

## TRANSESTERIFIED CORN OIL PRODUCTS

This application is derived from GB application number 9213393.3.

The present invention relates to transesterified corn oil products.

In one aspect, this invention provides a trans-esterification product of corn oil and glycerol comprising predominately of linoleic acid and oleic acid mono-, di- and tri-glycerides, and having a free glycerol content less than 10% by weight, treated so as to reduce the saturated fatty acid component content of mono-, di- and tri-glycerides, and to enhance the unsaturated fatty acid component content of mono-, di- and tri-glycerides so that the linoleic acid and oleic acid mono-, di- and tri-glyceride content is in total 85% by weight or more of the whole composition.

A pharmaceutical composition is disclosed in GB 9213393.3 comprising a cyclosporin as active ingredient in a carrier medium comprising:

- 1) 1,2-propylene glycol;
- 2) a mixed mono-, di-, tri-glyceride; and
- 3) a surfactant.

Components (2) in the compositions disclosed in GB 9213393.3 comprise mixtures of  $C_{12-20}$  fatty acid mono-, di- and tri-glycerides, especially  $C_{16-18}$  fatty acid mono-, di- and triglycerides. The fatty acid component of said mixed mono-, di- and tri-glycerides may comprise both saturated and unsaturated fatty acid residues. Preferably however they will predominantly be comprised of unsaturated fatty acid residues in particular,  $C_{18}$  unsaturated fatty acid residues for example linolenic, linoleic and oleic acid residues. Suitably component (2) will comprise at least 60%, preferably at least 75%, more preferably 85% or more by weight  $C_{18}$  unsaturated fatty acid, e.g. linolenic, linoleic and oleic acid mono-, di- and tri-glycerides. Suitably they will comprise less than 20%, e.g. ca. 15% or 10% by weight or less, saturated fatty acid, e.g. palmitic and stearic acid mono-, di- and tri-glycerides.

Components (2) in the above-mentioned compositions will preferably be predominantly comprised of mono- and di-glycerides, e.g. comprise at least 50%, more preferably at least 70%, e.g. 75%, 80%, 85% by weight or more, mono- and di-glycerides, based on the total weight of component (2).

Components (2) in the compositions will suitably comprise from about 25 to about 50%, preferably from about 30 to about 40%, e.g. 35 to 40%, monoglycerides, based on the total weight of component (2).

Components (2) in the composition will suitably comprise from about 30 to about 60%, preferably from about 40 to about 55%, e.g. about 48 to 50%, di-glycerides, based on the total weight of component (2).

Components (2) in the compositions will suitably comprise at least 5%, e.g. from about 7.5 to about 15%, e.g. 9 to 12%, by weight of triglycerides.

Components (2) in the compositions may be prepared by admixture of individual mono-, di- or tri-glycerides in appropriate relative proportion. Conveniently however they will comprise transesterification products of vegetable oils, for example almond oil, ground nut oil, olive oil, peach oil, palm oil or, preferably, corn oil, sunflower oil or safflower oil and most preferably corn oil, with glycerol.

In another aspect, this invention provides a transesterification product of corn oil and glycerol having a saturated fatty acid content of mono-, di-, and tri-glycerides, and having a free glycerol content less than 10% by weight, which product comprises

- i) from about 25% to about 50% by weight of mono-glycerides, from about 30% to about 60% by weight of di-glycerides, and at least 5% by weight of tri-glycerides; and
- ii) a linoleic acid, oleic acid and linolenic acid mono-, di- and tri-glyceride content of at least 85% by weight;

wherein the total saturated fatty acid content of mono-, di-, and tri-glycerides is less than 10% by weight.

Such transesterification products are generally obtained by heating of the selected vegetable oil with glycerol, at high temperature in the presence of an appropriate catalyst

under an inert atmosphere with continuous agitation, e.g. in a stainless steel reactor, to effect trans-esterification or glycerolysis. In addition to their mono-, di- and tri-glyceride components, such transesterification products will also generally comprise minor amounts of free glycerol. The amount of free glycerol present in components (2) for use in the compositions of the invention will preferably be less than 10%, more preferably less than 5%, most preferably ca. 1 or 2% by weight based on the total weight of free glycerol plus mono-, di- and tri-glycerides.

Preferably some of the glycerol is first removed e.g. by distillation (to give a substantially glycerol free batch), when soft gelatine capsules are to be made.

Components (2) thus preferably contain lesser quantities of saturated fatty acids (e.g. palmitic and stearic acids) and relatively greater quantities of unsaturated fatty acids (e.g. oleic and linoleic acids) than for the starting material.

Typical preferred components (2) preferably contain:

|        |                   |
|--------|-------------------|
| 32-36% | mono-glycerides,  |
| 45-55% | di-glycerides and |
| 12-20% | tri-glycerides    |

by weight based on the total weight of component (2).

Further preferred characteristics include the following:

Fatty acid content as determined as the methyl ester by chromatography

|                   |        |
|-------------------|--------|
| Methyl linoleate  | 53-63% |
| Methyl oleate     | 24-34% |
| Methyl linolenate | 0- 3%  |
| Methyl arachate   | 0- 3%  |
| Methyl palmitate  | 6-12%  |
| Methyl stearate   | 1- 3%  |

|                        |           |
|------------------------|-----------|
| Relative Density       | 0.94-0.96 |
| Hydroxyl Value         | 140-210   |
| Iodine Value           | 110-120   |
| Peroxide Value         | <4.0      |
| Free Glycerol          | <1.0      |
| Acid value max.        | ca. 2     |
| Saponification no. ca. | 150-185   |

Components (2) complying with the above outlined features are referred to herein as "refined glycerol-transesterified corn oils". Freshly prepared components (2) according to the preferred embodiments are of clear appearance and stay clear at storage temperature of 20°C - 25°C for more than 20 days.

