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Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2012/049639 A1

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

(57) Abstract: This invention is related to using of anti-adherents in pharmaceutical or dietary supplement formulations of cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate. In this invention, cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate are used as active pharmaceutical ingredients.

Description

Title of Invention: FORMULATIONS OF CETYL MYRISTATE AND/OR CETYL PALMITATE

[1] This invention is related to using of antiadherents in pharmaceutical or dietary supplement formulations of cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate. In this invention, cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate are used as active pharmaceutical ingredients and/or dietary supplements.

[2] 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 US3169099A (SOCONY MOBIL OIL CO INC) 02.09.1965 patent which discloses a biosynthetic method of producing cetyl palmitate.

[3] US 4,113,881A (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.

[4] US 5569676A (DIEHL, HARRY W) 29. 10. 1996 US 5,569,676 discloses the use of cetyl myristoleate in the treatment of osteo-arthritis.

[5] WO 01/85162A (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.

[6] WO 01/85163A (MERACOL CORP LTD ET.AL.) 15.1 1.2001 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).

[7] WO 2005/118070A (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.

[8] WO 03/018731A (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.

[9] WO 03/045374A (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 obstruc tive pulmonary disease and/or other respiratory difficulties.

[10] WO 03/026640A (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.

[11] WO 01/85164A (MERACOL CORP LTD ET.AL.) 15.11.2001 discloses the use of cetyl myristate and/or cetyl palmitate in the treatment of herpes.

[12] Cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate can be used as active pharmaceutical ingredients (API) in pharmaceutical formulations in addition to excipient properties. However both cetyl myristate and cetyl palmitate are waxy ingredients and thus in formulation stage, they are adhered onto the surfaces of formulation equipments. It brings about difficulties such as filling of capsules. Therefore it is needed that non-adhering and eligible formulations.

[13] It is invented that sticking problem is solved by using of antiadherents,further excipients and active ingredient(s) with certain percentages in formulations. Using of certain percentages of antiadherent provides to obstacle bedaubing.

[14] Cetyl myristate and cetyl palmitate are sticky and tend to adhere to surfaces of formulation equipments.

[15] This invention discloses processability of cetyl myristate and cetyl palmitate and also the ability not to stick or adhere to equipments.

[16] In accordance with this invention, antiadherents are used in certain percentages to prevent sticking. Antiadherents can be selected from excipients which have only antiadherent function or multifunction wherein at least one function is antiadherent.

[17] Antiadherents are but not limited to talc, colloidal silicon dioxide, calcium carbonate, magnesium trisilicate, calcium stearate,glyceryl behenate, poly(ethylene glycol), magnesium stearate,kaolin ,calcium sulfate, calcium chloride, corn

starch,hydrogenated vegetable oil, mineral oil, stearic acid, mixtures thereof and the like.

[18] The anti-adherent excipient or mixtures of excipients can be present in an amount in the range of 0.1% to 20.0%, preferably 5% to 10%, more preferably 8.3% by weight of pharmaceutical composition. Most preferably anti-adherent excipient or mixtures of excipients are 35 mg of 420 mg in toto formulation.

[19] In accordance with present invention, the pharmaceutical composition of cetyl myristate and cetyl palmitate combination comprises binder,diluent/filler,coating agents and the like.

[20] Binders are, but not limited to, sodium alginate, cellulose, methylcellulose, ethyl-cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, polypropylpyrrolidone, polyvinylprrolidone, gelatin, polyethylene glycol, starch, pre-gelatinized starch, sugars, trehalose, glucose,tragacanth, sorbitol, acacia, alginates, carrageenan, xanthan gum, locust bean gum and gum arabic, waxes, poly acrylamide , mixtures thereof, and the like.

[21] Diluents/fillers are, but not limited to, mannitol, sorbitol, xylitol, microcrystalline cellulose, silicified microcrystalline cellulose , hydroxypropyl methylcellulose, hydroxypropyl cellulose , pullulan and fast dissolving carbohydrates such as Pharmaburst™, mixtures thereof and the like.

[22] Plasticizers are , but not limited to, polyethylene glycol, propylene glycol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, castor oil , acetylated monoglycerides, mixtures thereof and the like. Plasticizer is used to have hard granulate.

[23] According to foregoing explanations fromulation comprises filler is from about 0,5 % to about 60 % , cetyl myrisate as active pharmaceutical ingredient is from about 50 % to about 99,5 % ,cetyl palmitate as active pharmaceutical ingredient is from about 0,5 % to about 10 %, plasticizer is from about 0,1 % to about 6 %, binder is from about 1 % to about 10 % by weight.

[24] Preferably formulation comprises filler is 4,7 % , cetyl myrisate as active pharmaceutical ingredient is 79,3 % ,cetyl palmitate as active pharmaceutical ingredient is 3,9 %, plasticizer is 1,1 %, binder is 2,3 % by weight .

