TRANSDERMAL FORMULATION CONTAINING COX INHIBITORS

Technical field

The present invention is related to transdermal formulations containing COX-inhibitors. Transdermal formulations, e.g., gels, are important and useful for delivering pharmaceutically active compounds. Such formulations offer a possibility for administering medicines to patients who have difficulty in swallowing oral formulations or in cases when prolonged parenteral medication should be replaced. Such formulations furthermore offer the possibility of localized administration of the medicament thus preventing side effects and are suitable for the administration of active ingredients which are metabolized rapidly and extensively subsequent to oral administration. Especially there is a need for transdermal gel formulations that deliver active compounds that are anti-inflammatory and/or pain relieving pharmaceutically active compounds, e.g., COX inhibitors, or selective COX inhibitors, e.g., COX-2 inhibitors, preferably, celecoxib, deracoxib, valdecoxib, rofecoxib, tilmacoxib, or other similar known compounds, especially celecoxib, including its various known crystalline forms and various salts thereof, e.g., crystalline forms I, II, III, IV and N.

Background of the invention

Transdermal pharmaceutical formulations are characterized in vitro by the measurement of the permeation of the active ingredient through natural or artificial membranes or in vivo by skin penetration studies. Such a measurement method and apparatus developed are disclosed in WO2010089619.

The delivery of COX-2 inhibitors, especially topically, has many challenges, as these compounds have a very low solubility, high melting point, and low penetration potential in known topical formulations that have acceptable organoleptic (sensory) characteristics.

There is a need that the formulation exhibit suitable skin penetration to achieve the required therapeutical objective and advantageous organoleptic properties, such as suitable consistency without adherence (sticking) to the skin or clothing, appropriate viscosity, agreeable odour and good spreadability.

There is furthermore a need for the formulation to have good physical-chemical stability, especially in the cold, and microbiological stability. In case of low-solubility active ingredient, such as celecoxib, the formulation should also improve the solubility of the active ingredient. Moreover, said formulations should be easily manufacturable on an industrial scale.

For example, during the reproduction of the experiments of Soliman and co-workers (S.M.Soliman, N.S.Abdel-Malak, O.N.El-Gazayerly, A.A.Abdel-Rehim: Formulation of microemulsion gel systems for transdermal delivery of celecoxib: In vitro permeation, anti-inflammatory activity and skin irritation tests. [DrugDisc&Ther.2010; 4(6):459-471.], although technically a gel was obtained, the product was not suitable for product development due to thermal instability and unsatisfactory consistence due to high stickiness.

Summary of the invention

Applicants have found a solution to the above discussed challenges to the topical delivery of COX-2 inhibitors by the use of a formulation that has excellent organoleptic characteristics, while also providing for good skin penetration and suitable stability.

Accordingly, the transdermal formulation according to the present invention is a gel composition which comprises an active ingredient which is a COX inhibitor, preferably a selective COX-2 inhibitor, a solubilizer, a wetting agent, a gel forming agent, a volatile

siloxane agent and a solvent. Optionally, the formulation may also contain a permeation enhancing agent and a precipitating agent.

The drugs preferred in the formulations according to the present invention are selective COX-2 inhibitors, which are known to be useful for treating inflammation, colorectal polyps (because they have effects on abnormally dividing cells such as those of precancerous colorectal polyps), menstrual cramps, sports injuries, osteoarthritis, rheumatoid arthritis, and pain, e.g., acute pain, and for reducing the risk of peptic ulceration. The embodiments of the invention are suitable for use with crystalline or amorphous forms of active ingredients. The preferred drug of the formulations is Celecoxib, which is a selective COX-2 inhibitor having about 7.6-times higher affinity towards COX-2 than towards COX-1. Thus the antiinflammatory activity of celecoxib is only rarely accompanied with gastrointestinal side effects which are often experienced with non-selective non-steroidal antiinflammatory active ingredients.

The invention also includes the use of the formulations for the indications known for the active ingredient. For example, a method of treating inflammation, colorectal polyps, menstrual cramps, sports injuries, osteoarthritis, rheumatoid arthritis, and pain, e.g., acute pain, and of reducing the risk of peptic ulceration, by administering a composition disclosed herein topically is included in the invention.

The advantage of the formulation according to the present invention resides in that it provides a way for convenient local administration of a stabile COX-2 inhibitor medicament, for example, for relieving pain while preventing side effects which may occur subsequent to oral administration.

