



(11)

EP 2 234 480 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
18.09.2013 Bulletin 2013/38

(21) Application number: **09704710.4**(22) Date of filing: **23.01.2009**

(51) Int Cl.:

A01N 43/80 (2006.01) **A01N 37/02** (2006.01)
A01N 31/04 (2006.01) **A61K 8/34** (2006.01)
A61K 8/37 (2006.01) **A61K 8/49** (2006.01)
A61Q 19/00 (2006.01)

(86) International application number:
PCT/US2009/000460(87) International publication number:
WO 2009/094198 (30.07.2009 Gazette 2009/31)

(54) **Liquid preservative compositions comprising glyceryl caprylate and 2-methyl-4-isothiazolin-3-one**

Flüssige Konservierungsmittelzusammensetzungen enthaltend Glycerylcaprylat und 2-Methyl-4-isothiazolin-3-on

Compositions liquides de conservation comprenant de glyceryl caprylate et de 2-methyl-4-isothiazolin-3-one

(84) Designated Contracting States:
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
 HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL
 PT RO SE SI SK TR**

(30) Priority: **25.01.2008 US 62356**(43) Date of publication of application:
06.10.2010 Bulletin 2010/40(73) Proprietor: **Rhodia Opérations
 93306 Aubervilliers (FR)**

(72) Inventors:
 • **BERG, Kenneth
 Saint John
 Indiana 46373 (US)**

- **GERMAIN, Teresa
 Orland Park
 Illinois 60667 (US)**

(74) Representative: **Schnappauf, Georg et al
 Dr. Volker Vossius
 Patentanwälte / Partnerschaftsgesellschaft
 Radlkoferstrasse 2
 81373 München (DE)**

(56) References cited:
**EP-A1- 1 541 124 EP-A1- 2 138 189
 EP-A2- 0 559 319 EP-A2- 0 659 404
 US-A1- 2006 093 634 US-A1- 2007 265 352**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Description**FIELD OF THE INVENTION**

5 [0001] This invention relates to liquid preservative compositions containing glyceryl caprylate that are free from formaldehyde, formaldehyde-releasing compounds, phenolic compounds, paraben compounds, and halogenated preservatives.

BACKGROUND OF THE INVENTION

10 [0002] It is widely known that there is a growing demand for personal care and cosmetic products that are free from certain components perceived to be potentially harmful, which are found in many common preservative (i.e., antimicrobial) compositions. In particular, there is a strong demand in the marketplace for use in consumer and industrial products generally for alternatives to common preservative materials such as formaldehyde-releasing compounds (due to the 15 known hazards of formaldehyde), phenolic compounds, certain paraben compounds (i.e., para-hydroxybenzoate esters), and certain halogenated compounds.

20 [0003] Known alternatives to such compounds are the fatty glyceryl monoester materials developed by Kabara, such as glyceryl laurate, glyceryl caprylate, and the like. These high monoester-containing materials tend to have relatively weak antimicrobial activity compared to traditional preservatives, however. In addition, many of the monoesters are 25 solids at room temperature, and may require excessive heating to incorporate them into cosmetic or personal care products. The use of heat to dissolve or admix components in cosmetic and personal care product manufacturing processes can lead to undesirable side reactions, degradation of key ingredients, and discoloration in some cases, and is uneconomically energy intensive.

25 [0004] There is an ongoing need for new liquid preservative compositions for use in cosmetics and personal care products, especially, which are free from formaldehyde, formaldehyde-releasing compounds, phenolic compounds, paraben compounds, and preferably free from halogenated compounds, while still maintaining a broad spectrum of antimicrobial activity, and which can be formulated into personal care and cosmetic products without undue heating. The present invention fulfills these needs.

30 SUMMARY OF THE INVENTION

35 [0005] The present invention provides a liquid preservative composition comprising (a) glyceryl caprylate; and (b) an aqueous isothiazolinone solution comprising 2- methyl- 4- isothiazolin- 3- one, wherein the composition contains less than 15 percent by weight of water and is free from halogenated preservatives, formaldehyde, formaldehyde- releasing compounds, phenolic compounds, and paraben compounds. Preferably, the aqueous isothiazolinone solution comprises 2- methyl- 4- isothiazolin- 3- one at an active concentration of 0.005 to 55 weight percent. In a preferred embodiment, the liquid preservative composition additionally comprises an alkanol- substituted aromatic compound wherein the alkanol- substituted aromatic compound is an aromatic compound bearing at least one alkanol substituent selected from the group consisting of alkyl and alkoxy moieties that bear a hydroxyl group. Preferably, the alkanol- substituted aromatic 40 compound is selected from the group consisting of phenethyl alcohol; benzyl alcohol; and phenoxyethanol. In a preferred embodiment, the liquid preservative composition comprises 5 to 99.9 percent by weight, preferably 5 to 95 percent by weight of glyceryl caprylate. In a preferred embodiment, the liquid preservative composition comprises an aqueous solution of 0.1 to 25 active percent by weight of 2- methyl- 4- isothiazolin- 3- one. In a preferred embodiment, the liquid preservative composition comprises 85 to 95 percent by weight of glyceryl caprylate and an aqueous solution of 0.5 to 45 2 active percent by weight of 2- methyl- 4- isothiazolin- 3- one.

