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(54) **Title:** USE OF DISINTEGRANTS IN CETYL MYRISTATE AND/OR CETYL PALMITATE FORMULATIONS

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

Description

Title of Invention:

USE OF DISINTEGRANTS IN CETYL MYRISTATE AND/OR CETYL PALMITATE FORMULATIONS

[1] This invention is related to using of superdisintegrants 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 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. Ac-

cordingly, 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] This invention discloses using of an superdisintegrant or mixtures of superdisintegrants in pharmaceutical or dietary supplement formulations of cetylated fatty acids, especially cetyl myristate or cetyl palmitate or combination of cetyl palmitate and cetyl myristate.

[13] 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 after ingestion they become gel thickness. It brings about difficulties for disintegration in gastrointestinal environment. Therefore it is needed that eligible formulation which has suitable disintegrating properties. Additionally, combination of cetyl myristate and cetyl palmitate is required high drug load and thus total pharmaceutical composition is weighted and volumed. Thus patients cannot easily ingest it. Ratherly low volume and low weight and having good disintegration properties are provided thanks to using of superdisintegrant instead of ordinary disintegrant.

[14] It is invented that gelling problem in gastrointestinal system is solved by use of superdisintegrants in formulations. Using of certain percentages provides to impede gelling in gastrointestinal system and provides having low volume and low weight

pharmaceutical compositions.

[15] In accordance with this invention, superdisintegrants are used to prevent gelation of cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate in gastrointestinal system.

[16] Superdisintegrant is but not limited to croscarmellose sodium, sodium starch glycolate,crospovidone, L-hydroxypropyl cellulose, sodium carboxymethyl cellulose, mixtures thereof and the like.

[17] The superdisintegrant or mixtures of superdisintegrants can be present in an amount in the range of 0.1% to 10.0%, preferably 1% to 5%, more preferably 1.19% by weight of pharmaceutical composition. Most preferably disintegrant or mixtures of disintegrants are 5 mg of 420 mg in toto formulation.

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

[19] Binders are, but not limited to, sodium alginate, cellulose, methylcellulose, ethylcellulose, 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.

[20] 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.

[21] 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.

[22] In another aspect,this invention provides a weight ratio of superdisintegrant or mixtures of superdisintegrants to total pharmaceutical composition froml:10 to 1:200. Preferably weight ratio is 1:84.

[23] In another aspect, this invention provides a weight ratio of superdisintegrant or mixtures of superdisintegrants to active ingredient(s) froml:15 to 1:180. Preferably weight ratio is 1:70.

[24] To obtain elegant formulation superdisintegrant or mixtures of superdisintegrants provide disintegration not more than four minutes. Test is performed with disc and media is water. If test is performed without disc superdisintegrant or mixtures of superdisintegrants provide disintegration not more than five minutes.

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)** superdisintegrant or mixtures of superdisintegrants are in the range of 0.1% to 10.0%, preferably 1% to 5%, more preferably 1.19% by weight of pharmaceutical composition or **(b)** weight ratio of superdisintegrant or mixtures of superdisintegrants to total pharmaceutical composition froml:10 to 1:200, preferably weight ratio is l:84.or **(c)** weight ratio of superdisintegrant or mixtures of superdisintegrants to active ingredient(s) is froml:15 to l:180,preferably 1:70 and preferably further includes excipients .

[Claim 2] As claimed in claim 1, most preferably superdisintegrant or mixtures of superdisintegrants are 5 mg in formulations of 420 mg in toto.

[Claim 3] According to preceding claims, superdisintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate,crospovidone, L-hydroxypropyl cellulose, sodium carboxymethyl cellulose and mixtures thereof.

[Claim 4] As claimed in claim 1, in pharmaceutical or dietary supplement compositions of cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate superdisintegrant or mixtures of superdisintegrants provide a disintegration wherein if test is performed with disc and media is water disintegration is occured not more than four minutes and/or if test is performed without disc disintegration is occured not more than five minutes.

[Claim 5] As claimed in claim 4, in pharmaceutical or dietary supplement compositions of cetyl myristate or cetyl palmitate or combination of cetyl myristate and cetyl palmitate superdisintegrant or mixtures of superdisintegrants provide a disintegration wherein if test is performed with disc and media is water disintegration is occurred in 2-3 minutes and/or if test is performed without disc disintegration is occured 3-4 minutes.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/054514

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.
Y	WO 02/45694 A1 (BYK GULDEN LOMBERG CHEM FAB [DE] ; DIETRICH RANGO [DE] ; LINDER RUDOLF [j 13 June 2002 (2002-06-13) page 15 - page 22	1-5
Y	GB 2 181 053 A (SAND0Z LTD SAND0Z LTD [CH]) 15 April 1987 (1987-04-15) examples 2,3	1-5

☐ 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

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

"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)

"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/IB2011/054514

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