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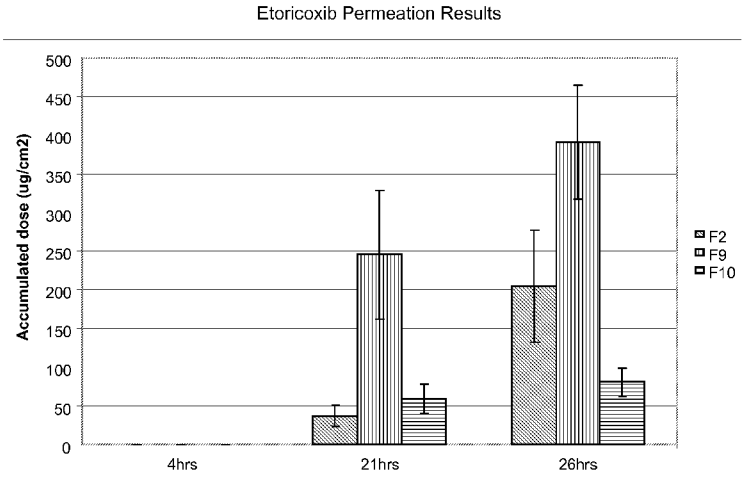

FIG. 1

(57) **Abstract**: The present invention provides topical pharmaceutical compositions, methods for preparation, and methods of treatment comprising a selective COX-2 inhibitor useful for the treatment of pain, particularly pain associated with osteoarthritis. The compositions provide good permeability and bioavailability at the target site. In certain preferred embodiments, the invention provides a composition comprising etoricoxib, 2-amino-2-methylpropanol (AMP), a cellulosic thickening agent, and urea.

WO 2011/041609 A2

TOPICAL FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 61/247,222, filed September 30, 2009. The contents of this priority document are incorporated herein in its 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) requires OA therapies to show superiority over placebo over a twelve-week period.

[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 GI 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. There has been widespread interest in this approach to treating OA, but data supporting the efficacy of topical NSAIDs in the treatment of OA is limited. For instance, a study of thirteen randomized placebo controlled trials (RCT's) of various topical NSAIDs tested specifically for use in the treatment of OA concluded that they were not generally efficacious for chronic use in OA. Lin *et al.*, Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomized controlled trials, *BMJ*, doi:10.1136/bmj.38159.639028.7C (2004).

[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 for topical NSAID treatment of OA partially arises from the difficulty associated with delivering a molecule through the skin both in a sufficient quantity to exert a therapeutic effect and in a manner that makes the treatment itself tolerable. It is generally believed that clinical efficacy in OA 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 composition I: relationship between topical vehicle

composition, 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 compositions. 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) the alteration of skin structure. *Id.*

[0012] Ho *et al.* 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. *Id.* The pH value affects the balance between ionized and non-ionized forms of the drug, which typically 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 a 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 satisfies these and other needs.

BRIEF SUMMARY OF THE INVENTION

[0017] The present invention provides pharmaceutical compositions, methods for preparation, and methods of treatment comprising a selective COX-2 inhibitor, a lower amino alcohol, a cellulosic thickening agent, and urea. In a preferred embodiment, the selective COX-2 inhibitor is etoricoxib. The formulations enhance permeability and bioavailability, and they are useful for topical treatment of pain and/or inflammation. In a 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 composition for topical administration, the composition consisting of, consisting essentially of, or comprising a selective COX-2 inhibitor (*e.g.*, etoricoxib), a lower amino alcohol, a cellulosic thickening agent, urea, a lower alcohol, and water. In a preferred aspect, the composition comprises 0.1% to 5% (w/w) etoricoxib, 0.5% to 5% of a lower amino alcohol, 0.5% to 5% of a cellulosic thickening agent, 0.5% to 10% urea, 35% to 65% of a lower alcohol, and 15% to 30% of water.

[0019] In a more preferred aspect, the composition comprises 1% to 3% (w/w) of a selective COX-2 inhibitor. Still more preferably, the composition comprises 1% (w/w) of a

selective COX-2 inhibitor. Alternatively, the composition comprises 2% (w/w) of a selective COX-2 inhibitor. Alternatively or yet still more preferably, the selective COX-2 inhibitor is etoricoxib.

[0020] In another aspect or preferred aspect of the embodiment, the lower amino alcohol is 2-amino-2-methylpropanol ("AMP"). In yet another aspect or preferred aspect of the embodiment, the lower alcohol is a monohydric alcohol.

[0021] In still another aspect of the embodiment or preferred aspect, the composition further comprises an additional molecular penetration enhancer (MPE™). More preferably, the MPE™ is the lower alcohol 2-(2-ethoxyethoxy)ethanol (Transcutol®). Still more preferably, the composition comprises 5% to 25% (w/w) 2-(2-ethoxyethoxy)ethanol, and yet still more preferably, 10% 2-(2-ethoxyethoxy)ethanol.

[0022] Alternatively, the MPE™ is a terpene. More preferably, the terpene is selected from the group consisting of limonene, geraniol and mixtures thereof. Still more preferably, the composition comprises 0.1% to 5% (w/w) terpene, and yet still more preferably, 3% terpene.

[0023] In yet still another aspect of the embodiment or preferred aspect, the composition further comprises a nonionic surfactant. More preferably, the nonionic surfactant is a polysorbitan ester. Still more preferably, the polysorbitan ester is polysorbate 20 (Tween® 20). Alternatively, the composition comprises from 0.5% to 15% (w/w) nonionic surfactant, and yet still more preferably, 2% to 10% nonionic surfactant.

[0024] In another embodiment, the present invention provides a pharmaceutical composition for topical administration, the composition consisting of, consisting essentially of, or comprising 1 to 3% (w/w) etoricoxib, 0.5% to 3% AMP, 1% to 3% hydroxypropyl cellulose, 2% to 10% urea, 10% 2-(2-ethoxyethoxy)ethanol, a lower monohydric alcohol, and water. Preferably, said composition consists of, consists essentially of, or comprises 2% to 5% urea. Alternatively and preferably, said composition consists of, consists essentially of, or comprises about 7.5% urea.

[0025] In yet another embodiment, the present invention provides a method for topically treating pain in a subject, the method comprising topically applying a pharmaceutical composition to treat pain in the subject; the composition consisting of, consisting essentially of, or comprising a selective COX-2 inhibitor (*e.g.*, etoricoxib), a lower amino alcohol, a cellulosic thickening agent, urea, a lower alcohol, and water. In a preferred aspect, the composition comprises 0.1% to 5% (w/w) etoricoxib, 0.5% to 5% of a lower amino alcohol,

0.5% to 5% of a cellulosic thickening agent, 0.5% to 10% urea, a lower alcohol, and water. More preferably, the composition comprises 35% to 65% of a lower alcohol and 15% to 30% water. In another aspect or preferred aspect of the embodiment, the lower amino alcohol is 2-amino-2-methylpropanol. In yet another aspect or preferred aspect of the embodiment, the lower alcohol is a monohydric alcohol. Alternatively or still more preferably, the pain is associated with OA.

[0026] These and other objects, aspects and embodiments and will become more apparent when read with the following detailed description and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] **FIG. 1** describes etoricoxib permeation through porcine skin from a first series of topical formulations (Table 1) at 4, 21, and 26 hours after application.

[0028] **FIG. 2** describes etoricoxib permeation through porcine skin from a second series of topical formulations (Table 2) at 4, 21, and 26 hours after application.

[0029] **FIG. 3** describes etoricoxib permeation through porcine skin from a third series of topical formulations (Table 3) at 4 and 20 hours after application at two different dosing levels.

[0030] **FIG. 4** describes etoricoxib permeation through porcine skin from a fourth series of topical formulations (Table 4) at 4, 20, and 24 hours after application.

[0031] **FIG. 5** describes etoricoxib permeation through porcine skin from a fifth series of topical formulations (Table 5) at 4, 21, and 24 hours after application.

[0032] **FIG. 6** describes etoricoxib permeation through porcine skin from a sixth series of topical formulations (Table 6) at 4, 21, and 26 hours after application.

[0033] **FIG. 7** describes etoricoxib permeation through porcine skin from a further series of topical formulations (Table 8) at 4, 21, and 26 hours after application.

[0034] **FIG. 8** describes etoricoxib permeation through porcine skin from a further series of topical formulations (Table 9) at 4, 21, and 26 hours after application.

[0035] **FIG. 9** describes etoricoxib permeation through porcine skin from a further series of topical formulations (Table 10) at 4, 21, and 26 hours after application.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0036] The terms "a," "an," or "the" as used herein not only include aspects with one member, but also include aspects with more than one member. For example, an embodiment including "a cellulosic thickening agent and a lower monohydric alcohol" should be understood to present certain aspects with at least a second cellulosic thickening agent, at least a second lower monohydric alcohol, or both.

[0037] The term "about" as used herein includes a close (*i.e.*, narrow) range around the explicit value for a variable. For example, in certain instances the term "about" includes 5%-10% higher or 5-10% lower than the value given. For example, "about 10" includes the range of values from 9.5 to 10.5.

[0038] 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%."

[0039] In compositions comprising an "additional" 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.

[0040] The term "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.

[0041] "Cellulosic thickening agent" as used herein includes a thickening agent that is a natural or synthetic polymeric carbohydrate (*e.g.*, cellulose, pharmaceutically acceptable vegetable gums) or a polymeric or oligomeric derivative of a polymeric carbohydrate that is produced by chemical modification (*e.g.*, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose). Representative cellulosic thickening agents include cellulose, hydroxypropyl cellulose ("HPC"), hydroxypropyl methyl cellulose, hydroxyethyl cellulose, methyl cellulose, carboxymethyl cellulose, and the like.

[0042] 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, patterned bar represents a single data value, which is the mean value of the distribution of data values.

[0043] "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.

[0044] "Formulation," "pharmaceutical composition," and "composition" as used herein are equivalent terms referring to a composition of matter suitable for pharmaceutical use.

[0045] "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.

[0046] "Lower amino alcohol" as used herein includes straight- or branched-chain alkyl compounds of 2 to 8 carbon atoms, and preferably, of 2 to 6 carbon atoms. Representative lower amino alcohols include 2-amino-2-methylpropanol, meglumine, serine methyl ester, serine ethyl ester, threonine ethyl ester, and the like.

[0047] "Lower alcohol" as used herein includes straight- or branched-chain alkyl alcohols of 1 to 6 carbon atoms. Representative lower monohydric alcohols include methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol, n-pentanol, 3-pentanol, 2-methoxyethanol, propylene glycol, and the like.

[0048] "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, oleyl alcohol, and the like.

[0049] "Nonionic surfactant" as used herein indicates a surface-active agent that is uncharged under the conditions of the formulation. Representative nonionic surfactants include the polysorbitans (*e.g.*, polysorbitan 20), fatty acid esters (*e.g.*, isopropyl myristate), and the like.

[0050] The term "or" as used herein should in general be construed non-exclusively. For example, an embodiment of "a composition comprising A or B" would typically present an aspect with a composition 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).

[0051] 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 the specific values of 17.36% and 21%. A percentage range of about 13% to 17% would also teach the specific values of 12.97%, 16%, and 17.1%.

[0052] "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 natural membrane such as skin or nail. 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 tissues surrounding the joint may be necessary to achieve therapeutic benefit. An MPE™ 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 underlying or near to the skin or nail; or iii) indirectly via systemic distribution to the site of the disease. If systemic distribution of an active agent would be likely to produce side effects (*e.g.*, etoricoxib), an MPE™ is preferably selected to maximize direct delivery and to minimize systemic distribution. An MPE™ may be a pure substance or may comprise, consist essentially of, or consist of a mixture of different chemical entities.

[0053] "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 cellulosic thickening agents, carbomer polymers, carbomer derivatives, cellulose derivatives, polyvinyl alcohol, poloxamers, polysaccharides, and mixtures thereof.

[0054] "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. Topical formulations can be used for topical, local, regional, or transdermal application of substances.

[0055] "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.

[0056] "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.

II. Selective COX-2 Inhibitor

[0057] 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. In another preferred aspect, the pharmaceutical composition comprises 0.1% to 5% (w/w) of etoricoxib, preferably 1% to 3%, and more preferably 2%.

[0058] In one aspect, a composition permits delivery of a selective COX-2 inhibitor daily dosage of about 0.01 mg to about 120 mg, preferably about 0.1 mg to 60 mg, more preferably about 1 mg to about 30 mg, and still more preferably about 1 to about 10 mg. Yet still more preferably, the formulation permits delivery of a daily dosage of about 3 mg. Preferably the concentration 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 (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.

