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(54) Title: SUSPENSION FORMULATIONS OF CETYL MYRISTATE AND/OR CETYL PALMITATE

(57) Abstract: This invention is related to pharmaceutical or dietary supplement suspension formulations of cetylated fatty acids, especially cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate.

Description**SUSPENSION FORMULATIONS OF CETYL MYRISTATE AND/OR CETYL PALMITATE****Technical Field**

[0001] This invention is related to pharmaceutical and/or dietary supplement suspension formulations of cetylated fatty acids, especially cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate.

Background Art

[0002] Cetyl palmitate is derived from the fatty acid, palmitic acid which occurs as the glycerol ester in many oils and fats such as palm oil or Chinese vegetable tallow. A synthetic method of preparation is to react palmitoyl chloride and cetyl alcohol in the presence of magnesium. See the Merck Index, 12th edition at page 336. Reference is also made to US US3169099 A (SOCONY MOBIL OIL CO INC) 02.09.1965 patent which discloses a biosynthetic method of producing cetyl palmitate.

[0003] US 4,1 13,881 A (DIEHL HARRY WELDON) 12.09.1978 discloses that the administration of an effective amount of cetyl myristoleate to a mammal is useful in inhibiting or relieving the symptoms of inflammatory rheumatoid arthritis in mammals.

[0004] US 5569676 A (DIEHL, HARRY W) 29.10.1996 US 5,569,676 discloses the use of cetyl myristoleate in the treatment of osteo-arthritis.

[0005] **WO** 01/85162 A (MERACOL CORP LTD ET.AL.) 15.1 1.2001 discloses the use of cetyl myristate and/or cetyl palmitate in the treatment of irritable bowel syndrome or disease. Patent embraces that cetyl myristate comprises 50-98 wt.% of the mixture, preferably, the myristate and palmitate are in a weight ratio of 95:5. The oral dosage unit is a capsule and contains 5-400 mg of the cetyl myristate or the mixture of the cetyl myristate and the cetyl palmitate. It also includes an excipient and/or diluent, preferably silicon dioxide, calcium phosphate and/or magnesium oxide. Preferably said mixture is in a capsule and it includes a pharmaceutically acceptable excipient and/or diluents. Preferably the dosage unit includes silicon dioxide, calcium phosphate and/or magnesium oxide. Liquid formulation, where an amount of liquid equivalent to at least

4 capsules is prescribed which is to be taken 3 times daily. That is 4200 mg of cetyl myristate or the mixture of cetyl myristate and cetyl palmitate. That mixture comprises by weight 95% cetyl myristate and 5% cetyl palmitate by weight. In addition added excipients were present in the non gelatin two part capsule case.

- [0006] **WO 01/85163** A (MERACOL CORP LTD ET.AL.) 15.11.2001 discloses the use of cetyl myristate and/or cetyl palmitate in the treatment of eczema and/or psoriasis. Accordingly, capsule also includes a pharmaceutically acceptable excipient and/or diluent. These are silicon dioxide, calcium phosphate and/or magnesium oxide. The dosage unit can also be a wax-like solid or can be an orally consumable liquid composition (eg; made up with a general pharmacy type carrier such as methyl cellulose).
- [0007] **WO 2005/1 18070** A (MERACOL CORP LTD ET.AL.) 15.12.2005 discloses the treatment of multiple sclerosis with the use of cetyl myristate and/or cetyl palmitate. The cetyl myristate; or combination of cetyl myristate and cetyl palmitate is administered simultaneously, separately or sequentially.
- [0008] **WO 03/018731** A (MERACOL CORP LTD) 06.03.2003 defines the process prepares a mixture of cetyl myristate (50-98 wt.%) and cetyl palmitate, for use in the formulation of cosmetics and pharmaceuticals.
- [0009] **WO 03/045374** A (MERACOL CORP LTD ET.AL.) 05.06.2003 discloses the use of cetyl myristate and/or cetyl palmitate in a method of treatment and/or prophylaxis of a mammal for at least the symptoms of treating asthma, chronic obstructive pulmonary disease and/or other respiratory difficulties.
- [0010] **WO 03/026640** A (MERACOL CORP LTD ET.AL.) 03.04.2003 discloses the use of cetyl myristate and/or cetyl palmitate in the treatment of food allergies and/or food intolerances.
- [0011] **WO 01/85164** A (MERACOL CORP LTD ET.AL.) 15.11.2001 discloses the use of cetyl myristate and/or cetyl palmitate in the treatment of herpes.