50 [0006] In another aspect, the present invention provides a method of preserving a consumer or industrial product comprising admixing a preservative effective amount of the preservative composition of the invention with said consumer or industrial product. In a preferred embodiment, the preservative effective amount of the preservative composition is in the range of 0.1 to 35 percent by weight based on the combined weight of the preservative composition and said consumer or industrial product.

55 [0007] In another aspect, the present invention provides a cosmetic or personal care product comprising 0.1 to 25 percent by weight glyceryl caprylate in combination with 0.02 to 10 percent by weight phenethyl alcohol and 2 to 200 ppm (active basis) of 2- methyl- 4- isothiazolin- 3- one; the cosmetic or personal care product being free from halogenated preservatives, formaldehyde, formaldehyde- releasing compounds, phenolic compounds, and paraben compounds.

[0008] The liquid preservative compositions of the invention are pourable, pumpable liquids, which provide a broad spectrum of protection against a variety of bacteria and fungi species. A preferred liquid preservative composition of the invention comprises glyceryl caprylate in combination with phenethyl alcohol and an aqueous solution of 2- methyl- 4- isothiazolin- 3- one. Such compositions provide a surprisingly enhanced activity against *Candida albicans* compared to

glyceryl caprylate, phenethyl alcohol, or aqueous 2- methyl- 4- isothiazolin- 3- one solution, when used as the sole preservative.

[0009] The liquid nature of the preservative composition of the invention facilitates efficient mixing of the preservative composition with other cosmetic or industrial ingredients without heating.

5

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0010] The liquid preservative compositions of the present invention comprise the alkanol fatty monoester glyceryl caprylate together with an aqueous isothiazolinone solution comprising 2- methyl- 4- isothiazolin- 3- one.

[0011] As used herein, the terms "alkanol fatty monoester" and "alkanol monoester of a C₈-C₂₂ alkanoic acid" are synonymous with one another and refer to monoesters of a diol or polyol with a C₈-C₂₂ carboxylic acid moiety. An alkanol fatty monoester can comprise a single ester compound or a combination of two or more esters. For example, the alkanol fatty monoester can comprise a monoester of a glycol or glycerin with a single carboxylic acid (e.g., caprylic acid) or with a combination of carboxylic acids, such as are often obtained by hydrolysis of natural oils. Preferred alkanol fatty monoesters are glycerin fatty acid monoesters. Particularly preferred alkanol fatty monoesters are glyceryl caprylate (i.e., glyceryl monoctanoate) and glyceryl caprate (i.e., glyceryl monodecanoate), which are commercially available from a variety of sources. Typically, alkanol fatty monoesters are prepared by direct reaction of a polyol with a fatty carboxylic acid. Alternatively, such mono esters can be prepared by transesterification of a fatty ester (e.g., a fatty methyl ester) with a polyol. Alkanol fatty monoesters useful in the practice of the present invention can be prepared by any suitable means.

[0012] The term "alkanol-substituted aromatic compound" as used herein and in the appended claims refers to an aromatic compound (e.g., a phenyl or naphthyl compound) bearing at least one alkanol substituent. Alkanol substituents are alkyl or alkoxy moieties that bear a hydroxyl group, such as hydroxyethyl, hydroxymethyl or 2-hydroxyethoxy substituents. Preferred alkanol-substituted aromatic compounds for use in the present invention include, phenoxyethanol, and benzyl alcohol, and particularly phenethyl alcohol.

[0013] The term "isothiazolinone solution" as used herein and in the appended claims refers to aqueous solutions comprising 2- methyl- 4- isothiazolin- 3- one (CAS No. 2682- 20- 4), preferably at an active concentration of 0.005 to 55 weight %, more preferably of 0.1 to 25 weight %, more preferably of 1 to 10 weight %. Aqueous isothiazolinone solutions optionally include a water- soluble inorganic salt, such as magnesium nitrate in an amount of up to about 25 weight %.