[0059] A person skilled in the art will appreciate that the dosage and application area will vary 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).

[0060] 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 most preferably less than 5%, yet provides local or regional delivery levels sufficient for therapeutic benefit. Preferably the concentration 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 (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.

[0061] In still another aspect, the pharmaceutical composition comprising etoricoxib provides better flux (as determined by the Franz cell procedure of Example 2) 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 greater than the flux of the comparative formulation's active. In other words, the ratio of: (i) the composition'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.

[0062] Still more preferably, the composition has an etoricoxib flux that is at least 2.0 times greater than the comparative formulation's coxib flux. Yet still more preferably, the composition has an etoricoxib flux that is at least 4.0 times greater than the comparative formulation's coxib flux.

[0063] In an alternative aspect, the composition has a selective COX-2 inhibitor flux equal to or greater than the selective COX-2 inhibitor flux from 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 greater than 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 selective COX-2 inhibitor flux from a comparative formulation with the same selective COX-2 inhibitor is preferably greater than 1.0, and more preferably at least about 1.5.

[0064] Still more preferably, the composition has a selective COX-2 inhibitor flux that is at least 2.0 times greater than the selective COX-2 inhibitor flux from a known comparative formulation with the same selective COX-2 inhibitor. Yet still more preferably, the composition has a selective COX-2 inhibitor flux that is at least 4.0 times greater than the selective COX-2 inhibitor flux from a comparative formulation with the same selective COX-2 inhibitor.

[0065] In another alternative aspect, the present invention provides a composition comprising etoricoxib and having an etoricoxib flux (as determined by the Franz cell

procedure of Example 2) of at least 0.1 μg/hr/cm^2 at 24 hours, preferably at least 0.2 μg/hr/cm^2 at 24 hours.

III. Lower Amino Alcohol, Cellulosic Thickening Agent, and Urea Components

[0066] In a preferred aspect, the composition comprises 2-amino-2-methylpropanol ("AMP"). More preferably, the composition comprises 0.5% to 5% AMP. Still more preferably, the composition comprises from 0.5% to 2% AMP. Yet still more preferably, the composition comprises 1% AMP. Alternatively, the composition comprises 1.5% AMP.

[0067] In another preferred aspect, the composition comprises a cellulosic thickening agent. Suitable cellulosic thickening agents include, but are not limited to, 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. Preferably, the cellulosic thickening agent is HPC.

[0068] Alternatively, the composition comprises 0.5% to 5% of a cellulosic thickening agent. More preferably, the composition comprises from 1% to 2% of a cellulosic thickening agent. Still more preferably, the composition comprises 1% of a cellulosic thickening agent. Alternatively, the composition comprises 2% of a cellulosic thickening agent.

[0069] In yet another preferred aspect, the composition comprises urea. More preferably, the composition comprises 0.5% to 10% urea. Still more preferably, the composition comprises 2% to 10% urea. Alternatively, the composition comprises 2% to 5% urea. Yet still more preferably, the composition comprises about 5% urea. Alternatively, the composition comprises about 2.5% urea, the composition comprises about 7.5% urea, or the composition comprises about 10% urea.

[0070] More preferably, the composition comprises a mixture of AMP and a cellulosic thickening agent. Alternatively, the composition comprises a mixture of AMP and urea, or the composition comprises a mixture of a cellulosic thickening agent and urea. Still more preferably, the composition comprises a mixture of AMP, a cellulosic thickening agent, and urea.

[0071] In certain aspects of the invention, urea may function as an MPE™ to assist in the delivery of a selective COX-2 inhibitor. In other aspects, AMP may function as an MPE™ to assist in the delivery of a selective COX-2 inhibitor. In yet other aspects, urea and AMP may function as MPE™s to assist in the delivery of a selective COX-2 inhibitor.

IV. Lower Alcohol

[0072] In one preferred aspect, the composition comprises a mixture of a lower monohydric alcohol and water. More preferably, the lower monohydric alcohol is ethanol or 2-(2-ethoxyethoxy)ethanol. In certain aspects, the composition comprises a second lower monohydric alcohol. In certain other aspects, the composition comprises a third lower monohydric alcohol. In one aspect, the formulation does not include isopropanol. In certain aspects, the lower monohydric alcohol may function as a MPE™.

[0073] In another aspect, the composition comprises at least about 3, 5, 7, 9.5, 10, 10.5, 11, 11.5, 12, 14, 15, 20, 25, 30, 31, 31.5, 32, 32.5, 33, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 44.5, 45, 46, 46.5, 47, 47.5, 48, 48.5, 49, 49.5, 50, 50.5, 51, 51.5, 52, 52.5, 53, 53.5, 54, 54.5, 55, 55.5, 56, 56.5, 57, 58, 59, 60, 63, or 65% (w/w) of a lower monohydric alcohol. In other aspects, the composition comprises at most about 3, 5, 7, 9.5, 10, 10.5, 11, 11.5, 12, 14, 15, 20, 25, 30, 31, 31.5, 32, 32.5, 33, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 44.5, 45, 46, 46.5, 47, 47.5, 48, 48.5, 49, 49.5, 50, 50.5, 51, 51.5, 52, 52.5, 53, 53.5, 54, 54.5, 55, 55.5, 56, 56.5, 57, 58, 59, 60, 63, or 65% (w/w) of a lower monohydric alcohol. In another aspect, the composition comprises 35% to 65% of a lower monohydric alcohol. In still other aspects, the composition comprises the same or differing amounts of a first and at least one additional monohydric alcohol. For example, the composition can include 44% to 54% of ethanol and 10% of 2-(2-ethoxyethoxy)ethanol.

[0074] In another aspect, the lower alcohol is a diol. Alternatively, the composition additionally comprises 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 mixtures thereof. For example, in one aspect the formulation comprises 0.1% to 15% (w/w) of propylene glycol; more preferably, the formulation comprises 0.1% to 5% (w/w) of propylene glycol.

V. Additional Molecular Penetration Enhancers

[0075] In another preferred aspect, an additional MPE™ is present in the carrier. In certain aspects, the MPE™ is selected the group consisting of terpenes, fatty acid esters, and fatty acid alcohols. More preferably, the MPE™ is a terpene. Examples include *d*-limonene, limonene oxide, geraniol, α-pinene, α-pinene oxide, thymol, menthone, menthol, neomenthol, 3-carene, *l*-carvol, carvone, carveol, 1,8-cineole (eucalyptol), citral,

dihydrocarveol, dihydrocarvone, 4-terpinenol, fenthone, menthone, pulegone, pulegol, isopulegol, piperitone, camphor, a-terpineol, terpinen-4-ol, linalool, carvacrol, trans-anethole, ascaridole, safrole, racemic mixtures thereof (*e.g.*, dl-limonene), and pharmaceutically acceptable isomers thereof. In certain preferred aspects, a second MPE™ can be present (*e.g.*, a fatty acid ester and a terpene).

[0076] In a specific embodiment, the composition of the present invention comprises limonene or geraniol. In one aspect, the composition comprises 0.1% to 5% (w/w) of limonene or geraniol. Preferably, the composition comprises 3% (w/w) of limonene or geraniol. In another aspect, the formulation does not include menthol or α-terpineol.

[0077] In certain aspects, the terpene MPE™ can be included within an essential oil. Essential oils that include a substantial proportion of at least one terpene MPE™ include oils of peppermint, eucalyptus, chenopodium, anise, and yling-yling.

[0078] Alternatively, a fatty acid ester is used as an MPE™ in the composition. Examples of preferred MPE™ are glyceryl monoesters. More preferably, the MPE™ is glyceryl monolaurate.

[0079] In another aspect, a fatty acid ester or a fatty alcohol ester is used as an MPE™ in the composition. Examples of fatty acid and fatty alcohol esters include butyl acetate, caproyl glycolate, cetyl lactate, cocoyl glycolate, decyl *N,N*-dimethylamino acetate, decyl *N,N*-dimethylamino isopropionate, diethyleneglycol oleate, diethyl sebacate, diisopropyl sebacate, dodecyl *N,N*-dimethylamino acetate, dodecyl *N,N*-dimethylamino butyrate, dodecyl *N,N*-dimethylamino isopropionate, dodecyl 2-(*N,N*-dimethylamino)propionate, ethylene oxide (EO)-5-oleyl ester, ethyl acetate, ethyl acetoacetate, ethyl propionate, glyceryl dilaurate, glyceryl dioleate, glyceryl monoesters (*e.g.*, glyceryl monolaurate, glyceryl monooleate, glyceryl monolinoleate, and the like), glycerol monoethers, isopropyl isostearate, isopropyl laurate, isopropyl linoleate, isopropyl myristate, isopropyl palmitate, isostearoyl glycolate, lauroyl glycolate, methyl acetate, methyl caprate, methyl laurate, methyl oleate, methyl propionate, methyl valerate, 1-monocaproyl glycerol, medium-chain-length monoglycerides, benzyl or substituted benzyl nicotinate, octyl acetate, octyl *N,N*-dimethylamino acetate, oleyl oleate, n-pentyl *N*-acetylprolinate, propylene glycol monolaurate, sodium lauroyl glycolate, tetradecyl *N,N*-dimethylamino acetate, and tromethamine lauroyl glycolate. Still other examples include sunscreens such as Padimate-O, homosalate, cinnamate esters, octocrylene, and the like.

[0080] Other MPE™s include fatty acids, lactic acid, fatty alcohols (*e.g.*, oleyl alcohol, stearyl alcohol, decanol), fatty alcohol ethers, hexahydro-1-dodecyl-2H-azepin-2-one (*i.e.*, laurocapram or Azone™) and derivatives thereof, dimethylsulfoxide (DMSO) and related sulfoxides (*e.g.*, n-decyl methylsulfoxide), salicylic acid and alkyl esters thereof (*e.g.*, methyl salicylate), N,N-dimethyl acetamide, dimethyl formamide, N,N-dimethyltoluamide, 2-pyrrolidinone and N-alkyl derivatives thereof (*e.g.*, N-methyl-2-pyrrolidone (NMP)) and N-octyl-2-pyrrolidinone), and 2-nonyl-1,3-dioxolane. *See* Osborne, D.W.; Henke, J. J. "Skin Penetration Enhancers Cited in the Technical Literature," *Pharmaceut. Tech.* 58-66 (Nov. 1997).

VI. Other Components

[0081] In yet another aspect, the composition additionally comprises at least one pharmaceutically acceptable surfactant. Preferably, the surfactant is a nonionic surfactant. More preferably, the surfactant is a polysorbate surfactant. Still more preferably, the surfactant is polysorbitan 20. In one aspect, the composition comprises 0.5% to 15% (w/w) of a nonionic surfactant, preferably 2 to 10%.

[0082] 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 (20) sorbitan monooleate, stearyl alcohol, sucrose coconut fatty ester mixtures, and sucrose monolaurate.

[0083] In one aspect, the composition 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, tocophereth-80, and the like.

[0084] In another aspect, the composition additionally comprises a chelating agent. Preferred chelating agents include ethylenediamine tetraacetic acid (EDTA), diammonium EDTA, dipotassium EDTA, calcium disodium EDTA, HEDTA, tetraethylammonium (TEA) EDTA, tetrasodium EDTA, tripotassium EDTA, trisodium phosphate, diammonium citrate, galactaric acid, galacturonic acid, gluconic acid, glucuronic acid, humic acid, cyclodextrin, sodium citrate, potassium citrate, the sodium salt of ethylenediamine-tetra (methylene phosphonic acid) (EDTMP), and potassium EDTMP.

[0085] In certain preferred aspects, the compositions of the invention optionally include a buffer or a pH-adjusting agent (*e.g.*, in addition, the topical formulations of the present invention can also comprise a pH-adjusting agent). In one particular embodiment, the pH-adjusting agent is a base. Suitable pH-adjusting bases include bicarbonates, carbonates, hydroxides (such as alkali or alkaline earth metal hydroxide as well as transition metal hydroxides), and the like. In an alternative aspect, suitable pH-adjusting bases include amines, such as diethanolamine, triethanolamine, or aminopropanol; bicarbonates; carbonates; and hydroxides, such as ammonium hydroxide, alkali or alkaline earth metal hydroxide, or transition metal hydroxides. Alternatively, the pH-adjusting agent can also be an acid, an acid salt, or mixtures thereof.

