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, a tocopherol and/or a derivative thereof, and water, in which yellowing that occurs with time or under high temperature conditions is suppressed, and excellent storage 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.

[0004]

Non Patent Literature 1 reported that tocopherol acetate is a representative blood circulation-promoting component, and reduces sides effects when used in combination with diclofenac sodium in rheumatic patients, to provide therapeutic effects for osteoarthritis, arthritis, joint pain, and the like.

Citation List

Non Patent Literature

[0005]

Non Patent Literature 1: Von H. Bartsch, Fat Sci. Technol. 92 jahrgang Nr. 5 1990, 197-201

Summary of Invention

Technical Problem

[0006]

As disclosed in Non Patent Literature 1, it is known that the use of diclofenac and/or a salt thereof in combination with a tocopherol and/or a derivative thereof reduces side effects when diclofenac sodium is used together in rheumatic patients, and is effective for the treatment of osteoarthritis, arthritis, joint pain, and the like. However, although diclofenac and a tocopherol and/or a derivative thereof can be formulated into an oral pharmaceutical composition such as a capsule or a tablet, they have a drawback in that when blended into a pharmaceutical composition for external use containing a relatively large amount of water, the pharmaceutical composition for external use is turned into yellow (yellowing) with time or under high temperature conditions, and cannot maintain transparent appearance characteristics, leading to reduced storage stability.

[0007]

It is accordingly an object of the present invention to provide a formulation technique that can suppress yellowing that occurs with time or under high temperature

conditions to provide excellent storage stability, while incorporating diclofenac and/or a salt thereof and a tocopherol and/or a derivative thereof into a pharmaceutical composition for external use containing water.

Solution to Problem

[0008]

The present inventor conducted extensive research to solve the above-mentioned problem, and found that when lactic acid and/or a salt thereof is blended into a pharmaceutical composition for external use containing diclofenac and/or a salt thereof, a tocopherol and/or a derivative thereof, and water, yellowing that occurs with time or under high temperature conditions can be suppressed, and excellent storage stability can be provided in the pharmaceutical composition for external use. 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) a tocopherol and/or a derivative thereof, (C) lactic acid and/or a salt thereof, and (D) water.

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

Item 3. The pharmaceutical composition for external use according to item 1 or 2, further containing (F) 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 0.05 to 1 wt%.

Item 5. The pharmaceutical composition for external use according to any of items 1 to 4, wherein a content of the component (D) is 15 to 50 wt%.

Item 6. The pharmaceutical composition for external use according to any of

items 2 to 5, wherein a content of the component (E) is 5 wt% or more.

Item 7. The pharmaceutical composition for external use according to any of items 1 to 6, wherein the component (B) is tocopherol acetate.

Item 8. The pharmaceutical composition for external use according to any of items 1 to 7, which is a liquid or a gel.

Item 9. A method for suppressing yellowing of a pharmaceutical composition for external use including blending (C) lactic acid and/or a salt thereof into a pharmaceutical composition for external use containing (A) diclofenac and/or a pharmacologically acceptable salt thereof, (B) a tocopherol and/or a derivative thereof, and (D) water.

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, a tocopherol and/or a derivative thereof, and water are present together, yellowing that occurs with time or under high temperature conditions can be suppressed, and excellent storage stability can be provided. Moreover, the pharmaceutical composition for external use of the present invention can have excellent storage stability even when it contains water in a relatively large amount, i.e., 15 wt% or more, and thus, it has less constraints on the formulation design, and can be used for various pharmaceutical formulae.

[0011]

Further, when the pharmaceutical composition of the present invention further contains menthol, precipitation and cloudiness that occur in the presence of diclofenac and/or a salt thereof, a tocopherol and/or a derivative thereof, and water can also be suppressed, leading to excellent appearance characteristics with high transparency.

[0012]

Moreover, the pharmaceutical composition for external use of the present invention, which contains diclofenac and/or a salt thereof and a tocopherol and/or a

derivative thereof, can exhibit an excellent antiinflammatory effect, and thus, can effectively alleviate or heal osteoarthritis, arthritis, joint pain, and the like.

