

DESCRIPTION

TITLE OF THE INVENTION: PHARMACEUTICAL COMPOSITION FOR
EXTERNAL USE

TECHNICAL FIELD

[0001]

The present invention relates to a pharmaceutical composition for external use containing a nonsteroidal anti-inflammatory drug and a monoterpene and having an improved cool sensation.

BACKGROUND ART

[0002]

Nonsteroidal anti-inflammatory drugs represented by loxoprofen sodium, diclofenac sodium, felbinac, and the like are widely used as an active component of a pharmaceutical composition for external use. In addition, since a monoterpene such as menthol gives a feeling of coolness, it is used for the purpose of improving usability of a pharmaceutical composition for external use.

[0003]

Conventionally, there have been various reports on formulation of a pharmaceutical composition for external use containing a nonsteroidal anti-inflammatory drug and a monoterpene. For example, Patent Document 1 describes that a pharmaceutical composition for external use containing loxoprofen and/or a salt thereof, menthol, ethanol, and water can suppress cloudiness. Patent Document 2 describes that a pharmaceutical composition for external use containing diclofenac and/or a salt thereof, tocopherol and/or a derivative thereof, menthol, and water can suppress cloudiness and generation of precipitates, and can have excellent appearance properties. Patent Document 3 describes that an oil-in-water type emulsified

preparation for external use having felbinac, l-menthol, a polyhydric alcohol, and triglyceride and having a pH of 6.5 to 8.0 can suppress a decrease in the content of felbinac.

[0004]

In recent years, there has been an increasing demand from consumers for improvement in feeling of use and functionality of a pharmaceutical composition for external use, and in order to follow such consumer needs, development of a formulation technique for further improving a cool sensation of a pharmaceutical composition for external use containing a nonsteroidal anti-inflammatory drug and a monoterpene is required.

PRIOR ART DOCUMENTS

PATENT DOCUMENTS

[0005]

Patent Document 1: Japanese Patent Laid-open Publication No. 2020-59666

Patent Document 2: Japanese Patent Laid-open Publication No. 2015-189760

Patent Document 3: Japanese Patent Laid-open Publication No. 2019-178110

SUMMARY OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0006]

An object of the present invention is to provide a technique for improving a feeling of coolness given by a pharmaceutical composition for external use containing a nonsteroidal anti-inflammatory drug and a monoterpene.

MEANS FOR SOLVING THE PROBLEM

[0007]

The present inventors have extensively conducted studies for achieving the

above-mentioned object, and resultantly found that when propylene glycol is contained at a content of more than 10 wt% in a pharmaceutical composition for external use containing a nonsteroidal anti-inflammatory drug and a monoterpene, a feeling of coolness can be improved. The present invention has been completed by further conducting studies based on such a finding.

[0008]

In other words, the present invention provides inventions of the following modes.

Item 1. A pharmaceutical composition for external use, containing:

(A) a nonsteroidal anti-inflammatory drug, (B) a monoterpene, and (C) propylene glycol,

wherein a content of the component (C) is more than 10 wt%.

Item 2. The pharmaceutical composition for external use according to item 1, wherein the component (A) is at least one selected from the group consisting of loxoprofen, diclofenac, felbinac, and salts thereof.

Item 3. The pharmaceutical composition for external use according to item 1 or 2, wherein the component (B) is menthol and a content of the menthol is 2 to 5 wt%.

Item 4. A method for improving a feeling of coolness of a pharmaceutical composition for external use containing a nonsteroidal anti-inflammatory drug and a monoterpene, the method including:

blending (A) a nonsteroidal anti-inflammatory drug, (B) a monoterpene, and (C) more than 10 wt% of propylene glycol into the pharmaceutical composition for external use.

