APPLICATION ACCEPTED AND ALLOWED 15.11.90

606681

FORM 1
REGULATION 9

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952–1973

APPLICATION FOR A PATENT

I/We SANSHO SEIYAKU CO., LTD.

of 26–7, Oike 2–chome, Onojo–shi, Fukuoka–ken, JAPAN

hereby apply for the grant of a Patent for an invention entitled: A composition for external application to skin, which is stable against discoloration".

which is described in the accompanying complete specification. This Application is a Convention Application and is based on the Application(s) numbered: 62–108226 for a Patent or similar protection made in Japan on 30 April 1987.

My/Our address for service is:

GRIFFITH HASSEL & FRAZER
71 YORK STREET
SYDNEY N.S.W. 2000
AUSTRALIA

DATED this 27th day of April, 1988.

SANSHO SEIYAKU CO., LTD.

By his/their Patent Attorneys

GRIFFITH HASSEL & FRAZER

LODGED AT SUB-OFFICE
27 APR 1988
Sydney

TO: THE COMMISSIONER OF PATENTS
COMMONWEALTH OF AUSTRALIA
2801A:rk

ASSIGNEE - APPLICANT

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952 (AS AMENDED)

DECLARATION IN SUPPORT OF AN APPLICATION FOR A PATENT

(Name of applicant) In support of an Application made by SANSHO SEIYAKU CO., LTD.

(Title) for a patent for an invention entitled

EXTERNAL PREPARATIONS

(Full name of signatory) I, Tsuneo Jinnai

(Address of signatory) of 26-7, Oike 2-chome, Onojo-shi, Fukuoka-ken, JAPAN

do solemnly and sincerely declare as follows:-

I. I am authorised by the abovementioned applicant for the the patent to make this Declaration on its behalf.

2. The name and address of each actual inventor of the invention is as follows:

Shinji Yamamoto

of Room 507 River Side Shibuta, 3-10-1, Higashiori, Onojo-shi, Fukuoka-ken, JAPAN

and the facts upon which the applicant is entitled to make this application are as follows:

(Insert details of assignment etc.) The applicant is the assignee of the said invention from the said inventor

(Delete paragraphs 3 and 4 for Non-Convention application)

3. The basic application(s) as defined by Section 141 of the Act was (were) made as follows:

Country Japan on 30 April 1987

in the name(s) Sansho Seiyaku Co., Ltd.

and in ..... on .....

in the name(s) .....

and in ..... on .....

and in the name(s) .....

4. The basic applications(s) referred to in the preceding paragraph of this Declaration was(were) the first application(s) made in a Convention country in respect of the invention the subject of this application.

(Place and date of signing) Declared at Fukuoka-ken,JAPAN this 20th day of April 19 88.

Signed: Tsuneo Jinnai

Position: .....

(12) PATENT ABRIDGMENT (11) Document No. AU-B-15222/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 606681

(54) Title
SUBLIMED KOJIC ACID COMPOSITION FOR EXTERNAL APPLICATION

International Patent Classification(s)
(51)[4] A61K 031/35 A61K 007/48

(21) Application No. : 15222/88 (22) Application Date : 27.04.88

(30) Priority Data

(31) Number	(32) Date	(33) Country
62-108226	30.04.87	JP JAPAN

(43) Publication Date : 03.11.88

(44) Publication Date of Accepted Application : 14.02.91

(71) Applicant(s)
SANSHO SEIYAKU CO., LTD.

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(57) Intensive studies to prevent discoloration of external preparations containing kojic acid as active ingredient have led us to discover the unexpected fact that this problem can be solved if kojic acid purified by sublimation is used. This invention was accomplished on the basis of these findings.

CLAIM

1. A composition for external application to skin containing, as an active ingredient, 0.01 to 5.00% by weight of kojic acid purified by sublimation, based on the total weight of base materials.

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COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952 Form 10

COMPLETE SPECIFICATION

FOR OFFICE USE

Short Title:

Int. Cl:

Application Number:
Lodged:

Complete Specification–Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: SANSHO SEIYAKU CO., LTD.

