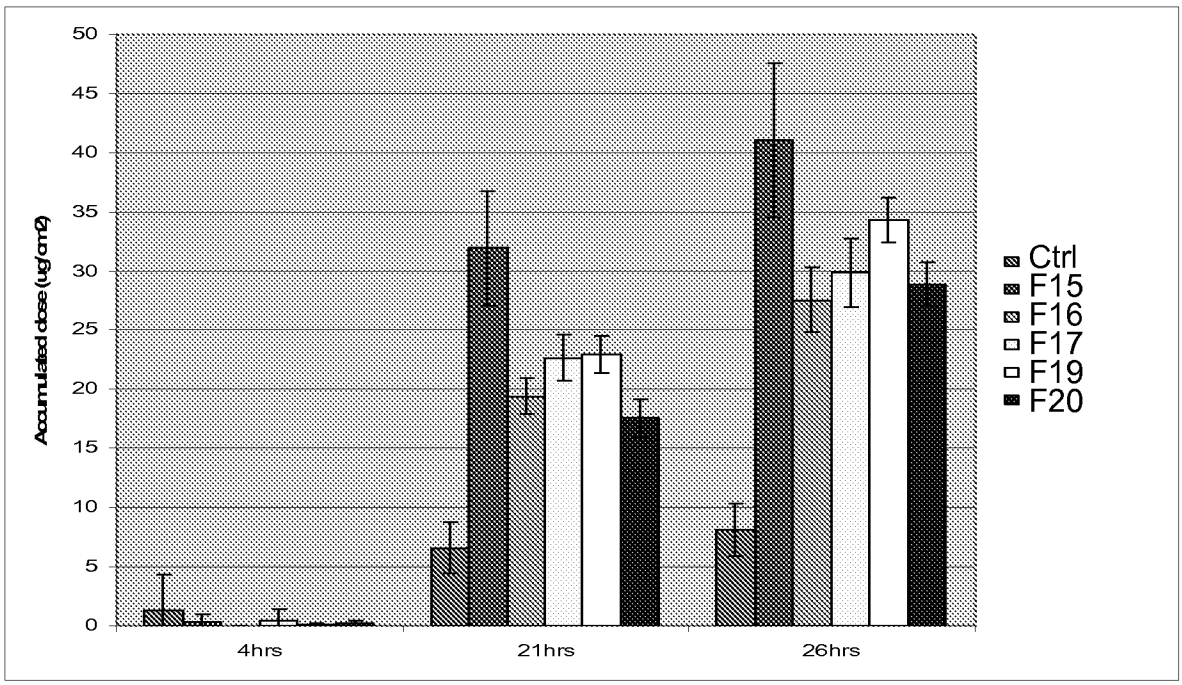
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FIG. 2

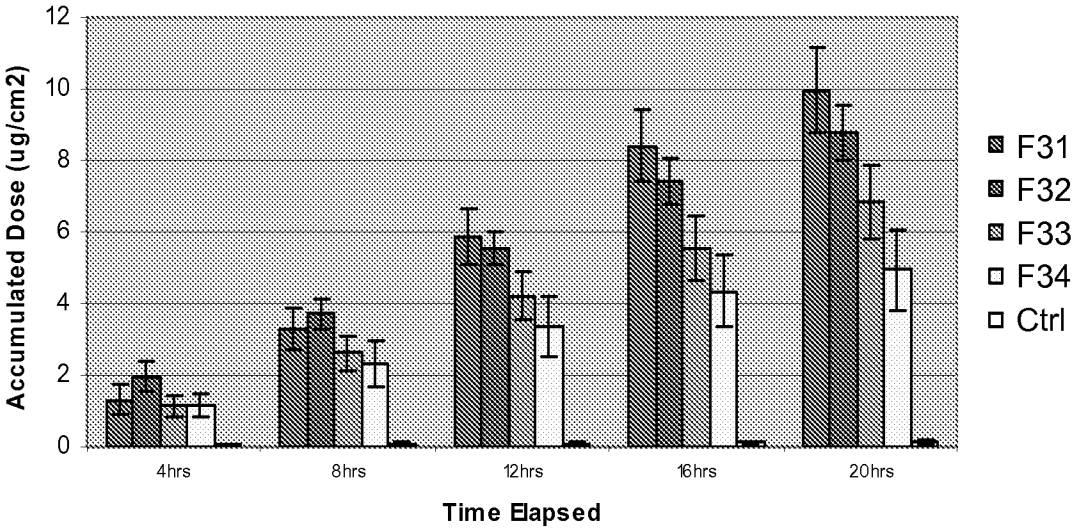
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FIG. 3

