

DESCRIPTION

TITLE OF THE INVENTION: AQUEOUS TOPICAL COMPOSITION

TECHNICAL FIELD

[0001]

The present invention relates to an aqueous topical composition in which an ester derivative of nicotinic acid and an ester derivative of myristic acid are contained in water at a predetermined ratio with their separation suppressed.

BACKGROUND ART

[0002]

Nicotinic acid ester derivatives such as nicotinic acid benzyl ester are known as drugs having a blood circulation promoting action, and are also used as topical compositions. In addition, since a nicotinic acid ester derivative is hardly soluble in water, it is formulated as an aqueous composition employing ethanol or isopropanol as shown in, for example, Patent Documents 1 and 2.

[0003]

In addition, a myristic acid ester derivative such as isopropyl myristate is an oily component known as a percutaneous absorption promoting agent, and is blended and used together with an active ingredient in an external patch or the like as shown in, for example, Patent Documents 3 and 4.

PRIOR ART DOCUMENTS

PATENT DOCUMENTS

[0004]

Patent Document 1: Japanese Patent Laid-open Publication No. 2017-200909

Patent Document 2: Japanese Patent Laid-open Publication No. 2018-104369

Patent Document 3: International Patent Publication No. WO 2004/084946

SUMMARY OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0005]

In order to enhance the efficacy of an ester derivative of nicotinic acid in an aqueous topical composition containing the ester derivative of nicotinic acid together with a monohydric lower alcohol, the present inventor has designed the aqueous topical composition so as to increase the content of the ester derivative of nicotinic acid while blending the ester derivative of myristic acid as a percutaneous penetration promoting agent. However, in the case that the ratio of the ester derivative of nicotinic acid to 1 weight of the ester derivative of myristic acid is 0.005 parts by weight or more, remarkable separation undesirably occurs although both the ester derivative of nicotinic acid and the ester derivative of myristic acid are dissolved in a lower monohydric alcohol.

[0006]

The purpose of the present invention is therefore to provide a pharmaceutical formulation with which it is possible to suppress separation in an aqueous topical composition containing 0.005 parts by weight or more of a nicotinic acid ester derivative with respect to 1 part by weight of a myristic acid ester derivative.

MEANS FOR SOLVING THE PROBLEM

[0007]

The present inventors have found, through intensive studies, that separation can be suppressed by blending menthol in an aqueous topical composition containing 0.005 parts by weight or more of an ester derivative of nicotinic acid with respect to 1 part by weight of an ester derivative of myristic acid. The present invention has been

completed by further conducting studies based on this finding.

[0008]

That is, the present invention provides inventions with the following aspects.

Item 1. An aqueous topical composition containing (A) an ester derivative of nicotinic acid, (B) an ester derivative of myristic acid, and (C) menthol, and having a content of the component (A) of 0.005 parts by weight or more with respect to 1 part by weight of the component (B).

Item 2. The aqueous topical composition according to item 1, wherein the component (A) is nicotinic acid benzyl ester.

Item 3. The aqueous topical composition according to item 1 or 2, wherein the component (B) is isopropyl myristate.

Item 4. The aqueous topical composition according to any of items 1 to 3, having a content of the component (A) of 0.011% by weight or more.

Item 5. The aqueous topical composition according to any of items 1 to 4, having a content of the component (C) of 4 parts by weight or more with respect to 1 part by weight of the component (A).

Item 6. The aqueous topical composition according to any of items 1 to 5, being a lotion, an emulsion, a gel, or a cream.

ADVANTAGES OF THE INVENTION

[0009]

According to the present invention, there is provided a pharmaceutical formulation with which it is possible to suppress separation in an aqueous topical composition containing 0.005 parts by weight or more of a nicotinic acid ester derivative with respect to 1 part by weight of a myristic acid ester derivative.

EMBODIMENTS OF THE INVENTION

[0010]

The aqueous topical composition of the present invention contains (A) an ester derivative of nicotinic acid (hereinafter, it may be referred to as "component (A)"), (B) an ester derivative of myristic acid (hereinafter, it may be referred to as "component (B)"), and (C) menthol (hereinafter, it may be referred to as "component (C)"), and the content of the component (A) is 0.005 parts by weight or more with respect to 1 part by weight of the component (B). Hereinafter, the aqueous topical composition of the present invention will be described in detail.

