DESCRIPTION

Title of Invention: COMPOSITION FOR EXTERNAL USE

Technical Field

[0001]

The present invention relates to a composition for external use.

Background Art

[0002]

Loxoprofen and pharmaceutically acceptable salts thereof (these are also collectively referred to as “loxoprofens” in the present specification), which are propionic acid-based non-steroidal antipyretic, analgesic, anti-inflammatory drugs (NSAIDs), have antipyretic action, analgesic action, and anti-inflammatory action based on the inhibitory action of prostaglandin biosynthesis, as with other NSAIDs.

[0003]

Various external preparations comprising loxoprofen as an active component for antipyretic action, analgesic action, and/or anti-inflammatory action have been developed (PTL 1). Moreover, various external preparations comprising diclofenac, which is also an NSAID, further in combination with a warm feeling component, have been proposed (PTL 2).

[0004]

For example, PTL 1 discloses a composition for external use comprising diclofenac in combination with capsaicinoid etc. as a warm feeling component.

Citation List

Patent Literature

[0005]

PTL 1: JP2015-98469A

PTL 2: JP2011-74032A

Summary of Invention

Technical Problem

[0006]

The present inventor found that a composition for external use comprising loxoprofen in combination with capsaicinoid etc. as a warm feeling component, and using a $C_{1-4}$ alcohol as a solvent (such alcohols are also collectively referred to as "lower alcohols" in the present specification) tended to brown with time. An object of the present invention is to provide a composition for external use that is prevented from browning with time.

Solution to Problem

[0007]

As a result of extensive research to achieve the above object, the present inventor found that when a composition was mixed with a lower alcohol in an amount of 55 mass% or more based on the entire composition, browning with time was prevented. The present invention has been completed upon further studies based on this finding, and includes the following embodiments.

[0008]

(I) Composition for External Use

(I-1) A composition for external use comprising loxoprofen or a pharmaceutically acceptable salt thereof, capsaicinoid, and a $C_{1-4}$ alcohol; wherein the alcohol is contained in an amount of 55 mass% or more based on the entire composition.

(I-2) The composition for external use according to (I-1), wherein the capsaicinoid is nonanoic acid vanillylamide.

(I-3) The composition for external use according to (I-1) or (I-2), further comprising an ester derivative of nicotinic acid.

(I-4) The composition for external use according to any one of (I-1) to (I-3), for use in analgesia.

(I-5) The composition for external use according to any one of (I-1) to (I-4), which is a liquid formulation.

[0009]

(II) Method for Preventing Browning with Time of Composition Comprising Loxoprofen and Capsaicinoid

(II-1) A method for preventing browning with time of a composition comprising loxoprofen or a pharmaceutically acceptable salt thereof, capsaicinoid, and a $C_{1-4}$ alcohol; the method comprising the step of adjusting the content ratio of the alcohol based on the entire composition to 55 mass% or more.

(II-2) The method according to (II-1), wherein the capsaicinoid is nonanoic acid vanillylamide.

(II-3) The method according to (II-1) or (II-2), wherein the composition further comprises an ester derivative of nicotinic acid.

(II-4) The method according to any one of (II-1) to (II-3), wherein the composition is a liquid formulation.

Advantageous Effects of Invention

[0010]

The present invention can provide a composition that comprises loxoprofen or a pharmaceutically acceptable salt thereof, capsaicinoid, and a $C_{1-4}$ alcohol, and that is prevented from browning with time.

Brief Description of Drawing

[0011]

Fig. 1 shows photographs showing the browning observation results of Example 1 and Comparative Example 3.

Description of Embodiments

[0012]

1. Composition for External Use and Preparation Method Thereof

The composition for external use of the present invention comprises loxoprofen or a pharmaceutically acceptable salt thereof (loxoprofens), capsaicinoid, and a $C_{1-4}$ alcohol; wherein the alcohol is contained in an amount of 55 mass% or more

based on the entire composition.

[0013]

1.1. Loxoprofen and Pharmaceutically Acceptable Salt Thereof (Loxoprofens)

The composition for external use of the present invention comprises loxoprofen as an active component for at least one action selected from antipyretic action, analgesic action, and anti-inflammatory action.

[0014]

Loxoprofen (2-[4-(2-oxocyclopentylmethyl)phenyl]propionic acid) is a propionic acid-based non-steroidal antipyretic, analgesic, anti-inflammatory drug (NSAID) having antipyretic action, analgesic action, and anti-inflammatory action.

[0015]

In the present invention, in addition to loxoprofen itself, a pharmaceutically acceptable salt thereof can also be used. Such salts include solvates of loxoprofen or a pharmaceutically acceptable salt thereof, and water or alcohol, etc. These are known compounds and can be produced by a known method. Further, commercially available products can also be used.