ADVANTAGES OF THE INVENTION

[0009]

According to the present invention, it is possible to improve a feeling of coolness given by a pharmaceutical composition for external use containing a nonsteroidal anti-inflammatory drug and a monoterpene, and to impart excellent feeling of use. In addition, according to the present invention, since it is possible to give an excellent feeling of coolness even when the content of a monoterpene is set to a low content (e.g., 5 wt% or less) at which skin irritation is unlikely to appear, it is also possible to cope with formulation having low skin irritation.

EMBODIMENTS OF THE INVENTION

[0010]

1. Pharmaceutical composition for external use

A pharmaceutical composition for external use of the present invention is characterized by containing (A) a nonsteroidal anti-inflammatory drug, (B) a monoterpene, and (C) propylene glycol, wherein a content of the component (C) is more than 10 wt%. Hereinafter, the pharmaceutical composition for external use of the present invention will be described in detail.

[0011]

[(A) Nonsteroidal anti-inflammatory drug]

The pharmaceutical composition for external use of the present invention contains a nonsteroidal anti-inflammatory drug (sometimes referred to as component (A)). The nonsteroidal anti-inflammatory drug is a generic term for anti-inflammatory drugs other than glucocorticoids.

[0012]

The type of the nonsteroidal anti-inflammatory drug used in the present invention is not particularly limited, and examples thereof include loxoprofen, diclofenac, felbinac, salicylic acid, acetylsalicylic acid, aspirin, salsalate, salicylamide,

ethenzamide, ibuprofen, ketoprofen, naproxen, flurbiprofen, piroxicam, tiaprofenic acid, suprofen, tolmetin, alminoprofen, benoxaprofen, benzydamine, sulindac, acemetacin, proglumetacin, amfenac, mofezolac, lornoxicam, ampiroxicam, fenoprofen, tiaprofenic acid, oxaprozin, mefenamic acid, flufenamic acid, azapropazone, fenbufen, etodolac, rofecoxib, diflunisal, zomepirac, celecoxib, zaltoprofen, ketorolac, nimesulide, and aceclofenac.

[0013]

In addition, the nonsteroidal anti-inflammatory drug may be in the form of a salt when it can be in the form of a salt. Examples of the nonsteroidal anti-inflammatory drug in the form of a salt include a salt of loxoprofen and a salt of diclofenac.

[0014]

Specific examples of the salt of loxoprofen include alkali metal salts such as sodium salts and potassium salts; and alkaline earth metal salts such as calcium salts. Among them, alkali metal salts are preferred, and sodium salts are further preferred. The salt of loxoprofen may be a hydrate.

[0015]

Specific examples of the salt of diclofenac include alkali metal salts such as sodium salts and potassium salts; alkaline earth metal salts such as calcium salts; salts with ammonia; and salts with primary, secondary, or tertiary alkylamines such as dimethylamine, diethylamine, trimethylamine, and triethylamine. Among them, alkali metal salts are preferred, and sodium salts are further preferred.

[0016]

These nonsteroidal anti-inflammatory drugs may be used one kind alone, or may be used in combination of two or more kinds thereof.

[0017]

Among these nonsteroidal anti-inflammatory drugs, loxoprofen, diclofenac, felbinac, and salts thereof are preferred.

[0018]

The content of component (A) in the pharmaceutical composition for external use of the present invention may be appropriately set according to the type of component (A) to be used, the drug efficacy to be provided, and the like, and is, for example, 0.1 to 15 wt%, preferably 0.5 to 10 wt%, and more preferably 0.5 to 5 wt%.

[0019]

[(B) Monoterpene]

The pharmaceutical composition for external use of the present invention contains a monoterpene (sometimes referred to as component (B)). The monoterpene is a known component having a structure containing two isoprene units in the molecule and having a cooling action or the like.

[0020]

The type of the monoterpene used in the present invention is not particularly limited as long as it is pharmaceutically acceptable, and examples thereof include alcoholic monoterpenes such as menthol, thymol, geraniol, linalool, borneol, cineole, and terpineol; aldehyde-based monoterpenes such as citral, citronellal, perillaldehyde, and safranal; and ketone-based monoterpenes such as camphor, menthone, carvomenthone, and ionone. These monoterpenes may be any of a d-form, an l-form, and a dl-form when optical isomers are present. These monoterpenes may be used one kind alone, or may be used in combination of two or more kinds thereof.