[0014] Aqueous 2- methyl- 4- isothiazolin- 3- one solutions are commercially available at a reported active concentration of 9.5- 9.9% in water sold under the brand names NEOZONE® 950 Preservative by Rohm and Haas Company; and MICROKARE® MT by Thor Products; and at a reported active concentration of 50- 52% in water sold under the brand name KORDEK® LX5000 Industrial Microbiocide by Rohm and Haas Company.

[0015] The alkanol fatty monoester glyceryl caprylate preferably constitutes 5 to 99.9 percent by weight, more preferably 5 to 95 percent by weight, of the liquid preservative composition. In one preferred embodiment, the liquid preservative composition comprises 85 to 95 percent by weight of glyceryl caprylate (e.g., 90 percent by weight glyceryl caprylate), and 0.5 to 2 active percent by weight of 2- methyl- 4- isothiazolin- 3- one (e.g., 10 weight percent of an aqueous solution of 9 to 10 active percent by weight 2- methyl- 4- isothiazolin- 3- one).

[0016] The preservative compositions of the present invention provide a variety of desirable Matures for use in consumer products, such as cosmetics and personal care products, including emolliency (i.e., due to the glyceryl caprylate component) and surprisingly unexpected broad spectrum antimicrobial activity. The compositions of the present invention provide surprisingly enhanced activity against *Candida albicans* compared to preservatives that include an alkanol fatty monoester alone, an alkanol- substituted aromatic compound alone, or an aqueous isothiazolinone solution alone. In addition, compositions that include phenethyl alcohol also provide a desirable fragrance characteristic. The presence in the liquid preservative composition of the alkanol- substituted aromatic compound and/or an aqueous isothiazolinone solution (e.g., 8 to 12 weight percent of an aqueous solution of 9 to 10 active weight percent 2- methyl- 4- isothiazolin- 3- one) also liquefies the normally solid alkanol fatty monoester. This liquefying characteristic allows highly concentrated, alkanol fatty monoester preservative compositions to be prepared, which are pumpable and pourable without requiring the addition of large amounts of solvents that do not contribute to the preservative activity of the compositions.

[0017] The preservative compositions of the invention are free from formaldehyde, formaldehyde-releasing compounds, phenolic compounds, paraben compounds, and halogenated preservatives. The compositions of the invention contain less than 15 percent by weight, preferably less than about 10 percent by weight water, mainly derived from the aqueous isothiazolinone solution.

[0018] As disclosed herein, the liquid preservative concentrates typically can be admixed with other ingredients of consumer products, such as cosmetic and personal care products, or industrial products in an energy conserving manner with minimal or no heating, which is an added advantage of the compositions of the present invention. The use of the terms "cosmetic" and "personal care" products, and grammatical variations thereof, individually or collectively, is intended to encompass topically applied toiletries, health care, beauty aids, over-the-counter pharmaceutical formulations, and

the like. The term "industrial" products is intended to encompass products used in institutional, industrial, or household environments, for cleaning and maintaining the facility.

[0019] Another aspect of the present invention is a method of preserving a consumer or industrial product comprising admixing a preservative effective amount of a liquid preservative composition of the invention with a consumer or industrial product. In a preferred embodiment, the preservative effective amount of the preservative composition is in the range of 0.1 to 35 percent by weight based on the combined weight of the preservative and the consumer or industrial product.

[0020] Yet another preferred aspect of the present invention is a cosmetic or personal care product comprising 0.1 to 25 percent by weight glyceryl caprylate in combination with 0.02 to 10 percent by weight phenethyl alcohol and an aqueous solution of 2 to 200 ppm (actives basis) of 2- methyl- 4- isothiazolin- 3- one; the product being free from formaldehyde, formaldehyde- releasing compounds, phenolic compounds, paraben compounds, and halogenated preservatives.

[0021] The preservative composition of the present invention can be employed in aqueous or non- aqueous liquid products, including emulsions of oil- in- water, water- in- oil, and multiple phase emulsions.

[0022] The following examples are provided to illustrate preferred embodiments of the present invention, and are not meant to limit the scope of the invention.

Example 1. Evaluation of Broad Spectrum Preservative Activity in a Cleansing Composition.