Description of the embodiments

The formulation according to the present invention contains the following ingredients in the following amounts (the amounts and percentages of amounts discussed in the present application are by weight, based on the composition as a whole unless indicated otherwise):

I) an active compound, e.g., a COX inhibitor, preferably a COX-2 inhibitor, e.g., celecoxib, deracoxib, valdecoxib, rofecoxib, and/or tilmacoxib, especially celecoxib, and particularly preferably a crystalline form thereof. The active ingredient is preferably in a particulate form. Although the active ingredient does not have to be micronized, but in preferred embodiments, micronized forms are advantageous to further enhance the solubility of the active ingredient. Nevertheless it is possible to produce delivery systems according to the present invention wherein the active ingredient is partly or fully dissolved.

The amount of active compound, e.g., of celecoxib, should be 0.5-10%, preferably 1-6%, more preferably 1.5-5%, and especially preferably about 2%.

II) a compound or a natural mixture capable of enhancing the penetration of the active ingredient, e.g. celecoxib may be present, including but not limited to menthol, thymol, essential oils such as lavender oil or kernel oils, such as almond oil and vegetable oils etc. The presence of a penetration enhancing agent is preferred.

Terpene compounds may also be useful as penetration enhancers, such as isoborneol, irone, ocimene, carveol, carvotanacetone, carvomenthone, carvone, carene, carone, camphene, camphor, geraniol, cymene, sabinene, safranal, cyclocitral, citral, citronellal, citronellic acid, citronellol, cineole, sylvestrene, thujyl alcohol, thujone, terpineol, terpinene, terpinolene, tricyclene, nerol, pinene, pinocampheol, pinol, piperitenone, phellandral, phellandrene, fenchene, fenchyl alcohol, perillyl alcohol, perillyl aldehyde, borneol, myrcene, menthol, menthone, ionol, ionone, linalool, or limonene. Essential oils containing such compounds can also be used.

Considerations in the selection of the compound, an essential oil or natural mixture should be concerns of allergies, aroma, e.g., bad smell versus pleasant smell, the potential of the compound to irritate the skin, potential in causing adverse effects etc. Preferred among the options is menthol and lavender oil, especially menthol.

The amount of the penetration enhancing compound e.g., of menthol or lavender oil, especially menthol, is 0.5-10%, preferably 0.7-5%, more preferably 1-2%, and especially preferably about 1%.

a solubilizer, or a solubilizer system having at least two solubilizer components. Solubilizers are well known in the state of the art. Applicants have found that in the formulation according to the present invention, the solubilizers can be preferably selected from polyethylene glycols, sorbitol esters with fatty acids, pegylated sorbitol esters with fatty acids (polysorbates), polyethylene glycol alkylethers, polyoxyethylene and polyoxypropylene block polymers and silicone alkyl glycols.

When a solubilizer system having at least two solubilizer components is used, the solubilizing ability of the system is generally significantly improved over the use of a single solubilizer. Solubilizers having large hydrophilic-lipophilic balance (HLB) values, i.e., above 10, preferably above 12, e.g., 13, and more preferably about 14-20, have been found to be particularly useful. As an example, the solubilizers Tween 60, Brij-58, Kolliphor P-407 can be used as a single solubilizer or as components of a solubilizer system in the formulation according to the present invention.

Applicants have found that a solubilizer known as Brij-58, also known as polyethylene glycol hexadecyl ether or polyoxyethylene (20) cetyl ether, is particularly suitable for the solubility enhancement of COX-2 inhibitor compounds, especially of celecoxib.

The amount of Brij-58 is in the range of 3-25%, preferably 4-15%, more preferably 5-10%, and especially preferably about 7%.

In one embodiment of the invention, the solubilizer used in the formulation is Brij-58.

It is particularly advantageous to use of the combination of Brij-58 with Kolliphor P407, which is also known as Poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol). Said combination results in enhanced solubilizing effect, especially in an increase in the physical stability of the formulation wherein the active ingredient is in the dissolved state, and is unexpectedly better for such formulations than other solubilizers alone or in combination, for example, the combination of Tween 60 and ethanol. Further advantageous combinations of solubilizers include but are not limited to the combination of polyethylene glycol 1000 (PEG 1000) and Brij-58 and PEG 1000, Brij-58 and Kolliphor P407.

Alternate combinations include Tween 60, which is also known as Polyoxyethylene (20) sorbitan monostearate, with either Brij-58 or Kolliphor P407, or other combinations

where both solubilizers have HLB values above 10, preferably above 12, e.g., 13, and more preferably about 14-20.

An additional advantage of Kolliphor P407 is its ability to act as a thickening agent and/or gel binder.

Solubilizers that may additionally be included in the solubilizer system are Span 60 and Emulsifier 10. Some of the solubilizers known from the prior art have been found inadequate alone in enhancing the solubility of the active compounds to the desired extent, but may provide some benefit when in combination with a solubilizer having a high HLB value.

