

Description

Title of Invention: AQUEOUS SOLID OINTMENT

Technical Field

[0001]

The present invention relates to an aqueous solid ointment comprising fatty acid salts, a lower alcohol, a sucrose fatty acid ester, water, and an active component. The aqueous solid ointment has a combination containing an active component and predetermined fatty acid salts.

Background Art

[0002]

Solid ointments have many advantages, as they can, by having them filled in appropriate containers such as airtight containers with a push-up mechanism or a turn-dial mechanism, be applied to affected areas without soiling the fingers during use, applied to a limited area, and carried conveniently, and thus various products have been proposed and put on the market.

[0003]

Among the solid ointments, aqueous solid ointments, which contain volatile components, as they are prepared by using volatile components such as lower alcohols and aqueous solidification components such as fatty acid salts, can have suppressed stickiness when applied to the skin, and achieve high refreshing feel as well as remarkably good feel of use compared to other oil-based solid ointments. However, an aqueous solid ointment in which a fatty acid salt is used as a solidification component may have varying effectiveness and safety due to crystals containing the fatty acid salt, or in some cases further containing an active component easily precipitated by storage at a low temperature.

Note that JP 2018-052902 A discloses a technology that allows suppression of crystal precipitation of a fatty acid salt even in the case of storing an aqueous solid ointment at a low temperature. However, the aqueous solid ointment needs to be alkaline with a pH above 9 to prepare an aqueous solid ointment having excellent transparency with visual refreshing effects and adequate shape retainability for application to affected areas. If used repeatedly, the resulting alkaline aqueous solid ointment with a pH above 9 may have a negative effect on the skin.

Disclosure of Invention

Technical Problem

[0004]

An object of the present invention is to provide an aqueous solid ointment which does not cause, at a pH from 6 to 9, precipitation of crystals containing fatty acid salts, or in some cases further containing an active component, by storage at a low temperature and has transparency and shape retainability.

Solution to Problem

[0005]

As a result of diligent study to solve the issues described above, the inventors of the present invention found that, in an aqueous solid ointment comprising fatty acid salts, a lower alcohol, a sucrose fatty acid ester, water, and an active component, by selecting a predetermined combination of fatty acid salts and a predetermined ratio of the fatty acid salts, it is possible to obtain the aqueous solid ointment which does not cause, at a pH from 6 to 9, precipitation of crystals containing the fatty acid salts, or in some cases further containing the active component, by storage at a low temperature and has transparency and shape retainability, and thus completed the present invention.

That is, the present invention provides an invention with the following key characteristics and aspects.

[0006]

Aspect 1: An aqueous solid ointment, comprising fatty acid salts, a lower alcohol, a sucrose fatty acid ester, water, and an active component,

the fatty acid salts comprising a palmitate, a stearate, and a behenate, and when the palmitate, the stearate, and the behenate contained in the aqueous solid ointment are converted to fatty acids corresponding thereto, and a total parts by weight of the fatty acids are taken as 100, a respective ratio of the palmitate to the stearate to the behenate being in a range of 35 - 90 : 5 - 55 : 5 - 28,

wherein the aqueous solid ointment comprises, with respect to a total amount of the aqueous solid ointment, three kinds of the fatty acid salts totaling from 3 to 8 wt.% in terms of fatty acids, from 50 to 90 wt.% of the lower alcohol, from 0.1 to 2.5 wt.% of the sucrose fatty acid ester, from 1 to 20 wt.% of the water, and from 0.1 to 10 wt.% of the active component, and has a pH of 6 to 9.

Aspect 2: The aqueous solid ointment according to Aspect 1, wherein the active component is an antiphlogistic analgesic component.

[0007]

Aspect 3: The aqueous solid ointment according to Aspect 2, wherein the antiphlogistic analgesic component is at least one selected from diclofenac, loxoprofen, flurbiprofen, and salts thereof.

Advantageous Effects of Invention

[0008]

As described above, the present invention can provide an aqueous solid ointment, which does not cause, at a pH from 6 to 9, precipitation of crystals containing fatty acid salts, or in some cases further containing an active component, by storage at a low temperature and has transparency and shape retainability.

Brief Description of Drawings

[0009]

FIG. 1 is a chart illustrating weight ratios (in terms of fatty acids) of palmitates, stearates, and behenates contained in aqueous solid ointments of Examples 1 to 7 and Comparative Examples 1 to 14 with respect to total weights of these fatty acid salts calculated as converted to fatty acids.

FIG. 2 is a chart illustrating weight ratios (in terms of fatty acids) of palmitates, stearates, and behenates contained in aqueous solid ointments of Examples 8 to 13 and Comparative Examples 15 to 18 with respect to total weights of these fatty acid salts calculated as converted to fatty acids.

