Description

Title of Invention: Pharmaceutical Composition for External Use

Technical Field

[0001]

The present invention relates to a pharmaceutical composition for external use containing diclofenac and/or a salt thereof and lactic acid and/or a salt thereof, in which the precipitation of diclofenac and/or a salt thereof is suppressed, and excellent stability is provided.

Background Art

[0002]

In the modern society, an increasing number of people are suffering from stiff shoulders, muscular pain, joint pain, and the like caused by the same posture maintained for long hours due to the prevalence of OA equipment, excessive stress, lack of exercise, and the like. Conventionally, for the treatment of stiff shoulders, muscular and joint pains, and the like as described above, antiinflammatory agents are applied to reduce inflammation in the affected areas, and improve the symptoms.

[0003]

Nonsteroidal antiinflammatory drugs such as diclofenac, felbinac, dexamethasone, indomethacin, and ibuprofen have been conventionally put into practical use as antiinflammatory agents. Among these nonsteroidal antiinflammatory drugs, diclofenac is known to have high cyclooxygenase inhibitory activity, and can exhibit an excellent antiinflammatory effect. When diclofenac is orally or intrarectally administered, it may cause gastrointestinal, kidney, or liver disorders as side effects, and in particular, may cause serious side effects in the gastrointestinal tract. Thus, the use of diclofenac as external preparations is recently increasing. Diclofenac, however, has a drawback in that because of its poor

percutaneous absorption, it cannot sufficiently exhibit its original antiinflammatory effect when percutaneously applied.

[0004]

Various formulation techniques have been studied in the past for improving the percutaneous absorption of diclofenac, or improving its drug efficacy. Patent Literature 1, for example, discloses that the percutaneous absorption of diclofenac or a salt thereof is improved by adding an alcohol and a carboxylate ester and/or a carboxylic acid to a composition for external use containing diclofenac or a salt thereof. Patent Literature 2 also discloses that the analgesic effect is improved by incorporating 0.5 to 1.5 wt% of diclofenac or a pharmacologically acceptable salt thereof and 5 to 15 wt% of a cooling agent into a pharmaceutical composition for external use.

Citation List

Patent Literature

[0005]

Patent Literature 1: Japanese Unexamined Patent Publication No. 10-182450

Patent Literature 2: Japanese Unexamined Patent Publication No. 2011-074032

Summary of Invention

Technical Problem

[0006]

Along with the increase in the number of people who suffer from stiff shoulders, muscular pain, joint pain, and the like, there is an increasing demand for an external preparation that can exhibit a superior antiinflammatory effect, and expectations are growing for the development of a formulation technique for further improving the percutaneous absorption of diclofenac and/or a salt thereof. Thus, the present inventor studied a formulation technique for improving the percutaneous absorption of diclofenac and/or a salt thereof in a pharmaceutical composition for

external use containing diclofenac and/or a salt thereof, and consequently found that lactic acid and/or a salt thereof contributes to improvement in the percutaneous absorption of diclofenac and/or a salt thereof, as shown in Test Example 3 below. The inventor, however, encountered a new problem in that when diclofenac and/or a salt thereof and 0.1 wt% or more of lactic acid and/or a salt thereof are simply present together, diclofenac and/or a salt thereof readily precipitates, which impairs the stability of the pharmaceutical formulation. While a pharmaceutical formula containing a high content of a lower alcohol, or a pharmaceutical formula containing a polyvalent alcohol or a polar oil would be effective to suppress such precipitation of diclofenac and/or a salt thereof, these pharmaceutical formulae have the drawback of adversely affecting the feeling of use, or having more constraints on the formulation design.

[0007]

It is accordingly an object of the present invention to provide a formulation technique for suppressing the precipitation of diclofenac and/or a salt thereof to provide excellent stability, even when diclofenac and/or a salt thereof and lactic acid and/or a salt thereof are present together.

Solution to Problem

[0008]

The present inventor conducted extensive research to solve the above-mentioned problem, and found that the use of menthol in combination with diclofenac and/or a salt thereof and 0.1 wt% or more of lactic acid and/or a salt thereof can prevent the precipitation of diclofenac and/or a salt thereof to provide excellent stability. The present invention was completed by conducting further research based on this finding.