Address of Applicant: 26-7, Oike 2-chome, Onojo-shi, Fukuoka-ken, JAPAN

Actual Inventor: Shinji Yamamoto

Address for Service: GRIFFITH HASSEL & FRAZER
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AUSTRALIA

Complete Specification for the invention entitled:

"A composition for external application to skin, which is stable against discoloration".

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

2801A:rk

A composition for external application to skin, which is stable against discoloration".

Background of the Invention

Filed of the Invention

This invention relates to external preparations with improved stability against discoloration comprising kojic acid purified by sublimation.

Description of the Prior Art

Kojic acid is known as a substance capable of effectivity inhibiting the formation of melanin in the human skin.

Cosmetics have also been disclosed which utilize the melanogenesis inhibitory action of this acid (for example, Japanese Patent Kokai No. 53-3538, and Japanese Patent Publication No. 56-18569, No. 61-109705, No. 62-3820).

Also known are external preparations utilizing the melanogenesis-inhibitory, anti-inflammatory and analgesic actions of kojic acid (for example, Japanese Patent Publication No. 61-10447, No. 58-3446, No. 60-27648, and Japanese Patent Kokai No. 61-143313, No. 61-143314).

Kojic acid contained in these cosmetics and external preparations that has been accepted as an excellent ingredient capable of inhibiting the formation of melanin with no side effect to the skin.

However, the external preparations containing kojic acid tend to become discolored with the passage of

time, thus lowering in commodity value, unless careful considerations are given to the removal of metal ions from the water, materials and equipment used for the manufacture thereof, the pH of final products and other factors.

Summary of the Invention

Intensive studies to prevent discoloration of external preparations containing kojic acid as active ingredient have led us to discover the unexpected fact that this problem can be solved if kojic acid purified by sublimation is used. This invention was accomplished on the basis of these findings.

In accordance with the present invention there is provided a composition for external application to skin containing as an active ingredient, 0.01 to 5.00% by weight of kojic acid purified by sublimation, based on the total weight of base materials.

Brief Description of the Drawings

Figure 1 illustrates the sublimation apparatus used in the Manufacturing Example for preparing purified kojic acid, in which a is a vessel or crude kojic acid, b is a trap, 1 is crude kojic acid being purified, 2 is an internal tube for cooling water circulation, and 3 is a freezing mixture.

Detailed Description of the Invention

This invention relates to external preparations containing, as active ingredient, kojic acid purified by sublimation which are free from discoloration with the passage of time.

Kojic acid used in this invention is obtained by growing a strain belonging to the genus Aspergillus, penicillium, Escherichia or Acetobacter and capable of producing kojic acid, and purifying the crude kojic acid recovered from the culture fluid by sublimation under normal or reduced pressure.

Sublimation may be carried out under normal pressure at a temperature ranging from 120°C to the melting point of the acid. However, better results can be obtained by sublimation under reduced pressure at an elevated temperature in terms of product yield.

The external preparations herein mean general pharmaceutical preparations for external use, such as ointments, emulsions, lotions, creams, emulsified lotions, skin lotions and packs. Kojic acid purified by sublimation is contained is these preparations in amounts of 0.01 to 5.00 weight %.

Known techniques may be used for the manufacture of these preparations form the purified kojic acid and base materials for external preparations.

Kojic acid purified by sublimation shows the same effect of inhibiting melanogenesis as the acid conventionally used. It also exhibits similar synergistic effects with vitamin E, derivatives thereof, placental extract and liver extract.

Thus, the external preparations of this invention containing, as active ingredient, kojic acid purified by sublimation show higher stability against discoloration

compared with conventional products containing otherwise purified kojic acid.

This invention will become more apparent from the following Examples and Manufacturing Example (purification of kojic acid by sublimation).