When a combination of solubilizers or a solubilizer system is used, the amount of an individual component thereof can be approximately the same as when used alone. As such, the amount of Brij-58 in the solubilizer system is the same as when used alone.

The amount of each of the solubilizers in the system can be the same. For example, the amount of Kolliphor P407 in the combination or even when used alone is in the range of 3-25%, preferably 4-15%, more preferably 5-10%, and especially preferably about 7%.

The ratio by weight of the each solubilizer in a solubilizer system, for example, when two are present, can be from 1:10 to 10:1, preferably 1:5 to 5:1, more preferably 1:2 to 2:1, and especially preferably 1:1.

The combination of Kolliphor P407 and Brij-58, for example, in a 1:1 mixture results in increased physical stability of the formulation wherein the active ingredient is in dissolved form.

IV) a wetting agent or lubricant, e.g., Polyethylene glycol (PEG). Preferred among the PEGs is PEG 1000. However, any PEG 200 to PEG 20,000 may be used. Preferable polyethylene glycols are those having a molecular weight equal or less than 1000 and are liquids or of semisolid state.

PEG 1000 improves the handling properties of the ingredients of the formulation which can be dissolved in PEG 1000 even in cold temperatures. However, increasing the concentration of PEG 400 from, for example, 10% to 20% neither improves stability nor membrane permeation, and therefore PEG was believed to be not regardable as a solvent, e.g., true solubilizer, in the formulations of the invention. The unexpected increase in the solubilizing effect and membrane permeation is the likely the result of the addition of the

combination of Kolliphor P407 and Brij-58, which may be even further enhanced, e.g., by PEG or other solubilizers and/or wetting agents, and/or the permeation enhancing component, such as menthol.

PEG in addition to serving as a wetting agent, also appears to enhancing the solubility of the active ingredient, e.g., of celecoxib.

The amount of PEG, preferably of PEG 1000, is in the range of 2-25%, preferably 5-20%, more preferably 8-15%, and especially preferably about 10%.

Other wetting agents in addition or alternate to PEG may be used as long as they provide comparable results to PEG in the composition.

V) a gel forming or thickening agent, preferably Carbopol compounds, preferably Carbopol 980, also known as polymerized prop-2-enoic acid ester. Carbopol 980 is a polymer that is a highly efficient thickener and is ideal for formulating clear aqueous and hydro-alcoholic gels. Other gel forming agents known from the state of the art are possible in addition to or alternate to Carbopol 980.

The amount of gel forming agent can be low, as long as sufficient to provide for the formation of a gel. For example, for Carbopol 980, the amount is in the range of 0.1-2%, preferably 0.2-1.5%, more preferably 0.3-1%, and especially preferably about 0.5%.

VI) optionally a precipitation agent or pH adjuster, e.g., a sodium hydroxide aqueous solution, provided that such an agent is required for setting a suitable pH range or precipitation of the gel in conjunction with a specific gel forming agent. Additional or alternate precipitation agents may be useful in the formulations. For example, when a Carbopol gel forming agent is used, it is possible to use the precipitation agent sodium hydroxide (NaOH) solution in order to obtain a gel. In case of other gel forming agents, a different precipitating agent known from the state of the art may be necessary. In case of some gel systems, no precipitation agent is required.

The strength of the precipitation agent or pH adjuster solution can vary, but is preferably 10 m/v%.

The amount of precipitating agent should be sufficient to bring about a pH of 5.5-7.5 for the gel forming agent swollen in water, and is typically in the range of 0.5-2%, preferably 0.7-1.5%, more preferably 0.8-1.2%, and especially preferably about 1%.

VII) a volatile siloxane agent, preferably present as a coating on the surface of active ingredient particles or preferably a siloxane coating agent system having at least two volatile siloxane coating agent components, which are used to coat the active ingredient particles. The volatile siloxane coating agent should be highly volatile to be able to evaporate from the skin upon application.

WO2009007764 and WO2010089617 disclose transdermal gel formulations, which are dispersions of solid active ingredient particles coated with a highly volatile siloxane or with a mixture of such siloxanes in aqueous gels. The siloxanes as defined regarding their volatility and which are disclosed in these applications, i.e., hexamethyldisiloxane, octamethyltrisiloxane and decamethylcyclopentasiloxane, are useful in the present invention for the coating of active compound particles. Other compounds capable of coating a particulate ingredient and evaporating upon application to the skin are also useful instead of the above siloxane compounds. Particularly advantageous volatile siloxanes for coating the particles of the active ingredients are apolar, non-functionalized siloxanes, i.e. they do not contain any polar functional group.