[0016]

In the present invention, the loxoprofen or the pharmaceutically acceptable salt thereof is preferably loxoprofen sodium hydrate.

[0017]

The content of loxoprofen may be an efficacy effective amount, and is not limited. The content thereof in terms of loxoprofen sodium anhydride can be set to, for example, 0.1 to 10 mass%, preferably 0.5 to 5 mass%, and more preferably 0.5 to 3 mass%, based on the entire composition for external use of the present invention.

[0018]

1.2. Capsaicinoid

The composition for external use of the present invention comprises capsaicinoid as an active component for warm feeling action.

[0019]

N-acylvanillylamide can be used as the capsaicinoid. N-acylvanillylamide is a compound known as a blood circulation promoter.

[0020]

The acyl group in N-acylvanillylamide may be linear or branched. The number of carbon atoms of the acyl group in N-acylvanillylamide is not limited, and is, for example, 5 to 15, and preferably 6 to 11.

[0021]

Specific examples of N-acylvanillylamide include nonanoic acid vanillylamide; capsaicins, such as capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, and homodihydrocapsaicin; and the like.

[0022]

In the present invention, the capsaicinoid may be a refined product, and a mixture containing other components in addition to capsaicinoid may also be used. Specific examples of the capsaicinoid-containing mixture include capsicums, such as capsicum extract, capsicum tincture, and capsicum powder.

[0023]

In the present invention, the capsaicinoids may be used singly or in combination of two or more. Of the capsaicinoids, nonanoic acid vanillylamide is preferable, because it is more likely to exhibit an effect of preventing browning with time when combined with ethanol.

[0024]

The content of capsaicinoid in the present invention may be an efficacy effective amount, and is not limited. The content can be set to, for example, 0.002 to 0.2 mass% based on the entire composition for external use of the present invention. In terms of the effect of preventing browning with time, the

content can be preferably set to 0.003 to 0.05 mass%, and more preferably 0.01 to 0.015 mass%.

[0025]

The ratio of capsaicinoid can also be set in consideration of the ratio thereof to loxoprofen contained in the composition for external use. Specifically, the ratio of capsaicinoid is generally set within a range of 0.002 to 0.2 parts by mass, preferably 0.003 to 0.05 parts by mass, and more preferably 0.01 to 0.015 parts by mass, based on 1 part by mass of loxoprofen contained in the composition for external use.

[0026]

1.3. Ester Derivative of Nicotinic Acid

The composition for external use of the present invention can further comprise an ester derivative of nicotinic acid as an active component for warm feeling action. According to the present invention, even if an ester derivative of nicotinic acid is contained, a composition for external use having excellent properties can be obtained, without further generating browning.

[0027]

In a preferable embodiment, the composition for external use of the present invention further comprises an ester derivative of nicotinic acid, thereby further increasing the effect of preventing browning with time.

[0028]

The ester derivative of nicotinic acid is not limited, as long as it is pharmaceutically acceptable. Ester derivatives of nicotinic acid can be widely used. Examples include nicotinic acid benzyl ester, nicotinic acid β-butoxy ethyl ester, nicotinic acid methyl ester, and the like. These ester derivatives of nicotinic acid may be used singly or in combination of two or more. Of the ester derivatives of nicotinic acid, nicotinic acid benzyl ester is preferable.

[0029]

The content of the ester derivative of nicotinic acid

in the present invention may be an efficacy effective amount, and is not limited. The content can be set to, for example, 0.002 to 0.2 mass% based on the entire composition for external use of the present invention. In terms of the effect of preventing browning with time, the content can be preferably set to 0.003 to 0.05 mass%, and more preferably 0.008 to 0.015 mass%.

[0030]

The ratio of the ester derivative of nicotinic acid can also be set in consideration of the ratio thereof to loxoprofen contained in the composition for external use. Specifically, the ratio of the ester derivative of nicotinic acid is generally set within a range of 0.002 to 0.2 parts by mass, preferably 0.003 to 0.05 parts by mass, and more preferably 0.008 to 0.015 parts by mass, based on 1 part by mass of loxoprofen contained in the composition for external use.

[0031]

1.4. $C_{1-4}$ Alcohol (Lower Alcohol)

The lower alcohol is not limited, and lower alcohols can be widely used as long as they function as bases effective for the above active components.

[0032]

Specific examples of lower alcohols include methanol, ethanol, propyl alcohol, isopropyl alcohol, and the like; and preferably ethanol.

[0033]

The composition for external use of the present invention comprises a lower alcohol in an amount of 55 mass% or more based on the entire composition. The composition for external use of the present invention is thereby prevented from browning with time.