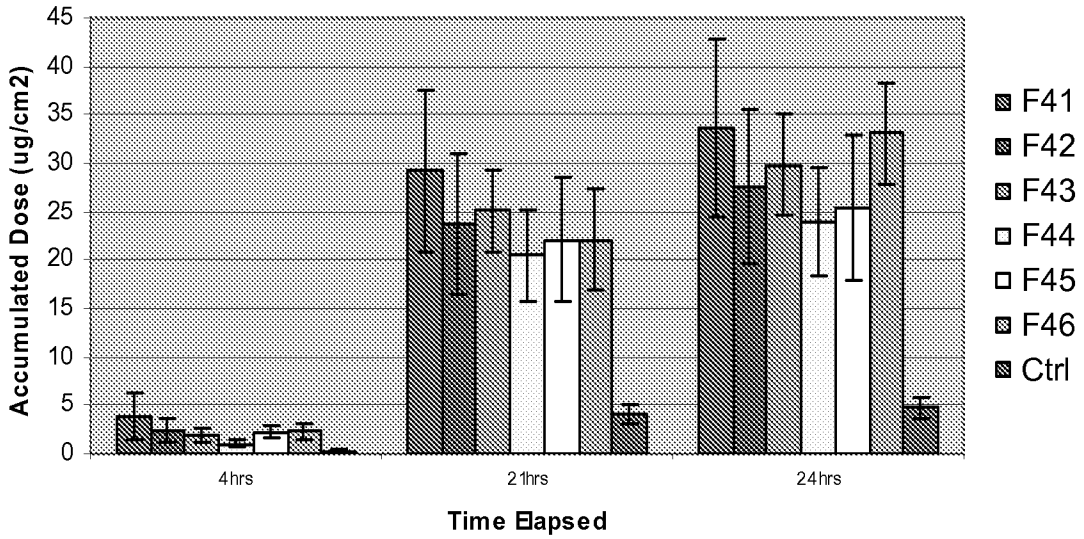
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FIG. 4

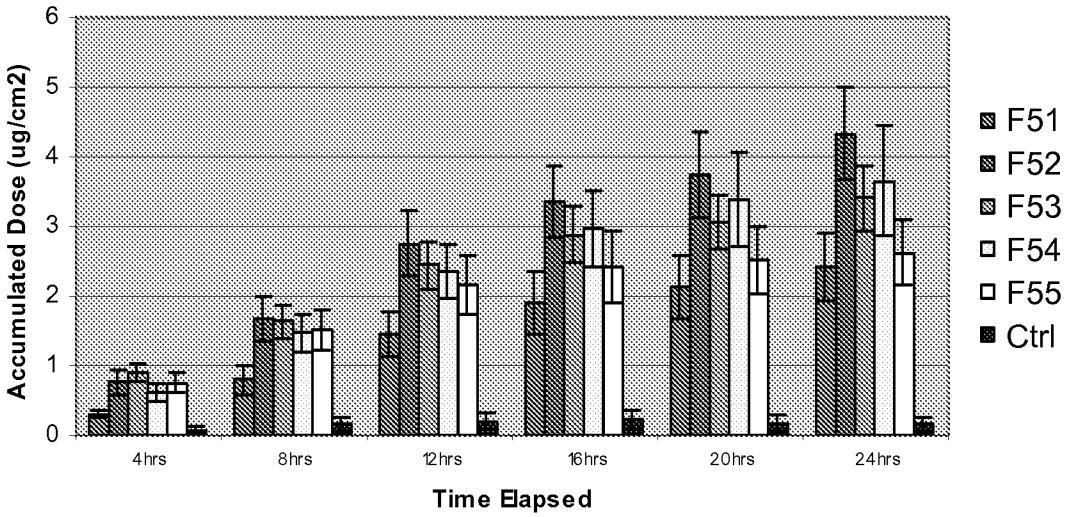
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FIG. 5