[0086] The pH-adjusting agent can be present in an amount sufficient to adjust the pH of the composition to between about pH 4.0 to about 10.0, more preferably about pH 7.0 to about 9.5. In certain embodiments, the unadjusted pH of the admixed components is between 8 and 10, such as 9, without the need for the addition of any pH-adjusting agents.

[0087] Preferably, the pH-adjusting agent is sodium hydroxide, hydrochloric acid, or a combination of both, and is present in an amount sufficient to adjust the pH of the composition to between about pH 4.0 to about 8.5, more preferably to between about pH 5.5 to about 7.0, such as 6.0 or 6.5. Even more preferably, the pH is adjusted to about 4.0, 4.2, 4.4, 4.6, 4.8, 5.0, 5.2, 5.4, 5.6, 5.8, 6.0, 6.2, 6.3, 6.4, 6.6, 6.8, 7.0, 7.2, 7.4, 7.6, 7.8, 8.0, 8.4, 8.5, or any fraction in-between.

[0088] In certain preferred aspects, a small amount of acid or base is included in the formulation. Non-limiting examples of amounts of acid or base that may be included in the formulation are about 0.000001%, 0.00001%, 0.0001%, 0.001%, 0.0012%, 0.01%, 0.012%, 0.1%, or 1.0%. Preferably, this amount is about 0.0001%. 0.0002%, 0.0003%, 0.0004%, 0.0005%, 0.0006%, 0.0007%, 0.0008%, 0.0009%, 0.0010%, 0.0011%, 0.0012%, 0.0015%, 0.0016%, 0.0017%, 0.0018%, 0.0019%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%,

0.008%, 0.009%, 0.01%, 0.012%, or 0.02%. More preferably, this amount is about 0.001%. 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.010%, 0.011%, 0.012%, 0.015%, 0.016%, 0.017%, 0.018%, 0.019%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1%, or as needed to adjust the formulation to the desired pH.

[0089] Further, the pH-adjusting agent can also be a buffer. Preferably, the pH of the composition of the invention can be adjusted or stabilized with a buffer. Suitable buffers include citrate/citric acid buffers, acetate/acetic acid buffers, phosphate/phosphoric acid buffers, formate/formic acid buffers, propionate/propionic acid buffers, lactate/lactic acid buffers, carbonate/carbonic acid buffers, ammonium/ammonia buffers, and the like. In certain instances, the buffer is an acidic buffer system such as, for example, benzocaine. In more preferred instances, the acidic acid buffer system is citric acid or a citric acid salt.

[0090] In certain preferred aspects, the buffer is present at a concentration of about 0.000001 M, 0.00001 M, 0.0001 M, 0.001 M, 0.0012 M, 0.01 M, 0.012 M, 0.1 M, or 1.0 M. Preferably, this amount is about 0.0010 M, 0.0015 M, 0.002 M, 0.003 M, 0.004 M, 0.005 M, 0.006 M, 0.007 M, 0.008 M, 0.009 M, 0.01 M. 0.012 M, or 0.02 M. More preferably, this amount is about 0.001 M. 0.002 M, 0.003 M, 0.004 M, 0.005 M, 0.006 M, 0.007 M, 0.008 M, 0.009 M, 0.010 M, 0.011 M, 0.012 M, 0.015 M, 0.016 M, 0.017 M, 0.018 M, 0.019 M, 0.02 M, 0.025 M, 0.03 M, 0.035 M, 0.04 M, 0.045 M, 0.05 M, 0.055 M, 0.06 M, 0.065 M, 0.07 M, 0.075 M, 0.08 M, 0.085 M, 0.09 M, 0.095 M, or 0.1 M. Still more preferably, this amount is about 0.10 M, 0.11 M, 0.12 M, 0.13 M, 0.14 M, 0.15 M, 0.16 M, 0.17 M, 0.18 M, 0.19 M, 0.20 M, 0.21 M, 0.22 M, 0.23 M, 0.24 M, 0.25 M, 0.26 M, 0.27 M, 0.28 M, 0.29 M, 0.30 M, 0.31 M, 0.32 M, 0.33 M, 0.34 M, 0.35 M, 0.36 M, 0.37 M, 0.38 M, 0.39 M, 0.40 M, 0.41 M, 0.42 M, 0.43 M, 0.44 M, 0.45 M, 0.46 M, 0.47 M, 0.48 M, 0.49 M, 0.50 M, 0.55 M, 0.60 M, 0.65 M, 0.7 M, 0.75 M, 0.8 M, 0.85 M, 0.9 M, 0.95 M, or 1.0 M.

[0091] In certain preferred aspects, the inventive formulation includes a buffer, and a second pH-adjusting agent (*e.g.*, sodium hydroxide or hydrochloric acid) to adjust the pH of the composition to a desired pH. More preferably, the second pH-adjusting agent comprises two agents (*e.g.*, sodium hydroxide and hydrochloric acid) that are included as needed to adjust the pH of the composition to a desired pH.

[0092] In certain aspects, the composition of the present invention comprises a preservative, such as propyl paraben or methyl paraben, or combinations thereof. The formulation may be made bacteriostatic by the addition of preservatives. For example, a composition can contain 0.001-8%, preferably 0.01-6%, more preferably 0.05-5% by weight

of the total composition of a preservative or a combination of preservatives. A variety of preservatives are suitable, including, but not limited to, benzoic acid, benzyl alcohol, benzylhemiformal, benzylparaben, 5-bromo-5-nitro-1,3-dioxane, 2-bromo-2-nitropropane-1,3-diol, butyl paraben, phenoxyethanol, methyl paraben, propyl paraben, diazolidinyl urea, calcium benzoate, calcium propionate, captan, chlorhexidine diacetate, chlorhexidine digluconate, chlorhexidine dihydrochloride, chloroacetamide, chlorobutanol, p-chloro-m-cresol, chlorophene, chlorothymol, chloroxylenol, m-cresol, o-cresol, diethylene glycol dimethyl ether ("DEDM") hydantoin, DEDM hydantoin dilaurate, dehydroacetic acid, dibromopropamidine diisethionate, and 1,3-bis(hydroxymethyl)-5,5-dimethylimidazolidine-2,4-dione ("DMDM") hydantoin. In certain aspects, the formulations herein may be (i) sterile or essentially free from microorganisms such as bacteria and viruses that can cause infection and (ii) optionally preservative-free.

[0093] In certain preferred aspects, the present invention provides a pharmaceutical composition for topical administration, said composition comprising, consisting essentially of, or consisting of: 0.1% to 5% (w/w) of a selective COX-2 inhibitor; 0.5% to 5% of a lower amino alcohol; 0.5% to 5% of a cellulosic thickening agent; 0.5% to 10% urea; at least one lower alcohol; and water. More preferably, the selective COX-2 inhibitor is etoricoxib.

[0094] In certain preferred aspects, the present invention provides a pharmaceutical composition for topical administration, said composition comprising, consisting essentially of, or consisting of: 2% (w/w) of a selective COX-2 inhibitor; 0.5% to 3% 2-amino-2-methylpropanol; 1% to 3% of hydroxypropyl cellulose; 2% to 5% urea; 10% 2-(2-ethoxyethoxy)ethanol; a lower monohydric alcohol; and water. More preferably, the selective COX-2 inhibitor is etoricoxib.

VII. Other Properties

[0095] In still yet another aspect, the composition is selected from the group of a gel, a cream, an emulsion, a foam, a lotion, an organogel, an ointment, and a transdermal patch. More preferably, the composition is a gel.

[0096] In yet another alternative 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, or 10,000 cP at STP. Preferably, the dynamic viscosity is from 100

to 1000 cP, from 250 to 2000 cP, from 500 to 5000 cP, or from 500 to 20,000 cP. In certain other aspects, the dynamic viscosity of the composition is at least about 10^4, 5 x 10^4, 10^5, 5 x 10^5, 10^6, 5 x 10^6, 10^7 or 10^8 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 addition of a cellulosic thickening agent or other thickening agents.

[0097] In another aspect, the composition is acidic. In certain aspects, the composition has a pH of below 7.5, of below 6.5, of below 5.5, of below 4.5, of below 3.5, or of below 2.5. In certain other aspects, the pH of the composition may range from about 1.5 to about 7, about 2 to about 7, about 3 to about 7, about 4 to about 7, or about 5 to about 7. In still other aspects, the pH of the composition may range from about 1.5 to about 5.5, about 2.5 to about 5.5, about 3.5 to about 5.5, or about 4.5 to about 5.5.

[0098] In yet another aspect, the composition is basic. In certain aspects, the composition has a pH of above 7, of above 8, of above 9, of above 10, of above 11, or of above 12. In certain other aspects, the pH of the composition may range from about 7 to about 12.5, about 7 to about 11.5, about 7 to about 10.5, about 7 to about 9.5, or about 7 to about 8.5. In still other aspects, the pH of the composition may range from about 9 to about 12.5, about 9 to about 11.5, about 9 to about 10.5, or about 8.5 to about 10.

[0099] In still yet another aspect, the composition is neutral. In certain aspects, the composition has a pH of about 7. In certain other aspects, the composition has a pH from about 6 to about 8.5, from about 5.5 to about 8, about 6 to about 8, about 6.5 to about 8.5, or from about 6.5 to about 7.5.

[0100] 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.

[0101] In another aspect, a composition is designed for topical efficacy with minimal systemic distribution of the coxib through the body by the circulatory system (*e.g.*, the cardiovascular system). 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.

[0102] In a preferred aspect, a composition 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.

[0103] In another preferred aspect, a composition 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.*, 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 composition.

[0104] 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.

[0105] 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.

VIII. Methods of Preparation

[0106] In one aspect, the pharmaceutical composition is formulated as a cream, an emulsion, a foam, 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 gel. Alternatively, the composition is a patch.

IX. Methods of Treatment

[0107] In certain embodiments, the invention describes a method for treating pain comprising the step of applying a topical, selective COX-2 inhibitor composition to a subject. In one aspect, the pharmaceutical composition is applied to the skin of the subject.

[0108] In another aspect, the selective COX-2 inhibitor is delivered locally to the skin with minimal systemic absorption. In yet another aspect, the selective COX-2 inhibitor is delivered to and through the skin with minimal systemic absorption. In a still yet another aspect, the selective COX-2 inhibitor is delivered to the tissue surrounding or under the area of skin application with minimal systemic absorption.

[0109] In other aspects, the subject is a human. Alternatively, the subject is a non-human mammal.

[0110] In still other aspects, the treatment is continued for at least 12 weeks. More preferably, the treatment is continued for at least six months.

[0111] 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.

[0112] Due to the properties of higher flux and greater *in vivo* absorption, it is believed that the compositions of the present invention can be administered at lower dosing than previously described etoricoxib compositions. In particular, it is expected that the compositions of the invention can be used at twice-a-day dosing 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.

[0113] Compositions of the present invention may, if desired, be presented in a bottle, jar, or other container-closure system approved by the FDA or other regulatory authority, which may provide one or more unit 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.

X. Examples

[0114] Below, the present invention will be described by way of examples, which are provided for illustrative purposes only. Accordingly, they are not to be construed as limiting the scope of the present invention as defined by the appended claims.

[0115] **Example 1: General Preparative Procedure for Compositions**

[0116] For small-scale preparation of a typical AMP/HPC/urea composition, etoricoxib and urea, were combined. The mixture was dissolved in a portion of the ethanol and water components.

[0117] After the components were dissolved, the remaining ingredients except for the cellulosic thickening agent were added, the AMP being added last. If the components precipitated or failed to dissolve completely, more of the ethanol and water components were added.

[0118] The cellulosic thickening agent was then added with the remainder, if any, of the ethanol and water components. The composition was thoroughly mixed by vortexing for about 30 min or until a clear and homogenous system formed.

[0119] **Example 2: General Procedure for Skin Permeation Measurement**

[0120] The permeation of etoricoxib through porcine skin from each of the present compositions was measured using Franz diffusion cells ("FDC"s). Porcine skin pieces were obtained from Lampire Biological Laboratories, Inc., Pipersville, PA. At Lampire, porcine skins were collected immediately following animal sacrifice, and the hairs were trimmed with clippers. Larger pieces of excess fat were removed with a filet knife. The skin was then trimmed to a set thickness of some 2 mm, cut into individual pieces, wrapped in aluminum foil, frozen, shipped, and stored at -78 °C.