Description of Embodiments

[0013]

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) a tocopherol and/or a derivative thereof, (C) lactic acid and/or a salt thereof, and (D) water. 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.

[0014]

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

[0015]

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.

[0016]

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.

[0017]

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) A tocopherol and/or a derivative thereof

The pharmaceutical composition for external use of the present invention contains a tocopherol and/or a derivative thereof (hereinafter sometimes also denoted as "component (B)") together with the above-described component (A), in order to enhance the antiinflammatory effect.

[0018]

A tocopherol is a known compound known as vitamin E. While the tocopherol may be in any of d-, l-, and dl-forms, the dl-form may be preferred. Moreover, while the tocopherol may be in any of α-, β-, γ-, and δ-forms, the α-form may be preferred.

[0019]

While the tocopherol derivative is not particularly limited as long as it is pharmacologically acceptable, examples thereof include esters with carboxylic acids such as acetic acid, nicotinic acid, and succinic acid, and diesters with phosphoric acid. Among these tocopherol derivatives, an ester with a carboxylic acid may be preferred, and tocopherol acetate may be more preferred.

[0020]

While the tocopherol derivative may be in any of d-, l-, and dl-forms, the dl-form may be preferred. Moreover, while the tocopherol derivative may be in any

of α-, β-, γ-, and δ-forms, the α-form may be preferred.

[0021]

As component (B) in the pharmaceutical composition for external use of the present invention, one of tocopherols and derivatives thereof may be selected and used alone, or two or more of them may be used in combination. Among components (B), a tocopherol derivative may be preferred, an ester of a tocopherol with a carboxylic acid may be more preferred, tocopherol acetate may be even more preferred, and d-α-tocopherol acetate, l-α-tocopherol acetate, and dl-α-tocopherol acetate may be particularly preferred.

[0022]

While the content of component (B) in the pharmaceutical composition for external use of the present invention is not particularly limited, it may be 0.01 to 2 wt%, for example, preferably 0.05 to 1.5 wt%, and more preferably 0.1 to 1 wt%.

(C) Lactic acid and/or a salt thereof

The pharmaceutical composition for external use of the present invention contains lactic acid and/or a salt thereof (hereinafter sometimes also denoted as "component (C)"). The inclusion of lactic acid and/or a salt thereof can suppress yellowing that occurs with time or under high temperature conditions to provide excellent storage stability.

[0023]

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.

[0024]

As component (C) 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 (C), 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 providing even further improved storage stability.

[0025]

While the content of component (C) in the pharmaceutical composition for external use of the present invention is not particularly limited, it may be 0.01 to 1.5 wt%, for example, preferably 0.05 to 1 wt%, and more preferably 0.05 to 0.6 wt%.

(D) Water

The pharmaceutical composition for external use of the present invention contains water (hereinafter sometimes also denoted as "component (D)") so that the above-described components (A) to (C)are present together in water.

[0026]

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 15 to 50 wt%, for example. In general, when diclofenac and/or a salt thereof and a tocopherol and/or a derivative thereof are present together under conditions having a high water content, i.e., 15 wt% or more, and particularly 20 wt% or more, yellowing that occurs with time or under high temperature conditions becomes 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, yellowing that occurs with time or under high temperature conditions 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 15 to 45 wt%, more preferably 20 to 45 wt%, particularly preferably 20 to 24 wt%, and most preferably 20.3 to 23.3 wt%.

(E) Menthol

The pharmaceutical composition for external use of the present invention may optionally contain menthol (hereinafter sometimes also denoted as "component (E)"). The inclusion of menthol can suppress cloudiness that occurs in the presence of

diclofenac and/or a salt thereof, a tocopherol and/or a derivative thereof, and water, leading to excellent appearance characteristics with high transparency. The inclusion of menthol can further impart a cool feeling to the skin upon application, leading to a good feeling of use.

[0027]

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

[0028]

In the pharmaceutical composition for external use of the present invention, an essential oil containing menthol may be used as component (E). 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.

[0029]

Among components (E), l-menthol and an essential oil containing l-menthol may be preferred, in view of even more effectively suppressing cloudiness and precipitation that occur in the presence of diclofenac and/or a salt thereof, a tocopherol and/or a derivative thereof, and water.