[0023] Several 200-gram samples of a cleanser base were admixed with a variety of preservative compositions, and challenged with selected bacteria and fungi (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus niger*, and *Candida albicans*) according to the following procedure:

[0024] About 0.5 mL of an aqueous suspension containing about 1×10^6 to about 2×10^7 colony forming units-per-milliliter (cfu/mL) of *Aspergillus niger* in a pH 7.2 phosphate buffer was transferred to a tube containing about 9.5 mL of a sample of a cleanser base composition to provide an inoculum level of about 1×10^5 to about 1×10^6 cfu/mL. The same procedure was used to challenge samples of the cleanser base with *Candida albicans* and with a mixed culture of *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*, at about the same inoculum levels. The challenged samples were stored at an ambient room temperature of about 22 °C. At 7 days and 14 days after challenge, aliquots from each sample were diluted according to the following procedure: about 1 mL of each challenged sample was aseptically transferred into a tube containing about 9 mL of Dey/Engley (D/E) neutralizing broth with thorough mixing to provide a dilution ratio of about 1:10. About 0.1 mL of each of the 1:10 diluted samples was then aseptically transferred into separate tubes, each tube containing about 9 mL of sterile buffered saline solution, (3.5g/L phosphoric acid in 0.9 wt. % NaCl solution, adjusted to pH 7.2 with 50 wt. % aqueous sodium hydroxide), with thorough mixing, to provide a dilution ratio of about 1:1000.

[0025] Finally, each of the 1: 10 diluted samples and each of the 1: 1000 diluted samples were plated according to the following procedure: about 1 mL of each of the diluted samples was plated with Lethen agar (bacteria samples) or Sabouraud dextrose agar (yeast and mold samples) . The Lethen agar plates were incubated at 35 ± 2 °C for about 48 hours (about 2 days) in an inverted position, and the resulting microbial colonies were counted. The Sabouraud dextrose agar plates were incubated at 25 ± 2 °C for about 120 hours (about 5 days) in an upright position and the resulting microbial colonies were counted.

[0026] The formulations of the cleanser base and the D/E Neutralizing Broth used in these evaluations are provided in Table 1 and Table 2, respectively. The preservative compositions and observed plate counts (in cfu) are shown in Tables 3 and 4.

Table 1. Cleanser Base Formulation.

Component (Common or INCI* Name)	Weight %
Water to 100 weight %	q.s.
PEG-80 sorbitan laurate	5
PEG-6000 distearate	1.1
Sodium lauroamphoacetate (44 % solids in water)	2
Sodium laureth sulfate (70 % solids in water)	3.7
Cocamidopropyl betaine (44 % solids in water)	6.4
Citric acid (25 % aq.) to pH 6.7	q.s.

* INCI = International Nomenclature Cosmetic Ingredient name assigned by the International Committee of the Personal Care Products Council (formerly Cosmetic, Toiletry, and Fragrance Association (CTFA)).

q.s.=quantity sufficient

Table 2. D/E Neutralizing Broth Formulation.

Component (Common or INCI Name)	Grams/Liter Water
Pancreatic digest of casein	5
Yeast extract	2.5
Dextrose	10
Sodium thioglycolate	1
Sodium thiosulfate	6
Sodium bisulfite	2.5
Polysorbate 80	5
Lecithin	7
Bromcresol purple	0.02

Table 3. Day-7 Plate Counts (cfu).

Ex.	Preservative added (wt. % or ppm)*	Plate Count, cfu				
		EC	PA	SA	AN	CA
A	0.9 % phenoxyethanol (POE)	<10	1500	18500	<10	9500
B	95 ppm 2-methyl-4-isothiazolin-3-one (MI)	155	115	215	1000	10500
C	0.5 % glyceryl caprylate (GC)	15	7500	<10	1000	500
D	0.5 % phenethyl alcohol (PEA)	380	10	7500	25	91000
E	0.15% sodium benzoate	TN	TN	9000	1500	336500
F	none	TN	TN	13500	2500	TN
G	95 ppm MI and 0.5 % GC**	<10	1000	10	<10	<10
H	0.5% PEA and 0.5 % GC	<10	9500	<10	10	<10

* Amount added to the base composition.

** Representative of an example of the Invention for amounts obtainable by adding to the base composition e.g., 0.56 % by weight of a liquid preservative composition containing about 90 wt. % glyceryl caprylate, about 1.7 active wt. % MI and about 8.3 wt % water.

EC = *Escherichia coli*; PA = *Pseudomonas aeruginosa*; SA = *Staphylococcus aureus*;

AN = *Aspergillus niger*; CA = *Candida albicans*.

TN = too numerous to count

Table 4. Day-14 Plate Counts (cfu).