Particularly preferred is a combination of hexamethyldisiloxane and decamethylcyclopentasiloxane. As such, in a preferred embodiment, the formulation contains Silicone Fluid 0.65 cSt (hexamethyldisiloxane) and StCyclomethicone 5-NF (decamethylcyclopentasiloxane).

Embodiments including St-Cyclomethicone 5-NF have improved organoleptic properties.

The amount of Silicone Fluid 0.65 cSt when used in the combination and even when used alone is in the range of 1-25%, preferably 5-20%, more preferably 8-15%, and especially preferably about 10%.

The amount of St-Cyclomethicone 5-NF when used in the combination and even when used alone is in the range of 1-25%, preferably 3-15%, more preferably 4-10%, and especially preferably about 5%.

When the active ingredient is in the form of a suspension, the amount of siloxane used should be sufficient to adequately coat the active ingredient particles to avoid their intermixing with the gel matrix containing solubilizers and penetration enhancing components before the

evaporation of the siloxane coating upon application to the skin. Too low an amount could lead to the partial dissolution of the active ingredient particles thus affecting skin penetration and stability.

The ratio by weight of the siloxane coating agents, for example, when two are present, can be from 1:10 to 10:1, preferably 1:5 to 5:1, most preferably 1:2 to 2:1, including 1:1.

VIII) and finally, purified water or in some embodiments, a solvent in addition to water, for example, an alcohol is added to achieve 100%.

In some embodiments, the above formulation will include additional solvents to water, for example, various alcohols, etc. Additional ingredients in the composition are possible, as long as they do not negatively affect the effectiveness or organoleptic characteristics thereof. For example, the composition may additionally contain colorants, fragrances, additional cosmoceuticals or nutriceuticals. Such compounds are known from the prior art.

In one embodiment, the composition of the invention contains

a selective COX-2 inhibitor compound,
at least one compound capable of enhancing the skin penetration of the active ingredient,
at least one solubilizer,
at least one wetting agent,
at least one gel forming agent,
at least one precipitating agent,
at least one volatile siloxane coating agent, and
at least one solvent.

The formulations may be either in the form of a solution gel, where the active ingredient is dissolved in the gel, or a suspension / dispersion gel, where the active ingredient is in a particulate form suspended and dispersed in the gel. It is possible, however, to produce a formulation wherein the active ingredient is present partly in a solution and partly in suspension gel form at the same time. In such formulations, the proportion of the active ingredient present in suspension (i.e. in particulate form) can be chosen freely.

In the case of suspension gels, the solid particles of active ingredient are coated with one or more siloxanes and dispersed in the gel, thus obtaining a transdermal formulation having similar properties to the solution gels according to the present invention, for example, cold stability and good skin penetration, but providing additional benefits, e.g., even further enhanced stability, e.g., storage stability, especially physicochemical and microbiological stability.

A preferred composition of the invention contains

Celecoxib	0.5-10%
Menthol	0.5-10%
Brij 58	3-25%
Kolliphor P407	3-25%, however, this ingredient may be absent,
PEG 1000	2-25%
Carbopol 980	0,25-2%
NaOH aqueous solution (10 m/v%)	0,1%-5%
Silicone Fluid 0.65 cSt	1-25%
St-Cyclomethicone 5-NF	1-25%
Purified water	ad 100%

A more preferred composition, which is a solution gel, contains

Celecoxib	2%
Menthol	1%
Brij 58	7%
Kolliphor P407	7%,
PEG 1000	10%
Carbopol 980	0.5%
NaOH aqueous solution (10 m/v%)	1%
Silicone Fluid 0.65 cSt	10%
ST-Cyclomethicone5-NF	5%

Purified water	ad 100%.

A more preferred composition, which is a suspension gel containing the active ingredient in particulate form, contains

Celecoxib	2%
Menthol	1%
Brij 58	5%
PEG1000	10%
Carbopol 980	0.5%
NaOH solution 10%	1%
Silicone 0.65 cSt	5%
St-Cyclomethicone 5-NF	5%
Purified water	ad 100%.

The amounts indicated herein may be varied for each ingredient, for example, by 20%, more preferably by 10%.

In the above formulations, the menthol may be exchanged for lavender oil or almond oil, for example.

In the above formulations, one or both of Silicone Fluid 0.65 cSt and St-Cyclomethicone 5-NF may be used, preferably both.

According to the actual application requirements, it is possible to change the viscosity of the gel by modifying the concentration of the gel forming agent and, as required, the amount of the precipitating agent. Lowering the concentration of the gel forming agent to 0.25-0.4 percent results in decreased viscosity.