[0030]

While the content of component (E) in the pharmaceutical composition for external use of the present invention is not particularly limited, it may be 1 wt% or more, for example, preferably 1 to 15 wt%, more preferably 3 to 10 wt%, particularly preferably 5 to 10 wt%, and most preferably 5 to 8 wt%.

(F) Lower alcohol

The pharmaceutical composition for external use of the present invention may optionally contain a lower alcohol (hereinafter sometimes also denoted as "component (F)"). The inclusion of a lower alcohol can suppress cloudiness and the formation of precipitate that occur in the presence of diclofenac and/or a salt thereof, a tocopherol and/or a derivative thereof, and water.

[0031]

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, isopropanol, and isopropanol may be preferred, and ethanol may be more preferred, in view of even more effectively suppressing cloudiness and precipitation that occur in the presence of diclofenac and/or a salt thereof, a tocopherol and/or a derivative thereof, and water. These lower alcohols may be used alone, or in combination or two or more.

[0032]

While the content of component (F) in the pharmaceutical composition for external use of the present invention is not particularly limited, it may be 50 to 80 wt%, for example, preferably 55 to 75 wt%, and more preferably 55 to 70 wt%.

Other components

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.

[0033]

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 (F), to be formulated into a desired dosage form.

[0034]

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

[0035]

Examples of oily bases include nonpolar oils and polar oils. Specific examples of nonpolar oils include hydrocarbons such as paraffins and isoparaffins; and squalane and waxes. Specific examples of polar oils include aliphatic monocarboxylic acid esters, triglyceride, aliphatic dicarboxylic acid diesters, aliphatic dicarboxylic acid alkylene glycol esters, and higher fatty acids.

[0036]

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

While the pH of the pharmaceutical composition for external use of the invention may be set as appropriate within a range where the pharmaceutical composition can be percutaneously applied, the pH may be 3.0 to 9.0, for example,

preferably 4.0 to 9.0, and more preferably 4.5 to 9.0.

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, 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.

[0037]

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 yellowing

The present invention also provides a method for suppressing yellowing that occurs with time or under high temperature conditions in a pharmaceutical composition for external use containing (A) diclofenac and/or a pharmacologically

acceptable salt thereof, (B) a tocopherol and/or a derivative thereof, and (D) water. Specifically, the method for suppressing yellowing of the present invention is characterized in that it includes blending (C) lactic acid and/or a salt thereof into a pharmaceutical composition for external use containing (A) diclofenac and/or a pharmacologically acceptable salt thereof, (B) a tocopherol and/or a derivative thereof, and (D) water. In the method for suppressing yellowing 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

[0038]

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 (only in Examples 1 and 2) were added and dissolved in a predetermined amount of ethanol, and a predetermined amount of tocopherol acetate (dl-α-tocopherol acetate) and a predetermined amount of lactic acid or sodium lactate were further added and stirred. Next, predetermined amounts of water and hydroxypropylcellulose (only in Example 2) were added and stirred, thus obtaining pharmaceutical compositions for external use (as liquids in the examples except for Example 2, and as a gel in Example 2).

[0039]

Each of the obtained pharmaceutical compositions for external use was stored at 60°C for 1 week under light-tight conditions. The appearance characteristics of each pharmaceutical composition for external use before and after storage were visually evaluated. Specifically, the appearance characteristics were evaluated in

accordance with the following determination criteria:

<Determination criteria for appearance characteristics>

A: not cloudy, colorless and transparent.

B: cloudy but colorless, and a yellow tone is not observed.

C: cloudy, and a yellow tone corresponding to PANTONE 712C is observed.

D: cloudy, and a yellow tone corresponding to PANTONE 713C is observed.

E: cloudy, and a yellow tone corresponding to PANTONE 714C or 715C is observed.

[0040]

Note that PANTONE 712C, 713C, 714C, and 715C are color sample numbers in the color sample Formula Guide Solid Coated published by Pantone LLC, and all assume yellow tones, with the depth of yellow increasing in the order of 712C<713C<714C<715C.