[0009]

In summary, the present invention provides aspects of invention as itemized below.

Item 1. A pharmaceutical composition for external use containing (A) diclofenac and/or a pharmacologically acceptable salt thereof, (B) 0.1 wt% or more of lactic acid and/or a salt thereof, and (C) menthol.

Item 2. The pharmaceutical composition for external use according to item 1, further containing (D) water.

Item 3. The pharmaceutical composition for external use according to item 1 or 2, further containing (E) a lower alcohol.

Item 4. The pharmaceutical composition for external use according to any of items 1 to 3, wherein a content of the component (C) is 1 wt% or more.

Item 5. The pharmaceutical composition for external use according to any of items 1 to 4, wherein a content of the component (D) is 5 to 50 wt%.

Item 6. The pharmaceutical composition for external use according to any of items 1 to 5, wherein a content of the component (E) is 30 to 90 wt%.

Item 7. The pharmaceutical composition for external use according to any of items 1 to 6, which is a liquid or a gel.

Item 8. A method for suppressing precipitation of diclofenac and/or a pharmacologically acceptable salt thereof, the method including blending (C) menthol into a pharmaceutical composition for external use containing (A) diclofenac and/or a pharmacologically acceptable salt thereof and (B) 0.1 wt% or more of lactic acid and/or a salt thereof.

Advantageous Effects of Invention

[0010]

In the pharmaceutical composition for external use according to the present invention, even though diclofenac and/or a salt thereof is present with lactic acid and/or a salt thereof, the precipitation of diclofenac and/or a salt thereof is suppressed, such that the pharmaceutical composition for external use can exhibit good appearance characteristics, and have excellent stability. Moreover, in the pharmaceutical composition for external use of the present invention, the inclusion of

menthol can suppress the precipitation of diclofenac and/or a salt thereof to achieve stabilization, and therefore, in the formulation of the pharmaceutical composition for external use of the present invention, the lower alcohol content can be reduced (to 80 wt% or less, for example), or a polyhydric alcohol or a polar oil may not be used, for example. Thus, the pharmaceutical composition for external use according to the present invention has less constraints on the formulation design, and can be used for various pharmaceutical formulae.

[0011]

Further, the pharmaceutical composition for external use of the present invention provides dramatically improved percutaneous absorption of diclofenac and/or a salt thereof, and thus, can exhibit an excellent antiinflammatory effect, and effectively alleviate or heal stiff shoulders, muscular pain, joint pain, and the like.

Description of Embodiments

[0012]

1. Composition for external use

The pharmaceutical composition for external use of the present invention is characterized in that it contains (A) diclofenac and/or a pharmacologically acceptable salt thereof, (B) 0.1 wt% or more of lactic acid and or a salt thereof, and (C) menthol. The pharmaceutical composition for external use of the present invention will be described hereinafter in detail.

(A) Diclofenac and/or a salt thereof

The pharmaceutical composition for external use of the present invention contains diclofenac and/or a salt thereof (hereinafter sometimes also denoted as "component (A)") as an antiinflammatory component.

[0013]

Diclofenac is a known nonsteroidal compound also referred to as 2-(2-(2,6-dichlorophenylamino)phenyl)acetate.

[0014]

While the salt of diclofenac is not particularly limited as long as it is pharmacologically acceptable, examples thereof include alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt; salts with ammonia; salts with primary, secondary, or tertiary alkylamines such as dimethylamine, diethylamine, trimethylamine, and triethylamine; and salts with primary, secondary, or tertiary alkanolamines such as monoethanolamine, diethanolamine, diisopropanolamine, triethanolamine, and triisopropanolamine. Among the above, an alkali metal salt may be preferred, and sodium salt may be more preferred. These pharmacologically acceptable salts of diclofenac may be used alone, or in combination of two or more.

[0015]

As component (A) in the pharmaceutical composition for external use of the present invention, one of diclofenac and salts thereof may be selected and used alone, or two or more of them may be used in combination. Among components (A), a salt of diclofenac may be preferred, an alkali metal salt of diclofenac may be more preferred, and diclofenac sodium may be particularly preferred.