Description of Embodiments

[0010]

Hereinafter, the aqueous solid ointment of the present invention will be described in detail; however, the present invention is not limited by specific examples and technical terms used in the present description.

A "pH" value of an aqueous solid ointment of the present invention is based on measurement of a pH of a small amount of liquid present on a solid surface of the aqueous solid ointment.

[0011]

The pH intended for the aqueous solid ointment of the present invention is from 6 to 9, from 7 to 9, from 6 to 8.5, or from 7 to 8.5. In a case where a pH of an aqueous solid ointment using a fatty acid salt as a solidification component is adjusted to lower than 6, the shape retainability may be lost. Furthermore, in a case where a pH is adjusted to higher than 9, repeated use may affect the skin.

[0012]

"Crystal precipitation" of the aqueous solid ointment of the present invention is determined by visual confirmation of the aqueous solid ointment after storage at a low temperature from 1°C to 15°C for 4 weeks. A case where no crystals were observed in the aqueous solid ointment is defined as no crystal precipitation occurred.

[0013]

"Transparency" of the aqueous solid ointment of the present invention is determined by measuring a light transmittance of the aqueous solid ointment of 15 to 25°C charged in a cell having an optical path length of 10 mm using a spectrophotometer at a wavelength of 660 nm. A case where the light transmittance is 30% or greater is defined as having transparency. A case where the light transmittance is less than 30% may not achieve visual refreshing effects.

[0014]

"Shape retainability" in the present invention is determined by the total amount of energy (g · mm) required for a spherical probe made of stainless steel and having a diameter of 7 mm to

penetrate 3.5 mm at a speed of 0.07 mm/sec in a vertical direction with respect to a bottom face of one bottom central part of an aqueous solid ointment, which is at $24^{\circ}\text{C} \pm 2^{\circ}\text{C}$, cut into a cylindrical shape having a diameter of 37 mm or greater and a height of 20 mm to 40 mm. A case where the total amount of energy is 900 g · mm or greater is defined as having shape retainability. In a case where the total amount of energy is less than 900 g · mm, adequate shape retainability for application to affected areas may be difficult to be maintained.

The aqueous solid ointment of the present invention contains three kinds of fatty acid salts, which are a palmitate, a stearate, and a behenate, as essential components.

[0015]

As the palmitate, sodium palmitate alone or a combination of sodium palmitate and other palmitate can be used. Examples of such other palmitates include potassium palmitate, monoethanolamine palmitate, diethanolamine palmitate, and triethanolamine palmitate.

[0016]

Similarly, as the stearate, sodium stearate alone or a combination of sodium stearate and other stearate can be used. Examples of such other stearates include potassium stearate, monoethanolamine stearate, diethanolamine stearate, and triethanolamine stearate.

[0017]

Similarly, as the behenate, sodium behenate alone or a combination of sodium behenate and other behenate can be used. Examples of such other behenates include potassium behenate, monoethanolamine behenate, diethanolamine behenate, and triethanolamine behenate.

[0018]

As for the palmitate, the stearate, and the behenate contained in the aqueous solid ointment, when converted to fatty acids corresponding thereto, and total parts by weight of the fatty acids are taken as 100, a respective ratio of the palmitate to the stearate to the behenate is in a range of 35 - 90 : 5 - 55 : 5 - 28, respectively, or 40 - 90 : 5 - 50 : 5 - 25, respectively, or 35 - 80 : 10 - 55 : 10 - 28, respectively, or 40 - 80 : 10 - 50 : 10 - 25, respectively.

[0019]

From 3 to 8 wt.% total, from 3 to 6 wt.% total, from 3.5 to 7 wt.% total, or from 3.5 to 6 wt.% total, in terms of fatty acids of the three kinds of the fatty acid salts are contained with respect to the total amount of the aqueous solid ointment.

[0020]

Note that, in addition to the three kinds of the fatty acid salts, the aqueous solid ointment may contain another fatty acid salt in a range that does not impair the effect of the present invention. When another fatty acid salt is contained, examples thereof include a caprylate, a caprate, a myristate, an oleate, a laurate, an arachidate, an erucate, a linoleate, a linolenate, and a lignocerate. These are typically derived from one kind or two or more kinds of fats and/or oils and are raw materials from which various fatty acid salts are produced, and they may not be removed completely or easily when the three kinds of the fatty acid salts described above are provided.

The fatty acid salt may be a fatty acid salt obtained by neutralizing a corresponding fatty acid in advance or may be a fatty acid salt formed by neutralizing a predetermined fatty acid and a base in a preparation process.