Ex.	Preservative added (wt. % or ppm)	Plate Count, cfu				
		EC	PA	SA	AN	CA
A	0.9 % phenoxyethanol (POE)	<10	<10	100	<10	<10
B	95 ppm 2-methyl-4-isothiazolin-3-one (MI)	10	<10	6500	500	15000
C	0.5 % glyceryl caprylate (GC)	10	117500	1000	280	485
D	0.5 % phenethyl alcohol (PEA)	1000	1000	1000	<10	2000
E	0.15% sodium benzoate	TN	TN	500	3500	TN
F	none	TN	TN	1000	6500	TN
G	95 ppm MI and 0.5 % GC	<10	<10	1000	<10	<10
H	0.5% PEA and 0.5 % GC	<10	900	500	<10	<10

[0027] The data in Tables 3 and 4 clearly indicate that the preservative composition of the invention (Example G) exhibited desirably good activity in the cleanser base against the various bacteria and yeast species tested, as well as a surprisingly and unexpectedly improved activity against *Candida albicans* compared to the preservatives that included glyceryl caprylate alone (Ex. C), phenethyl alcohol alone (Ex. D), and 2- methyl- 4- isothiazolin- 3- one alone (Ex. B) .

5 In addition, the antimicrobial activities of the composition of the invention were comparable to or superior to various other known formaldehyde- free and paraben- free preservatives (i.e., Examples A and E) for most or all of the tested microbial species. The composition of the invention met or exceeded the standard United States Pharmacopeia (USP) requirement for antimicrobial effectiveness, having reduced bacterial levels by a minimum of one log level in seven days and having reduced bacterial levels by three or more log levels in 14 days, and showing no increase over the initial inoculum level 10 of fungi at any time during the test.

Example 2. Evaluation of Preservative Activity by Minimum Inhibitory Concentration

[0028] A Minimum Inhibitory Concentration (MIC) evaluation was conducted for five preservative liquids; i.e., Ex. A: an aqueous liquid preservative composition of the invention comprising about 90 weight % glyceryl caprylate (GC), and about 1 active weight % 2- methyl- 4- isothiazolin- 3- one (MI) with the balance being water (GCM) ; Ex. B: a liquid preservative composition comprising about 60 weight % PEA and about 40 weight % GC (GCP) ; as well as the individual components: i.e., Ex. C: glyceryl caprylate (GC) ; Ex. D: an aqueous 2- methyl- 4- isothiazolin- 3- one (MI) solution of about 9.5 % active MI; and Ex. E: phenethyl alcohol (PEA) . In this evaluation, nutrient broth solutions were made with different concentrations of the test compounds, and then all the solutions were spiked with the same concentration of test organism. Growth was indicated by a solution becoming hazy after 24 hours of incubation time. The highest dilution without observable growth is the Minimal Inhibitory Concentration (MIC) .

Procedures:

[0029] The following procedure was adopted from the Manual of Clinical Microbiology, 2nd Ed. published by the American Society for Microbiology, ISBN 0914826-00-X.

Growth Media:

[0030] Prepare and sterilize Mueller-Hinton Broth (MH broth) (Fluka) per the manufacturer's instructions (dissolve 23 grams in one liter water and autoclave at 121°C for 15 minutes minimum).

Dilution of Antimicrobial agent:

[0031] The stock antimicrobial solution is diluted (in MH broth) to twice the highest final test concentration desired. Sterile 13x100mm screw-capped culture tubes are used. Two-fold dilutions are made directly in the tubes. To the first tube is added 2 mL of the working solution of antimicrobial agent. To each remaining tube is added 1 mL of broth. Using aseptic technique, an amount of 1 mL is transferred from the first tube to the second tube and is thoroughly mixed. After thorough mixing, 1 mL is transferred from the second tube to the third tube. This process is repeated through the second to last tube, from which 1 mL is removed and discarded. The final tube receives no antimicrobial agent and serves as a growth control.

Preparation of inoculums:

Reagents

[0032] Buffered saline (3.5g/L phosphoric acid in a 0.9% NaCl solution, pH adjusted to 7.2 with 50 wt. % aqueous NaOH, sterilized by autoclave).

[0033] The organisms used were:

S. aureus 6538 EPWR E7 (Fisher cat# 23- 003- 378)
P. aeruginosa 9027 EPWR E7 (Fisher cat# 23- 003- 377)
A. niger 16404 E PWR 10PK (Fisher cat# 23- 003- 3397)

[0034] The organisms are preferably lyophilized Microbiologics Epower E7 microorganisms (mean assay value of between 10 million and 100 million colony forming units or equivalent concentration). The final concentrations of the microorganism in the inoculum should be in the order of 10⁶-10⁷ cfu/mL.