[0016]

While the content of component (A) in the pharmaceutical composition for external use of the present invention is not particularly limited, it may be 0.2 to 2 wt%, for example, preferably 0.5 to 1.5 wt%, and more preferably 0.7 to 1.3 wt%.

(B) Lactic acid and/or a salt thereof

The pharmaceutical composition for external use of the present invention contains 0.1 wt% or more of lactic acid and/or a salt thereof (hereinafter sometimes also denoted as "component (B)").

[0017]

While the salt of lactic acid is not particularly limited as long as it is pharmacologically acceptable, examples thereof include alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt and magnesium salt; and salts with ammonia. These salts of lactic acid may be used

alone, or in combination or two or more.

[0018]

As component (B) in the pharmaceutical composition for external use of the present invention, one of lactic acid and salts thereof may be selected and used alone, or two or more of them may be used in combination. Among components (B), lactic acid and an alkali metal salt of lactic acid may be preferred, lactic acid and sodium lactate may be more preferred, and lactic acid may be particularly preferred, in view of further improving the percutaneous absorption of diclofenac and/or a salt thereof, along with the effect of suppressing the precipitation of diclofenac and/or a salt thereof.

[0019]

While the content of component (B) in the pharmaceutical composition for external use of the present invention may be 0.1 wt% or more, it may be preferably 0.1 to 5 wt%, more preferably 0.1 to 4 wt%, particularly preferably 0.1 to 3 wt%, and more particularly preferably 0.1 to 1 wt%, in view of even further improving the percutaneous absorption of diclofenac and/or a salt thereof, along with the effect of suppressing the precipitation of diclofenac and/or a salt thereof.

(C) Menthol

The pharmaceutical composition for external use of the present invention contains menthol (hereinafter sometimes also denoted as "component (C)"). The inclusion of menthol can suppress the precipitation of diclofenac and/or a salt thereof that occurs in the presence of diclofenac and/or a salt thereof and 0.1 wt% or more of lactic acid and/or a salt thereof, which allows excellent stability to be provided in the pharmaceutical composition for external use. Moreover, the inclusion of menthol can also dramatically improve the percutaneous absorption of diclofenac and/or a salt thereof, through the interaction with 0.1 wt% or more of lactic acid and/or a salt thereof. Further, the inclusion of menthol can also impart a cool feeling to the skin upon application, leading to a good feeling of use.

[0020]

While menthol may be in any of d-, l-, and dl-forms, the l-form may be preferred.

[0021]

In the pharmaceutical composition for external use of the present invention, an essential oil containing menthol may be used as component (C). While the essential oil containing menthol to be used may be selected as appropriate from known ones, examples thereof include mentha oil, peppermint oil, and spearmint oil.

[0022]

Among components (C), menthol and an essential oil containing menthol may be preferred, and l-menthol and an essential oil containing l-menthol may be more preferred, in view of even further improving the percutaneous absorption of diclofenac and/or a pharmacologically acceptable salt thereof.

[0023]

The content of component (C) in the pharmaceutical composition for external use of the present invention may be 1 wt% or more, for example, preferably 1 to 15 wt%, more preferably 3 to 10 wt%, and particularly preferably 5 to 10 wt%, in view of even further improving the effect of suppressing the precipitation of diclofenac and/or a salt thereof.

(D) Water

The pharmaceutical composition for external use of the present invention may optionally contain water (hereinafter sometimes also denoted as "component (D)"), to be formulated into a desired dosage form.

[0024]

While the content of component (D) in the pharmaceutical composition for external use of the present invention may be set as appropriate, depending on the dosage form, it may be 5 to 50 wt%, for example. In general, when diclofenac and/or a salt thereof and 0.1 wt% or more of lactic acid and/or a salt thereof are present together under conditions having a water content of 15 wt% or more, and particularly 20 wt% or more, there is a tendency for the formation of precipitate to become

pronounced. In contrast, in the pharmaceutical composition for external use of the present invention, even when the water content is relatively high as described above, the precipitation of diclofenac and/or a salt thereof can be suppressed. In view of this effect of the present invention, the content of component (D) in the pharmaceutical composition for external use of the present invention may be preferably 10 to 40 wt%, more preferably 15 to 40 wt%, particularly preferably 15 to 39 wt%, and most preferably 20 to 38.9 wt%.