[0011]

(A) Ester derivative of nicotinic acid

The aqueous topical composition of the present invention contains an ester derivative of nicotinic acid as the component (A). The ester derivative of nicotinic acid is a known component whose blood circulation promoting action, cell activating action, and the like are known.

[0012]

The ester derivative of nicotinic acid is an ester of nicotinic acid and alcohol, and specific examples thereof include nicotinic acid benzyl ester, nicotinic acid β -butoxyethyl ester, and nicotinic acid methyl ester. These ester derivatives of nicotinic acid may be used singly, or may be used in combination of two or more thereof. Among these ester derivatives of nicotinic acid, nicotinic acid benzyl ester is preferable.

[0013]

The content of the component (A) in the aqueous topical composition of the present invention is 0.005 parts by weight or more with respect to 1 part by weight of the component (B). In the case that the aqueous topical composition contains the component (A) in an amount of 0.005 parts by weight or more with respect to 1 part by

weight of the component (B), separation basically occurs but is suppressed in the aqueous topical composition of the present invention.

[0014]

Since the aqueous topical composition of the present invention is excellent in the separation suppressing effect, separation can be effectively suppressed even if the content of the component (A) with respect to 1 part by weight of the component (B) is large. From such a viewpoint, suitable examples of the content of the component (A) with respect to 1 part by weight of the component (B) include 0.007 parts by weight or more, 0.009 parts by weight or more, 0.012 parts by weight or more, 0.02 parts by weight or more, 0.03 parts by weight or more, 0.04 parts by weight or more, 0.05 parts by weight or more, 0.06 parts by weight or more, 0.07 parts by weight or more, and 0.08 parts by weight or more.

[0015]

The upper limit of the content of the component (A) with respect to 1 part by weight of the component (B) is not particularly limited, but is, for example, 0.2 parts by weight or less, 0.15 parts by weight or less, 0.1 parts by weight or less, or 0.09 parts by weight or less.

[0016]

The specific content of the component (A) in the aqueous topical composition of the present invention may be appropriately set according to the drug efficacy and the like to be provided to the aqueous topical composition, but is, for example, 0.005% by weight or more, and is preferably 0.008% by weight or more, more preferably 0.011% by weight or more, still more preferably 0.018% by weight or more, and even still more preferably 0.03% by weight or more. The specific upper limit of the content of the component (A) is, for example, 0.5% by weight or less, preferably 0.1% by weight or

less, more preferably 0.05% by weight or less, and still more preferably 0.03% by weight or less.

[0017]

(B) Ester derivative of myristic acid

The aqueous topical composition of the present invention contains an ester derivative of myristic acid as the component (B). The ester derivative of myristic acid is a known component whose percutaneous penetration promoting action and the like are known.

[0018]

The ester derivative of myristic acid is an ester of myristic acid and alcohol, and specific examples thereof include isopropyl myristate, butyl myristate, and octyldodecyl myristate. These ester derivatives of myristic acid may be used singly, or may be used in combination of two or more thereof. Among these ester derivatives of myristic acid, isopropyl myristate is preferable.

[0019]

The content of the component (B) in the aqueous topical composition of the present invention is determined according to the content (parts by weight) of the component (A) with respect to 1 part by weight of the component (B) and the specific content (% by weight) of the component (A), and is, for example, 1 to 8% by weight, and preferably 2 to 6% by weight.

[0020]

(C) Menthol

The aqueous topical composition of the present invention contains menthol as the component (C). The menthol may be any of d-isomer, l-isomer, and dl-isomer. In addition, an essential oil containing menthol may be blended for blending of menthol.

[0021]

The content of the component (C) in the aqueous topical composition of the present invention is not particularly limited, but is, for example, 1% by weight or more, and is preferably 2.5% by weight or more, more preferably 3.5% by weight or more, still more preferably 4.5% by weight or more, even still more preferably 5.5% by weight or more from the viewpoint of further enhancing the separation suppressing effect. The upper limit of the content of the component (C) is not particularly limited, but is, for example, 8% by weight or less, 7% by weight or less, or 6.5% by weight or less.

[0022]

In the aqueous topical composition of the present invention, the ratio of the component (A) to the component (C) is determined according to the content of each of the above components, but from the viewpoint of further enhancing the separation suppressing effect, the content of the component (C) with respect to 1 part by weight of the component (A) is preferably 4 parts by weight or more, more preferably 10 parts by weight or more, still more preferably 50 parts by weight or more, even still more preferably 70 parts by weight or more, further more preferably 100 parts by weight or more, 150 parts by weight or more, 200 parts by weight or more, 250 parts by weight or more, 300 parts by weight or more, 400 parts by weight or more, or 500 parts by weight or more. The upper limit of the content of the component (C) with respect to 1 part by weight of the component (A) is not particularly limited, but is, for example, 600 parts by weight or less, 550 parts by weight or less, 450 parts by weight or less, 350 parts by weight or less, or 250 parts by weight or less.