[0021]

The ratio of the number of moles of the fatty acid salt to the number of moles of the fatty acid corresponding to the fatty acid salt contained in the aqueous solid ointment of the present invention is in a range of 80 - 100 : 0 - 20, or 90 - 100 : 0 - 10, or 95 - 100 : 0 - 5, in a case where the total of the number of moles of the fatty acid salt to the number of moles of the fatty acid corresponding to the fatty acid salt is 100.

[0022]

For the base used when a fatty acid is neutralized in a preparation process, a base forming a sodium salt of the fatty acid can be used alone, or a combination of a base forming a sodium salt of the fatty acid and a base forming another fatty acid salt can be used. Examples of the base forming a sodium salt of the fatty acid include sodium hydroxide, sodium carbonate, and sodium hydrogencarbonate, and one kind alone, or a combination of two or more kinds thereof can be used. Examples of another base forming a fatty acid salt include potassium hydroxide, monoethanolamine, diethanolamine, and triethanolamine, and one kind alone, or a combination of two or more kinds thereof can be used.

[0023]

Examples of the lower alcohol used in the present invention include lower alcohols having 6 or less carbons, such as methanol, ethanol, propanol, isopropanol, butanol, pentanol, and hexanol, and modified products of these, and one kind alone, or a combination of two or more kinds thereof can be used. From 50 to 90 wt.%, from 50 to 80 wt.%, from 55 to 85 wt.%, or from 55 to 80 wt.%, of the lower alcohol is contained with respect to the total amount of the aqueous solid ointment.

[0024]

Examples of the sucrose fatty acid ester used in the present invention include sucrose fatty acid esters in which one kind, or two or more kinds of fatty acids selected from caprylic acid, capric acid, stearic acid, palmitic acid, myristic acid, oleic acid, lauric acid, arachidic acid, behenic acid, erucic acid, linolic acid, and linolenic acid are ester-bonded to sucrose. One kind alone, or a combination of two or more kinds thereof can be used. From 0.1 to 2.5 wt.%, from 0.3 to 1 wt.%, from 0.1 to 0.7 wt.%, or from 0.3 to 0.7 wt.%, of the sucrose fatty acid ester is contained with respect to a total amount of the aqueous solid ointment.

[0025]

Examples of the water used in the present invention include purified water, sterile water, natural water, regular water, and water for injection, and one kind alone, or a combination of two or more kinds thereof can be used. From 1 to 20 wt.%, from 5 to 15 wt.%, from 1 to 10 wt.%, or from 5 to 10 wt.%, of the water is contained with respect to a total amount of the aqueous solid ointment.

[0026]

The active component used in the present invention is not particularly limited, as long as the active component is medically or pharmaceutically acceptable, and is preferably an active component having excellent percutaneous absorbability with a molecular weight of 500 or less. Examples thereof include local anesthesia components such as lidocaine, procaine, tetracaine, and ethyl aminobenzoate, antihistamine components such as diphenhydramine and chlorpheniramine maleate, and antiphlogistic analgesic components such as loxoprofen, indomethacin, diclofenac, flurbiprofen, and salts of these. One kind alone, or a combination of two or more kinds thereof can be used. From 0.1 to 10 wt.%, from 0.5 to 5 wt.%, from 0.1 to 3 wt.%, or from 0.5 to 3 wt.%, of the active component is contained with respect to the total amount of the aqueous solid ointment. Blending can be performed with proper adjustment taking the properties, dose, percutaneous absorbability, effective blood concentration, and the like of the active component into consideration.

[0027]

In addition to the components described above, the aqueous solid ointment of the present invention may properly contain various components that are acceptable upon preparation of pharmaceuticals in a range that does not impair the effect of the present invention. That is, the aqueous solid ointment may properly contain a polyhydric alcohol, a pH control agent, a higher alcohol, a surfactant, an active component solubilizing agent, an essential oil, a humectant, an antioxidant, an active component stabilizing agent, and a transdermal absorption promoting agent.

[0028]

Examples of the polyhydric alcohol include ethylene glycol, diethylene glycol, polyethylene glycol, 1,3-butylene glycol, propylene glycol, and dipropylene glycol, and one kind alone, or a combination of two or more kinds thereof can be used.

[0029]

Examples of the pH control agent include hydrochloric acid, acetic acid, sodium acetate, potassium acetate, tartaric acid, sodium tartrate, lactic acid, sodium lactate, malic acid, and sodium malate, and one kind alone, or a combination of two or more kinds thereof can be used.

[0030]

Examples of the higher alcohol include oleyl alcohol, stearyl alcohol, cetanol, myristyl alcohol, and lauryl alcohol, and one kind alone, or a combination of two or more kinds thereof can be used.