Summary of invention

- [0012] This invention discloses eligible suspension formulations of cetylated fatty acids, especially cetyl myristate or cetyl palmitate or combination of cetyl palmitate and cetyl myristate.

Technical Problem

[0013] Cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate can be used as active pharmaceutical ingredients (API) in pharmaceutical or dietary supplement formulations in addition to their excipient properties. However suspending of those is very hard, since particles of cetyl myristate and cetyl palmitate are immediately sedimented and resuspending becomes problematic or impossible. Suspension needs adequate shaking of the container to resuspend the drug uniformly prior to dosing. Redispersion difficulty of the drug from a sediment will result in under- and overdosing. Therefore suspension should maintain its content uniformity for a period of time at least patients can be properly ingest it.

Solution to Problem

[0014] It is invented that in formulations, when certain excipients are used in specific ranges, agglomeration is not occurred and/or resuspending is improved. In the terms of solution, rapid sedimentation is reduced by increasing the viscosity of the liquid. Departing from this point of view, rapid sedimentation of a solution is reduced as the viscosity of the liquid is increased. The problem is eliminated via use of viscosity increasing agent in a specific concentration.

Description of embodiments

[0015] Rapid sedimentation can be reduced by increasing the viscosity of the liquid phase. It is achieved by using of viscosity increasing agent in a specific amount per ml. Thus viscosity enhancing agent is used from about 0.1 mg/ml to about 50 mg/ml. Preferably, viscosity enhancing agent is from about 0.1 mg/ml to about 25 mg/ml. More preferably, viscosity enhancing agent is from about 1 mg/ml to about 15 mg/ml. Most preferably viscosity enhancing agent is about 5 mg/ml.

[0016] Viscosity enhancing agent is, but not limited to xantham gum, guar gum, acacia, alginic acid, sodium alginate, propylene glycol alginate, povidone, carbomer, salts of carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, bentonite, polydextrose, carrageenan, sucrose, sorbitol,

xylitol, dextrose, fructose, malitol, gelatin, tragacanth, a polyvinyl alcohol, cetearyl alcohol, colloidal silicon dioxide, mixtures thereof and the like.

- [0017] In accordance with this invention cetyl myristate is used from about 10 mg/ml_ to about 200 mg/ml_. Preferably, cetyl myristate is from about 30 mg/ml_ to about 100 mg/ml_. More preferably, cetyl myristate is from about 50 mg/ml_ to about 80 mg/ml_. Most preferably cetyl myristate is about 66,66 mg/ml_.
- [0018] In another aspect of this invention, cetyl palmitate is used from about 0.1 mg/ml_ to about 30 mg/ml_. Preferably, cetyl palmitate is from about 1 mg/ml_ to about 10 mg/ml_. More preferably, cetyl palmitate is from about 2 mg/ml_ to about 5 mg/ml_. Most preferably cetyl palmitate is about 3.34 mg/ml_.
- [0019] In accordance with this invention preservative is used from about 0.1 mg/ml_ to about 30 mg/ml_. Preferably, preservative is from about 0.2 mg/ml_ to about 20 mg/ml_. More preferably, preservative is from about 0.3 mg/ml_ to about 6 mg/ml_. Most preferably preservative is about 3 mg/ml_.
- [0020] Preservative is, but not limited to, sodium benzoate, benzoic acid, ethylenediaminetetraacetic acid, sorbic acid, benzethonium chloride, benzalkonium chloride, bronopol, butyl paraben, methyl paraben, ethylparaben, propyl paraben, thiomerosol, sodium propionate, chlorhexidine, chlorobutanol, chlorocresol, cresol, imidurea, phenol, phenylmercuric salts, potassium sorbate, propylene glycol, mixtures thereof and the like.
- [0021] In accordance with this invention sweetener is also used. Accordingly sweetener is used from about 10 mg/ml_ to about 500 mg/ml_. Preferably, sweetener is from about 30 mg/ml_ to about 200 mg/ml_. More preferably, sweetener is from about 110 mg/ml_ to about 180 mg/ml_. Most preferably sweetener is about 150 mg/ml_.
- [0022] Sweeteners are but not limited to, corn syrup, dextrose, invert sugar, fructose, saccharin, aspartame, acesulfame-K, Stevia rebaudiana, sucralose, sorbitol, mannitol, xylitol, mixtures thereof and the like.
- [0023] In accordance with this invention flavor is also used. Accordingly flavour is used from about 0.01 mg/ml_ to about 3 mg/ml_. Preferably, flavor is from