[0121] Prior to use, the skin pieces were dermatoned to a thickness of 0.5 to 1 mm and were allowed to thaw, in air, to room temperature. The FDCs had a 3 ml receptor well volume that was filled with isotonic phosphate buffered saline solution ("PBS") doped with 0.01% sodium azide. The flanges of the FDCs 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 from VWR Scientific, West Chester, PA). After the FDCs were assembled, the porcine skin was allowed to pre-hydrate for 45 min with isotonic PBS. Isotonic PBS was then removed, and the composition was applied to the donor well or directly to the skin

surface, depending on the amount of the composition applied. The receptor wells were maintained at 37°C (the temperature on the surface of the skin is about 30 °C) in a stirring block with continual agitation via a stir bar.

[0122] The flux rates were calculated by assuming a radius of 0.42 cm in the donor well (i.e., an area of 0.55 cm^2). Samples were drawn from the receptor wells at various times, as provided in the examples that follow. Franz diffusion cell measurements were typically made in 6-fold replicates for each composition. The concentration of etoricoxib in the samples was measured using HPLC analysis using a C18 column and acetonitrile and water as the mobile phase. Flux rates, F, were calculated based on the total transference of etoricoxib across the skin after time, t, according to

$$F = \frac{D * V}{t * A},$$

where D is the concentration of the drug in the receptor well after incubation time t, V is the volume of the receptor well, and A is the surface area of skin.

[0123] Example 3: Etoricoxib Composition Investigation I

[0124] Table 1: Etoricoxib Composition Investigation I

Ingredients	Formulations		
	F2	F9	F10
Etoricoxib	2	2	2
Ethanol	52.5	52.5	63
Water	22.5	22.5	35
Urea	5	5	
DL-Limonene	3	3	
DL-Lactic acid	1		
Polysorbate 20	2	2	
2-(2-Ethoxy-ethoxy)ethanol	10	10	
HPC HY121	2	2	
2-Amino-2-methylpropanol		1	

[0125] The objective for the preparation of F9 was to evaluate whether the delivery of etoricoxib would be increased in the presence of AMP together with other ingredients as MPE™s. As shown in Figure 1, the formulation including AMP in combination with urea and HPC (F9) showed significantly enhanced delivery of etoricoxib relative to the control (F10).

[0126] Example 4: Etoricoxib Composition Investigation II

[0127] Table 2: Etoricoxib Composition Investigation II

Ingredients	Compositions									
	F21	F22	F23	F24	F25	F26	F27	F28	F29	Ctl
Etoricoxib	2	2	2	2	2	2	2	2	2	2
Ethanol	51.5	52	48	51.5	51.5	51.5	54.5	53	53.5	63
Water	22.5	24.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	35
Urea	5	2.5	2.5	5	5	5	2.5	2.5	5	
DL-Limonene	3	3	3	3	3	3	3	3	3	
Polysorbate 20	3	3	9	3	3	3	3	3	3	
Diisopropanol -amine				1						
Meglumine					1					
Sodium lauryl sulfate (SLS)							2			
Sodium docusate								2		
Transcutol®	10	10	10	10	10	10	10	10	10	
Trolamine						1				
HPC HY121	2	2	2	2	2	2	2	2		
2-Amino-2-methyl-propanol	1	1	1						1	

Ctl is a control

[0128] The results are shown in Fig. 2. Surprisingly, agents chemically similar to AMP do not increase the delivery of etoricoxib (F24 through F28). This suggests an advantage specific to topical formulations comprising AMP.

[0129] A reduction in the urea content diminishes the delivery (F21 vs. F22). Increasing the amount of polysorbate 20 does not significantly enhance etoricoxib delivery (F22 vs. F23).

[0130] Example 5: Etoricoxib Composition Investigation III

[0131] Table 3: Etoricoxib Composition Investigation III

Ingredients	Formulations		
	F33-a,b	F34-a,b	Ctl-a,b
Etoricoxib	2	2	2
Ethanol	51.5	51.5	63
Transcutol®	10	10	
Water	22.5	22.5	35
Urea	5	5	
DL-Limonene	3	3	
Polysorbate 20	3	3	

Ingredients	Formulations		
	F33-a,b	F34-a,b	Ctl-a,b
HPC HY121	2		
2-Amino-2-methylpropanol	1	1	
HPC HY117		2	

Ctl-a,b are controls

a= 50 µl
b= 25 µl

[0132] The results are shown in Fig. 3. The two types of hydroxypropyl cellulose in a chassis containing AMP afford similar etoricoxib delivery through porcine skin.

[0133] Example 6: Etoricoxib Composition Investigation IV

[0134] Table 4: Etoricoxib Composition Investigation IV

Ingredients	Formulations								
	F41	F42	F43	F44	F45	F46	F47	F48	Ctl
Etoricoxib	2	2	2	2	2	2	2	2	2
Ethanol	63	53.5	51	42	42	56	52	52.5	63
Water	35	20	22	20	15	21	22	23.5	35
Urea		5	2.5	5	5	5	2.5	2.5	
DL-Limonene		3	3	3	3	3	3	3	
Polysorbate 20		3	6	3	3	3	3	3	
Transcutol®		10	10	10	10	10	10	10	
Isopropanol				11.5	11.5				
Propylene glycol					5				
HPC HY117		2	2	2	2		2	2	
2-Amino-2-methyl-propanol		1.5	1.5	1.5	1.5				
Sodium isethionate							1.5	1.5	
DL-Lactic acid							2		

Ctl is a control

[0135] The results are shown in Fig. 4. The addition of other alcohol combinations reduces etoricoxib delivery (F44, F45 vs. F42). In particular, the formulations containing isopropanol evidenced reduced delivery. The use of higher amounts of alcohol or a higher amount of polysorbate 20 also reduced etoricoxib permeation.

[0136] Example 7: Etoricoxib Composition Investigation V

[0137] Table 5: Etoricoxib Composition Investigation V

Ingredients	Formulations						
	F51	F52	F53	F54	F55	F56	Ctl-2
Etoricoxib	2	2	2	2	2	2	2
Ethanol	44.5	46.5	46	48	44.5	44.5	48

Ingredients	Formulations						
	F51	F52	F53	F54	F55	F56	Ctl-2
Water	20	20	20	20	20	20	50
Urea	3	3	3	3	3	3	
DL-Limonene	3	3	3	3			
Propylene glycol	5	5	5	5	5		
2-Amino-2-methyl-propanol	1.5	1.5			1.5	1.5	
Polysorbate 20	9	9	9	9	9	9	
Transcutol®	10	10	10	10	10	10	
Geraniol					3		
Oleic acid						3	
HPC HY121	2		2		2	2	

Ctl is a control

[0138] The results are shown in Fig. 5. In contrast to polysorbate 20 alone, the terpene geraniol with 9% polysorbate 20 enhances the delivery of etoricoxib (F55 vs. F51).

[0139] Example 8: Etoricoxib Composition Investigation VI

[0140] Table 6: Etoricoxib Composition Investigation VI

Ingredients	Formulations									
	F61	F62	F63	F64	F65	F66	F67	F68	F69	Ctl-2
Etoricoxib	2	2	2	2	2	2	2	2	2	2
Ethanol	53.5	48.5	48.5	56.5	52.5	53.5	52	53.5	48.5	48
Water	20	25	25	20	22.5	22	25	20	20	50
Urea	5		5	5	5	5	5	5	5	
DL-Limonene	3	3		3	3	3	3		3	
Caffeine		5								
Transcutol®	10	10	10	10	10	10	10	10	10	
2-Amino-2-methylpropanol	1.5	1.5	1.5	1.5		1.5		1.5	1.5	
Polysorbate 20	3	3	3		3	3	3	3	3	
Geraniol								3		
Propylene glycol									5	
HPC HY121	2	2	2	2	2			2	2	

Ctl-2 is a control

[0141] The results are shown in Fig. 6. In contrast with certain previously mentioned formulations, incorporation of polysorbate 20 did not reduce etoricoxib permeation.

[0142] It also generally appears that a combination of AMP with HPC exhibits an additional increase in etoricoxib permeation (F61, F64, F66, and F69).

[0143] Example 9: Etoricoxib Composition Investigation VII

[0144] Table 7: Etoricoxib Composition Investigation VII

Ingredients	Formulations					
	III (F69)	IIIA (F9)	IIIB (F22)	IIIC (F34)	IIID (F55)	IIIE (F61)
Etoricoxib	2	2	2	2	2	2
Ethanol	48.5	52.5	52	51.5	44.5	53.5
Urea	5	5	2.5	5	3	5
Transcutol®	10	10	10	10	10	10
DL-Limonene	3	3	3	3		3
Polysorbate 20	3	2	3	3	9	3
2-Amino-2-methylpropanol	1.5	1	1	1	1.5	1.5
HPC HY121	2	2	2		2	2
Water	20	22.5	24.5	22.5	20	20
Propylene glycol	5				5	
HPC HY117				2		
Geraniol					3	

[0145] In this example, the compositions contain AMP, cellulosic thickener, urea, and a terpene (*i.e.*, limonene, geraniol) at different levels. The amount of formulation applied to each donor cell was 25 µl, except for IIIA and IIIB (50 µl). Various alcohol mixtures were used as solvents. Polysorbitans (especially polysorbate 20) were added at different levels as non-ionic surfactants.

[0146] Example 10: Etoricoxib Composition Investigation VIII

[0147] The purpose of this experiment was to identify optimal excipients, compositions and concentrations based on Formulation IIIA (F9) of Table 7. The impact of varying the concentrations of various excipients on etoricoxib delivery across intact pig skin *in vitro* were evaluated and used to identify the optimal concentration and combination of selected excipients. In addition, the physical stability and esthetic characteristics of each of the formulations were also analyzed.

[0148] **Experimental Design**

[0149] All *in vitro* permeation studies in this example were carried out using Franz diffusion cells and excised pig skin at 32°C. Only formulations that were physically stable based on visual inspection immediately prior to the permeability experiments were tested for their respective abilities to delivery etoricoxib across pig skin. Experiments were carried out in five- or six-fold replicates for each formulation using a once-daily, finite dosing regimen (5 µl/cell). Etoricoxib concentrations in the receiver fluid were periodically measured by

HPLC, and the amounts of etoricoxib that accumulated in the receptor phases over a 24-hour period were quantified.

[0150] In these *in vitro* delivery studies, the etoricoxib concentration was maintained at 2% for all formulations; a formulation containing 2% etoricoxib, 48% ethanol and 50% water was included as a control. The etoricoxib-delivery enhancement ratios were calculated as the ratios of etoricoxib delivery from test formulations to those from the control formulation.

[0151] Results

A. Formulation Optimization

[0152] Three sets of permeability studies were conducted to identify the optimal composition of Formulation IIIA (F9) of Table 7 based, for each respective formulation, on measurements of both formulation physical stability and the etoricoxib flux across intact pig skin.

(I) At Constant Ethanol and Polysorbate 20 Concentrations

[0153] In the first set of formulation optimization studies, ethanol and polysorbate 20 concentrations were maintained at constant concentrations while varying the concentrations of other formulation excipients (Table 8).