Organism hydration:

[0035]

- 5 1. Allow unopened vial of microorganism pellets to equilibrate to room temperature.
2. Warm 1 tube of 10 mL buffered saline per organism used to about 35-37 °C.
3. Using sterile forceps, transfer 2 pellets to the saline and return unused pellets to storage.
4. Incubate the hydrated material at about 35-37 °C for about 30 minutes.
5. Vortex the vials until homogeneous.
- 10 6. Add 1.0 ml of the diluted culture suspension to each of the previously prepared tubes containing the preservative compositions. The final concentration of preservative is now one-half of the original concentration in each tube.

[0036] All tubes were incubated at about 35 °C for about 24 hours. The tubes were then examined for visible signs of bacterial growth. The highest concentration without observed growth was recorded as the observed MIC values and are shown in Table 5.

Table 5. MIC Values, (%)

Ex.	Preservative	<i>A. niger</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>
A	GCM	0.19	0.25	0.125
B	GCP	1.0	0.63	0.63
C	GC	2.0	1.0	1.0
D	MI	0.1	0.008	0.1
E	PEA	1.0	0.9	0.9

[0037] The MIC values from Table 5 were then used to calculate the Fractional Inhibitory Concentration Index (FICI) (sometimes called the Synergy Index) of GCM and GCP versus the various individual test organisms using the following equation.

$$\text{FICI} = (\text{MICa}/\text{MICA}) + (\text{MICb}/\text{MICB})$$

Where:

35 MICa= concentration of component A at the MIC of the combination of A & B;

MICA= MIC of component A alone;

MICb= concentration of component B at the MIC of the combination of A & B; and

MICB= MIC of component B alone.

40 [0038] A description of the FICI is provided in an article by Greene et al., entitled "Synergistic Inhibition of Microbial Sulfide Production by Combinations of the Metabolic Inhibitor Nitrite and Biocides", Applied and Environmental Microbiology, 72, 7997-7901 (2006).

45 [0039] The FICI equation is equivalent to what is commonly referred to as the Synergy Index measurement published in a paper by Kull et al., entitled "Mixtures of Quaternary Ammonium Compounds and Long-chain Fatty Acids as Antifungal Agents", in Applied Microbiology, V9, 538-541 (1961), and discussed in the articles by Steinberg, "Measuring Synergy", Cosmetics & Toiletries®, 115, 59-62 (2000) and by Schmaus et al. "1,2-Alkanediols for Cosmetic Preservation", Cosmetics & Toiletries®, 123, 53-64 (2008). The calculated FICI values are provided in Table 6.

50 Table 6. Fractional Inhibitory Concentration Index

Ex.	Preservative	<i>A. niger</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>
A	GCM	0.1	0.5	0.1
B	GCP	0.8	0.7	0.7

55 [0040] A Fractional Inhibitory Calculated Index of less than 1.0 indicates synergistic action between the two components. Values of 0.5 or less indicate strong synergistic action between the two components. Values between 0.5 and 1.0 are indicative of mild synergy.

[0041] The results in Table 6 clearly indicate an unexpected synergy for GCP against all the organisms tested in this example. GCM exhibited a surprisingly strong synergy against all test organisms.

[0042] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0043] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention.

Claims

20. 1. A liquid preservative composition comprising (a) glyceryl caprylate; and (b) an aqueous isothiazolinone solution comprising 2- methyl- 4- isothiazolin- 3- one, wherein the composition contains less than 15 percent by weight of water and is free from halogenated preservatives, formaldehyde, formaldehyde- releasing compounds, phenolic compounds, and paraben compounds.
25. 2. The liquid preservative composition of claim 1 wherein the aqueous isothiazolinone solution comprises 2- methyl- 4- isothiazolin- 3- one at an active concentration of 0.005 to 55 weight percent.
30. 3. The liquid preservative composition of claim 1 or claim 2 wherein the composition additionally comprises an alkanol- substituted aromatic compound wherein the alkanol-substituted aromatic compound is an aromatic compound bearing at least one alkanol substituent selected from the group consisting of alkyl and alkoxy moieties that bear a hydroxyl group.
35. 4. The liquid preservative composition of claim 3 where the alkanol-substituted aromatic compound is selected from the group consisting of phenethyl alcohol; benzyl alcohol; and phenoxyethanol.
40. 5. The liquid preservative composition of any one of claims 1-4 wherein the composition comprises 5 to 99.9 percent by weight of glyceryl caprylate.
45. 6. The liquid preservative composition of any one of claims 1-5 wherein the composition comprises an aqueous solution of 0.1 to 25 active percent by weight of 2- methyl- 4- isothiazolin- 3- one.
50. 7. The liquid preservative composition of any one of claims 1-6 wherein the composition comprises 5 to 95 percent by weight of glyceryl caprylate.
55. 8. The liquid preservative composition of any one of claims 1- 7 wherein the composition comprises 85 to 95 percent by weight of glyceryl caprylate and an aqueous solution of 0.5 to 2 active percent by weight of 2- methyl- 4- isothiazolin- 3- one.
9. A method of preserving a consumer or industrial product comprising admixing a preservative effective amount of the preservative composition of any one of claims 1-8 with said consumer or industrial product.
10. The method of claim 9 wherein the preservative effective amount of the preservative composition is in the range of 0.1 to 35 percent by weight based on the combined weight of the preservative composition and said consumer or industrial product.
11. A cosmetic or personal care product comprising 0.1 to 25 percent by weight glyceryl caprylate in combination with 0.02 to 10 percent by weight phenethyl alcohol and 2 to 200 ppm (active basis) of 2- methyl- 4- isothiazolin- 3- one; the cosmetic or personal care product being free from halogenated preservatives, formaldehyde, formaldehyde-

