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(71) Applicant *(for all designated States except US):* NOVO-NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK).

(72) Inventors; and
(75) Inventors/Applicants *(for US only) :* HANSEN, Tomas, Tage [DK/DK]; Tonedraget 5, DK-3450 Alleroed (DK). GODTFREDSEN, Sven, Erik [DK/DK]; Smedegade 15B, DK-3500 Vaerloese (DK). FROEKJAER, Sven [DK/DK]; Langebjerg 56, DK-2850 Naerum (DK).

(74) Common Representative: NOVO-NORDISK A/S; Patent Dept., Novo Allé, DK-2880 Bagsvaerd (DK).

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(54) Title: EMULSION AND USE OF THE EMULSION AS A PARENTERAL PREPARATION

(57) Abstract

The emulsion has an aqueous, continuous phase and contains as the discontinuous phase the triglyceride 2-eicosapentaenoyl-1,3-dioctanoyl glycerol, formulated for parenteral use. This emulsion exhibits a better bioavailability than hitherto known parenteral emulsions used as a source for EPA (eicosapentaenoic acid).

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EMULSION AND USE OF THE EMULSION AS A PARENTERAL PREPARATION

The invention relates to an emulsion and a use of the emulsion as a parenteral preparation.

The triglyceride 2-eicosapentaenoyl-1,3-dioctanoyl glycerol is described in US 4,407,052 and S. E. Boustani et al., Lipids, 22, 711-14 (1987). Also, an emulsion for enteral use of this triglyceride is described. Eicosapentaenoic acid is abbreviated EPA.

As the above triglyceride is important as a nutrient, especially for diseased humans, there is a need for an emulsion of 2-eicosapentaenoyl-1,3-dioctanoyl glycerol, which can be used for parenteral nutrition, and which exhibits a better bioavailability than hitherto known parenteral emulsions used as a source for EPA.

A very important clinical aspect in regard to the bioavailability is the slower metabolism in comparison to emulsions containing MCT, which are known to cause metabolic acidosis when infused intravenously.

The emulsion according to the invention with an aqueous continuous phase and containing as the discontinous phase the triglyceride 2-eicosapentaenoyl-1,3-dioctanoyl glycerol, is characterized by the fact that it is formulated for parenteral use. Any worker skilled in the art will know in principle how to compose such formulation.

Surprisingly it has been found that the emulsion according to the invention exhibits a better bioavailability than hitherto known parenteral emulsions used as a source for EPA. Moreover, the above-mentioned triglycerides turn out, surprisingly, to be very efficient sources of energy in when applied in parenteral nutrition - the EPA acid moiety of the triglycerides being in an optimal position in the molecule in respect to their cleavage by lipoprotein lipase.

Surprisingly, the above triglycerides appear to exhibit physical properties which allow facile formulation of the compounds in liquid products as well as in powdered products exhibiting excellent wetability properties. In the

liquid form the products of the invention possess excellent stabilities making sterilization of e.g. parenteral products containing the above-mentioned triglycerides reliable, easy and safe.

The above-mentioned triglycerides are advantageously applied in such emulsions due to their fast conversion by lipoprotein lipase and endothelial lipase and the consequential avoidance of the discomfort and side effects of lipolipaedemia. Arachidonic acid applied in above triglycerides is thus cleared quickly and efficiently thereby providing the essential fatty acid concomitantly with short chain acids useful as energy substrates.

The use of the above-mentioned triglycerides in parenteral nutritional products is further particularly advantageous since the relatively high polarity of the triglycerides favour the stability of their emulsions which are subjected to severe heat treatments during their manufacturing. Use of such emulsion is particularly advantageous for nutrition of severely ill patients e.g. post-operatively.

Another advantage of the products of the invention has to do with the stability of the EPA towards oxidation and thus the avoidance of problems associated with oxidation of polyunsaturated fatty acids. It thus turns out that products according to the invention allows preparation of EPA containing lipids with an improved quality of EPA as compared to other sources of the essential fatty acid. Detrimental processes of polyunsaturated fats and oils leading to negative nutritional forms are thus commonly associated with gastric and intestinal problems due to oxidation and polymerisation products of the polyunsaturated fatty acid. Such oxidized forms of EPA can interfere with nitrogen uptake by interacting with sensitive amino acids. These highly undesired effects are diminished or even avoided by applying triglycerides according to the invention.

A preferred embodiment of the emulsion according to the invention is characterized by the fact that the average

diameter of the triglyceride globules is between 5 and 1000 nm, and that less than 5% of the triglyceride globules exhibits a diameter above 5000 nm. This emulsion is well suited as a parenteral emulsion and shows a good bioavailability.

