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 cloudiness and the formation of precipitate are suppressed.

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, diclofenac and/or a salt thereof and a tocopherol and/or a derivative thereof differ in polarity from each other, and therefore, although they 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, they cannot be solubilized, and causes cloudiness or the formation of precipitate.

[0007]

It is accordingly an object of the present invention to provide a formulation technique that can suppress cloudiness and the formation of precipitate to provide excellent appearance characteristics, while incorporating diclofenac 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 menthol 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, cloudiness and the formation of precipitate due to diclofenac and/or a salt thereof and a tocopherol and/or a derivative thereof can be suppressed, and excellent appearance characteristics can be provided in the pharmaceutical composition for external use. The inventor also found that although the pharmaceutical composition for external use containing diclofenac and/or a salt thereof, a tocopherol and/or a derivative thereof, and water is turned into yellow (yellowing) with time or under high temperature conditions, such yellowing can be reduced by blending menthol into 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) menthol, and (D) water.

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

Item 3. The pharmaceutical composition for external use according to item 1 or 2, wherein a content of the component (C) is 3 wt% or more.

Item 4. The pharmaceutical composition for external use according to any of items 1 to 3, wherein a content of the component (D) is 15 to 45 wt%.

Item 5. The pharmaceutical composition for external use according to any of items 2 to 4, wherein a content of the component (E) is 50 wt% or more.

Item 6. The pharmaceutical composition for external use according to any of items 1 to 5, wherein the component (B) is tocopherol acetate.

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 cloudiness and precipitation in a pharmaceutical composition for external use, the method including blending (C) menthol 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.

Item 9. A method for reducing yellowing of a pharmaceutical composition for external use, the method including blending (C) menthol 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, cloudiness and the formation of precipitate can be suppressed, and excellent appearance characteristics can be provided. Moreover, in the pharmaceutical composition for external use of the present invention, even when the water content is relatively high, i.e., 15 wt% or more, cloudiness and the formation of precipitate can be effectively suppressed, and excellent appearance characteristics can be provided, such that the pharmaceutical composition for external use of the present invention has less constraints on the formulation design, and can be used for various pharmaceutical formulae. Further, in

the pharmaceutical composition for external use of the present invention, yellowing that occurs with time or under high temperature conditions can also be reduced.

[0011]

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

[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) a tocopherol and/or a derivative thereof, (C) menthol, 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.

[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) 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.

[0017]

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.

[0018]

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.

[0019]

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.

[0020]

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.

[0021]

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) 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 cloudiness and the formation of precipitate, and can provide excellent appearance characteristics. The inclusion of menthol can also reduce yellowing that occurs with time or under high temperature conditions. The inclusion of menthol can further impart a cool feeling to the skin upon application, leading to a good feeling of use.

[0022]

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

[0023]

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.

[0024]

Among components (C), l-menthol and an essential oil containing l-menthol may be preferred, in view of even more effectively suppressing cloudiness and the formation of precipitate, and even more effectively reducing yellowing that occurs with time or under high temperature conditions.

[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 1 wt% or more, for example, and preferably 1 to 15 wt%. In view of even more effectively suppressing cloudiness and the formation of precipitate, and even more effectively reducing yellowing that occurs with time or under high temperature conditions, the content of component (C) is preferably 3 wt% or more, more preferably 3 to 15 wt%, particularly preferably 3 to 10 wt%, and most preferably 5 to 10 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 water content of 15 wt% or more, and particularly 20 wt% or more, cloudiness or the formation of precipitate 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, cloudiness or the formation of precipitate can be suppressed, and excellent appearance characteristics can be provided. 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 15 to 40 wt%, particularly preferably 18 to 36 wt%, and most preferably 18.9 to 28.9 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)"). The inclusion of a lower alcohol can even more effectively suppress cloudiness and the formation of precipitate.

[0027]

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, and ethanol and isopropanol 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.

[0028]

While the content of component (E) in the pharmaceutical composition for external use of the present invention is not particularly limited, it may be 45 wt% or more, for example. In view of even more effectively suppressing cloudiness and the formation of precipitate, the content of component (E) may be 50 wt% or more, preferably 50 to 80 wt%, more preferably 55 to 80 wt%, particularly preferably 60 to 75 wt%, and most preferably 65 to 75 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.

[0029]

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.

[0030]

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.

[0031]

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.

[0032]

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 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, 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.

[0033]

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 precipitation 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 precipitation of the present invention is 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, (B) a tocopherol and/or a derivative thereof, and (D) water. 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.

3. Method for reducing yellowing

The present invention also provides a method for reducing 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 reducing yellowing of the present invention is 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, (B) a tocopherol and/or a derivative thereof, and (D) water. In the method for reducing 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

[0034]

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 then a predetermined amount of tocopherol acetate (dl-α-tocopherol acetate) was further added and stirred. Next, predetermined amounts of water and hydroxypropylcellulose (only in Example 7) were added and stirred, thus obtaining pharmaceutical compositions for external use (as liquids in the examples except for Example 7, and as a gel in Example 7).

[0035]

The appearance characteristics of each of the pharmaceutical compositions for external use after being stored at 25°C for 1 day under light-tight conditions were evaluated. Moreover, the degree of cloudiness of each of the pharmaceutical compositions for external use was also evaluated by measuring the absorbance at a wavelength of 400 nm using a UV-VIS spectrophotometer (UV-2600 from Shimadzu Corporation). 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: A clear state accompanied by no formation of precipitate and cloudiness.

B: A practically acceptable level of semi-transparent state accompanied by no formation of precipitate and slight cloudiness.

C: An opaque state accompanied by visible cloudiness, but without formation of precipitate.

D: An opaque state accompanied by significant cloudiness, but without formation of precipitate.