(E) Lower alcohol

The pharmaceutical composition for external use of the present invention may optionally contain a lower alcohol (hereinafter sometimes also denoted as "component (E)"), for, for example, improving the water solubility of the components contained therein, for example.

[0025]

While the lower alcohol is not particularly limited, examples thereof include monovalent lower alcohols with one to four carbon atoms, such as ethanol, propanol, isopropanol, n-butanol, sec-butanol, and tert-butanol. Among the above, ethanol, propanol, and isopropanol may be preferred. These lower alcohols may be used alone, or in combination or two or more.

[0026]

While the content of component (E) in the pharmaceutical composition for external use of the present invention may be set as appropriate depending on the dosage form and the like, it may be 30 to 90 wt%, for example. In the pharmaceutical composition for external use of the present invention, the inclusion of the above-described components (A) to (C) improves the water solubility of diclofenac and/or a salt thereof to make the precipitation thereof unlikely, leading to a reduction in the amount of the lower alcohol to be contained. In view of this effect of the present invention, when component (E) is contained in the pharmaceutical composition for external use of the present invention, the content of component (E) may be preferably 45 to 80 wt%, more preferably 50 to 75 wt%, and particularly

preferably 55 to 70 wt%.

Other components

The pharmaceutical composition for external use of the present invention may also contain a base such as an aqueous base or an oily base other than the above-described components (D) and (E), to be formulated into a desired dosage form.

[0027]

Examples of aqueous bases other than the above-described components (D) and (E) include polyhydric alcohols such as glycerol, propylene glycol, dipropylene glycol, and butylene glycol.

[0028]

Examples of oily bases include nonpolar oils and polar oils. Examples of nonpolar oils include hydrocarbons such as paraffins and isoparaffins; and squalane and waxes. Examples of polar oils include aliphatic monocarboxylic acid esters, triglyceride, aliphatic dicarboxylic acid diesters, aliphatic dicarboxylic acid alkylene glycol esters, and higher fatty acids. A polar oil is generally used for, for example, improving the water solubility of lipid-soluble components; however, the inclusion of the above-described components (A) to (C) in the pharmaceutical composition for external use of the present invention improves the water solubility of diclofenac and/or a salt thereof to make the precipitation thereof unlikely, and therefore, the pharmaceutical composition for external use of the present invention can be formulated without substantially containing a polar oil. In view of this effect of the present invention, one preferred embodiment of the pharmaceutical composition for external use of the present invention may be substantially free of a polar oil. As used herein, the expression "substantially free of a polar oil" means that the content of a polar oil is such that it does not affect the water solubility of diclofenac and/or a salt thereof, and specifically means that the content of a polar oil is 5 wt% or less, preferably 3 wt% or less, and more preferably 0 wt%.

[0029]

The pharmaceutical composition for external use of the present invention may

optionally contain pharmacological components other than the above-described components, as long as they do not hinder the effects of the present invention. While the pharmacological components that can be blended into the pharmaceutical composition for external use of the present invention are not particularly limited, examples thereof include antiinflammatory agents such as glycyrrhetic acid, glycyrrhizinate dipotassium, ammonium glycyrrhizinate, and stearyl glycyrrhizinate; antihistamines such as diphenylimidazole, diphenhydramine and pharmacologically acceptable salts thereof, and chlorpheniramine maleate; local anesthetics such as lidocaine and pharmacologically acceptable salts thereof, dibucaine and pharmacologically acceptable salts thereof, and ethyl aminobenzoate; blood circulation promoters such as benzyl nicotinate, nonanoic acid vanillylamide, and red pepper tincture; and herbal medicines such as arnica tincture, *Phellodendron amurense* bark extract, gardenia Florida fruit extract, *Aesculus hippocastanum* extract, scopolia extract, belladonna extract, *Angelica acutiloba* extract, *Lithospermi* radix extract, and *Zanthoxylum piperitum* extract.