[0154] Table 8A: Formulation Optimization Study (Constant Ethanol and Polysorbate 20 Concentrations)

Ingredient/Lot #	Formulations / Concentration (%, w/w)							
	1	2	3	4	5	6	7	8
	F71	F72	F73	F74	F75	F76	F77	E091027-08
Etoricoxib	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
EtOH	50	50	50	50	50	50	50	50
Urea	5.0	0.0	2.5	10	5.0	5.0	5.0	5.0
Transcutol®	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
DL-Limonene	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Polysorbate 20	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
AMP	1.5	1.5	1.5	1.5	1.0	2.0	3.0	0
HPC, HY121	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Water	24.5	29.5	27.0	19.5	25.0	24	23.0	26.0
24 hr Cumulative ($\mu g/cm^2$)[a]	**36.3**	**29.4**	**29.0**	**18.8**	**23.4**	**32.9**	**47.7**	**n/a**
SEM[b]	**2.9**	**1.5**	**3.4**	**4.7**	**3.6**	**6.6**	**3. 5**	**n/a**
ER[c] over Control	**8.9**	**7.2**	**7.1**	**4.6**	**5.7**	**8.1**	**11.7**	**n/a**
Physical Stability*	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**

[0155] Table 8B: Formulation Optimization Study (Constant Ethanol and Polysorbate 20 Concentrations)

Ingredient/Lot #	Formulations / Concentration (%, w/w)					
	9	10	11	12	13	Ctrl
	F78	F79	E091027-11	E091027-12	E091027-13	
Etoricoxib	2.0	2.0	2.0	2.0	2.0	2.0
EtOH	50	50	50	50	50	48.0
Urea	5.0	5.0	5.0	5.0	5.0	
Transcutol®	10.0	10.0	10.0	5.0	0	
DL-Limonene	0	1.5	6.0	3.0	3.0	
Polysorbate 20	2.0	2.0	2.0	2.0	2.0	
AMP	1.5	1.5	1.5	1.5	1.5	
HPC, HY121	2.0	2.0	2.0	2.0	2.0	
Water	27.5	26.0	21.5	29.5	34.5	50.0
24 hr Cumulative ($\mu g/cm^2$) [a]	**20.5**	**25.7**	**n/a**	**n/a**	**n/a**	**4.1**
SEM[b]	**3.6**	**5.0**	**n/a**	**n/a**	**n/a**	**0.9**
ER[c] over Control	**5.04**	**6.3**	**n/a**	**n/a**	**n/a**	**1**
Physical Stability*	**Y**	**Y**	**N**	**N**	**N**	**Y**

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

[0156] The results are shown in Figure 7. Based on the etoricoxib accumulated in the receiver phase at the end of the 24-hour study and the physical stability of the formulation, the following conclusions may be made:

i) **Urea:** The optimal concentration of urea appears to be at 5%; changing the urea concentrations outside of 5% led to the reduction of etoricoxib delivery across pig skin (F71 vs. F72, F73, and F74).
ii) **AMP:** The optimal concentration of AMP appears to be at 3.0% (F75, F76, and F77); excluding AMP from the formulation led to unstable formulation (E091027-08).
iii) **DL-Limonene**: The optimal concentration of DL-limonene appears to be at 3% since the reduction of limonene levels to 0 and 1.5 % led to diminished etoricoxib delivery (F71 vs. F78, and F79).
iv) **Transcutol®:** The absence of Transcutol® or at a lower (5%) level impacted negatively on the physical stability of the formulation (E091027-12 and E091027-13). This result suggests that Transcutol® may be important for stability.

(II) At Constant Water and Gelling Agents (Hydroxypropyl Cellulose, HPC; HY117 and HY121, Respectively) Concentrations

[0157] In the second and third sets of optimization studies, the concentrations of water and the gelling agents (HY117 or HY121) were maintained as constants while the concentrations of other excipients were varied. Two separate studies were conducted to evaluate the

etoricoxib delivery across pig skin from formulations containing two different cellulosic gelling agents, *i.e.*, HY117 and HY121. In the second study, both water and HY117 concentrations were maintained as constants while varying the concentrations of other excipients.

[0158] Table 9: Formulation Optimization Study (Constant Water and the Gelling Agent HPC HY117 Concentrations)

Ingredient /Lot #	Formulations / Concentration (% w/w)													
	1	2	3	4	5	6**	7**	8	9	10	11	12	13	Ctrl
	F80	F81	F82	E091 027-30	F83	F84	F85	F86	F87	F88	E091 027-37	F89	F90	
Etoricoxib	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Ethanol	50	55	52.5	45	50.5	49.5	48.5	51.5	53	51.5	47	55	60	48.0
Urea	5.0	0.0	2.5	10	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	
Transcutol®	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	5.0	0	
DL-Limonene	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	0	1.5	6.0	3.0	3.0	
Polysorbate 20	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	
AMP	1.5	1.5	1.5	1.5	1.0	2.0	3.0	0	1.5	1.5	1.5	1.5	1.5	
HPC, HY117	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	
Water	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	50.0
24-hr Cumulative ($\mu g/cm^2$) [a]	**51.9**	**28.2**	**34.7**	**n/a**	**28.2**	**45.0**	**41.9**	**33.0**	**29.2**	**42.1**	**n/a**	**29.1**	**29.6**	**2.7**
SEM[b]	**5.8**	**5.0**	**8.9**	**n/a**	**8.1**	**7.0**	**7.3**	**7.1**	**1.9**	**4.7**	**n/a**	**3.8**	**2.5**	**0.8**
ER[c] over Control	**19.5**	**10.6**	**13.0**	**n/a**	**10.6**	**16.9**	**15.8**	**12.4**	**11.0**	**15.8**	**n/a**	**11.0**	**10.0**	**1**
Physical Stability*	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**

[a]24-hour accumulated amount of etoricoxib
[b]standard error of the mean
[c]enhancement ratio over control
*Y=physically stable formulation based on visual inspection; N= physically unstable formulation based on visual inspection
**Precipitation was observed after the completion of the permeability study
Ctrl=control

[0159] The results are shown in Figure 8. Based on the amount of etoricoxib accumulated in the receiver phase at the end of the 24-hour study and the physical stability of the formulation, the following conclusions may be made:

i) **Urea:** The optimal level of urea appears to be at 5% (F80 vs. F81 and F82), consistent with the conclusion from the previous study.
ii) **AMP:** The incorporation of AMP enhanced the etoricoxib delivery (F80 vs. F86). Increasing the AMP amount from 1% to 1.5% further enhanced the permeation (F80 and F83), but beyond the 1.5% AMP concentrations, the formulations were no longer physically stable (F84 and F85).
iii) **DL-Limonene:** The optimal DL-limonene concentration in enhancing etoricoxib delivery across intact pig skin appears to be 3%. Reducing the DL-limonene levels to 0 or 1.5% led to reduced etoricoxib delivery (F80 vs. F87 and F88).

iv) **Transcutol®:** Transcutol® at 10% concentration is optimal. Removing Transcutol® from the formulation or reducing the Transcutol® concentration to a lower level (*i.e.*, 5%) led to reduction of the etoricoxib delivery (F80 vs. F90 and F89).

[0160] In addition to evaluating HY117 as a gelling agent in this particular formulation, a second HPC gelling agent (*i.e.*, HY121) was also considered. In the third study, both water and HY121 concentrations were maintained as constants while varying the concentrations of other excipients. Visual inspection of formulations incorporating either HY117 or HY121 as the gelling agent indicated that HY121 is a more effective gelling agent for this particular formulation and produces the desired formulation viscosity of the final formulation.

[0161] Table 10: Formulation Optimization Study (Constant Water and the Gelling Agent HPC HY121 Concentrations)

Ingredient/ Lot #	Formulations / Concentration (% w/w)													
	1	**2**	**3**	**4**	**5**	**6****	**7****	**8**	**9**	**10**	**11**	**12**	**13**	**Ctrl**
	F91	F92	F93	E0910 27-17	F94	F95	F96	F97	F98	F99	E091 027-24	F100	F101	
Etoricoxib	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Ethanol	50	55	52.5	45	50.5	49.5	48.5	51.5	53	51.5	47	55	60	48.0
Urea	5.0	0.0	2.5	10	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	
Transcutol®	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	5.0	0	
DL-Limonene	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	0	1.5	6.0	3.0	3.0	
Polysorbate 20	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	
AMP	1.5	1.5	1.5	1.5	1.0	2.0	3.0	0	1.5	1.5	1.5	1.5	1.5	
HPC, HY121	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	
Water	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	50.0
24 hr Cumulative (μug/cm^2) [a]	**46.4**	**45.2**	**47.0**	**n/a**	**39.0**	**40.6**	**48.3**	**33.5**	**47.8**	**52.6**	**n/a**	**34.4**	**39.1**	**6.9**
SEM[b]	**8.2**	**9.1**	**12.5**	**n/a**	**4.9**	**12.9**	**16.1**	**7.1**	**10.9**	**6.2**	**n/a**	**6.6**	**15.8**	**1.5**
ER[c] over Control	**6.7**	**6.5**	**6.8**	**n/a**	**5.6**	**5.9**	**7.0**	**4.8**	**6.9**	**7.6**	**n/a**	**5.0**	**5.6**	**1**
Physical Stability*	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**	**Y**

[a]24-hour accumulated amount of etoricoxib
[b]standard error of the mean
[c]enhancement ratio over control
*Y=physically stable formulation based on visual inspection; N= physically unstable formulation based on visual inspection
**Precipitation was observed after the completion of the permeability study
Ctrl=control

[0162] The results are shown in Figure 9. Based on the visual inspection, the physical stability of the formulations, and etoricoxib delivery, the following conclusions may be made:

i) **Urea:** It appears that at constant water concentration and using HPC HY121 as the gelling agent, the incorporation of urea at 2.5% and 5% concentrations

has minimal impact on etoricoxib delivery (F91 vs. F92 and F93). However, the incorporation of urea increases etoricoxib delivery in studies where the ethanol concentrations were maintained constant (see above). Based on this result, urea at a 5% concentration appears optimal.

ii) **AMP:** Increasing the AMP concentration beyond the 1.5% level led to formulation instability (F95 and F96) in this study.

iii) **DL-Limonene:** The reduction of limonene to 0 and 1.5% levels had minimal influence on etoricoxib delivery in this study (F91 vs. F98 and F99);

iv) **Transcutol®:** Removing Transcutol® from the formulation or reducing to a 5% level led to reduction of the etoricoxib permeation (F100 and F101).

(III) Etoricoxib Formulation Based on Optimization Studies

[0163] The formulation provided in Table 11 is based on the collective results from the three studies discussed above.

Table 11: Etoricoxib Formulation Based on Optimization Studies

Ingredient	Concentration (%)
Etoricoxib	2.0
Ethanol	50.0
Urea	7.5
Transcutol®	10.0
DL-Limonene	3.0
Polysorbate 20; Tween 20	2.0
AMP	1.5
HPC; HY121	2.0
Water	22.0

[0164] It is understood that the examples and embodiments described herein are for illustrative purposes only and that 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 pharmaceutical composition for topical administration, said composition comprising:

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

0.5% to 5% of a lower amino alcohol;

0.5% to 5% of a cellulosic thickening agent;

0.5% to 10% urea;

at least one lower alcohol; and

water.

2. The pharmaceutical composition of claim **1**, wherein said composition comprises 1% to 3% (w/w) etoricoxib.

3. The pharmaceutical composition of claim **2**, wherein said composition comprises 2% (w/w) etoricoxib.

4. The pharmaceutical composition of any one of claims **1**, **2**, or **3**, wherein said lower amino alcohol is 2-amino-2-methylpropanol.

5. The pharmaceutical composition of any one of claims **1**, **2**, or **3**, wherein at least one said lower alcohol is a lower monohydric alcohol.

6. The pharmaceutical composition of claim **1**, wherein said composition further comprises an additional molecular penetration enhancer.

7. The pharmaceutical composition of claim **6**, wherein said additional molecular penetration enhancer is 2-(2-ethoxyethoxy)ethanol.

8. The pharmaceutical composition of claim **6**, wherein said additional molecular penetration enhancer is a terpene.

9. The pharmaceutical composition of claim **8**, wherein said terpene is selected from the group consisting of limonene, geraniol, and mixtures thereof.

10. The pharmaceutical composition of claim **7**, wherein said composition comprises 10% (w/w) 2-(2-ethoxyethoxy)ethanol.

11. The pharmaceutical composition of claim **8** or **9**, wherein said composition comprises 3% (w/w) terpene.

12. The pharmaceutical composition of claim **1**, wherein said composition further comprises a nonionic surfactant.

13. The pharmaceutical composition of claim **12**, wherein said nonionic surfactant is a polysorbitan ester.

14. The pharmaceutical composition of claim **12** or **13**, wherein said composition comprises from 2% to 10% (w/w) nonionic surfactant.

15. The pharmaceutical composition of any one of claims **1**, **2**, **3**, **6**, **7**, **8**, **9**, **10**, **12**, or **13**, wherein said composition is a gel.

16. A pharmaceutical composition for topical administration, said composition comprising:

2% (w/w) etoricoxib;

0.5% to 3% 2-amino-2-methylpropanol;

1% to 3% of hydroxypropyl cellulose;

2% to 10% urea;

10% 2-(2-ethoxyethoxy)ethanol;

a lower monohydric alcohol; and

water.

17. The pharmaceutical composition of claim **16**, wherein said composition comprises 2% to 5% urea.

18. The pharmaceutical composition of claim **16**, wherein said composition comprises about 7.5% urea.

19. The pharmaceutical composition of claim **16**, wherein said composition comprises 35% to 65% of the lower monohydric alcohol and 15% to 30% water.