E: An opaque state accompanied by the formation of precipitate and significant cloudiness.

[0036]

The obtained results are shown in Tables 1 and 2. When diclofenac sodium and tocopherol acetate were present together in the presence of water, the formation of precipitate or significant cloudiness was observed (Comparative Examples 1 to 3). On the other hand, when menthol was present together with diclofenac sodium and tocopherol acetate in the presence of water, the formation of precipitate or cloudiness was suppressed, and transparency was improved, resulting in excellent appearance characteristics (Examples 1 to 10). Moreover, when l-menthol was present together with diclofenac sodium and tocopherol acetate in the presence of water, further addition of isopropanol as a lower alcohol thereto resulted in appearance characteristics having transparency even higher than that in the cases where ethanol was added (Examples 8 and 9).

[0037]

[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	0.5	1.0	0.1	0.1	0.1	0.1	0.1
l-Menthol	3.0	3.0	5.0	5.0	10.0	3.0	5.0	3.0	3.0	3.0
Ethanol	75.0	70.0	70.0	70.0	70.0	65.0	65.0	60.0	-	55.0
Isopropanol									60.0	
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	A	A	A	A	A	A	A	A	A	B
Absorbance (400 nm)	0.004	0.005	0.001	0.008	0.02	0.005	0.015	0.057	0.005	0.175

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

[0038]

[Table 2]

	Comparative Examples		
	1	2	3
Diclofenac Sodium	1.0	1.0	1.0
Tocopherol Acetate	0.1	0.1	0.1
l-Menthol	-	-	-
Ethanol	70.0	60.0	55.0
Isopropanol	-	-	-
Hydroxypropylcellulose	-	-	-
Purified Water	Balance	Balance	Balance
Total Amount	100	100	100
Appearance Characteristics	E	D	D
Absorbance (400 nm)	Not Measured	0.453	1.353

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

[0039]

Test Example 2

Pharmaceutical compositions for external use of the compositions shown in Table 3 were prepared in the same manner as that in Test Example 1 described above. Each of the obtained pharmaceutical compositions for external use was stored at 60°C for 1 week under light-tight conditions. The appearance characteristics before and after storage were evaluated using the same method as that in Test Example 1 described above. Further, the degree of yellowing after storage was evaluated in accordance with the following determination criteria:

<Determination criteria for yellowing>

A: A yellow tone corresponding to PANTONE 712C is observed.

B: A yellow tone corresponding to PANTONE 713C is observed.

C: A yellow tone corresponding to PANTONE 714C is observed.

D: A yellow tone corresponding to PANTONE 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 Table 3. The results show that as in Test Example 1 above, when l-menthol was present together with diclofenac sodium and tocopherol acetate in the presence of water, the formation of precipitate or cloudiness was suppressed to improve the transparency (Examples 11 to 13). In particular, when the content of ethanol was 55 wt% or more, the effect of suppressing the formation of precipitate or cloudiness was improved, and appearance characteristics with remarkably high transparency were achieved, even after storage. Moreover, when l-menthol was present together with diclofenac sodium and tocopherol acetate in the presence of water, yellowing after storage was reduced (Examples 11 to 13).

[0042]

[Table 3]

	Examples			Comparative Examples		
	11	12	13	4	5	6
Diclofenac Sodium	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
l-Menthol	5.0	5.0	5.0	-	-	-
Ethanol	70.0	55.0	50.0	70.0	55.0	50.0
Purified Water	Balance	Balance	Balance	Balance	Balance	Balance
Total Amount	100	100	100	100	100	100
Appearance Characteristics before Storage	A	A	B	D	D	D
Appearance Characteristics after Storage	A	A	B	D	D	D
Degree of Yellowing after Storage	A	B	B	C	D	C

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

[0043]

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. All of the obtained pharmaceutical compositions for external use had excellent appearance characteristics with high transparency, with the formation of precipitate or cloudiness being suppressed. Moreover, the effect of reducing yellowing after storage was also observed in these pharmaceutical compositions for external use.

[0044]

[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) 0.2 to 2 wt% of a pharmacologically acceptable salt of diclofenac, (B) 0.1 to 1 wt% of at least one member selected from the group consisting of tocopherol, esters of tocopherol and carboxylic acid, and diesters of tocopherol and phosphoric acid, (C) 1 wt% or more of menthol, (D) water, and (E) 50 to 75 wt% of a lower alcohol.

[Claim 2]

The pharmaceutical composition for external use according to claim 1, wherein a content of the component (D) is 15 to 45 wt%.

[Claim 3]

The pharmaceutical composition for external use according to claim 1 or 2, wherein the component (B) is tocopherol acetate.

[Claim 4]

The pharmaceutical composition for external use according to any of claims 1 to 3, which is a liquid or a gel.

[Claim 5]

A method for suppressing cloudiness and precipitation in a pharmaceutical composition for external use, the method comprising blending (C) 1 wt% or more of menthol into a pharmaceutical composition for external use comprising (A) 0.2 to 2 wt% of a

pharmacologically acceptable salt of diclofenac, (B) 0.1 to 1 wt% of at least one member selected from the group consisting of tocopherol, esters of tocopherol and carboxylic acid, and diesters of tocopherol and phosphoric acid, (D) water, and (E) 50 to 75 wt% of a lower alcohol.

[Claim 6]

A method for reducing yellowing of a pharmaceutical composition for external use, the method comprising blending (C) 1 wt% or more of menthol into a pharmaceutical composition for external use comprising (A) 0.2 to 2 wt% of a pharmacologically acceptable salt of diclofenac, (B) 0.1 to 1 wt% of at least one member selected from the group consisting of tocopherol, esters of tocopherol and carboxylic acid, and diesters of tocopherol and phosphoric acid, (D) water, and (E) 50 to 75 wt% of a lower alcohol.