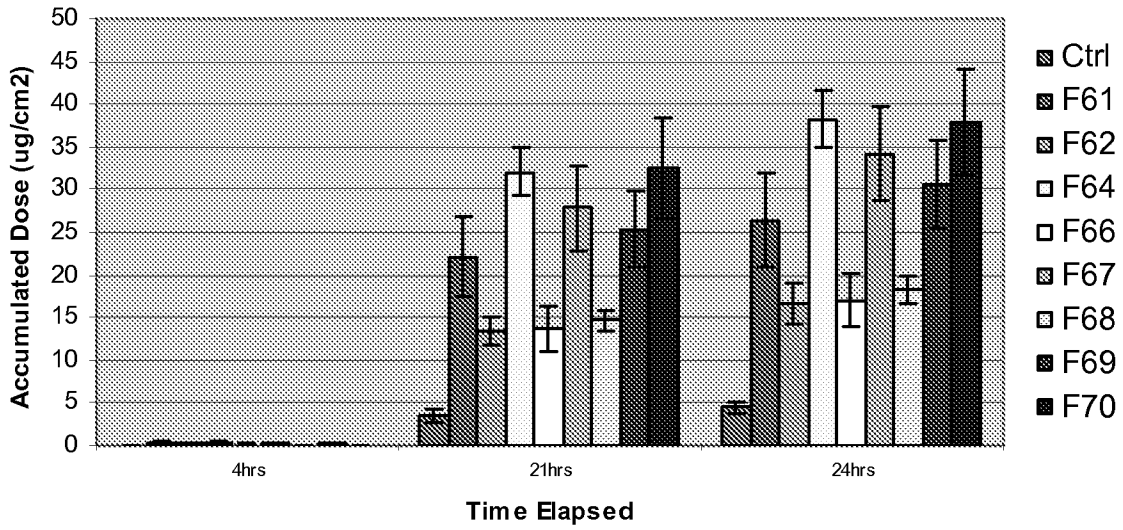
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FIG. 6

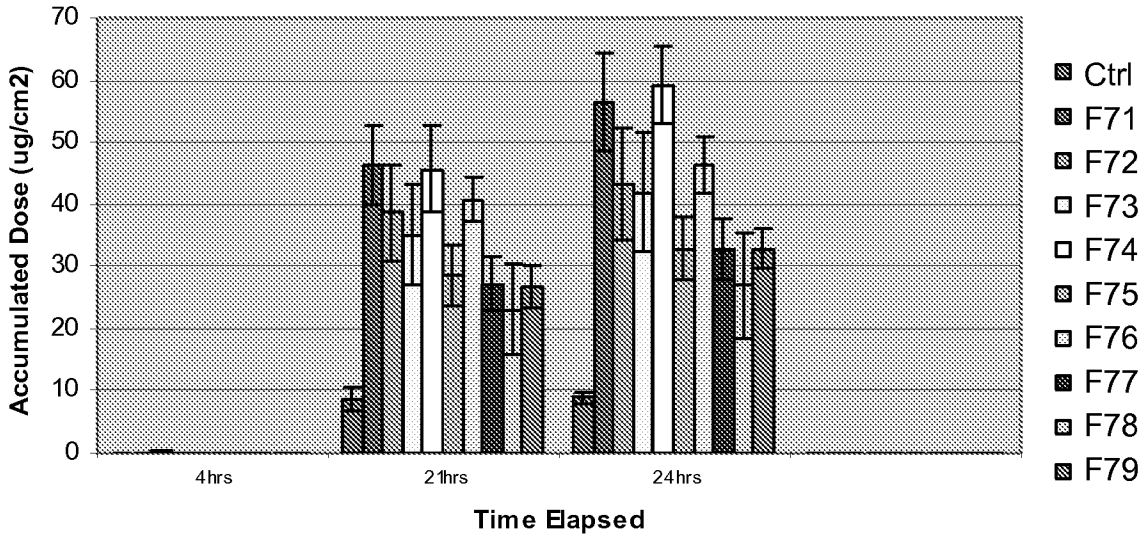
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FIG. 7