[0034]

The composition for external use of the present invention preferably comprises a lower alcohol in an amount of 90 mass% or less, and more preferably 80 mass% or less, based on the entire composition, in terms of preventing skin irritation.

[0035]

The composition for external use of the present invention preferably comprises a lower alcohol in an amount of 60 mass% or more based on the entire composition, in terms of the effect of preventing browning with time.

[0036]

Therefore, the composition for external use of the present invention comprises a lower alcohol in an amount of 55 to 90 mass% based on the entire composition, whereby browning with time of the composition for external use can be prevented while preventing skin irritation. In this respect, the lower alcohol is preferably contained in an amount of 60 to 90 mass%, and more preferably 60 to 80 mass%, based on the entire composition.

[0037]

1.5. Other Components

The composition for external use of the present invention may further comprise a cooling agent in addition to the above components, as long as the effects of the present invention are not impaired.

[0038]

Examples of such cooling agents include l-menthol, d-menthol, dl-menthol, d-camphor, dl-camphor, d-borneol, dl-borneol, menthane, menthyl lactate, geraniol, eucalyptus oil, turpentine oil, bergamot oil, fennel oil, mentha oil (peppermint), rose oil, cool mint, and the like. These cooling agents may be used singly or in combination of two or more.

[0039]

Preferable examples of the cooling agent contained in the composition for external use of the present invention include l-menthol, d-menthol, dl-menthol, d-borneol, dl-borneol, menthane, mentha oil (peppermint), and cool mint; more preferably menthol; and particularly preferably l-menthol.

[0040]

The composition for external use of the present invention may further comprise a drug effect adjuvant in addition

to the above components, as long as the effects of the present invention are not impaired.

[0041]

Examples of such drug effect adjuvants include anti-inflammatory agents and skin protective agents, such as glycyrrhetic acid, dipotassium glycyrrhizinate, ammonium glycyrrhizinate, and stearyl glycyrrhizinate; antihistamines, such as diphenylimidazole, diphenhydramine and pharmaceutically acceptable salts thereof, and chlorpheniramine maleate; blood circulation promoters, such as tocopherol acetate; herbal medicines, such as arnica tincture, phellodendron bark extract, gardenia fruit extract, horse chestnut extract, scopolia extract, belladonna extract, Angelica acutiloba extract, lithospermum root extract, Sichuan pepper extract, and the like.

[0042]

In addition to the above components, the composition for external use of the present invention may suitably contain active components that can be used in combination, and additives used for general compositions for external use, such as pH regulators, antiseptics, preservatives, antioxidants, and stabilizers.

[0043]

1.6. Form and Production Method

The form of the composition for external use of the present invention is not limited, and is preferably a liquid formulation (including lotions, sprays, aerosols, and milky lotions).

[0044]

The composition for external use of the present invention can be prepared by a standard method depending on the dosage form. For example, loxoprofen, capsaicinoid, and optionally an ester derivative of nicotinic acid, are mixed with a general-purpose base comprising a lower alcohol for use in external preparations described below, and dissolved or dispersed. Then, the pH is adjusted to a desired value. The pH is

not limited within a range in which the skin is not adversely affected. The pH is generally adjusted to 3.5 to 8.5, preferably 4 to 8, and more preferably 4 to 7.5.

[0045]

For example, when the composition for external use of the present invention is prepared as a liquid formulation, it can be prepared by mixing loxoprofen, capsaicinoid, and further optionally an ester derivative of nicotinic acid, with a base comprising a lower alcohol as a main component. The base can be mixed with at least one member selected from glycols, water, and emulsifiers.

[0046]

The glycols are not limited. Examples include glycerol, propylene glycol, 1,3-butylene glycol, octanediol, ethylene glycol, polyethylene glycol, D-sorbitol, and the like. Glycerol, propylene glycol, and 1,3-butylene glycol are preferable. The glycols may be used singly or in combination of two or more.

[0047]

The emulsifiers are not limited. Examples include nonionic surfactants, such as sorbitan fatty acid esters, glycerol fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyl stearate, and lauromacrogol; and the like. The emulsifiers may be used singly or in combination of two or more.

[0048]

The composition for external use of the present invention is preferably prepared as an external preparation in a coating form, and can be externally administered locally. The dose of the composition for external use of the present invention depends on the degree of symptom to be treated; however, a desired amount is such that the application dose of loxoprofen, which is an active component contained therein, per day is 100 mg or less.

[0049]

The composition for external use of the present invention can be suitably used, as an anti-inflammatory,

analgesic drug for external use, for the purpose of relieving pain, such as shoulder pain caused by stiff shoulders, arthritic pain, low back pain, muscular pain, tenosynovitis (pain in the hand and wrist), elbow pain (tennis elbow etc.), blow pain, sprain pain, bone fracture pain, and neuralgia.