[0031]

Examples of the surfactant include alkyl allyl polyether alcohols, higher alcohol sulfated products, self-emulsification glyceryl monostearate, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene polyoxypropylene glycols, propylene glycol fatty acid esters, polyglycerin fatty acid esters, monoglycerin fatty acid esters, lauromacrogol, sodium

lauryl sulfate, quaternary ammonium salts, lecithin, and hydrogenated lecithin, and one kind alone, or a combination of two or more kinds thereof can be used.

[0032]

Examples of the active component solubilizing agent include diisopropyl adipate, diethyl sebacate, isopropyl palmitate, isopropyl myristate, medium-chain triglyceride, cetyl myristate, myristyl myristate, castor oil, crotamiton, squalane, squalene, and propylene carbonate, and one kind alone, or a combination of two or more kinds thereof can be used.

[0033]

Examples of the essential oil include dl-menthol, l-menthol, l-menthone, limonene, pinene, piperitone, terpinene, terpinolene, terpinol, carveol, and d-camphor, and one kind alone, or a combination of two or more kinds thereof can be used.

[0034]

Examples of the humectant include urea, glycerin, sorbitol, acetylglucosamine, and hyaluronic acid, and one kind alone, or a combination of two or more kinds thereof can be used.

[0035]

Examples of the antioxidant include tocopherols such as dl- α -tocopherol acetate, dl- α -tocopherol, and d- δ -tocopherol, dibutylhydroxyanisole, dibutylhydroxytoluene, propyl gallate, L-ascorbic acid, and sodium ascorbate, and one kind alone, or a combination of two or more kinds thereof can be used.

[0036]

Examples of the active component stabilizing agent include sodium hydrogen sulfite, sodium hydrogen phosphate, and sodium edetate, and one kind alone, or a combination of two or more kinds thereof can be used.

[0037]

Examples of the transdermal absorption promoting agent include polyhydric alcohols such as ethylene glycol, 1,3-butylene glycol, propylene glycol, and glycerin; esters such as diisopropyl adipate, isopropyl myristate, ethyl acetate, cetyl lactate, and glyceryl monooleate; surfactants such as sucrose oleate and sucrose laurate; essential oils such as dl-menthol, l-menthol, limonene, and peppermint oil; pyrrolidones such as N-methyl-2-pyrrolidone and pyrrolidonecarboxylic acid; α -hydroxy moieties such as lactic acid and glycolic acid; and aliphatic alcohols such as stearyl alcohol, myristyl alcohol, lauryl alcohol, 2-ethyl-1,3-hexanediol. One kind alone, or a combination of two or more kinds thereof can be used.

[0038]

The aqueous solid ointment of the present invention can be prepared by a known ordinary method or a novel method that will be available hereafter. As a typical preparation method thereof, in addition to the fatty acid salts or the fatty acids and bases, the lower alcohol, the sucrose fatty acid ester, the water, and the active component, a polyhydric alcohol, a pH control agent, a higher alcohol, a surfactant, an active component solubilizing agent, an essential oil, a humectant, an antioxidant, an active component stabilizing agent, a transdermal absorption

promoting agent, and the like are charged in a dissolution bath and stirred until the mixture becomes homogeneous while heated to reflux. This is filled in a container and cooled to room temperature to solidify, and thus the preparation can be completed. Examples of the container include airtight containers and containers with a push-up mechanism or a turn-dial mechanism.

Examples

[0039]

The present invention will be described in more detail below with specific examples; however, the present invention is not limited to these.

[0040]

Example 1

Each component was weighed based on the composition listed in Table 1. Preparation was performed by Preparation Method 1 described below, and an aqueous solid ointment was obtained. Subjected to the pH evaluation, the crystal precipitation evaluation, the transparency evaluation, and the shape retainability evaluation in accordance with Test Examples 1 to 4 described below, the obtained aqueous solid ointment had a proper pH, did not cause precipitation of crystals by storage at a low temperature, and achieved transparency and shape retainability. The results are presented in Table 1.

[0041]

Preparation Method 1

Each of the weighed components were charged in a dissolution bath and allowed to be refluxed and stirred until the mixture became homogeneous while heated to 85°C. Thereafter, this mixture was charged in a container appropriate for performing Test Examples 1 to 4 described below, cooled to room temperature, and solidified, and thus an aqueous solid ointment was obtained.

[0042]

Test Example 1

pH Evaluation

The pH of each of the aqueous solid ointments of Example 1 described above and Examples 2 to 20 and Comparative Examples 1 to 24 described below was measured by using a pH composite electrode (GST-5723S, available from DKK-TOA Corporation). A case where the pH was from 6 to 9 was evaluated as the proper pH.