20. The pharmaceutical composition of claim **16**, wherein said composition is a gel.

21. A method for topically treating pain in a subject, said method comprising:

topically applying a physiologically acceptable pharmaceutical composition to treat pain in said subject, said composition comprising:

0.1% to 5% (w/w) of a selective COX-2 inhibitor;

0.5% to 5% 2-amino-2-methylpropanol;

0.5% to 5% of a cellulosic thickening agent;

0.5% to 10% urea;

a lower monohydric alcohol; and

water.

22. The method of claim **21**, wherein said composition comprises 35% to 65% of the lower monohydric alcohol and 15% to 30% water.

23. The method of claim **21** or **22**, wherein said selective COX-2 inhibitor is etoricoxib.

24. The method of any one of claims **21**, **22**, or **23**, wherein said pain is associated with osteoarthritis.

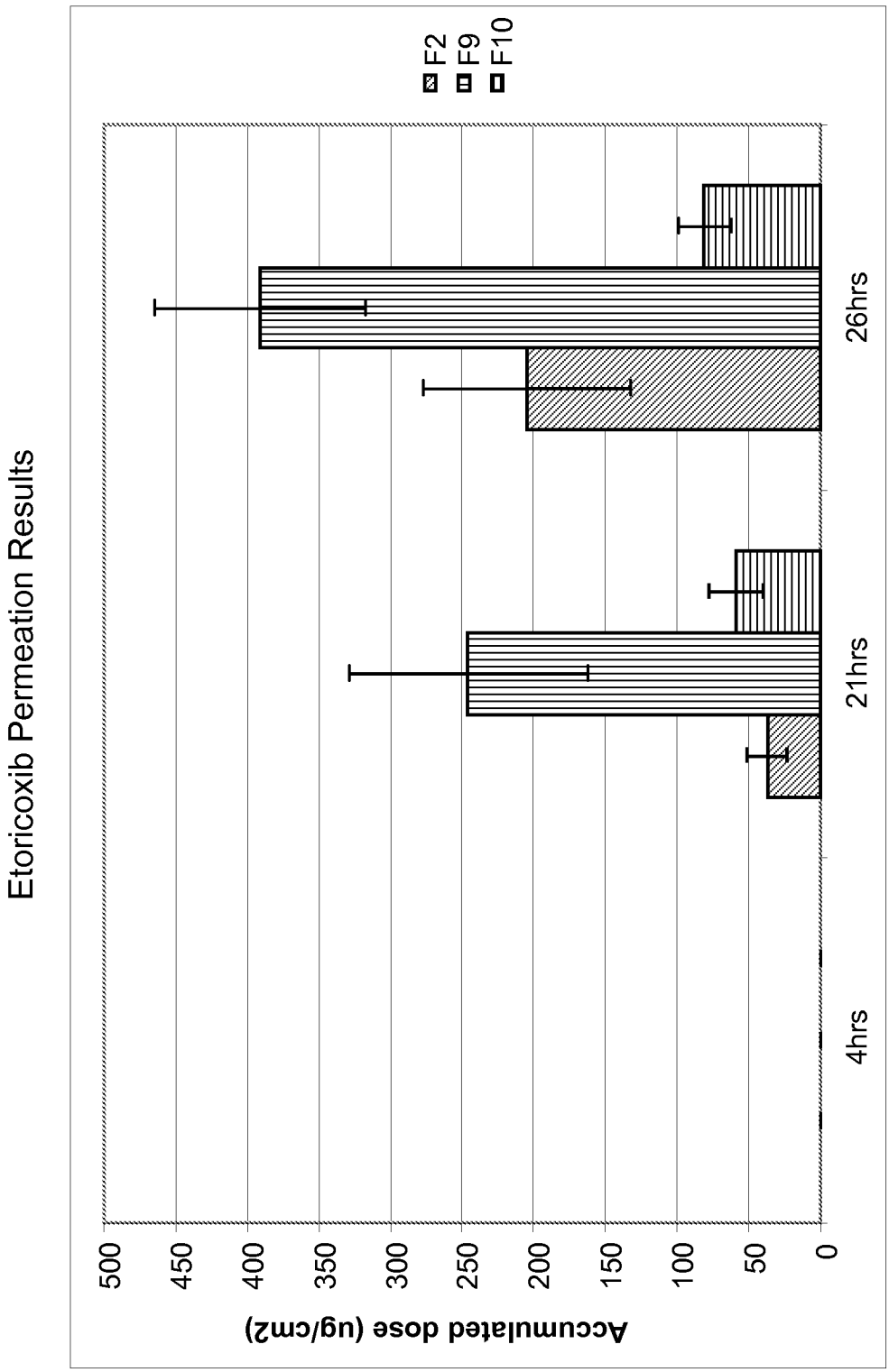
Etoricoxib Permeation Results
Accumulated dose (ug/cm2)
500
450
400
350
300
250
200
150
100
50
0
4hrs
21hrs
26hrs
F2
F9
F10

FIG. 1

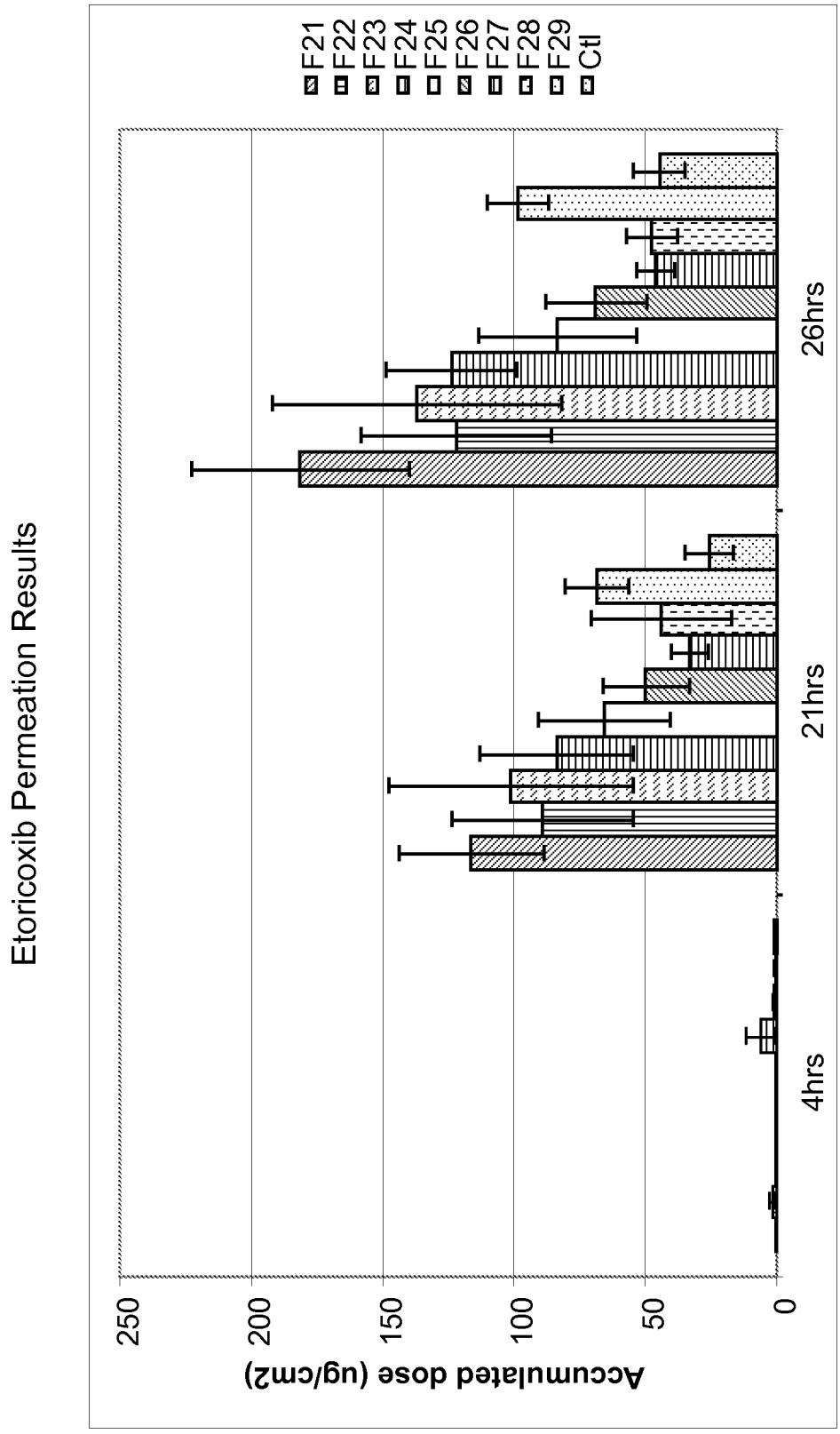
Etoricoxib Permeation Results
F21
F22
F23
F24
F25
F26
F27
F28
F29
Ctl
Accumulated dose (ug/cm2)
250
200
150
100
50
0
4hrs
21hrs
26hrs

FIG. 2

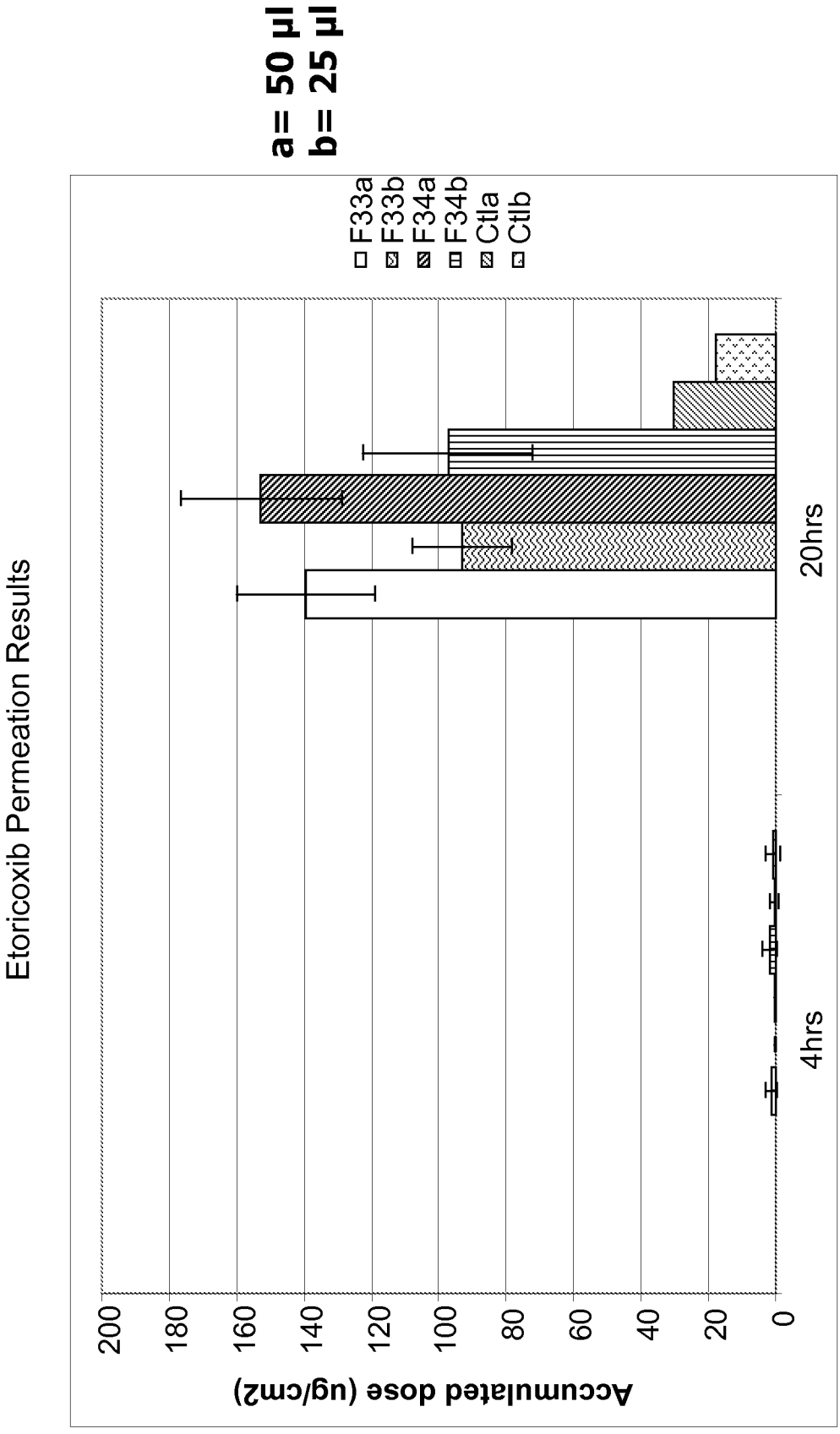
a= 50 µl
b= 25 µl
Etoricoxib Permeation Results
F33a
F33b
F34a
F34b
Ctla
Ctlb
Accumulated dose (ug/cm2)
0
20
40
60
80
100
120
140
160
180
200
4hrs
20hrs