[0030]

In addition to the above-described components, the pharmaceutical composition for external use of the present invention may further optionally contain other additives generally used in pharmaceutical compositions for external use. Examples of such additives include a pH adjuster, a surfactant, an emulsifier, a solubilizer, an antiseptic, a preservative, an antioxidant, a stabilizer, a chelating agent, a thickener, a perfume, and a colorant. While the thickener that can be blended into the pharmaceutical composition for external use of the present invention is not particularly limited, examples thereof include hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethyl cellulose, carboxyvinyl polymer, hyaluronic acid, and xanthan gum.

pH

When the pharmaceutical composition for external use of the invention is prepared in the form of a liquid, the pH may be 3.0 to 9.0, for example, preferably 4.0

to 9.0, and more preferably 4.5 to 8.5.

Dosage form

While the dosage form of the pharmaceutical composition for external use of the present invention is not particularly limited as long as it can be percutaneously applied, examples thereof include liquids (including lotions, sprays, aerosols, and emulsions), foams, ointments, plasters, creams, gels, and patches. Among the above, liquids or gels may be preferred. The pharmaceutical composition for external use of the present invention can be prepared into these dosage forms, using additives suitable for the dosage forms, in accordance with known methods described in the General Rules for Preparations in the Japanese Pharmacopoeia 16th Edition, for example.

Usage

The pharmaceutical composition for external use of the invention is used by being externally administered to a local site (skin) where pain relief is required. While the dose of the pharmaceutical composition for external use of the present invention is set as appropriate depending on the site for administration, the severity of the symptoms to be treated, and the like, it is desirably such that the amount of diclofenac and/or a pharmacologically acceptable salt thereof administered per dose, per cm^2 of the local site for administration, is approximately 10 to 500 mg.

[0031]

The pharmaceutical composition for external use of the present invention can be used as an antiinflammatory agent for external use, for the purpose of treating pain in the shoulders caused by stiff shoulders, joint pain, low back pain, muscular pain, peritendinitis (pain in the hands and wrists), pain in the elbows (such as tennis elbow), bruise pain, sprain pain, bone fracture pain, neuralgia, osteoarthritis, arthritis, and the like.

2. Method for suppressing precipitation

The present invention also provides a method for suppressing the precipitation of diclofenac and/or a pharmacologically acceptable salt thereof. Specifically, the method for suppressing precipitation of the present invention is a method for

suppressing the precipitation of diclofenac and/or a pharmacologically acceptable salt thereof characterized in that it includes blending (C) menthol into a pharmaceutical composition for external use containing (A) diclofenac and/or a pharmacologically acceptable salt thereof and (B) 0.1 wt% or more of lactic acid and/or a salt thereof. In the method for suppressing precipitation of the present invention, the types or amounts of the components to be used, the pH or dosage form of the pharmaceutical composition for external use, and so forth are as described in the "1. Composition for external use" section above.

Examples

[0032]

The present invention will be hereinafter described in more detail with reference to examples, which are not intended to limit the present invention.

Test Example 1

Pharmaceutical compositions for external use of the compositions shown in Tables 1 and 2 were prepared. Specifically, predetermined amounts of diclofenac sodium and l-menthol were added and dissolved in a predetermined amount of ethanol or isopropanol, and a predetermined amount of lactic acid was further added and stirred. Next, predetermined amounts of water and hydroxypropylcellulose (only in Example 3) were added and stirred, thus obtaining pharmaceutical compositions for external use (as liquids in the examples except for Example 3, and as a gel in Example 3).

[0033]

The appearance characteristics of each of the pharmaceutical compositions for external use immediate after the preparation were evaluated, and moreover, the appearance characteristics of each of the pharmaceutical compositions for external use after being stored at 25°C for 3 days under light-tight conditions were evaluated. The appearance characteristics of the pharmaceutical composition for external use were evaluated in accordance with the following determination criteria:

<Determination criteria for appearance characteristics>

A: An extremely good solubilized state without the formation of precipitate.

B: A good solubilized state accompanied by slight formation of precipitate, which is practically not problematic.

C: An insufficient solubilized state for practical use, accompanied by visible formation of precipitate.

D: A non-solubilized state accompanied by significant precipitation.