releasing compounds, phenolic compounds, and paraben compounds.

Patentansprüche

- 5 1. Flüssige Konservierungsmittelzusarumensetzung, die (a) Glycerylcaprylat und (b) eine wässrige Isothiazolinon- Lösung umfasst, die 2- Methyl- 4- isothiazolin- 3- on umfasst, wobei die Zusammensetzung weniger als 15 Gewichtsprozent Wasser enthält und frei von halogenierten Konservierungsmitteln, Formaldehyd, Verbindungen, die Formaldehyd freisetzen, phenolischen Verbindungen und Parabenverbindungen ist.
- 10 2. Flüssige Konservierungsmittelzusammensetzung nach Anspruch 1, wobei die wässrige Isothiazolinon- Lösung 2- Methyl- 4- isothiazolin- 3- on bei einer aktiven Konzentration von 0, 005 bis 55 Gewichtsprozent umfasst.
- 15 3. Flüssige Konservierungsmittelzusammensetzung nach Anspruch 1 oder Anspruch 2, wobei die Zusammensetzung zusätzlich eine alkanolsubstituierte aromatische Verbindung umfasst, wobei die alkanolsubstituierte aromatische Verbindung eine aromatische Verbindung ist, die mindestens einen Alkanol-Substituenten trägt, der ausgewählt ist aus der Gruppe, bestehend aus Alkyl- und Alkoxygruppen, die eine Hydroxylgruppe tragen.
- 20 4. Flüssige Konservierungsmittelzusammensetzung nach Anspruch 3, wobei die alkanolsubstituierte aromatische Verbindung ausgewählt ist aus der Gruppe, bestehend aus Phenethylalkohol, Benzylalkohol und Phenoxyethanol.
- 25 5. Flüssige Konservierungsmittelzusammensetzung nach einem jeglichen der Ansprüche 1-4, wobei die Zusammensetzung 5 bis 99,9 Gewichtsprozent an Glycerylcaprylat umfasst.
6. Flüssige Konservierungsmittelzusammensetzung nach einem jeglichen der Ansprüche 1- 5, wobei die Zusammensetzung eine wässrige Lösung von 0, 1 bis 25 aktiven Gewichtsprozent an 2- Methyl- 4- isothiazolin- 3- on umfasst.
- 30 7. Flüssige Konservierungsmittelzusammensetzung nach einem jeglichen der Ansprüche 1-6, wobei die Zusammensetzung 5 bis 95 Gewichtsprozent an Glycerylcaprylat umfasst.
8. Flüssige Konservierungsmittelzusammensetzung nach einem jeglichen der Ansprüche 1- 7, wobei die Zusammensetzung 85 bis 95 Gewichtsprozent an Glycerylcaprylat und eine wässrige Lösung von 0, 5 bis 2 aktiven Gewichtsprozent an 2- Methyl- 4- isothiazolin- 3- on umfasst.
- 35 9. Verfahren zum Konservieren eines Konsumartikels oder Industrieprodukts, umfassend ein Mischen einer konservierenden wirksamen Menge der Konservierungsmittelzusammensetzung nach einem jeglichen der Ansprüche 1-8 mit dem Konsumartikel oder Industrieprodukt.
10. Verfahren nach Anspruch 9, wobei die konservierende wirksame Menge der Konservierungsmittelzusammensetzung in dem Bereich von 0,1 bis 35 Gewichtsprozent, basierend auf dem vereinigten Gewicht der Konservierungsmittelzusammensetzung und des Konsumartikels oder Industrieprodukts, liegt.
- 45 11. Kosmetisches Mittel oder Körperpflegeprodukt, das 0, 1 bis 25 Gewichtsprozent an Glycerylcaprylat zusammen mit 0, 02 bis 10 Gewichtsprozent an Phenethylalkohol und 2 bis 200 ppm (aktive Basis) an 2- Methyl- 4- isothiazolin- 3- on umfasst, wobei das kosmetische Mittel oder Körperpflegeprodukt frei von halogenierten Konservierungsmitteln, Formaldehyd, Verbindungen, die Formaldehyd freisetzen, phenolischen Verbindungen und Parabenverbindungen ist.