[0043]

Test Example 2

Crystal Precipitation Evaluation

The aqueous solid ointment charged in the airtight container of each of Example 1 described above and Examples 2 to 20 and Comparative Examples 1 to 24 described below and stored at 5°C for 4 weeks was visually observed to check presence of crystal precipitation and

evaluated as follows. Note that this test was not conducted for the aqueous solid ointments evaluated as not having the proper pH in Test Example 1.

○: No crystal precipitation occurred

×: Crystal precipitation occurred

[0044]

Test Example 3

Transparency Evaluation

The light transmittance of the aqueous solid ointment at 15 to 25°C charged in a polystyrene cell having an optical path length of 10 mm of each of Example 1 described above and Examples 2 to 20 and Comparative Examples 1 to 24 described below was measured by using a spectrophotometer (V-560, available from JASCO Corporation) at a wavelength of 660 nm. A case where the light transmittance was 30% or greater was evaluated as having transparency. Note that this test was not conducted for the aqueous solid ointments evaluated as "crystal precipitation occurred" in Test Example 2.

[0045]

Test Example 4

Shape Retainability Evaluation

The total amount of energy (g·mm) required for a spherical probe made of stainless steel and having a diameter of 7 mm to penetrate 3.5 mm at a speed of 0.07 mm/sec in a vertical direction with respect to a bottom face of one bottom central part of an aqueous solid ointment, which was at 24°C ± 2°C, cut into a cylindrical shape having a diameter of 40 mm and a height of 20 mm to 40 mm of each of Example 1 described above and Examples 2 to 20 and Comparative Examples 1 to 24 described below was measured by using a texture analyzer (TA-XT Plus, available from Stable Micro Systems). The measurement was performed three times total, and a case where an average value of the total amounts of energy was 900 g·mm or greater was evaluated as having shape retainability. Note that this test was not conducted for the aqueous solid ointments evaluated as "crystal precipitation occurred" in Test Example 2.

Table 1:

(wt. %)

Component	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7	Comparative Example 1	Comparative Example 2	Comparative Example 3	Comparative Example 4
	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7	Remainder	Remainder	Remainder	Remainder
Diclofenac sodium	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
l-Menthol	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Palmitic acid (NAA-160, NOF Corporation)	1.50	2.40	2.10	1.65	1.20	1.65	1.20	-	3.00	1.50	0.30
Stearic acid (NAA-180, NOF Corporation)	0.90	0.30	0.60	1.05	1.50	0.60	1.05	-	-	1.50	0.30
Behenic acid (NAA-222S, NOF Corporation)	0.60	0.30	0.30	0.30	0.30	0.75	0.75	3.00	-	-	2.40
1,3-Butylene glycol (Daicel Corporation)	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
Sucrose fatty acid ester (DK-Ester F-10, DKS Co., Ltd.)	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70
Sodium hydroxide (Kozakai Pharmaceutical Co., Ltd.)	0.43	0.45	0.45	0.44	0.44	0.43	0.43	0.35	0.47	0.45	0.37
Purified water	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Isopropanol (Kosumenoru S, ENEOS Corporation)	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Weight ratio of fatty acid salts (in terms of fatty acids)	Palmitic acid	50	80	70	55	40	55	40	0	100	50
	Stearic acid	30	10	20	35	50	20	35	0	0	50
	Behenic acid	20	10	10	10	10	25	25	100	0	0
pH	7.85	7.91	7.91	7.89	7.82	7.95	7.89	7.51	8.03	7.86	7.54
Crystal precipitation	○	○	○	○	○	○	○	○	○	○	○
Light transmittance (%)	67.4	72.0	66.2	62.3	62.0	67.3	63.2	0.1	22.6	45.9	0.0
Total amount of energy (g·mm)	1655	1254	1221	1217	1164	1324	1297	508	686	810	484

Table 2:

Component	(wt.%)												
	Comparative Example 5	Comparative Example 6	Comparative Example 7	Comparative Example 8	Comparative Example 9	Comparative Example 10	Comparative Example 11	Comparative Example 12	Comparative Example 13	Comparative Example 14			
Diclofenac sodium	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00			
l-Menthol	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00			
Palmitic acid (NAA-160, NOF Corporation)	1.50	-	-	0.30	1.50	1.20	0.70	1.05	0.70	1.05			
Stearic acid (NAA-180, NOF Corporation)	-	3.00	1.50	2.40	0.60	0.90	1.05	1.40	2.10	2.10			
Behenic acid (NAA-222S, NOF Corporation)	1.50	-	1.50	0.30	0.90	0.90	1.75	1.05	0.70	0.35			
1,3-Butylene glycol (Daicel Corporation)	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00			
Sucrose fatty acid ester (DK-Ester F-10, DKS Co., Ltd.)	0.70	0.70	0.70	0.70	0.70	0.70	0.50	0.50	0.50	0.50			
Sodium hydroxide (Kozakai Pharmaceutical Co., Ltd.)	0.41	0.42	0.39	0.42	0.43	0.42	0.45	0.47	0.47	0.49			
Purified water	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00			
Isopropanol (Kosumotoru S. ENEOS Corporation)	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder			
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00			
Weight ratio of fatty acid salts (in terms of fatty acids)	50	0	0	10	50	40	20	30	20	30			
Palmitic acid													
Stearic acid	0	100	50	80	20	30	30	40	60	60			
Behenic acid	50	0	50	10	30	30	50	30	20	10			
pH	7.71	7.67	7.51	7.70	7.81	7.80	7.74	7.85	7.87	7.96			
Crystal precipitation	×	×	×	×	×	×	×	×	×	×			

The relevance of the data in Tables 1 and 2 above is illustrated in FIG. 1.

[0046]

Example 2 to Example 7

Each component was weighed based on the composition listed in Table 1. Preparation was performed by Preparation Method 1 described above, and aqueous solid ointments were obtained. Subjected to the pH evaluation, the crystal precipitation evaluation, the transparency evaluation, and the shape retainability evaluation in accordance with Test Examples 1 to 4, the obtained aqueous solid ointments had the proper pH, did not cause precipitation of crystals by storage at a low temperature, and achieved transparency and shape retainability. The evaluation results are also presented in Table 1.

[0047]

Comparative Example 1 to Comparative Example 4

Each component was weighed based on the composition listed in Table 1. Preparation was performed by Preparation Method 1 described above, and aqueous solid ointments were obtained. When the obtained aqueous solid ointments were subjected to the pH evaluation, the crystal precipitation evaluation, the transparency evaluation, and the shape retainability evaluation in accordance with Test Examples 1 to 4, the pH was proper and no precipitation of crystals occurred by storage at a low temperature; however, the aqueous solid ointments having transparency and shape retainability were not obtained. The evaluation results are also presented in Table 1.

[0048]

Comparative Example 5 to Comparative Example 14

Each component was weighed based on the composition listed in Table 2. Preparation was performed by Preparation Method 1 described above, and aqueous solid ointments were obtained. When the obtained aqueous solid ointments were subjected to the pH evaluation and the crystal precipitation evaluation in accordance with Test Examples 1 and 2, the pH was proper; however, the aqueous solid ointments that did not cause precipitation of crystals by storage at a low temperature were not obtained. The evaluation results are also presented in Table 2.

Table 3:

(wt.%)

Component	Example 8	Example 9	Example 10	Example 11	Example 12	Example 13	Comparative Example 15	Comparative Example 16	Comparative Example 17	Comparative Example 18
Loxoprofen sodium hydrate	1.00	1.00	1.00	-	-	-	1.00	-	1.00	-
Flurbiprofen	-	-	-	1.00	1.00	1.00	-	1.00	-	1.00
l-Menthol	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Palmitic acid (NAA-160, NOF Corporation)	1.65	2.10	1.20	1.65	2.10	1.20	0.30	0.30	0.30	0.30
Stearic acid (NAA-180, NOF Corporation)	0.60	0.60	1.50	0.60	0.60	1.50	2.40	2.40	0.30	0.30
Behenic acid (NAA-222S, NOF Corporation)	0.75	0.30	0.30	0.75	0.30	0.30	0.30	0.30	2.40	2.40
1,3-Butylene glycol (Daicel Corporation)	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
Sucrose fatty acid ester (DK-Ester F-10, DKS Co., Ltd.)	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70	0.70
Sodium hydroxide (Kozakai Pharmaceutical Co., Ltd.)	0.43	0.45	0.44	0.60	0.61	0.60	0.42	0.59	0.37	0.54
Purified water	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Isopropanol (Kosumenoru S, ENEOS Corporation)	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Weight ratio of fatty acid salts (in terms of fatty acids)	55	70	40	55	70	40	10	10	10	10
Palmitic acid										
Stearic acid	20	20	50	20	20	50	80	80	10	10
Behenic acid	25	10	10	25	10	10	10	10	80	80
pH	8.04	8.09	8.05	7.95	8.01	7.94	7.93	7.81	7.78	7.69
Crystal precipitation	○	○	○	○	○	○	×	×	○	○
Light transmittance (%)	71.0	70.3	70.5	66.6	41.0	68.5			0.1	0.1
Total amount of energy (g·mm)	1209	1104	1056	1377	1096	1146			447	428

The relevance of the data in Table 3 above is presented in FIG. 2.