[0034]

The obtained results are shown in Tables 1 and 2. The results show that the formation of precipitate was not observed when diclofenac sodium and lactic acid were not present together, and when diclofenac sodium and less than 0.1 wt% of lactic acid were present together (Referential Examples 1 and 2); whereas significant formation of precipitate was observed immediately after the preparation or after the storage of 3 days when diclofenac sodium and 0.1 wt% or more of lactic acid were present together, and l-menthol was not contained (Comparative Examples 1 to 6). On the other hand, when l-menthol was contained together with diclofenac sodium and 0.1 wt% or more of lactic acid, the formation of precipitate was suppressed immediately after the preparation and the storage of 3 days (Examples 1 to 9). In particular, when 5 wt% or more of l-menthol was contained together with diclofenac sodium and 0.1 wt% or more of lactic acid, a pronounced effect of suppressing the formation of precipitate was achieved, resulting in an extremely good solubilized state.

[0035]

[Table 1]

	Examples								
	1	2	3	4	5	6	7	8	9
Diclofenac Sodium	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Lactic Acid	0.1	0.15	0.3	0.3	0.3	0.6	0.6	0.6	0.3
l-Menthol	5.0	5.0	5.0	5.0	5.0	5.0	5.0	10.0	3.0
Ethanol	55	55	60	60	-	70	-	55	60
Isopropanol	-	-	-	-	55	-	70	-	-
Hydroxypropylcellulose				3.0					
Purified Water	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance
Total Amount	100	100	100	100	100	100	100	100	100
pH	6.20	6.06	5.53	5.82	5.41	5.35	5.35	4.99	5.76
Appearance Characteristics Immediately after Preparation	A	A	A	A	A	A	A	A	A
Appearance Characteristics after Storage of 3 Days	A	A	A	A	A	A	A	A	B

In the table, the amount of each component is in "wt%".

[0036]

[Table 2]

	Referential Examples		Comparative Examples					
	1	2	1	2	3	4	5	6
Diclofenac Sodium	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Lactic Acid		0.05	0.1	0.15	0.3	0.3	0.6	0.6
l-Menthol	-	-	-	-	-	-	-	-
Ethanol	55	55	55	55	55	60	55	70
Isopropanol								
Hydroxypropylcellulose								
Purified Water	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance
Total Amount	100	100	100	100	100	100	100	100
pH	8.16	6.46	5.95	6.02	5.42	5.44	4.98	5.28
Appearance Characteristics immediately after the Preparation	A	A	A	D	D	D	D	D
Appearance Characteristics immediately after Storage of 3 Days	A	A	D	D	D	D	D	D

In the table, the amount of each component is in "wt%".

[0037]

Test Example 3

Pharmaceutical compositions for external use (in the form of liquids) of the compositions shown in Table 3 were prepared. The following test was performed to evaluate the percutaneous absorption of each of the pharmaceutical compositions for external use. YMP (Yucatan Micropig) skin (Charles River Japan) frozen at –30°C was allowed to stand at room temperature for about 30 minutes and thawed, fat and pieces of meat found subcutaneously were then removed, and the resulting material was used as the test skin. The test skin was loaded into a Franz diffusion cell (effective permeation size: about 25 mm; glass), the receptor was filled with 0.2 M PBS buffer (pH 7.4), and the Franz diffusion cell was soaked in warm water at 37°C ± 3°C. After the temperature of the Franz diffusion cell reached 37°C ± 3°C, 1 g of each of the pharmaceutical compositions for external use was applied to the epidermal side of the test skin, and maintained at 37°C ± 3°C for 5 hours. After 3 and 5 hours from the application of the pharmaceutical composition for external use, 0.5 ml of the PBS buffer in the receptor was sampled, and the concentration of diclofenac in the PBS buffer was measured by liquid chromatography, to calculate the amount of diclofenac sodium that penetrated through the test skin (the amount of percutaneous absorption of diclofenac sodium, μg). Note that all the test skin used in this test was from the same lot.