Manufacturing Example

Kojic acid was purified by sublimation using an apparatus shown in Figure 1. Powder of crude acid (2g) was placed at the bottom of vessel a fitted with an internal tube for cooling water circulation 2. Trap b was externally cooled with a freezing mixture 3 (acetone/dry ice), and the vessel a was evacuated to 5 torr by a vacuum pump and heated to 140°C with its bottom immersed in an oil of the depth. Treatment under the conditions described above gave sublimate of kojic acid deposited on the bottom of internal tube 2. This sublimate was colleted eight times at 60-minute intervals. The total yield of purified acid was one gram.

The pure acid thus prepared has the following properties:

(1) Appearance	white powder	
(2) Melting point	154.4°C	
(3) Color tone (3%), 420nm	0.002	(absorbance)
(4) Turbidity (3%), 570nm	0.002	(absorbance)
(5) pH (1%)	4.57	
(6) Purity	100.0%	

Example 1 (skin lotion)

Polyethylene adduct of hardened castor oil (60 E.O.)	1.00%
Ethanol	15.00
Methyl p-oxybenzoate	0.10
Citric acid	0.10
Sodium citrate	0.30
1,3-Butylene glycol	4.00
Disodium edetate	0.01
Sublimed kojic acid	0.50
Pure water	Balance

Example 2 (emulsified lotion)

Polyxyethylene-sorbitan monostearate (20 E.O.)	1.00%
Polyoxyethylene-sorbitan tetraoleate (60 E.O.)	0.50
Lipophilic glycerol monostearate	1.00
Stearic acid	0.50%
Behenyl alcohol	0.50
Avocado oil	4.00
Glycerol trioctanoate	4.00
Ethyl p-oxybenzoate	0.20
1,3-Butylene glycol	5.00
Xanthan gum	0.14
Disodium edetate	0.01
Sublimed kojic acid	1.00

Pure water	Balance

Example 3 (cream)

Polyethylene glycol monostearate (40 E.O.)	2.00%
Self-emulsifiable glycerol monostearate	5.00
Stearic acid	5.00
Behenyl alcohol	1.00
Liquid paraffin	10.00
Glycerol trioctanoate	10.00
p-Oxybenzoic acid ester	0.20
1.3-Butylene glycol	5.00
Disodium edetate	0.01
Sublimed kojic acid	1.00
Pure water	Balance

Example 4 (cream pack)

Polyethylene glycol monostearate (40 E.O.)	2.00%
Self-emulsifiable glycerol monostearate	5.00
Stearic acid	5.00
Behenyl alcohol	0.50
Squalane	15.00
Cetyl octanoate	5.00
p-Oxybenzoic acid ester	0.20
1,3-Butylene glycol	5.00

Disodium edetate	0.01
Sublimed kojic acid	1.00
Pure water	Balance

Described below are the tests on the stability of sublimed kojic acid and external preparations containing the same against discoloration.

(1) Test samples

a) Sublimed kojic acid obtained in Manufacturing Example

b) Cream prepared in Example 3 containing 1% of the sublimed kojic acid

c) Kojic acid purified by a method other than sublimation

d) Cream prepared according to the formulation of Example 3 in which the sublimed kojic acid is replaced with the kojic acid purified by a method other than sublimation

(2) Testing procedure

Each of the samples (10g) was filled in a glass bottle and allowed to stand at 45°C for 30 days. Color of each sample was visually observed at the start of test, and on the 5th, 10th, 20th and 30th days.

(3) Result

The result of test is summarized in the table below.

Sample	At start	5th day	10th day	20th day	30th day
a	-	-	-	±	+
b	-	-	-	±	±
c	-	±	+	++	++
d	-	±	+	++	+++

-: No discoloration; ±: Faint yellowing;

+: Slight yellowing; ++: Appreciable yellowing

As is apparent from the a table, the external preparations containing kojic acid purified by sublimation showed higher stability against discoloration.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A composition for external application to skin containing, as an active ingredient, 0.01 to 5.00% by weight of kojic acid purified by sublimation, based on the total weight of base materials.

2. A composition for external application to skin, substantially as herein described, with reference to any one of Examples 1 to 4.

DATED this 22nd day of October 1990

SANSHO SEIYAKU CO., LTD.
By Their Patent Attorney
GRIFFITH HACK & CO.



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