[0041]

The obtained results are shown in Tables 1 and 2. When diclofenac sodium and tocopherol acetate were present together in the presence of water, yellowing was observed after storage (Comparative Examples 1 to 3). In particular, in Comparative Example 1, the formation of precipitate was also observed. Further, when acetic acid was present together with diclofenac sodium and tocopherol acetate in the presence of water, yellowing was observed after storage (Comparative Example 2). On the other hand, when lactic acid or sodium lactate was present together with diclofenac sodium and tocopherol acetate in the presence of water, no change in color tone was seen even after storage, and yellowing was suppressed (Examples 1 to 10). Moreover, when lactic acid and menthol were present together with diclofenac sodium and tocopherol acetate in the presence of water, cloudiness was suppressed, and a colorless and transparent state was retained even after storage (Examples 1 and 2).

[0042]

[Table 1]

	Examples									
	1	2	3	4	5	6	7	8	9	10
Diclofenac Sodium	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Tocopherol Acetate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Lactic Acid	0.6	0.6	0.6	0.3	0.3	0.15	0.15	0.05	0.05	-
Sodium Lactate	-	-	-	-	-	-	-	-	-	0.3
Acetic Acid	-	-	-	-	-	-	-	-	-	-
l-Menthol	5.0	5.0	-	-	-	-	-	-	-	-
Ethanol	70.0	70.0	70.0	70.0	55.0	70.0	55.0	70.0	55.0	70.0
Hydroxypropylcellulose	-	3.0	-	-	-	-	-	-	-	-
Purified Water	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance
Total Amount	100	100	100	100	100	100	100	100	100	100
Appearance Characteristics before Storage	A	A	B	B	B	B	B	B	B	B
Appearance Characteristics after Storage	A	A	B	B	B	B	B	B	B	B

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

[0043]

[Table 2]

	Comparative Examples			
	1	2	3	4
Diclofenac Sodium	1.0	1.0	1.0	1.0
Tocopherol Acetate	0.1	0.1	0.1	0.1
Lactic Acid	-	-	-	-
Sodium Lactate	-	-	-	-
Acetic Acid	-	-	-	0.3
l-Menthol	-	-	-	-
Ethanol	70.0	55.0	50.0	70.0
Hydroxypropylcellulose	-	-	-	-
Purified Water	Balance	Balance	Balance	Balance
Total Amount	100	100	100	100
Appearance Characteristics before Storage	B	B	B	B
Appearance Characteristics after Storage	E	E	E	D

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

[0044]

Formulation Examples

Pharmaceutical compositions for external use of the compositions shown in Table 3 (as liquids in Formulation Examples 1, 3 and 5, and gels in Formulation Examples 2, 4 and 6) were prepared. All of the obtained pharmaceutical compositions for external use had excellent appearance characteristics that were colorless and transparent, and no yellowing or cloudiness was observed even after storage at 60°C for 1 week.

[0045]

[Table 3]

	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) a tocopherol and/or a derivative thereof, (C) lactic acid and/or a salt thereof, and (D) water.

[Claim 2]

The pharmaceutical composition for external use according to claim 1, further comprising (E) menthol.

[Claim 3]

The pharmaceutical composition for external use according to claim 1 or 2, further comprising (F) a lower alcohol.

[Claim 4]

The pharmaceutical composition for external use according to any of claims 1 to 3, wherein a content of the component (C) is 0.05 to 1 wt%.

[Claim 5]

The pharmaceutical composition for external use according to any of claims 1 to 4, wherein a content of the component (D) is 15 to 50 wt%.

[Claim 6]

The pharmaceutical composition for external use according to any of claims 2 to 5, wherein a content of the component (E) is 5 wt% or more.

[Claim 7]

The pharmaceutical composition for external use according to any of claims 1

to 6, wherein the component (B) is tocopherol acetate.

[Claim 8]

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

[Claim 9]

A method for suppressing yellowing of a pharmaceutical composition for external use comprising blending (C) lactic acid and/or a salt thereof into a pharmaceutical composition for external use comprising (A) diclofenac and/or a pharmacologically acceptable salt thereof, (B) a tocopherol and/or a derivative thereof, and (D) water.