[0021]

In the present invention, as the monoterpene, an essential oil containing a

monoterpene may be used. The essential oil containing a monoterpene can be appropriately selected from known essential oils and then used, and examples of the essential oil containing menthol include *Mentha* oil, peppermint oil, and spearmint oil. Incidentally, the description regarding the content and the ratio of a monoterpene in the present specification is, when an essential oil containing a monoterpene is used, a value converted to the amount of a monoterpene contained in the essential oil.

[0022]

Among these monoterpenes, menthol, geraniol, d-borneol, dl-camphor are preferred, and l-menthol is more preferred.

[0023]

The content of component (B) in the pharmaceutical composition for external use of the present invention may be appropriately set according to the type of component (B), the feeling of coolness to be given, and the like, and is, for example, 0.01 to 10 wt%, preferably 0.1 to 8 wt%, more preferably 1 to 6 wt%, still more preferably 2 to 5 wt%, and particularly preferably 2 to 4 wt% in the total amount of component (B). The pharmaceutical composition for external use of the present invention contains a nonsteroidal anti-inflammatory drug and a monoterpene, and propylene glycol to be described later at a content of more than 10 wt%, thereby improving a feeling of coolness. Therefore, even when the content of component (B) is about 5 wt% or less, which hardly causes skin irritation, an excellent feeling of coolness can be provided.

[0024]

In the pharmaceutical composition for external use of the present invention, the ratio of component (B) to component (A) is determined according to the content of each of these components, and for example, component (B) is 0.001 to 100 parts by weight,

preferably 0.01 to 10 parts by weight, and more preferably 0.1 to 10 parts by weight per 1 part by weight of component (A).

[0025]

[(C) Propylene glycol]

The pharmaceutical composition for external use of the present invention contains propylene glycol (sometimes referred to as component (C)) at a content of more than 10 wt% in addition to the above components. In the pharmaceutical composition for external use of the present invention, propylene glycol is contained at a content of more than 10 wt% together with a nonsteroidal anti-inflammatory drug and a monoterpene, so that a cool sensation can be improved. Propylene glycol is a dihydric lower alcohol also referred to as propane-1,2-diol.

[0026]

The content of component (C) in the pharmaceutical composition for external use of the present invention may be more than 10 wt%, and specific examples thereof include more than 10 wt% and 50 wt% or less. From the viewpoint of further improving the feeling of coolness, the content of component (C) in the pharmaceutical composition for external use of the present invention is preferably 11 to 40 wt%, more preferably 13 to 30 wt%, still more preferably 15 to 30 wt%, and particularly preferably 15 to 20 wt%.

[0027]

In the pharmaceutical composition for external use of the present invention, the ratio of component (C) to component (A) is determined according to the content of each of these components, and for example, component (C) is 0.1 to 100 parts by weight, preferably 0.5 to 100 parts by weight, and more preferably 1 to 40 parts by weight per 1 part by weight of component (A).

[0028]

[Monohydric lower alcohol]

The pharmaceutical composition for external use of the present invention may further contain a monohydric lower alcohol. In the present invention, the monohydric lower alcohol refers to a monohydric alcohol having 1 to 5 carbon atoms.

[0029]

The type of the monohydric lower alcohol is not particularly limited as long as it is pharmaceutically acceptable, and examples thereof include ethanol, n-propanol, and isopropanol. These monohydric lower alcohols may be used one kind alone, or may be used in combination of two or more kinds thereof.

[0030]

Among these monohydric lower alcohols, ethanol is preferred.

[0031]

When a monohydric lower alcohol is contained in the pharmaceutical composition for external use of the present invention, the content thereof is not particularly limited, and is, for example, 0.1 to 88 wt%, preferably 25 to 80 wt%, and more preferably 50 to 80 wt%.