about 0.02 mg/mL to about 1 mg/mL. More preferably, flavor is from about 0.04 mg/mL to about 0.5 mg/mL. Most preferably flavor is about 0.08 mg/mL.

[0024] Flavors are, but not limited to, cinnamon oil, essence of apple, essence of pear, essence of peach, essence of grape, essence of strawberry, essence of raspberry, essence of cherry, essence of plum, essence of pineapple, essence of apricot, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, oil of bitter almonds, cassia oil, citrus oils such as lemon, orange, grape, lime and grapefruit, vanilla, benzaldehyde, aldehyde C-8, aldehyde C-9, aldehyde C-12, tolyl aldehyde, mixtures thereof and the like.

[0025] According to this invention flavour enhancer is also used. Accordingly flavour enhancer is used from about 0.1 mg/mL to about 10 mg/mL. Preferably, flavour enhancer is from about 0.5 mg/mL to about 5 mg/mL. More preferably .flavour enhancer is from about 0.8 mg/mL to about 3 mg/mL. Most preferably flavour enhancer is about 1mg/mL.

[0026] Flavor enhancer is but not limited to citric acid monohydrate, ethyl maltol, maltol, monosodium glutamate, neohesperidin dihydrochalcone, neotame, thaumatin, trehalose, disodium guanylate, disodium inosinate, mixtures thereof and the like.

[0027] According to this invention antifoaming agent is also used. Antifoaming agent is used from about 0.01 mg/mL to about 5 mg/mL. Preferably, antifoaming agent is from about 0.2 mg/mL to about 3 mg/mL. More preferably, antifoaming agent is from about 0.4 mg/mL to about 1 mg/mL. Most preferably antifoaming agent is about 0.5 mg/mL.

[0028] Anti-foaming agent is selected from the group consisting of silicon oil, simethicone, dimethicone, oleyl alcohol, polypropylene glycol, mixtures thereof and the like.

[0029] In another aspect, pH adjuster is used from about 0.01 mg/mL to about 10 mg/mL. Preferably, pH adjuster is from about 1 mg/mL to about 8 mg/mL. More preferably, pH adjuster is from about 1.5 mg/mL to about 6 mg/mL. Most preferably pH adjuster is about 2.1 mg/mL.

[0030] pH adjuster is but not limited to hydrochloric acid, sodium hydroxide, citric

acid, phosphoric acid, lactic acid, tartaric acid, succinic acid, mixtures thereof and the like.

[0031] Deionized water is used as solvent in this invention.