[25] Most preferably, formulation comprises filler is 20 mg , cetyl myrisate as active pharmaceutical ingredient is 333,3 mg ,cetyl palmitate as active pharmaceutical ingredient is 16,7 mg, plasticizer is 5 mg, binder is 10 mg.

[26] In another aspect ,this invention provides a weight ratio of antiadherent or mixtures of antiadherents to total pharmaceutical composition froml:3 to 1:20. Preferably weight ratio is 1:12.

[27] In another aspect ,this invention provides a weight ratio of antiadherent or mixtures

of antiadherents to active ingredient(s) from 1:2 to 1:20. Preferably weight ratio is 1:10.

[28] In yet another aspect, it is invented that pharmaceutical composition of cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate should be pressed as a tablet or should be filled under 45°C. Exceeding 45°C, active ingredient becomes a coagulated and smeared form and pressing or filling is very difficult. As tablet press or capsule filling machine warms itself while working, the condition of 45°C should be maintained in the course of filling or pressing and or tablet press or capsule filling machine contains a cooling system.

[29] **Example**

[Table 1]

INGREDIENTS	**mg**
Cetyl Myristate/API	333.3
Cetyl Palmitate/API	16.7
Diluent/Filler	20.0
Binder	10.0
Plasticizer	5.0
Antiadherent Agents	35
TOTAL	420.0

Claims

[Claim 1] A pharmaceutical or dietary supplement composition of cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate characterized in that **(a)** anti-adherent or mixtures of anti-adherents are in the range of 0.1% to 20.0%, preferably 5% to 10%, more preferably 8.3% by weight of pharmaceutical composition or **(b)** weight ratio of antiadherent or mixtures of antiadherents to total pharmaceutical composition is froml:3 to 1:20, preferably 1:12 or **(c)** weight ratio of anti-adherent or mixtures of antiadherents to active ingredient(s) is froml:2 to l:20,preferably 1:10 and preferably further includes filler, binder and plasticizer .

[Claim 2] As claimed in claim 1, most preferably anti-adherent excipient or mixtures of excipients are 35 mg in formulations of 420 mg in toto.

[Claim 3] As claimed in claim 1, antiadherents are selected from group consisting of talc, colloidal silicon dioxide, calcium carbonate, magnesium trisilicate, calcium stearate,glyceryl behenate, poly(ethylene glycol), magnesium stearate,kaolin ,calcium sulfate, calcium chloride, corn starch,hydrogenated vegetable oil, mineral oil, stearic acid and mixtures thereof.

[Claim 4] As claimed in claim 1,composition further comprises filler is from 0,5 % to 60 % , cetyl myrisate as active pharmaceutical ingredient is from 50 % to 99,5 % ,cetyl palmitate as active pharmaceutical ingredient is from 0,5 % to 10 %, plasticizer is from 0,1 % to 6 %, binder is from 1 % to 10 % by weight, preferably formulation comprises filler is 4,7 % , cetyl myrisate as active pharmaceutical ingredient is 79,3 % ,cetyl palmitate as active pharmaceutical ingredient is 3,9 %, plasticizer is 1,1 %, binder is 2,3 % by weight , most preferably, formulation comprises filler is 20 mg , cetyl myrisate as active pharmaceutical ingredient is 333,3 mg ,cetyl palmitate as active pharmaceutical ingredient is 16,7 mg, plasticizer is 5 mg, binder is 10 mg.

[Claim 5] A pharmaceutical or dietary composition of cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate characterized in that ingredients are filled into capsule and/or pressed as tablet under 45°C environment through using a tablet press or a capsule filling machine which includes a cooling system wherein its temperature does not exceed 45°.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/054512

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/215
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)
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, EMBASE, MEDLINE, 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	GB 2 181 053 A (SANDOZ LTD SANDOZ LTD [CH]) 15 April 1987 (1987-04-15)	1,3
Y	examples 1-19	1-4

X	WO 2004/062643 A1 (LIFECYCLE PHARMA AS [DK]; SCHULTZ KIRSTEN [DK]; HANSEN TUE [DK]; HOLM) 29 July 2004 (2004-07-29)	1,3
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[X] Further documents are listed in the continuation of Box C. [X] 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

"E" earlier document but published on or after the international filing date

"L" documentwhich 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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2012	20/02/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sindel , Ulrike

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/054512

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 02/00203 A1 (VECTURA LTD [GB] ; STANIFORTH JOHN NICHOLAS [GB] ; TOBYN MICHAEL JOHN [G) 3 January 2002 (2002-01-03) page 14, line 22 - line 27 example 4	5
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2011/054512

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2011/054512

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4

   Pharmaceutical composition comprising cetyl palmitate and/or cetyl myristate together with an anti-adherent

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2. claim: 5

   Pharmaceutical composition comprising cetyl palmitate and/or cetyl myristate and process for making it

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