FIG. 3

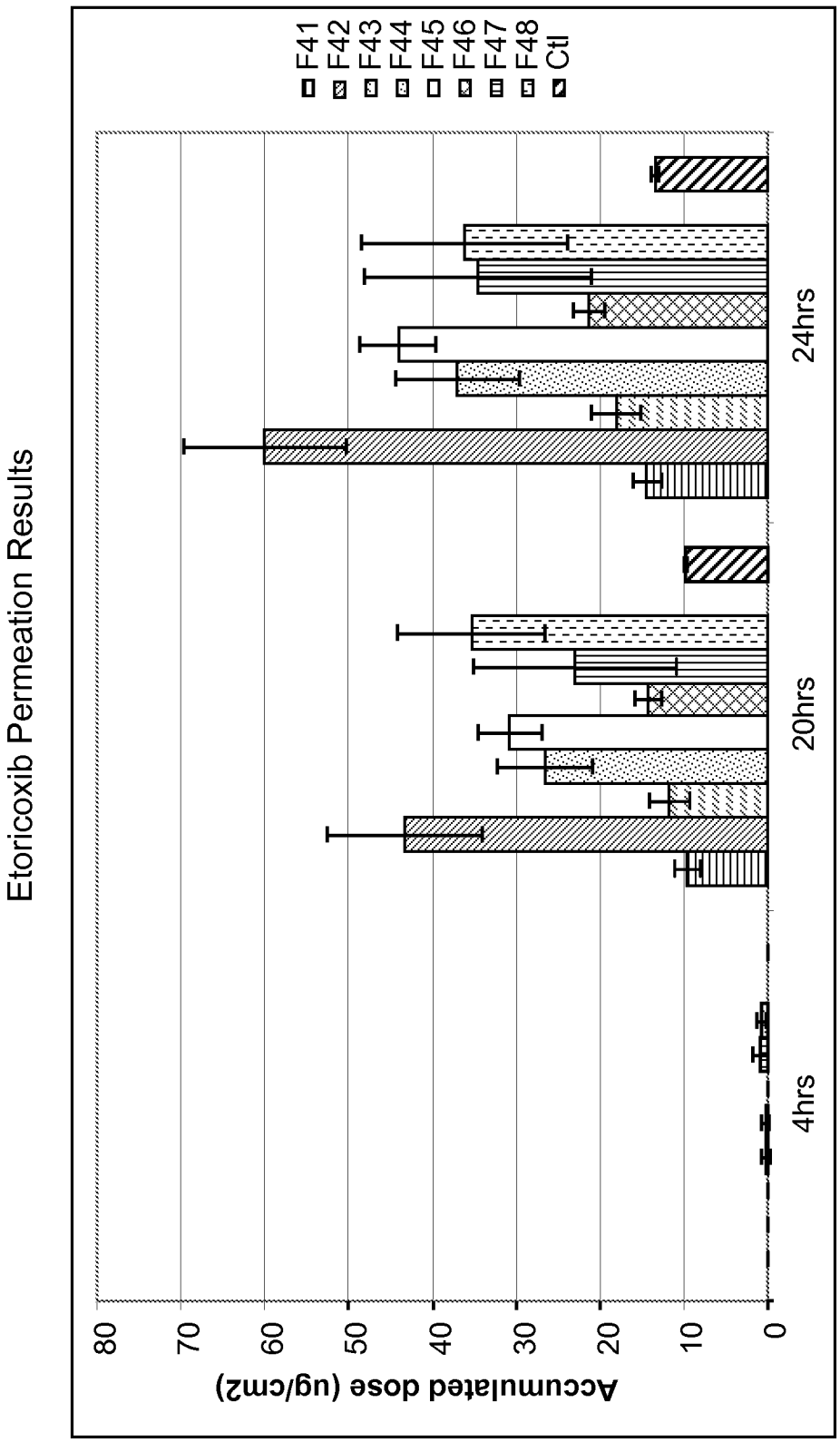
Etoricoxib Permeation Results
F41
F42
F43
F44
F45
F46
F47
F48
Ctl
Accumulated dose (ug/cm2)
0
10
20
30
40
50
60
70
80
4hrs
20hrs
24hrs

FIG. 4

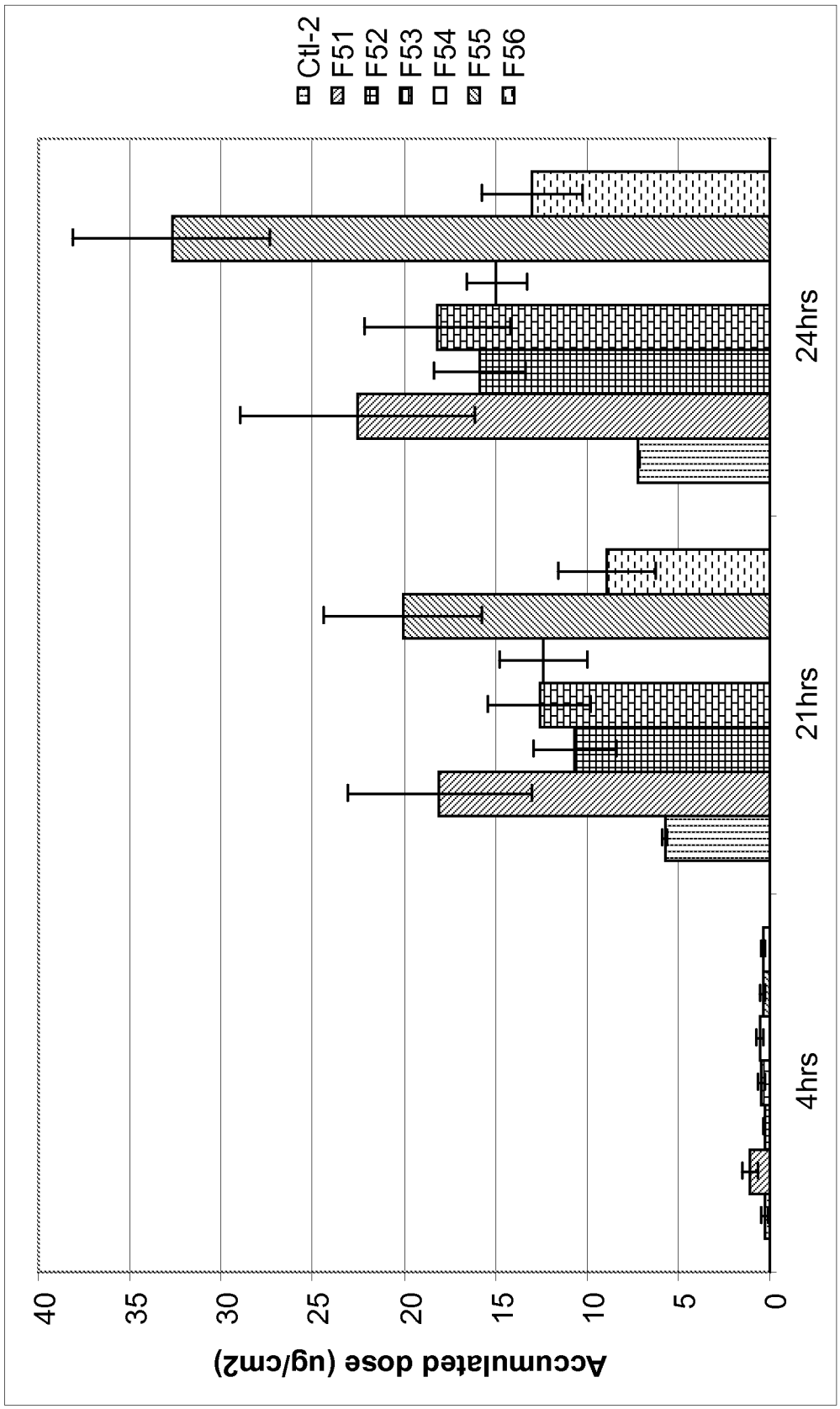
Etoricoxib Permeation Results
Ctl-2
F51
F52
F53
F54
F55
F56
Accumulated dose (ug/cm2)
0
5
10
15
20
25
30
35
40
4hrs
21hrs
24hrs

FIG. 5

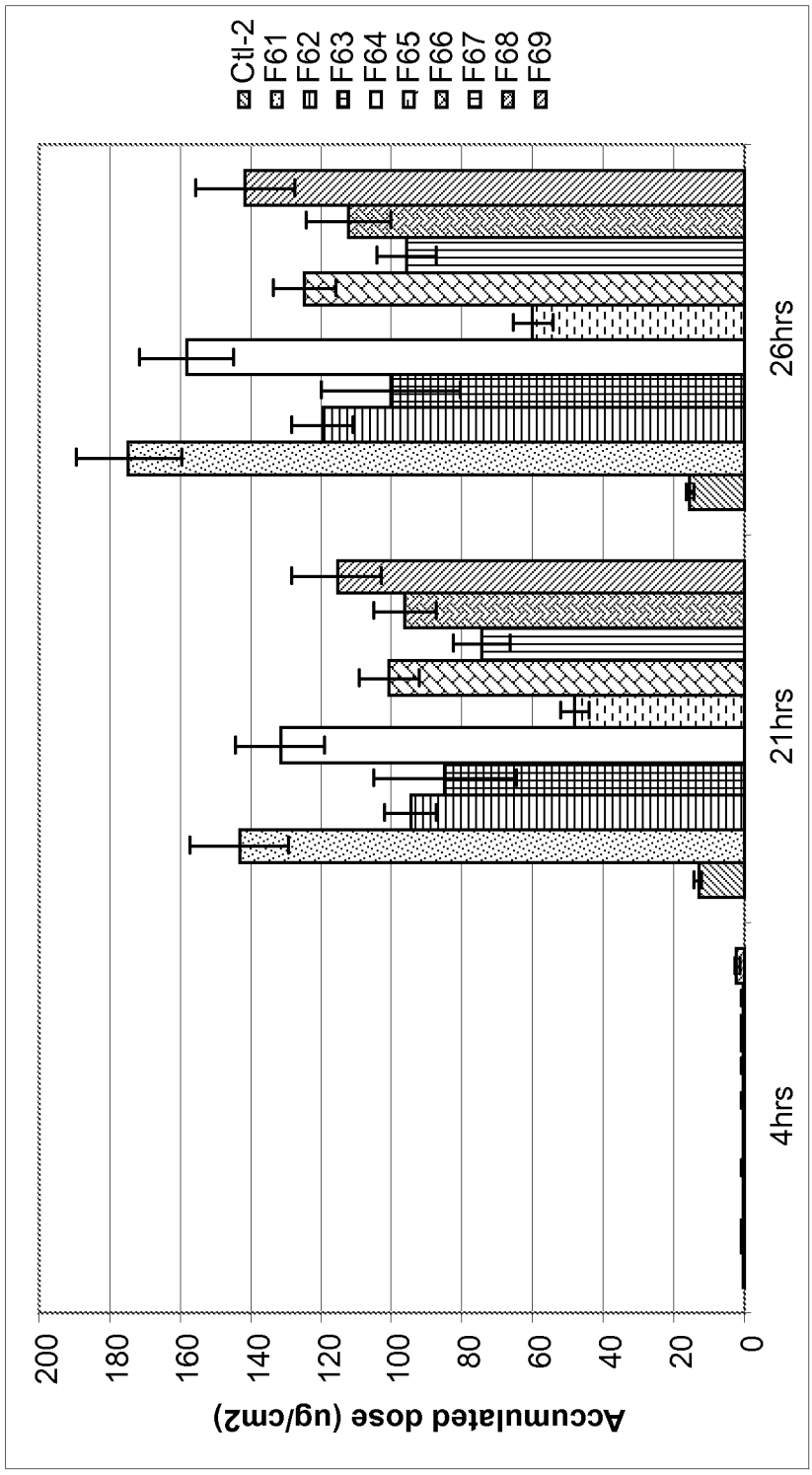
Etoricoxib Permeation Results
Ctl-2
F61
F62
F63
F64
F65
F66
F67
F68
F69
Accumulated dose (ug/cm2)
0
20
40
60
80
100
120
140
160
180
200
4hrs
21hrs
26hrs