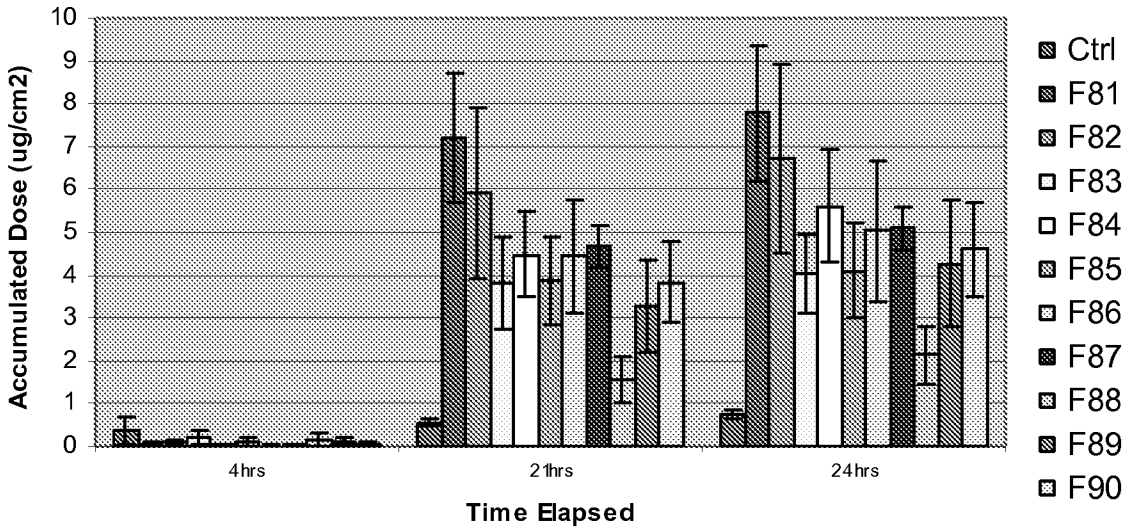
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FIG. 8

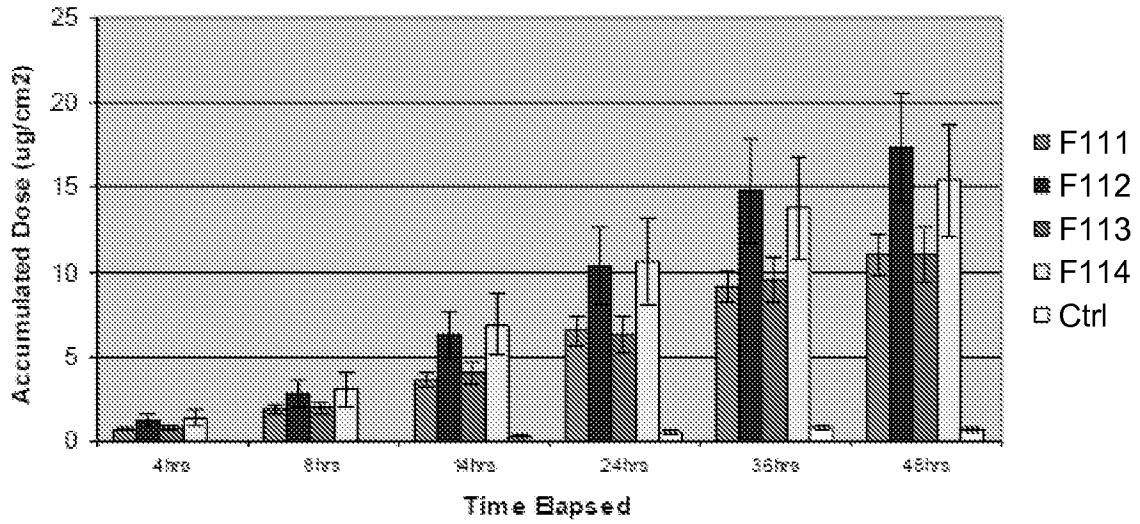
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FIG. 9

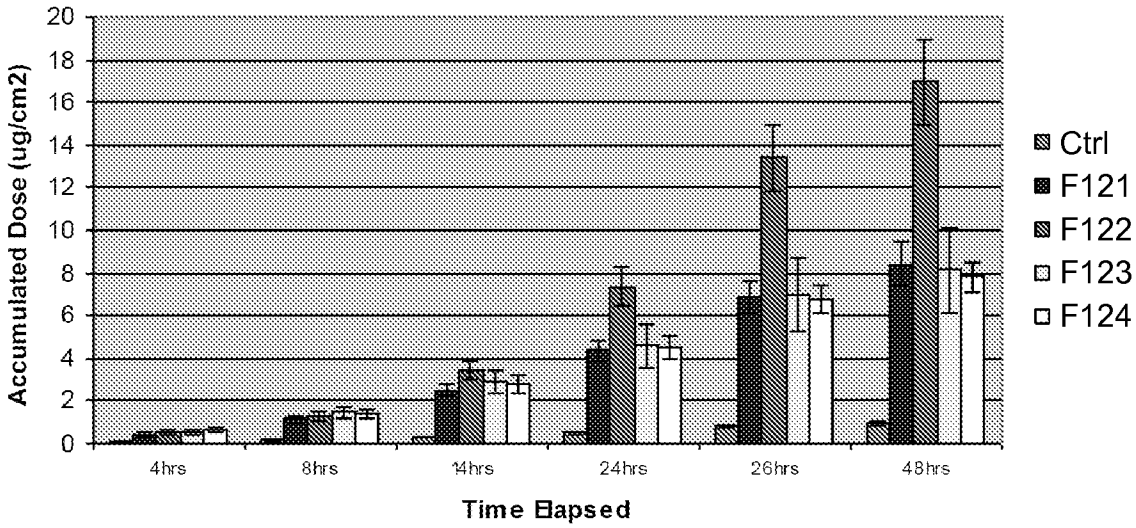
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FIG. 10