In preferred embodiments of the present invention, the particles of active ingredient, e.g., celecoxib, are surrounded by a volatile siloxane coating. In this coating, none of the active ingredient, the solubilizing agents, and the gel are soluble. Thus, the physical form of suspension is maintained, even though by direct contact celecoxib would dissolve in the

solubilizer, and the formulation is even more stable than when the active compound would be dissolved.

As soon as the formulation is transferred to the skin and the volatile siloxane coating evaporates, the barrier for dissolution disappears, and the active ingredient is contacted with and dissolved in the excipients, especially the solubilizers. Such a change in physical form of the formulation enhances absorption and skin penetration. This formulation thus exhibits controlled release as well as controlled absorption of the active ingredient.

When the gel containing celecoxib particles coated with siloxanes (i.e., a suspension gel as opposed to the solution gel) is spread onto the skin or other body surface and the temperature of the formulation would increase to, for example, between 24 to 32 °C, the volatile siloxanes evaporate. During the course of the evaporation of the volatile siloxanes, the formulation becomes a solution (i.e. particles of celecoxib are solubilized, dissolved) and the solution is absorbed by the skin.

In a preferred embodiment using celecoxib as the active ingredient in a suspension-type gel, the gel base is created from a Carbopol 980, water, and NaOH solution (Carbopol: an acrylate-type gel forming copolymer). Menthol is provided for enhancing the penetration of the active ingredient after the evaporation of the siloxanes and serves also as fragrance. Brij-58 functions as solubilizer and PEG 1000 functions as a wetting agent. Finally the siloxane coating agents used are SF 0.65 and St-Cyclomethicone 5-NF.

In general, the compositions can be prepared by a process that includes

swelling the at least one gel forming agent in the at least one solvent, and if required, neutralizing with the at least one precipitating agent until pH 5.5-7.5, or otherwise producing a gel base,

warming up the at least one solubilizer to approximately 50 °C and dissolving therein the at least one wetting agent and the at least one compound capable of enhancing the penetration of the active ingredient, thereby forming a melt, stirring the melt into the gel,

if more than one, then mixing together the siloxane coating agents,

the selective COX-2 inhibitor compound, optionally in micronized form is dispersed in the at least one siloxane coating agent and homogenized, optionally by a colloid mill, thereby forming a suspension, and

the suspension is stirred into the gel and homogenized, optionally by a colloid mill,

wherein the process includes the interchanging of the at least one compound capable of enhancing the penetration of the active ingredient and the selective COX-2 inhibitor compound in the above process steps.

In a preferred embodiment, the method of manufacture for the suspension formulation is as follows:

i) Carbopol 980 is allowed to swell in the water and neutralized by the NaOH solution until pH 5.5-7.5, thereby forming a gel.

ii) Brij-58 is warmed up to approximately 40-50 °C and PEG-1000 and menthol are dissolved in their mixture, thereby forming a melt.

iii) The melt is slowly stirred into the gel.

iv) The two siloxane components are mutually dissolved (i.e., mixed).

v) Micronized celecoxib is dispersed in the mixture of the siloxanes and homogenized, preferably by using a colloid mill.

vi) The suspension of the active ingredient in the siloxanes are stirred into the gel and homogenized, preferably by a colloid mill.

According to a further preferred embodiment, the method for preparation of a suspension formulation is carried out as follows. After preparing a gel by swelling the gel forming agent and addition of the precipitating agent, the solubilizer or components of solubilizer system and the wetting agent are mixed to the gel base to form a first mixture. The volatile siloxane components and menthol are mixed separately and the active ingredient, preferably celecoxib is suspended in the thus obtained mixture, forming a suspension. Finally the suspension is added to the first mixture and homogenized.

In the case of solution gels, the active ingredient is in a dissolved state in the gel, which contains the solubilizers. No particles of the active ingredient are present. However, in an embodiment, the menthol (which is used as penetration enhancer for the active ingredient, e.g.,

celecoxib) is coated with the siloxanes. Notwithstanding the above, it is possible to produce a formulation wherein the active ingredient is partly in dissolved state and partly present as particles.

Production of the solution-type gels is carried out in an essentially similar way to that of the suspension type gels with a few modifications. The active ingredient, e.g. celecoxib is dissolved in the solubilizer-wetting agent mixture heated to approx. 50 °C. The siloxane ingredient and the penetration enhancing component, e.g. menthol are dispersed in the gel base prepared according to the method described above and homogenized, for example, using a colloidal mill. Finally, the solution of the active ingredient in the solubilizer-wetting agent mixture is stirred into the gel base and homogenized, e.g. using a colloidal mill.