[0023]

Water

The aqueous topical composition of the present invention contains water. The water is not particularly limited, and examples thereof include purified water, distilled water, ion-exchanged water, ultrapure water, and sterilized water, and preferably include purified water.

[0024]

The content of water is not particularly limited as long as the effect of the present invention is not hindered, but is, for example, 5 to 0% by weight, and preferably 10 to 30% by weight.

[0025]

Other components

The aqueous topical composition of the present invention may contain other pharmacological components as necessary in addition to the above-described components as long as the effects of the present invention are not hindered. The other pharmacological components that can be blended in the aqueous topical composition of the present invention are not particularly limited, but examples thereof include anti-inflammatory agents such as glycyrrhetic acid, dipotassium glycyrrhizinate, ammonium glycyrrhizinate, stearyl glycyrrhizinate, indomethacin, felbinac, sodium diclofenac, and sodium loxoprofen; antihistamines such as diphenylimidazole, diphenhydramine and pharmaceutically acceptable salts thereof, and chlorpheniramine maleate; local anesthetic agents such as lidocaine and pharmaceutically acceptable salts thereof, dibucaine and pharmaceutically acceptable salts thereof, and ethyl aminobenzoate; blood circulation promoting agents (other than the component (A)) such as capsaicinoids (specifically, nonanoic acid vanillylamide; and capsaicins such as capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, and homodihydrocapsaicin) and tocopherol acetate; and crude drugs such as Arnica tincture,

a Phellodendron bark extract, Gardenia fruit extract, Rosskastanien extract, Scopolia extract, Belladonna extract, Angelica sinensis extract, Lithospermum root extract, and Zanthoxylum fruit extract.

[0026]

Furthermore, the aqueous topical composition of the present invention may contain, in addition to the components described above, a solvent and other additives commonly used for an aqueous topical composition, as necessary. Examples of such a solvent include monohydric lower alcohols having 1 to 5 carbon atoms, such as ethanol, propanol, isopropanol, n-butanol, sec-butanol, tert-butanol, and pentanol, preferably include ethanol and isopropanol, and more preferably include ethanol. In the aqueous topical composition of the present invention, the content of the monohydric lower alcohol is not particularly limited as long as the effect of the present invention is not hindered, but is, for example, 60 to 80% by weight. Examples of the additives include pH adjusters, surfactants, emulsifiers, solubilizers, antiseptic agents, preservatives, antioxidants, stabilizers, chelating agents, thickeners, fragrances, and colorants.

[0027]

Formulation

The formulation of the aqueous topical composition of the present invention is not particularly limited as long as it is percutaneously applicable. Separation is suppressed in the aqueous topical composition of the present invention, whereby the active ingredient is well dissolved and thus can effectively act in any formulation.

[0028]

Specific examples of the formulation of the aqueous topical composition of the present invention include solutions (lotions, sprays, aerosols, and emulsions), foams, ointments, gels, creams, and patches, and preferably include lotions, emulsions, gels,

and creams. The preparation for these formulations can be carried out by formulating using additives corresponding to the formulation according to a known method described in General Rules for Preparations of the Japanese Pharmacopoeia 17th edition.

EXAMPLES

[0029]

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

[0030]

Test Example 1

Aqueous topical compositions (lotions) having the composition shown in Tables 2 to 4 were prepared, and the degree of separation at the time of completion of the preparation was evaluated according to the following criteria.

[0031]

[Evaluation of Separation Suppressing Effect]

The prepared aqueous topical composition (10 g) was placed in a transparent screw tube having a body diameter of 21 mm, the appearance was visually observed from the side surface, and the separation suppressing effect was evaluated based on the criteria in Table 1. When the score is 5 or more, a predetermined separation suppressing effect is exhibited, and the separation suppressing effect is higher as the score is higher. The results are shown in Tables 2 to 4.