[0050]

2. Method for Preventing Browning with Time of Composition Comprising Loxoprofen and Capsaicinoid

The method of the present invention is a method for preventing browning with time of a composition comprising loxoprofen or a pharmaceutically acceptable salt thereof, capsaicinoid, and a $C_{1-4}$ alcohol; the method comprising the step of adjusting the content ratio of the alcohol based on the entire composition to 55 mass% or more.

[0051]

The components, including loxoprofen and capsaicinoid, mixed in the composition are as described in item (I) above regarding the composition for external use of the present invention.

[0052]

The step of adjusting the content ratio of the alcohol based on the entire composition to 55 mass% or more is not limited, and can be performed by mixing each component, as described in item (I) above regarding the composition for external use of the present invention. The mixing order is not limited.

[0053]

Moreover, an embodiment of the method of the present invention in which the method can exhibit a higher effect is an embodiment in which the composition further comprises an ester derivative of nicotinic acid, in addition to loxoprofen and capsaicinoid.

Examples

[0054]

The present invention is described below with reference to Examples; however, the present invention is not limited to these Examples etc. The unit in the table represents mass (g) per 100 g of the composition (i.e., mass%).

[0055]

As shown in Table 1, each component was weighed in each amount and dissolved by stirring, thereby preparing liquid compositions (Examples 1 to 6 and Comparative Examples 1 to 4).

[0056]

Table 1

| | Example | | | | | | Comparative Example | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 1 | 2 | 3 | 4 |
| Loxoprofen sodium hydrate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | - | 1 | 1 |
| Nonanoic acid vanillylamide | 0.012 | 0.012 | 0.012 | 0.012 | 0.012 | 0.012 | - | 0.012 | 0.012 | 0.012 |
| Nicotinic acid benzyl ester | - | - | - | 0.010 | 0.1 | 0.010 | - | - | - | 0.010 |
| Ethanol | 55 | 70 | 80 | 55 | 55 | 70 | 20 | 20 | 20 | 20 |
| Purified water | Remnant | Remnant | Remnant | Remnant | Remnant | Remnant | Remnant | Remnant | Remnant | Remnant |
| Total amount | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Properties of composition stored at 60°C for 1 month | ◎ | ◎ | ◎ | ◎ | ◎ | ◎ | × | △ | × | × |

[0057]

The obtained compositions were each placed in a screw tube (No. 5, produced by Maruemu Corporation; diameter: 27 mm, height: 55 mm) and stored at 60°C for one month. Then, their properties were observed. Compositions that were transparent by visual observation were evaluated as "◎," and compositions that most tended to brown were evaluated as "×." The compositions were evaluated on four scales "×," "△," "○," and "◎," in decreasing order of badness. Table 1 shows the results. Fig. 1 shows photographs evaluated as "◎" and "×." The left side is a photograph evaluated as "◎" (Example 1), and the right side is a photograph evaluated as "×" (Comparative Example 3).

[0058]

As shown in Table 1, the compositions comprising 20 mass% of ethanol and one or both of loxoprofen sodium hydrate and nonanoic acid vanillylamide tended to brown with time (Comparative Examples 1 to 4).

[0059]

In contrast, the compositions comprising 55 mass% or more of ethanol did not tend to brown even after storage in the same manner, and were still highly transparent (Examples 1 to 6).

[0060]

Based on Comparative Example 3 in which the ethanol content was 20 mass%, even when nicotinic acid benzyl ester was further added thereto, browning was still observed (Comparative Example 4). In contrast, browning could be prevented only by changing the ethanol content to 55 mass% or more (Examples 4 to 6), based on Comparative Example 3. This demonstrates that a browning preventing effect is obtained by adjusting the ethanol content to 55 mass% or more.

[0061]

The browning prevention effect in the presence of nicotinic acid benzyl ester (Examples 4 to 6) tended to be more significant than the browning prevention effect in the absence of nicotinic acid benzyl ester (Examples 1 and 2). Thus, it was

revealed that the browning prevention effect due to an ethanol content of 55% or more was significantly increased in the presence of nicotinic acid benzyl ester.

5

# CLAIMS

[Claim 1]

A composition for external use comprising loxoprofen or a pharmaceutically acceptable salt thereof, capsaicinoid, a $C_{1-4}$ alcohol and an ester derivative of nicotinic acid,

wherein the alcohol is contained in an amount of 55 mass% or more based on the entire composition.

[Claim 2]

The composition for external use according to claim 1, wherein the capsaicinoid is nonanoic acid vanillylamide.

[Claim 3]

The composition for external use according to claim 1 or 2, for use in analgesia.

[Claim 4]

The composition for external use according to any one of claims 1 to 3, which is a liquid formulation.