In an alternative preparation method to the processing method disclosed above, instead of the active agent being dispersed in the siloxanes, the menthol used as penetration enhancer is dispersed in the siloxanes, and the active compound is dissolved in the solubilizers.

In a further alternative preparation method, the gel forming agent is dispersed in water and allowed to swell. The precipitating agent is dissolved in a suitable solvent, preferably in water and the swollen gel is neutralized. The solubilizers Brij-58, Kolliphor P-407 and PEG-1000 are melted together at approximately 40 °C. Subsequently the active ingredient, for example, celecoxib and if present, the penetration enhancing agent, for example, menthol are dissolved in the composite melt. The siloxane component is mixed into the thus obtained mass comprising the solubilizers and active ingredient and homogenized. Finally, the neutralized gel and the mixture of solubilizers, active ingredient and siloxane component are slowly mixed and homogenized.

The formulations can be alternatively produced by inline manufacturing using a closed controlled manufacturing system.

The formulations of the invention can be administered by the use of a patch. However, preferably, no patch is utilized.

The formulation of the invention, preferably omit the use of higher alcohols and esters thereof, e.g., of saturated or unsaturated higher aliphatic alcohols having 8 to 22 carbon atoms.

Evaluation of membrane permeationis measured by static Hanson-cell with closed membrane surface, acceptor phase is an aqueous buffer, where the sample is deposed on the membrane. The results are given as a cumulative amount of the active ingredient during a 6-hour testing period permeating the membrane, expressed in micrograms/square centimeters. The membrane used for penetration testing was a cellulosic mixed ester membrane and the acceptor phase was phosphate buffer.

Examples

Reference preparations have been produced according to the method disclosed in WO2009007764 by coating the particles of the active ingredient with a volatile siloxane.

Example 1

Gel formulation wherein the active ingredient is in dissolved state (solution type gel)

Celecoxib	2%	active ingredient
Menthol	0.66%	penetration enhancer
Brij-58	7%	solubilizer
Kolliphor P407	7%	solubilizer
PEG1000	10%	wetting agent
Carbopol980	0.5%	gel-forming agent
NaOH solution 10%	1%	precipitating agent
Silicone 0.65 cSt	5%	siloxane additive
Purified water ad	100%	base, solvent

Properties:

White gel of excellent consistency with menthol odour and with a membrane permeation (6 hours) of 1398 micrograms/square cm.

Evaluation:

A gel containing the active ingredient is solubilized form. It can be easily manufactured on an industrial scale. The membrane permeation is good, as well as the consistency and organoleptic properties.

The active ingredient has been micronized using a Fritsch Pulverisette 14 milling equipment. There is no crystallization. The resulting composition has excellent consistency and applicability. The in vitro membrane penetration is immediate.

Example 2 provides a suspension gel formulation of the active ingredient prepared by a process described above.

Example 2

Gel formulation wherein the active ingredient is present in solid state (suspension gel)

Celecoxib	2%	active ingredient
Menthol	1%	penetration enhancer
Brij 58	5%	solubilizer
PEG1000	10%	wetting agent
Carbopol 980	0.5%	gel-forming agent
NaOH solution 10%	1%	precipitating agent
Silicone Fluid 0.65 cSt	5%	siloxane coating agent
ST-Cyclomethicone 5-NF	5%	siloxane coating agent

Purified water	ad	100%	base, solvent

Properties:

White gel of excellent consistency with menthol odour and with a membrane permeation (cumulative, 6 hours) of 478 micrograms/ square cm.

Evaluation:

A gel containing the active ingredient is suspended form. It can be easily manufactured on an industrial scale. The membrane permeation is immediate, the consistency and organoleptic properties are excellent.

Comparative examples 1 and 2 are experiments with gels, which are closely tailored to the approach taken in WO2009007764 and WO2010089617.

Comparative example 1

Composition:

Celecoxib		3%	active ingredient
Carbopol 980		0.5%	gel-forming agent
NaOH solution 10 (w/v)%		1%	precipitating agent
Silicone 0.65 cSt		3.3%	siloxane coating material
Silicone 100 cSt		10%	siloxane coating material
Purified water	ad	100%	base, solvent

Features:

Easily spreadable, odourless, non-sticking gel, with a cumulative permeation (6 hours) 3.1 micrograms/square cm.

Evaluation:

A classic, stable gel, which can be easily manufactured. Although the gel can be easily used and is of good consistency, the skin permeation is poor.

Comparative example 2

Celecoxib	3%	active ingredient
Carbopol 980	0.5%	gel-forming agent
NaOH solution 10 (w/v)%	1%	precipitating agent
Silicone 0.65 cSt	10%	siloxane coating material
Silicone 100 cSt	1%	siloxane coating material
Purified water ad	100%	base, solvent

Features:

Easily spreadable, odourless, non-sticking gel with a cumulative permeation (6 hours) of 4.8 micrograms/square cm.