[0032]

[Other components]

The pharmaceutical composition for external use of the present invention may contain other commonly used additives in addition to the above-described components as necessary. Examples of such an additive include water, a surfactant, a vegetable oil, an animal oil, a mineral oil, a fatty acid alkyl ester, a fatty acid, a higher alcohol, a pH adjuster, a buffer, a solubilizer, an antiseptic, a preservative, an antioxidant, a stabilizer, a fragrance, and a colorant. When these additives are contained in the pharmaceutical

composition for external use of the present invention, the content thereof may be appropriately set according to the type of additives to be used and the like.

[0033]

The pharmaceutical composition for external use of the present invention may contain a pharmacological component in addition to the above-described components. Examples of such a pharmacological component include an antihistamine, a local anesthetic, a moisturizing agent, a disinfectant, an antibacterial agent, an antipruritic agent, a skin protectant, a blood circulation promoting component, and vitamins. These pharmacological components may be used one kind alone, or may be used in combination of two or more kinds thereof. When these pharmacological components are contained in the pharmaceutical composition for external use of the present invention, the concentration thereof may be appropriately set according to the type of the pharmacological component to be used, the expected effect, and the like.

[0034]

[Formulation form]

The formulation form of the pharmaceutical composition for external use of the present invention is not particularly limited as long as it is a transdermally applicable dosage form, and may be either a liquid form or a semisolid form (gel, ointment, paste), but a liquid form is preferred.

[0035]

Specific examples of the formulation form of the pharmaceutical composition for external use of the present invention include a liquid preparation, a cream preparation, a lotion preparation, a gel preparation, an emulsion preparation, and an aerosol preparation. Among them, a liquid preparation is preferred. Preparation into these formulation forms can be carried out by formulation using additives

corresponding to the formulation forms according to a known method described in General Rules for Preparations of the Japanese Pharmacopoeia Seventeenth Edition or the like.

[0036]

2. Method for improving feeling of coolness

The present invention further provides a method for improving a feeling of coolness of a pharmaceutical composition for external use containing a nonsteroidal anti-inflammatory drug and a monoterpene, the method including: blending (A) a nonsteroidal anti-inflammatory drug, (B) a monoterpene, and (C) more than 10 wt% of propylene glycol into the pharmaceutical composition for external use.

[0037]

In the method for improving a cool sensation of the present invention, the types of components (A) and (B), the blending amounts of components (A) to (C), the types and contents of other components to be blended, the formulation form of the pharmaceutical composition for external use, and the like are the same as those in the above "1. Pharmaceutical composition for external use".

EXAMPLES

[0038]

Hereinafter, the present invention will be described more specifically with reference to Examples, but the present invention is not limited thereto.

[0039]

Test Example

Pharmaceutical compositions for external use (liquid preparations) having the composition described in Tables 1 to 3 were prepared. A feeling of coolness given by each of the obtained pharmaceutical compositions for external use was evaluated.

Specifically, about 2 g of each pharmaceutical composition for external use was applied to the inner arm of 10 subjects, and 30 minutes after the application, the feeling of coolness at the application site was evaluated on a 20-point scale. In the evaluation of the feeling of coolness, rating was performed on a 20-point scale consisting of 1 to 20 points according to the degree of the feeling of coolness with the score of "no feeling of coolness at all" as 1 point, the score of "feeling of coolness given when pharmaceutical composition for external use of Reference Example 1-1, 2-1, or 3-1 is used" as 15 points, and the score of "very good and high feeling of coolness" as 20 points, and the average score of the scores of 10 subjects was obtained. Then, taking the average score of the scores when the pharmaceutical composition for external use of Comparative Example 1-1, 2-1, or 3-1 was used as 100, the ratio of the average score of the scores when each pharmaceutical composition for external use was used was calculated, and the value obtained by rounding off the average score to the nearest whole number was taken as the score of feeling of coolness.