[0038]

The obtained results are shown in Table 3. As is clear from Table 3, when lactic acid was contained in addition to diclofenac sodium and l-menthol (Example 10), the amount of percutaneous absorption of diclofenac sodium dramatically increased, compared to the case where lactic acid was not contained (Comparative Example 7). On the other hand, when acetic acid was contained together with diclofenac sodium and l-menthol (Comparative Example 8), the amount of percutaneous absorption of diclofenac sodium was not increased as in the case where lactic acid was used. Further, when l-menthol was not contained even though

diclofenac sodium and lactic acid were contained (Comparative Example 9), the amount of percutaneous absorption of diclofenac sodium was not increased. The foregoing results reveal that the dramatic increase in the amount of percutaneous absorption of diclofenac sodium was achieved by the inclusion of diclofenac sodium, l-menthol, and lactic acid in an inseparable relationship.

[0039]

[Table 3]

	Example	Comparative Examples		
	10	7	8	9
Diclofenac Sodium	1.0	1.0	1.0	1.0
Lactic Acid	0.5	-	-	0.5
l-Menthol	5.0	5.0	5.0	-
Acetic Acid	-	-	0.5	-
Propylene Glycol	7.0	7.0	7.0	7.0
Ethanol	66.5	66.5	66.5	66.5
Purified Water	Balance	Balance	Balance	Balance
Total Amount	100	100	100	100
pH	5.54	8.48	5.90	5.42
Amount of Percutaneous Absorption of Diclofenac Sodium (Amount of Permeation after 3 hr) (μg)	40.61	0	21.12	0
Amount of Percutaneous Absorption of Diclofenac Sodium (Amount of Permeation after 5 hr) (μg)	204.85	84.71	54.38	5.42

In the table, the amount of each component is in "wt%".

[0040]

Formulation Examples

Pharmaceutical compositions for external use of the compositions shown in Table 4 (as liquids in Formulation Examples 1, 3 and 5, and gels in Formulation Examples 2, 4 and 6) were prepared. In all of the obtained pharmaceutical

compositions for external use, the percutaneous absorption of diclofenac sodium was excellent, and the formation of precipitate was also suppressed, and thus, excellent stability was provided.

[0041]

[Table 4]

	Formulation Examples					
	1	2	3	4	5	6
Diclofenac Sodium	1.0	1.0	1.0	1.0	1.0	1.0
Lactic Acid	0.3	0.3	0.3	0.3	0.3	0.3
l-Menthol	3.0	3.0	5.0	5.0	7.0	7.0
Tocopherol Acetate	0.1	0.1	0.1	0.1	0.1	0.1
Nonanoic Acid Vanillylamide	0.01	0.01	0.01	0.01	0.01	0.01
Benzyl Nicotinate	0.01	0.01	0.01	0.01	0.01	0.01
Ethanol	70.0	60.0	70.0	60.0	70.0	60.0
Propylene Glycol	5.0	5.0	5.0	5.0	5.0	5.0
Hydroxypropylcellulose	-	3.0	-	3.0	-	3.0
Water	Balance	Balance	Balance	Balance	Balance	Balance
Total Amount	100	100	100	100	100	100

In the table, the amount of each component is in "wt%".

Claims

[Claim 1]

A pharmaceutical composition for external use comprising (A) diclofenac and/or a pharmacologically acceptable salt thereof, (B) 0.1 wt% or more of lactic acid and/or a salt thereof, (C) menthol, (D) water, and (E) 30 to 90 wt% of a lower alcohol.

[Claim 2]

The pharmaceutical composition for external use according to claim 1, wherein a content of the component (C) is 1 wt% or more.

[Claim 3]

The pharmaceutical composition for external use according to claim 1 or 2, wherein a content of the component (D) is 5 to 50 wt%.

[Claim 4]

The pharmaceutical composition for external use according to any of claims 1 to 3, wherein a content of the component (E) is 45 to 80 wt%.

[Claim 5]

The pharmaceutical composition for external use according to any of claims 1 to 4, which is a liquid or a gel.

[Claim 6]

A method for suppressing precipitation of diclofenac and/or a pharmacologically acceptable salt thereof, the method comprising blending (C) menthol into a pharmaceutical composition for external use comprising (A) diclofenac

and/or a pharmacologically acceptable salt thereof, (B) 0.1 wt% or more of lactic acid and/or a salt thereof, (D) water, and (E) 30 to 90 wt% of a lower alcohol.