50

Revendications

1. Composition de conservateur liquide comprenant (a) du caprylate de glycéryle ; et (b) une solution aqueuse d'isothiazolinone comprenant de la 2- méthyl- 4- isothiazolin- 3- one, laquelle composition contient moins de 15 % en poids d'eau et est exempte de conservateurs halogénés, de formaldéhyde, de composés libérant du formaldéhyde, de composés phénoliques, et de composés de paraben.
- 55 2. Composition de conservateur liquide selon la revendication 1, dans laquelle la solution aqueuse d'isothiazolinone

comprend de la 2- méthyl- 4- isothiazolin- 3- one à une concentration active de 0, 005 à 55 % en poids.

3. Composition de conservateur liquide selon la revendication 1 ou 2, laquelle composition comprend en plus un composé aromatique à substitution alcool, lequel composé aromatique à substitution alcool est un composé aromatique portant au moins un substituant alcool choisi dans le groupe constitué par les fragments alkyle et alcoxy qui portent un groupe hydroxyle.
4. Composition de conservateur liquide selon la revendication 3, dans laquelle le composé aromatique à substitution alcool est choisi dans le groupe constitué par l'alcool phénéthylque, l'alcool 'benzylique, et le phénoxyéthanol.
5. Composition de conservateur liquide selon l'une quelconque des revendications 1 à 4, laquelle composition comprend de 5 à 99,9 % en poids de caprylate de glycéryle.
6. Composition de conservateur liquide selon l'une quelconque des revendications 1 à 5, laquelle composition comprend une solution aqueuse de 0, 1 à 25 % en poids d'agent actif 2- méthyl- 4- isothiazolin- 3- one.
7. Composition de conservateur liquide selon l'une quelconque des revendications 1 à 6, laquelle composition comprend de 5 à 95 % en poids de caprylate de glycéryle.
8. Composition de conservateur liquide selon l'une quelconque des revendications 1 à 7, laquelle composition comprend de 85 à 95 % en poids de caprylate de glycéryle et une solution aqueuse de 0, 5 à 2 % en poids d'agent actif 2- méthyl- 4- isothiazolin- 3- one.
9. Procédé de conservation d'un produit de consommation ou industriel, comprenant le mélange d'une quantité efficace du point de vue de la conservation de la composition de conservateur selon l'une quelconque des revendications 1 à 8 avec ledit produit de consommation ou industriel.
10. Procédé selon la revendication 9, dans lequel la quantité efficace du point de vue de la conservation de la composition de conservateur se situe dans une plage comprise entre 0,1 et 35 % en poids par rapport au poids combiné de la composition de conservateur et dudit produit de consommation ou industriel.
11. Produit cosmétique ou de soin personnel comprenant de 0, 1 à 25 % en poids de caprylate de glycéryle en combinaison avec 0, 02 à 10 % en poids d'alcool phénéthylque et 2 à 200 ppm (sur la base de l'agent actif) de 2- méthyl- 4- isothiazolin- 3- one ; le produit cosmétique ou de soin personnel étant exempt de conservateurs halogénés, de formaldéhyde, de composés libérant du formaldéhyde, de composés phénoliques, et de composés de paraben.

40

45

50

55

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Non-patent literature cited in the description

- Manual of Clinical Microbiology. American Society for Microbiology [0029]
- **GREENE et al.** Synergistic Inhibition of Microbial Sulfide Production by Combinations of the Metabolic Inhibitor Nitrite and Biocides. *Applied and Environmental Microbiology*, 2006, vol. 72, 7997-7901 [0038]
- **KULL et al.** Mixtures of Quaternary Ammonium Compounds and Long-chain Fatty Acids as Antifungal Agents. *Applied Microbiology*, 1961, vol. 9, 538-541 [0039]
- **STEINBERG.** Measuring Synergy. *Cosmetics & Toiletries®*, 2000, vol. 115, 59-62 [0039]
- **SCHMAUS et al.** 1,2-Alkanediols for Cosmetic Preservation. *Cosmetics & Toiletries®*, 2008, vol. 123, 53-64 [0039]