FIG. 6

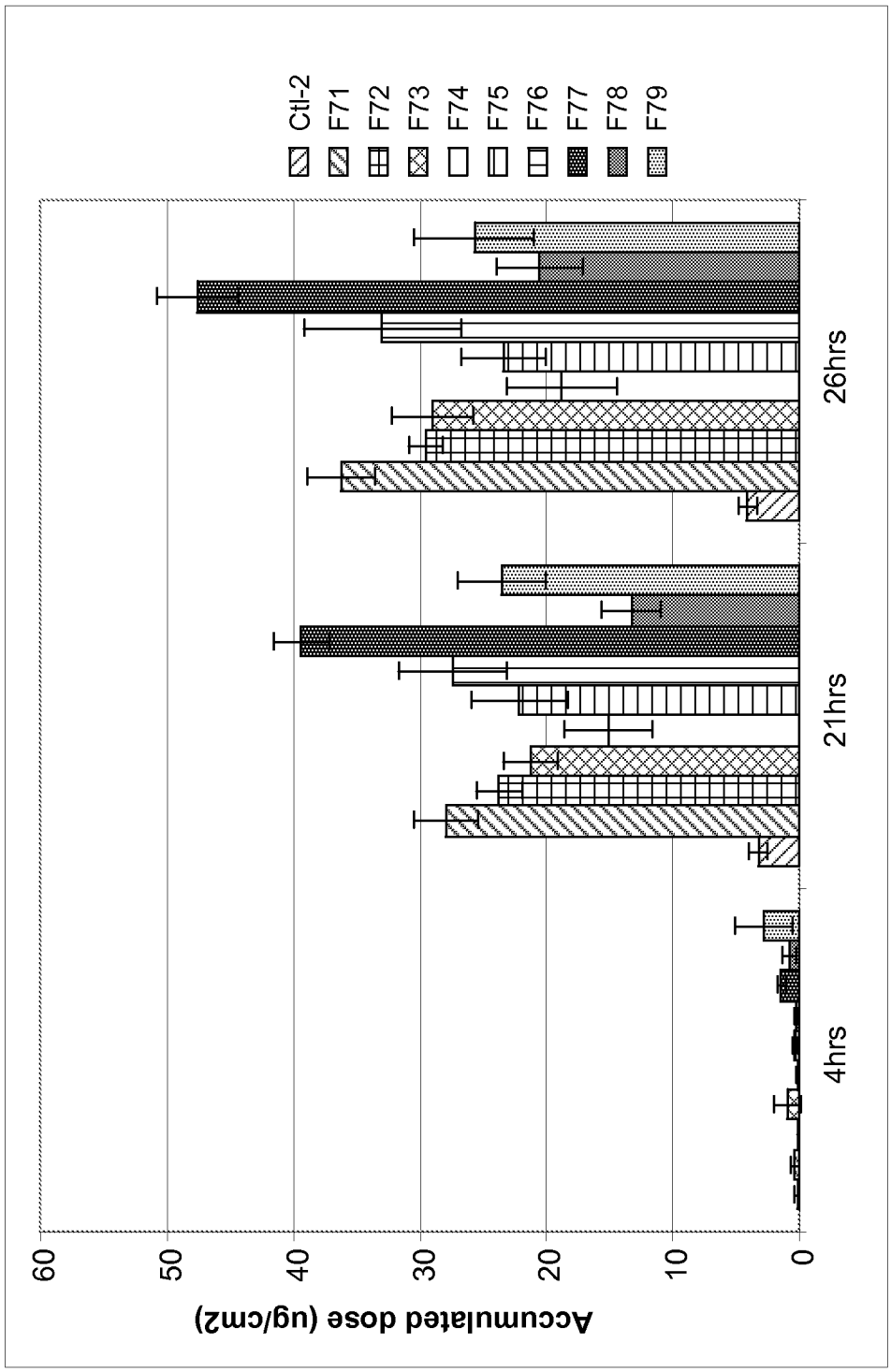
Etoricoxib Permeation Results
Ctl-2
F71
F72
F73
F74
F75
F76
F77
F78
F79
Accumulated dose (ug/cm2)
0
10
20
30
40
50
60
4hrs
21hrs
26hrs

FIG. 7

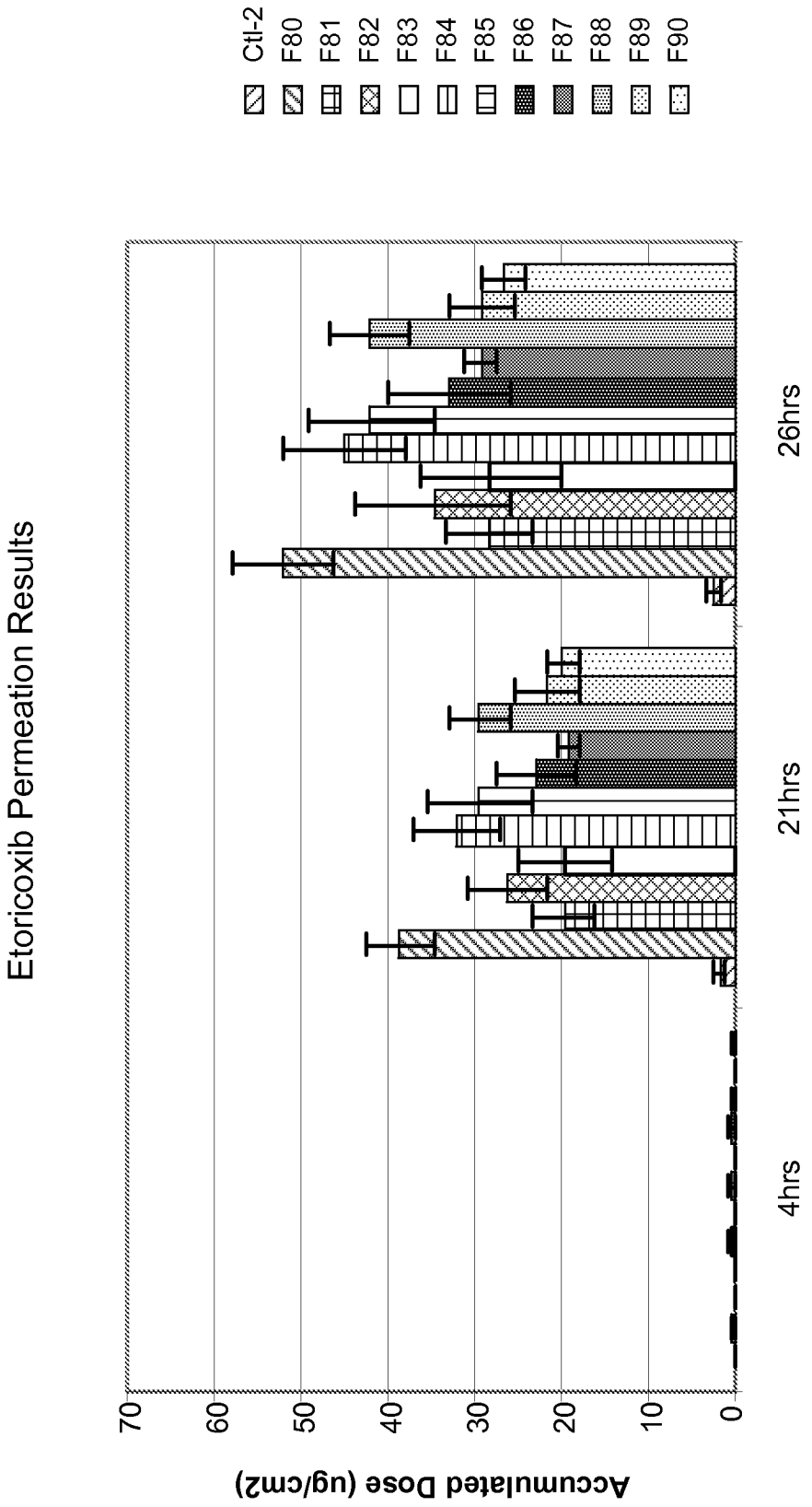
Etoricoxib Permeation Results
Ctl-2
F80
F81
F82
F83
F84
F85
F86
F87
F88
F89
F90
Accumulated Dose (ug/cm2)
0
10
20
30
40
50
60
70
4hrs
21hrs
26hrs
Time Elapsed

FIG. 8

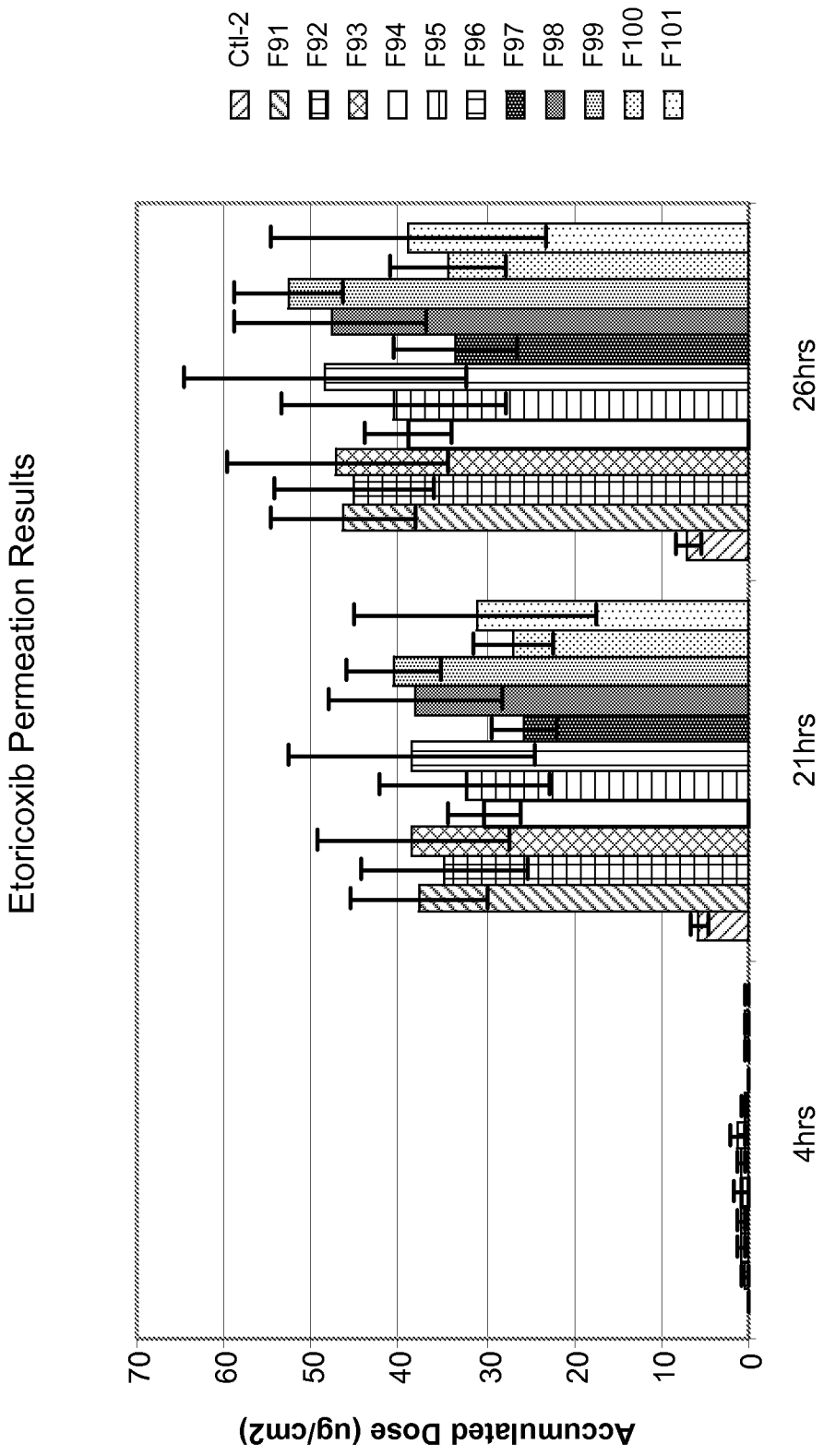
Etoricoxib Permeation Results
Ctl-2
F91
F92
F93
F94
F95
F96
F97
F98
F99
F100
F101
Accumulated Dose (ug/cm2)
0
10
20
30
40
50
60
70
4hrs
21hrs
26hrs
Time Elapsed

FIG. 9