Example

[0032]

Table 1

Function	mg/mL
Cetyl Myristate(Active Pharmaceutical Ingredient)	333.30 mg / 5 mL
Cetyl Palmitate(Active Pharmaceutical Ingredient)	16.70 mg / 5 mL
Preservative	15.00 mg / 5 mL
Flavor Enhancer	5.00 mg / 5 mL
Sweetener	750.00 mg / 5 mL
Antifoaming agent	2.50 mg / 5 mL
Viscosity Enhancer	25.00 mg / 5 mL
Flavor	0.4 mg / 5 mL
pH adjuster	10.50 mg / 5 mL

Claims

1. A pharmaceutical or dietary supplement suspension formulation of combination of cetyl myristate and cetyl palmitate comprising cetyl myristate is from 10 mg/mL to 200 mg/mL, cetyl palmitate is from 0.1 mg/mL to 30 mg/mL, viscosity enhancing agent is from 0.1 mg/mL to 50 mg/mL, preservative is from 0.1 mg/mL to 30 mg/mL, sweetener is from 10 mg/mL to 500 mg/mL, flavour is from 0.01 mg/mL to 3 mg/mL, flavour enhancer agent is from 0.1 mg/mL to 10 mg/mL, antifoaming is from 0.01 mg/mL to 5 mg/mL, pH adjuster is from 0.01 mg/mL to 10 mg/mL.
2. As claimed in claim 1, suspension formulation preferably comprising viscosity enhancing agent is from 0.1 mg/mL to 25 mg/mL, cetyl myristate is from 30 mg/mL to 100 mg/mL, cetyl palmitate is from 1 mg/mL to 10 mg/mL, preservative is from 0.2 mg/mL to 20 mg/mL, sweetener is from 30 mg/mL to 200 mg/mL, flavor is from 0.02 mg/mL to 1 mg/mL, flavour enhancer agent is from 0.5 mg/mL to 5 mg/mL, antifoaming agent is from 0.2 mg/mL to 3 mg/mL, pH adjuster is from 1 mg/mL to 8 mg/mL.
3. As claimed in claim 2, suspension formulation more preferably comprising viscosity enhancing agent is from 1 mg/mL to 15 mg/mL, cetyl myristate is from 50 mg/mL to 80 mg/mL, cetyl palmitate is from 2 mg/mL to 5 mg/mL, preservative is from 0.3 mg/mL to 6 mg/mL, sweetener is from 110 mg/mL to 180 mg/mL, flavor is from 0.04 mg/mL to 0.5 mg/mL, flavour enhancer agent is from 0.8 mg/mL to 3 mg/mL, antifoaming is from 0.4 mg/mL to 1 mg/mL, pH adjuster is from about 1,5 mg/mL to about 6 mg/mL.
4. As claimed in claim 3, suspension formulation most preferably comprising viscosity enhancing agent is 5 mg/mL, cetyl myristate is 66,66 mg/mL, cetyl palmitate is 3,34 mg/mL, preservative is 3 mg/mL, sweetener is 150 mg/mL, flavor is 0.08 mg/mL, flavour enhancer is 1mg/mL, antifoaming agent is 0.5 mg/mL, pH adjuster is 2.1 mg/mL.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/074146

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23L1/30 A61K31/23 A61K9/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	wo 01/85162 AI (MERACOL CORP LTD [NZ] ; MEAKIN TIMOTHY DAVID [NZ] ; HEATLEY CRAIG LEONAR) 15 November 2001 (2001-11-15) page 4, lines 26-29 page 5, lines 3-5	1-4
Y	US 4 113 881 A (DI EHL HARRY WELDON) 12 September 1978 (1978-09-12) column 3, lines 26-35	1-4
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 23 January 2012	Date of mailing of the international search report 01/02/2012
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Gimenez Miralles, J
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/074146

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>EFSA PANEL ON DIETETIC PRODUCTS ET AL: "Scientific Opinion on the safety of 'Cetyl myristolate complex' as a Novel Food ingredient", EFSA JOURNAL, XX, XX , vol . 8, no. 7 30 July 2010 (2010-07-30) , pages 1-14, XP002632859 , DOI : DOI : 10.2903/J .EFSA.2010. 1686 Retrieved from the Internet: URL: http://www.efsa.europa.eu/fr/efsajournal/doc/1686.pdf [retrieved on 2011-04-14] page 6, paragraph 2 -----</p>	1-4

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/EP2011/074146
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