[0049]

Example 8 to Example 13

Each component was weighed based on the composition listed in Table 3. Preparation was performed by Preparation Method 1 described above, and aqueous solid ointments were obtained. Subjected to the pH evaluation, the crystal precipitation evaluation, the transparency evaluation, and the shape retainability evaluation in accordance with Test Examples 1 to 4, the obtained aqueous solid ointments had the proper pH, did not cause precipitation of crystals by storage at a low temperature, and achieved transparency and shape retainability. The evaluation results are also presented in Table 3.

[0050]

Comparative Example 15 and Comparative Example 16

Each component was weighed based on the composition listed in Table 3. Preparation was performed by Preparation Method 1 described above, and aqueous solid ointments were obtained. When the obtained aqueous solid ointments were subjected to the pH evaluation and the crystal precipitation evaluation in accordance with Test Examples 1 and 2, the pH was proper; however, the aqueous solid ointments that did not cause precipitation of crystals by storage at a low temperature were not obtained. The evaluation results are also presented in Table 3.

[0051]

Comparative Example 17 and Comparative Example 18

Each component was weighed based on the composition listed in Table 3. Preparation was performed by Preparation Method 1 described above, and aqueous solid ointments were obtained. When the obtained aqueous solid ointments were subjected to the pH evaluation, the crystal precipitation evaluation, the transparency evaluation, and the shape retainability evaluation in accordance with Test Examples 1 to 4, the pH was proper and no precipitation of crystals occurred by storage at a low temperature; however, the aqueous solid ointments having transparency and shape retainability were not obtained. The evaluation results are also presented in Table 3.

Table 4:

Component	(wt.%)			
	Comparative Example 19	Comparative Example 20	Comparative Example 21	Comparative Example 22
Diclofenac sodium	1.00	1.00	1.00	1.00
Sodium stearate (NONSOL SN-MK, NOF Corporation)	6.00	6.00	6.00	6.00
Polyethylene glycol 200 (Macrogol 200, NOF Corporation)	15.00	15.00	15.00	15.00
Sucrose fatty acid ester (DK-Ester F-160, DKS Co., Ltd.)	0.50	0.50	0.50	0.50
Sodium lactate solution (sodium L-lactate solution (50%), Showa Kako Corp.)	5.00	-	-	-

Lactic acid (DL-lactic acid, Showa Kako Corp.)	-	0.50	-	-
5N (15.45%) Hydrochloric acid (Muto Pure Chemicals Co., Ltd.)	-	-	0.32	0.97
Purified water	2.50	5.00	4.73	4.18
Isopropanol (Kosumenoru S, ENEOS Corporation)	Remainder	Remainder	Remainder	Remainder
Total	100.00	100.00	100.00	100.00
pH	9.17	7.80	7.97	7.62
Crystal precipitation		×	×	×

[0052]

Comparative Example 19

Each component was weighed based on the composition listed in Table 4. Preparation was performed by Preparation Method 1 described above, and thus an aqueous solid ointment was obtained. When the obtained aqueous solid ointment was subjected to the pH evaluation in accordance with Test Example 1, the aqueous solid ointment having the proper pH was not obtained. The evaluation results are also presented in Table 4.

[0053]

Comparative Example 20 to Comparative Example 22

Each component was weighed based on the composition listed in Table 4. Preparation was performed by Preparation Method 1 described above, and aqueous solid ointments were obtained. When the obtained aqueous solid ointments were subjected to the pH evaluation and the crystal precipitation evaluation according to Test Examples 1 and 2, the pH was proper; however, the aqueous solid ointments that did not cause precipitation of crystals by storage at a low temperature was not obtained. The evaluation results are also presented in Table 4.

Table 5:

(wt.%)