[0032]

[Table 1]

Rating	Appearance
1	Complete separation state, corresponding to the appearance of Comparative Example 5
2	A separation phase floats on a liquid surface. The higher the rating, the smaller the amount of a separation phase.
3	
4	
5	No separation phase floats on a liquid surface. Cloudiness is observed. The higher the rating, the lower the degree of cloudiness.
6	
7	
8	
9	
10	Clear state, corresponding to the appearance of Reference Example 1.

[0033]

[Table 2]

	Reference Example 1	Reference Example 2	Reference Example 3	Comparative Example 1	Example 1	Example 2	Example 3	Example 4
(A) Nicotinic acid benzyl ester	-	-	0.005	0.011	0.011	0.011	0.012	0.012
(B) Isopropyl myristate	-	2	2	2	2	2	2	2
(C) Menthol	-	-	-	-	3	6	3	6
Ethanol	75	75	75	75	75	75	75	75
Purified water	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance
Total (%)	100	100	100	100	100	100	100	100
(A)/(B)	-	-	0.0025	0.0055	0.0055	0.0055	0.006	0.006
Separation suppressing effect	10	9	6	3	10	10	10	10

In the table, the unit of the numerical value indicating the content of each component is % by weight.

[0034]

[Table 3]

	Comparative Example 2	Example 5	Example 6	Comparative Example 3	Example 7	Example 8
(A) Nicotinic acid benzyl ester	0.015	0.015	0.015	0.02	0.02	0.02
(B) Isopropyl myristate	2	2	2	2	2	2
(C) Menthol	-	3	6	-	3	6
Ethanol	75	75	75	75	75	75
Purified water	Balance	Balance	Balance	Balance	Balance	Balance
Total (%)	100	100	100	100	100	100
(A)/(B)	0.0075	0.0075	0.0075	0.01	0.01	0.01
Separation suppressing effect	3	10	10	1	10	10

In the table, the unit of the numerical value indicating the content of each component is % by weight.

[0035]

[Table 4]

	Reference Example 4	Comparative Example 4	Example 9	Example 10	Example 11	Comparative Example 5	Example 12	Example 13
(A) Nicotinic acid benzyl ester	0.01	0.05	0.05	0.05	0.05	0.5	0.5	0.5
(B) Isopropyl myristate	4	4	4	4	4	6	6	6
(C) Menthol	-	-	3	4	6	-	4	6
Ethanol	75	75	75	75	75	75	75	75
Purified water	Balance	Balance	Balance	Balance	Balance	Balance	Balance	Balance
Total (%)	100	100	100	100	100	100	100	100
(A)/(B)	0.0025	0.0125	0.0125	0.0125	0.0125	0.0833	0.0833	0.0833
Separation suppressing effect	6	1	9	10	10	1	8	10

In the table, the unit of the numerical value indicating the content of each component is % by weight.

[0036]

As shown in Tables 2 to 4, in the case that the ratio of nicotinic acid benzyl ester to isopropyl myristate (numerical values represented by "(A)/(B)" in the tables) was to the extent shown in Reference Examples 2 to 4, remarkable separation did not occur, but in the case that the ratio was to the extent shown in Comparative Examples 1 to 5, separation was remarkable. In particular, in Comparative Examples 3 to 5 in which the ratio (A)/(B) of nicotinic acid benzyl ester to isopropyl myristate was 0.01 or more, the separation was particularly remarkable. On the other hand, a high separation suppressing effect was exhibited as shown in Examples 1 to 13 by further adding menthol to the composition having such a ratio as shown in Comparative Examples 1 to 5. Also, the separation suppressing effect was exhibited similarly to Examples 1 to 13 in the case that the content of ethanol in Examples 1 to 13 was changed to 60% or 80% by weight.

CLAIMS

1. An aqueous topical composition comprising (A) an ester derivative of nicotinic acid, (B) an ester derivative of myristic acid, and (C) menthol, and having a content of the component (A) of 0.005 parts by weight or more with respect to 1 part by weight of the component (B).
2. The aqueous topical composition according to claim 1, wherein the component (A) is nicotinic acid benzyl ester.
3. The aqueous topical composition according to claim 1 or 2, wherein the component (B) is isopropyl myristate.
4. The aqueous topical composition according to any of claims 1 to 3, having a content of the component (A) of 0.011% by weight or more.
5. The aqueous topical composition according to any of claims 1 to 4, having a content of the component (C) of 4 parts by weight or more with respect to 1 part by weight of the component (A).
6. The aqueous topical composition according to any of claims 1 to 5, being a lotion, an emulsion, a gel, or a cream.