A preferred embodiment of the emulsion according to the invention is characterized by the fact that the average diameter of the triglyceride globules is between 5 and 1000 nm, that less than 5% of the triglyceride globules exhibits a diameter above 5000 nm, that the amount of the triglyceride in relation to the amount of the entire emulsion is between 2 and 30% by weight, and that the emulsion contains glycerol to isotonicity and 0.2 - 10% by weight of an emulsifier. This emulsion is very well suited as a parenteral emulsion and shows a superior absorption ability. A preferred emulsifier is a phospholipid.

A preferred embodiment of the emulsion according to the invention is characterized by the fact that the triglyceride has a purity of at least 10%, preferably at least 30%, more preferably at least 50%, even more preferably at least 75%, and most preferably at least 90%. The higher the purity of the triglyceride, the more efficient the absorption of the triglyceride in the intestines.

Also the invention comprises a use of the emulsion according to the invention as a parenteral preparation.

EXAMPLE 1

A parenteral feeding product was prepared according to the following formula:

Composition for 1000 ml

I	Lipid		100.0 g
II	Egg yolk phospholipids (Lipoid E80)		12.0 g
III	Glycerol		22.5 g
IV	Water for injection	to	1000 ml

Production Procedure

II was dispersed in 500 ml of IV by a high shear mixer (Ultra turrax) followed by the addition of I and III. Fianlly water (IV) was added to a total volume of 1000 ml. The whole mixture was further prehomogenized for another 2-3 minutes (ultra turrax). The pre-emulsion was homogenized in a high pressure homogenizer (M110 Microfluidizer, Microfluidics Corporation, Newton, Mass.). The product was processed 5 times through the Microfluidizer. In order to keep the product temperature below 20°C the product was passed through an ice slurry by each cycle. The oxidation of lipids was prevented by running the process under Argon and by using liquids saturated with Argon.

The product was filled in a suitable package and sterilized in an autoclave at 120°C for 20 minutes.

Analytical data

pH = 6.1
Osmolality = 304 mOsm/kg water
Particle size (d_2) = 285 nm
Limulus test = < 0.5 EU/ml

CLAIMS

1. An emulsion with an aqueous, continuous phase and containing as the discontinuous phase the triglyceride 2-eicosapentaenoyl-1,3-dioctanoyl glycerol, formulated for parenteral use.

2. An emulsión according to Claim 1, wherein the average diameter of the triglyceride globules is between 5 and 1000 nm, and wherein less than 5% of the triglyceride globules exhibits a diameter above 5000 nm.

3. An emulsion according to Claim 2, wherein the amount of the triglyceride in relation to the amount of the entire emulsion is between 2 and 30% by weight, and the emulsion contains glycerol to isotonicity and 0.2 - 10% by weight of an emulsifier.

4. Emulsion according to Claims 1 - 3, wherein the triglycerides have a purity of at least 10%, preferably at least 30%, more preferably at least 50%, even more preferably at least 75%, and most preferably at least 90%.

5. Use of the emulsion according to Claims 1 - 4, as a parenteral preparation.

INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 89/00235

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 31/23, 9/107, C 11 C 3/08

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System [8]	Classification Symbols
IPC5	A 61 K; C 07 C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
P,X	WO, A1, 88/09325 (THE NISSHIN OIL MILLS LTD) 1 December 1988, see the whole document --	1-5
X	US, A, 4607052 (F MENDY ET AL) 19 August 1986, see column 2, line 55 - line 65; column 5, line 34 - line 50 --	1-5
X	EP, A2, 0265699 (THE NISSHIN OIL MILLS LTD) 4 May 1988, see page 2, line 10 - line 34; page 3, line 31 - line 38 --	1-5
Y	Lipids, Vol. 22, No. 10, 1987 S. El Boustani et al: "Enteral absorption in man of eicosapentaenoic acid in different chemical forms ", see page 711 - page 714 --	1-5

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
5th January 1990	1990 -01- 17
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Niklas Forslund

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	Patent Abstracts of Japan, Vol 11, No 357, C458, abstract of JP 62-129216, publ 1987-06-11 NIPPON SUISAN KAISHA LTD --	1-5

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/DK 89/00235

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 88/09325	01/12/88	JP-A- 63297342	05/12/88
US-A- 4607052	19/08/86	US-A- 4701468	20/10/87
		US-A- 4701469	20/10/87
EP-A2- 0265699	04/05/88	JP-A- 63087988	19/04/88