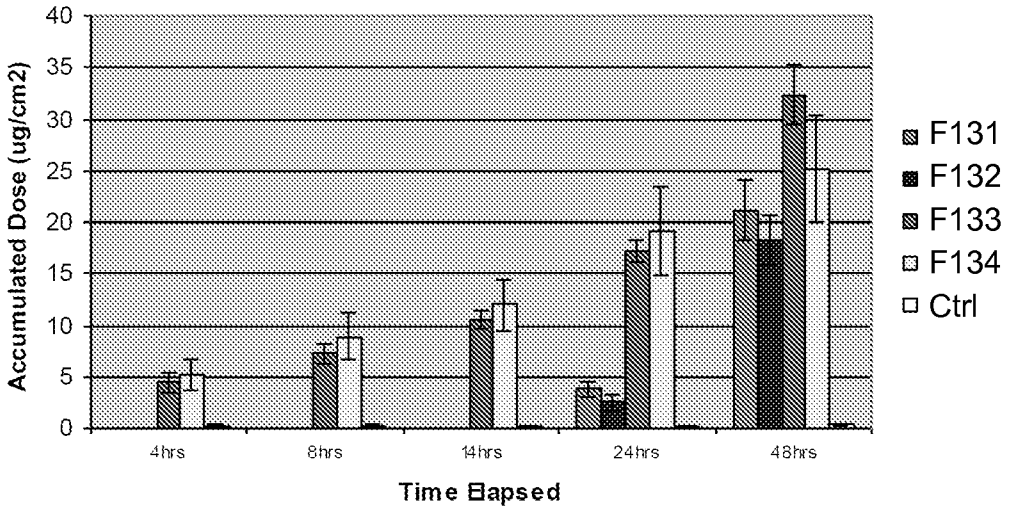
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FIG. 11

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/035788

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/444 A61K9/00 A61P19/02 A61P29/00
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 A61P

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 practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/096435 A2 (PHARMACIA CORP [US]; LU GUANG WEI [US]; EWING GARY D [US]; TYLE PRAVEE) 5 December 2002 (2002-12-05) claims 4,5; examples 8,11,16,18 -----	1-4, 9-12,36, 37,40,41
X	WO 2005/044227 A1 (GLENMARK PHARMACEUTICALS LTD [IN]; KRISHNAN ANANDI [IN]; SEN NILENDU []) 19 May 2005 (2005-05-19) page 12, paragraph 31; claim 3; example 2 ----- -/--	1-4,9, 12,36, 37,40,41

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 August 2011	21/09/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Pacreu Largo, Marta

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/035788

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PRAKASH P R ET AL: "Formulation, evaluation and anti-inflammatory activity of topical etoricoxib gel", ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH : AJPCR, INDORE, IN, vol. 3, no. 2, 1 April 2010 (2010-04-01), pages 126-129, XP009150982, ISSN: 0974-2441 the whole document	1-4, 9-12,36, 39-41
X,P	WO 2011/044540 A1 (NUVO RES INC [CA]; BUYUKTIMKIN SERVET [US]; BUYUKTIMKIN NADIR [US]; SI) 14 April 2011 (2011-04-14) examples 6,8,19	1-4, 9-14,20, 21, 23-32, 36,37, 40-43
X,P	WO 2011/041609 A2 (NUVO RES INC [CA]; BUYUKTIMKIN SERVET [US]; BUYUKTIMKIN NADIR [US]; SI) 7 April 2011 (2011-04-07) examples 3,4,5,6,8,9; tables 9,10	1,2, 4-12, 20-27, 36,37, 40-42
E	WO 2011/060195 A2 (NUVO RES INC [CA]; BUYUKTIMKIN SERVET [US]; BUYUKTIMKIN NADIR [US]; SI) 19 May 2011 (2011-05-19) examples 5-7,10-14,16-19	1-43

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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WO 2011060195 A2	19-05-2011	NONE	