The refined glycerol-transesterified corn oils have especially been proposed for the preparation of the compositions disclosed in GB 9213393.3. They may also have uses for the solubilization of other active agents and have the advantage of remaining stable, e.g. clear, for a long time.

The following example illustrates the present invention.

#### EXAMPLE 1:

Preparation of refined glycerol-transesterified corn oil.

Substantially-glycerol free glycerol-transesterified corn oil (if necessary after heating to give a clear mixture) is slowly cooled to a temperature of +20°C and kept at this temperature for one night. In a first-step centrifugation, at an acceleration of 12 000 G and a flow rate of 103 kg/h in a continuous flow centrifuge, a liquid phase (62 kg/h) and a sediment-containing phase (41 kg/h) are obtained. The liquid phase is slowly cooled to +8°C and kept at this temperature for one night. In a second-step centrifugation at an acceleration of 12 000 G and a flow rate of 112 kg/h a liquid phase (76.2 kg/h) and a sediment-containing phase (35.8 kg/h) are obtained. The liquid phase is "refined glycerol-transesterified corn oil". Alternatively an improved product may be obtained by effecting the centrifugation in three steps, e.g. at +20°C, +10°C and +5°C.

The process is characterised by a slight percentage reduction in the mono-glyceride component in the refined glycerol transesterified corn oil as compared to the starting material (e.g. 35.6% compared to 38.3%).

A typical analytical comparison between the sediment and clear solution is as follows:

| Compound                           | Sediment (%) | Clear Solution (%) |
|------------------------------------|--------------|--------------------|
| 1. Mono palmitate                  | 19.1         | 3.4                |
| 2. Mono linoleate +<br>Mono oleate | 23.4         | 27.0               |
| 3. Mono stearate                   | 5.7          | <2                 |
| 4. Dilinoleate +<br>Dioleate       | 35.4         | 44.7               |
| 5. Other di-glycerides             | 7.7          | 10.4               |
| 6. Tri-glycerides                  | 8.7          | 12.5               |

Typical contents of components in the refined product obtained from these preparations are listed in the following Table:

#### COMPOSITION OF COMPONENTS (% w/w)

| Components            | refined glycerol-trans-<br>esterified corn oil |
|-----------------------|------------------------------------------------|
| Glycerides: mono      | 33.3                                           |
| di                    | 52.1                                           |
| tri                   | 14.6                                           |
| Fatty acids:          |                                                |
| palmitic acid (C16)   | 7.8                                            |
| stearic acid (C18)    | 1.7                                            |
| oleic acid (C18:1)    | 31.6                                           |
| linoleic acid (C18:2) | 57.7                                           |
| Glycerol content      | <1%                                            |



## CLAIMS

1. A trans-esterification product of corn oil and glycerol comprising predominately of linoleic acid and oleic acid mono-, di- and tri-glycerides, and having a free glycerol content less than 10% by weight, wherein the product has been treated so as to
  - a) reduce the saturated fatty acid component content of mono-, di- and tri-glycerides; and to
  - b) enhance the unsaturated fatty acid component content of mono-, di- and tri-glycerides so that the linoleic acid and oleic acid mono-, di- and tri-glyceride content is in total 85% by weight or more of the whole composition.
2. A product as claimed in claim 1 having 30% to 40% by weight of mono-glycerides.
3. A product as claimed in claim 1 or claim 2 having 45% to 55% by weight of di-glycerides.
4. A product as claimed in any preceding claim having from about 7.5 to about 15 % by weight of tri-glycerides.
5. A product as claimed in any preceding claim having a free glycerol content of less than 5% by weight.
6. A product as claimed in any preceding claim having a free glycerol content of less than 2% by weight.
7. A product as claimed in any preceding claim, having a total palmitic acid and stearic acid content of mono-, di- and tri-glycerides of less than 10% by weight.



8. A transesterification product of corn oil and glycerol having a saturated fatty acid content of mono-, di-, and tri-glycerides, and having a free glycerol content less than 10% by weight, which product comprises

- i) from about 25% to about 50% by weight of mono-glycerides, from about 30% to about 60% by weight of di-glycerides, and at least 5% by weight of tri-glycerides; and
- ii) a linoleic acid, oleic acid and linolenic acid mono-, di- and tri-glyceride content of at least 85% by weight;

wherein the total saturated fatty acid content of mono-, di-, and tri-glycerides is less than 10% by weight.

9. A product as claimed in claim 8 having 30% to 40% by weight of mono-glycerides.

10. A product as claimed in claim 8 or claim 9 having 45% to 55% by weight of di-glycerides.

11. A product as claimed in any one of claims 8 to 10 having from about 7.5 to about 15 % by weight of tri-glycerides.

12. A product as claimed in any one of claims 8 to 11 having a free glycerol content of less than 5% by weight.

13. A product as claimed in any one of claims 8 to 12 having a free glycerol content of less than 2% by weight.

14. A product as claimed in any one of claims 8 to 13, having a total palmitic acid and stearic acid content of mono-, di- and tri-glycerides of less than 10% by weight.

15. A process for obtaining a refined glycerol-transesterified corn oil according to any preceding claim, comprising heating of corn oil with glycerol at high temperature in the presence of a suitable catalyst under an inert atmosphere with continuous agitation to effect glycerol-transesterification, and refining said product by freezing procedures coupled with separative techniques.



16. A transesterified corn oil substantially as hereinbefore described with reference to Example 1.

17. A process substantially as hereinbefore described with reference to Example 1.