[0040]

The results are shown in Tables 1 to 3. In the pharmaceutical compositions for external use containing loxoprofen sodium, diclofenac sodium or felbinac, and l-menthol, improvement in feeling of coolness was hardly observed even when dipropylene glycol or glycerin was contained (Comparative Examples 1-2, 1-3, 2-2, 2-3, 3-2, and 3-3).

[0041]

On the other hand, although all of propylene glycol, dipropylene glycol, and glycerin do not give a feeling of coolness (Reference Examples 1-2 to 1-4, 2-2 to 2-4, and 3-2 to 3-4), it was found that when propylene glycol was contained in pharmaceutical compositions for external use containing loxoprofen sodium, diclofenac

sodium or felbinac, and l-menthol, the feeling of coolness was dramatically improved (Examples 1-1 to 1-4, 2-1 to 2-4, and 3-1 to 3-4). In particular, although the content of l-menthol in the pharmaceutical compositions for external use of these Examples was half of that in the pharmaceutical compositions for external use of Reference Examples 1-1, 2-1, and 3-1, a feeling of coolness equal to or higher than that of the pharmaceutical compositions for external use of these Reference Examples was observed. In addition, in the pharmaceutical compositions for external use in which the content of l-menthol was changed to 6 wt% in Examples 1-3, 2-3, and 3-3, the feeling of coolness was further improved as compared with the pharmaceutical compositions for external use of Examples 1-3, 2-3, and 3-3. In addition, also in the pharmaceutical compositions for external use in which l-menthol was changed to geraniol, d-borneol, or dl-camphor in Examples 1-3, 2-3, and 3-3, the feeling of coolness was dramatically improved as compared with the case where propylene glycol was not contained from these pharmaceutical compositions for external use.

[0042]

[Table 1]

	Reference Example				Comparative Example				Example			
	1-1	1-2	1-3	1-4	1-1	1-2	1-3	1-4	1-1	1-2	1-3	1-4
Loxoprofen sodium	1	1	1	1	1	1	1	1	1	1	1	1
l-Menthol	6	-	-	-	3	3	3	-	3	3	3	3
Propylene glycol	-	11	-	-	-	-	-	-	11	13	15	20
Dipropylene glycol	-	-	11	-	-	11	-	-	-	-	-	-
Glycerin	-	-	-	11	-	-	11	-	-	-	-	-
Ethanol	75	75	75	75	75	75	75	75	75	75	75	75
Purified water	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder
Total (wt%)	100	100	100	100	100	100	100	100	100	100	100	100
Score of feeling of coolness ^{#1}	197	14	14	14	100	96	93	14	199	229	253	263

#1: With the score of "feeling of coolness given when pharmaceutical composition for external use of Reference Example 1-1 is used" as 15 points, the average score of the scores of the feeling of coolness by 10 subjects was obtained according to the above criterion, and taking the average score of the scores when the pharmaceutical composition for external use of Comparative Example 1-1 was used as 100, the ratio of the average score of the scores when each pharmaceutical composition for external use was calculated. (rounding off the average score to the nearest whole number)

[0043]

[Table 2]

	Reference Example				Comparative Example				Example			
	2-1	2-2	2-3	2-4	2-1	2-2	2-3	2-4	2-1	2-2	2-3	2-4
Diclofenac sodium	1	1	1	1	1	1	1	1	1	1	1	1
l-Menthol	6	-	-	-	3	3	3	-	3	3	3	3
Propylene glycol	-	11	-	-	-	-	-	-	11	13	15	20
Dipropylene glycol	-	-	11	-	-	11	-	-	-	-	-	-
Glycerin	-	-	-	11	-	-	11	-	-	-	-	-
Ethanol	75	75	75	75	75	75	75	75	75	75	75	75
Purified water	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder
Total (wt%)	100	100	100	100	100	100	100	100	100	100	100	100
Score of feeling of coolness ^{#1}	202	14	14	14	100	104	100	14	205	245	270	270