Component	Example 14	Example 15	Example 16	Example 17	Example 18	Example 19	Example 20	Comparative Example 23	Comparative Example 24
Diclofenac sodium	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
l-Menthol	-	-	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Palmitic acid (NAA-160, NOF Corporation)	1.50	1.50	2.50	3.00	3.50	4.00	1.60	0.50	5.00
Stearic acid (NAA-180, NOF Corporation)	0.90	0.90	1.50	1.80	2.10	2.40	1.40	0.30	3.00
Behenic acid (NAA-222S, NOF Corporation)	0.60	0.60	1.00	1.20	1.40	1.60	0.50	0.20	2.00
1,3-Butylene glycol (Daicel Corporation)	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
Sucrose fatty acid ester (DK-Ester F-160, DKS Co., Ltd.)	0.30	1.00	-	-	-	-	-	-	-
Sucrose fatty acid ester (DK-Ester F-10, DKS Co., Ltd.)	-	-	0.70	0.70	0.70	0.70	0.60	0.70	0.70
Isopropyl myristate (Nippon Fine Chemical Co., Ltd.)	-	-	-	-	-	-	3.00	-	-
Sodium hydroxide (Kozakai Pharmaceutical Co., Ltd.)	0.42	0.43	0.72	0.86	1.01	1.15	0.52	0.14	1.44
Purified water	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Isopropanol (Kosumoru S, ENEOS Corporation)	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder	Remainder
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Weight ratio of fatty acid salts (in terms of fatty acids)	50	50	50	50	50	50	46	50	50
Palmitic acid	30	30	30	30	30	30	40	30	30
Stearic acid	20	20	20	20	20	20	14	20	20
Behenic acid	3.00	3.00	5.00	6.00	7.00	8.00	3.50	1.00	10.00
Total amount of fatty acids	7.99	7.81	7.91	8.00	8.04	7.80	7.82	7.99	7.82
pH	○	○	○	○	○	○	○	○	○
Crystal precipitation	63.3	70.3	57.3	53.1	38.9	45.2	69.4	4.3	23.1
Light transmittance (%)	1403	1597	2163	2664	3451	4060	1751	45	5030
Total amount of energy (g·mm)									

[0054]

Example 14 to Example 20

Each component was weighed based on the composition listed in Table 5. Preparation was performed by Preparation Method 1 described above, and aqueous solid ointments were obtained. Subjected to the pH evaluation, the crystal precipitation evaluation, the transparency evaluation, and the shape retainability evaluation in accordance with Test Examples 1 to 4, the obtained aqueous solid ointment had the proper pH, did not cause precipitation of crystals by storage at a low temperature, and achieved transparency and shape retainability. The evaluation results are also presented in Table 5.

[0055]

Comparative Example 23

Each component was weighed based on the composition listed in Table 5. Preparation was performed by Preparation Method 1 described above, and an aqueous solid ointment was obtained. When the obtained aqueous solid ointment was subjected to the pH evaluation, the crystal precipitation evaluation, the transparency evaluation, and the shape retainability evaluation in accordance with Test Examples 1 to 4, the pH was proper and no precipitation of crystals occurred by storage at a low temperature; however, the aqueous solid ointment having transparency and shape retainability was not obtained. The evaluation results are also presented in Table 5.

[0056]

Comparative Example 24

Each component was weighed based on the composition listed in Table 5. Preparation was performed by Preparation Method 1 described above, and thus an aqueous solid ointment was obtained. When the obtained aqueous solid ointment was subjected to the pH evaluation, the crystal precipitation evaluation, the transparency evaluation, and the shape retainability evaluation according to Test Examples 1 to 4, the pH was proper, no precipitation of crystals occurred by storage at a low temperature, and shape retainability was achieved; however, the aqueous solid ointment having transparency was not obtained. The evaluation results are also presented in Table 5.

Industrial Applicability

[0057]

The present invention relates to an aqueous solid ointment, which does not cause, at a pH from 6 to 9, precipitation of crystals containing fatty acid salts, or in some cases further containing an active component, by storage at a low temperature and has transparency and shape retainability, and thus can be satisfactorily and industrially used.

Claims

[Claim 1]

An aqueous solid ointment, comprising fatty acid salts, a lower alcohol, a sucrose fatty acid ester, water, and an active component,

the fatty acid salts comprising a palmitate, a stearate, and a behenate, and when the palmitate, the stearate, and the behenate contained in the aqueous solid ointment are converted to fatty acids corresponding thereto, and a total parts by weight of the fatty acids are taken as 100, a respective ratio of the palmitate to the stearate to the behenate being in a range of 35 - 90 : 5 - 55 : 5 - 28,

wherein the aqueous solid ointment contains, with respect to a total amount of the aqueous solid ointment, three kinds of the fatty acid salts totaling from 3 to 8 wt.% in terms of fatty acids, from 50 to 90 wt.% of the lower alcohol, from 0.1 to 2.5 wt.% of the sucrose fatty acid ester, from 1 to 20 wt.% of the water, and from 0.1 to 10 wt.% of the active component, and has a pH of 6 to 9.

[Claim 2]

The aqueous solid ointment according to claim 1, wherein the active component is an antiphlogistic analgesic component.

[Claim 3]

The aqueous solid ointment according to claim 2, wherein the antiphlogistic analgesic component is at least one selected from diclofenac, loxoprofen, flurbiprofen, and salts thereof.