Evaluation:

A classic, stable gel which can be easily manufactured. Although the gel can be easily used and of good consistency, the skin permeation is poor.

Conclusions from experiments above:

The permeation of the active ingredient can be somewhat increased by varying the amounts of the siloxane ingredients, but the desired range cannot be achieved.

Comparative example 3 takes the approach of enhancing the penetration of celecoxib using menthol along with various solubilizers. The mixture of celecoxib and menthol was found to dissolve in most solubilizers tested (comparative example 3 provides the embodiment with Tween 60), but only those having a high HLB value can maintain it in the aqueous phase. None of the solubilizers were found to be suitable for forming an emulsion alone in these experiments, since the active ingredient starts crystallizing instantly. Using a complex emulgent (high+low HLB solubilizers), an emulsion can be formed which crystallizes after a few hours. The solution is stable on the short term (24 hours) only.

Comparative example 3

Composition:

Celecoxib		3%	active ingredient
Menthol		3%	fragrance, penetration enhancer
Tween 60		12%	solubilizer
Ethanol		10%	solubilizer
Carbopol980		0.5%	gel-forming agent
NaOH solution 10%		1%	precipitating agent
Silicone 0.65 cSt		5%	siloxane ingredient
Purified water	ad	100%	base, solvent

Features:

A yellowish, honey-like, viscous, sticky gel with a membrane permeation (6 hours) of 2341 micrograms/square cm.

Evaluation:

The manufacture of this composition is easily feasible. The *in vitro* permeation is excellent. However, the physical state, consistency and applicability of the gel is poor.

On the basis of the above composition of comparative example 3, further similar compositions were prepared by varying the amount of the active ingredient, from 3-6%, the

amount of menthol from 1-2% and the amount of Tween 60 from 12-24%, each time using 1% Carbopol to obtain a suitable gel consistency.

The membrane permeation increases with increasing active ingredient content but not proportionally. Increasing viscosity of the gel significantly degrades membrane permeation.

In the composition of comparative example 3 and in those based thereon, crystallization was observed after 3-4 days of storage.

The preceding examples can be repeated with similar success by substituting the generically or specifically described ingredients and/or operating conditions of this invention for those used in the preceding examples.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The preceding preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

The entire disclosures of all applications, patents and publications cited herein are incorporated by reference herein for the disclosure of materials mentioned herein regarding said applications, patents and publications.

Claims

1. A gel composition comprising:
a selective COX-2 inhibitor compound,
at least one solubilizer,
at least one wetting agent,
at least one gel forming agent,
at least one precipitating agent,
at least one volatile siloxane agent, and
at least one solvent.

2. Composition according to claim 1, further comprising a permeation enhancing compound.

3. The composition of claim 1, characterized by that the selective COX-2 inhibitor is present in the composition in solid particulate form.

4. The composition of claim 1, characterized by the selective COX-2 inhibitor is dissolved in the composition.

5. A pharmaceutical composition, comprising:
a selective COX-2 inhibitor, forming a plurality of solid particle;
at least one solubilizer;
a wetting agent;
a gel forming agent;
a solvent comprising water; and
at least one volatile siloxane agent coating the selective COX-2 inhibitor,
wherein the solid particles are dispersed in the composition, and
wherein the composition comprises a suspension gel.

6. The composition of claim 5, wherein the solubilizer comprises polyethylene glycol hexadecyl ether.

7. The composition of claim 5, wherein the polyethylene glycol hexadecyl ether comprises about 5-10% of the composition.

8. The composition of claim 6, wherein the solubilizer comprises poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene) glycol.

9. The composition of claim 8, wherein the poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene) glycol comprises about 5-10% of the composition.

10. The composition of claim 5, wherein the solubilizer comprises at least one of polyethylene glycol hexadecyl ether, poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene) glycol, polyethylene glycol 1000, polyoxyethylene (20) sorbitan monostearate, Span 60, and Emulsifier 10.

11. The composition of claim 5, wherein the solubilizer comprises a polyethylene glycol derivative having 2 to 25 oxyethylene groups.

12. The composition of claim 5, wherein the HLB value of the solubilizer is between 14 and 20.

13. The composition of claim 5, wherein the solubilizer comprises polyethylene glycol hexadecyl ether and polyethylene glycol 1000.

14. The composition of claim 5, wherein the wetting agent comprises polyethylene glycol.

15. The composition of claim 5, wherein the gel forming agent comprises polymerized prop-2-enoic acid ester.

16. The composition of claim 5, wherein the polymerized prop-2-enoic acid ester comprises about 0.3-1% of the composition.