#1: With the score of "feeling of coolness given when pharmaceutical composition for external use of Reference Example 2-1 is used" as 15 points, the average score of the scores of the feeling of coolness by 10 subjects was obtained according to the above criterion, and taking the average score of the scores when the pharmaceutical composition for external use of Comparative Example 2-1 was used as 100, the ratio of the average score of the scores when each pharmaceutical composition for external use was calculated. (rounding off the average score to the nearest whole number)

[0044]

[Table 3]

	Reference Example				Comparative Example				Example			
	3-1	3-2	3-3	3-4	3-1	3-2	3-3	3-4	3-1	3-2	3-3	3-4
Felbinac	3	3	3	3	3	3	3	3	3	3	3	3
l-Menthol	6	-	-	-	3	3	3	-	3	3	3	3
Propylene glycol	-	11	-	-	-	-	-	-	11	13	15	20
Dipropylene glycol	-	-	11	-	-	11	-	-	-	-	-	-
Glycerin	-	-	-	11	-	-	11	-	-	-	-	-
Ethanol	75	75	75	75	75	75	75	75	75	75	75	75
Purified water	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder
Total (wt%)	100	100	100	100	100	100	100	100	100	100	100	100
Score of feeling of coolness ^{#1}	220	15	15	15	100	103	103	15	222	228	279	294

#1: With the score of "feeling of coolness given when pharmaceutical composition for external use of Reference Example 3-1 is used" as 15 points, the average score of the scores of the feeling of coolness by 10 subjects was obtained according to the above criterion, and taking the average score of the scores when the pharmaceutical composition for external use of Comparative Example 3-1 was used as 100, the ratio of the average score of the scores when each pharmaceutical composition for external use was calculated. (rounding off the average score to the nearest whole number)

[0045]

Formulation Example

Pharmaceutical compositions for external use having the composition shown in Table 4 were prepared in the same manner as in Test Example 1, and the feeling of coolness was evaluated in the same manner as in Test Example 1. In any of the pharmaceutical compositions for external use of Formulation Examples 1 to 12, the feeling of coolness was dramatically improved as compared with the pharmaceutical compositions for external use in which propylene glycol was changed to being not blended in Formulation Examples 1 to 12.

[0046]

[Table 4]

	Formulation Example											
	1	2	3	4	5	6	7	8	9	10	11	12
Loxoprofen sodium	1	-	-	1	1	1	-	-	-	-	-	-
Diclofenac sodium	-	1	-	-	-	-	1	1	1	-	-	-
Felbinac	-	-	3	-	-	-	-	-	-	3	3	3
l-Menthol	6	6	6	-	-	-	-	-	-	-	-	-
Geraniol	-	-	-	3	-	-	3	-	-	3	-	-
d-Borneol	-	-	-	-	3	-	-	3	-	-	3	-
dl-Camphor	-	-	-	-	-	3	-	-	3	-	-	3
Propylene glycol	15	15	15	15	15	15	15	15	15	15	15	15
Ethanol	75	75	75	-	-	-	-	-	-	-	-	-
Purified water	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder
Total (wt%)	100	100	100	100	100	100	100	100	100	100	100	100

CLAIMS

1. A pharmaceutical composition for external use, comprising:
(A) a nonsteroidal anti-inflammatory drug, (B) a monoterpene, and (C) propylene glycol,
wherein a content of the component (C) is more than 10 wt%.
2. The pharmaceutical composition for external use according to claim 1, wherein the component (A) is at least one selected from the group consisting of loxoprofen, diclofenac, felbinac, and salts thereof.
3. The pharmaceutical composition for external use according to claim 1 or 2, wherein the component (B) is menthol and a content of the menthol is 2 to 5 wt%.
4. A method for improving a feeling of coolness of a pharmaceutical composition for external use containing a nonsteroidal anti-inflammatory drug and a monoterpene, the method comprising:
blending (A) a nonsteroidal anti-inflammatory drug, (B) a monoterpene, and (C) more than 10 wt% of propylene glycol into the pharmaceutical composition for external use.