17. The composition of claim 5, wherein the volatile siloxane agent comprises at least one of hexamethyldisiloxane and decamethylcyclopentasiloxane.

18. The composition of claim 17, wherein the hexamethyldisiloxane comprises about 8-15% of the composition.

19. The composition of claim 17, wherein the decamethylcyclopentasiloxane comprises about 4-10% of the composition.

20. The composition of claim 5, wherein the selective COX-2 inhibitor comprises celecoxib.

21. The composition of claim 5, wherein the selective COX-2 inhibitor comprises about 0.5-10% of the composition.

22. The composition of claim 5, further comprising a precipitation agent.

23. The composition of claim 22, wherein the precipitation agent comprises NaOH.

24. The composition of claim 22, wherein the precipitation agent comprises about 0.5-1.2% of the composition.

25. The composition of claim 5, further comprising a permeation enhancing agent.

26. The composition of claim 5, wherein the solvent consists essentially of an aqueous solvent.

27. The composition of claim 5, comprising
celecoxib in an amount of 2%;
menthol in an amount of 1%;

polyethylene glycol hexadecyl ether in an amount of 5%;
polyethylene glycol 1000 in an amount of 10%;
polymerized prop-2-enoic acid ester in an amount of 0.5%;
a 10% NaOH solution in an amount of 1%
hexamethyldisiloxane in an amount of 5%;
decamethylcyclopentasiloxane in an amount of 5%; and
purified water.

28. A pharmaceutical composition, comprising:
a selective COX-2 inhibitor;
at least one solubilizer;
a wetting agent;
a gel forming agent;
a solvent comprising water; and
at least one volatile siloxane agent,
wherein the composition comprises a solution gel.

29. The composition of claim 28, wherein the solubilizer comprises polyethylene glycol hexadecyl ether.

30. The composition of claim 28, wherein the polyethylene glycol hexadecyl ether comprises about 5-10% of the composition.

31. The composition of claim 29, wherein the solubilizer comprises poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene) glycol.

32. The composition of claim 31, wherein the poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene) glycol comprises about 5-10% of the composition.

33. The composition of claim 28, wherein the solubilizer comprises at least one of polyethylene glycol hexadecyl ether, poly(ethylene glycol)-block-poly(propylene glycol)-

block-poly(ethylene) glycol, polyethylene glycol 1000, polyoxyethylene (20) sorbitan monostearate, Span 60, or Emulsifier 10.

34. Composition according to claim 28, characterized by that the HLB value of the solubilizer is between 14 and 20.

35. The composition of claim 28, wherein the solubilizer comprises polyethylene glycol hexadecyl ether and polyethylene glycol 1000.

36. The composition of claim 28, wherein the solubilizer comprises polyethylene glycol hexadecyl ether, polyethylene glycol 1000, and poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene) glycol.

37. The composition of claim 28, wherein the wetting agent comprises polyethylene glycol.

38. The composition of claim 28, wherein the gel forming agent comprises polymerized prop-2-enoic acid ester.

39. The composition of claim 28, wherein the polymerized prop-2-enoic acid ester comprises about 0.3-1% of the composition.

40. The composition of claim 28, wherein the volatile siloxane agent comprises at least one of hexamethyldisiloxane and decamethylcyclopentasiloxane.

41. The composition of claim 40, wherein the hexamethyldisiloxane comprises about 8-15% of the composition.

42. The composition of claim 40, wherein the decamethylcyclopentasiloxane comprises about 4-10% of the composition.

43. The composition of claim 28, wherein the selective COX-2 inhibitor comprises celexocib.

44. The composition of claim 28, wherein the selective COX-2 inhibitor comprises about 0.5-10% of the composition.

45. The composition of claim 28, further comprising a precipitation agent.

46. The composition of claim 45, wherein the precipitation agent comprises NaOH.

47. The composition of claim 45, wherein the precipitation agent comprises about 0.5-1.2% of the composition.

48. The composition of claim 28, further comprising a permeation enhancing agent.

49. The composition of claim 28, wherein the solvent consists essentially of an aqueous solvent.

50. The composition of claim 28, comprising
celecoxib in an amount of 2%;
menthol in an amount of 0.66%;
polyethylene glycol hexadecyl ether in an amount of 7%;
poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene) glycol in an amount of 7%;
polyethylene glycol 1000 in an amount of 10%;
polymerized prop-2-enoic acid ester in an amount of 0.5%;
a 10% NaOH solution in an amount of 1%
hexamethyldisiloxane in an amount of 5%; and
purified water.