SPECIFICATION

New galenical compositions containing cyclosporins

This invention relates to galenical compositions containing a pharmacologically active mono-cyclic peptide, more particularly a cyclosporin, as active ingredient.

Because of the hydrophobic and/or lipophilic character of such peptides, pharmaceutical formulations thereof with conventional solid or liquid pharmaceutical excipients tend to have disadvantages. For example the peptide may not be satisfactorily absorbed, the composition may not be well tolerated, the composition may not be sufficiently stable on storage e.g. against crystallizing-out of the peptide, and/or the concentration of the peptide capable of being solubilized without crystallizing-out may be low, e.g. of the order of 3% or lower.

Problems of this nature arise not only with liquid formulations, but such solid forms such as solid "solutions", e.g. in the form of oral pellets, produced for example by melting a solid carrier, mixing in the active ingredient and allowing the mixture to solidify.

While there are many known proposals to alleviate or overcome problems of this type, it has been found after exhaustive trials that many of these proposals are inadequate in the area of the monocyclic peptides, in particular cyclosporins, with which the invention is concerned. It has, however, surprisingly been found that certain classes of glycerides used as carrier components do assist in alleviating these difficulties; in particular they, for example, may enable achievement of higher blood levels of active agent or avoid other problems each as instability.

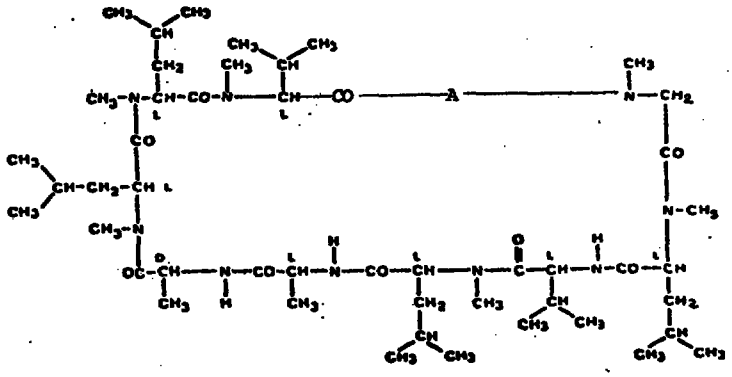
The present invention accordingly provides a pharmaceutical composition comprising a pharmacologically active cyclosporin as active ingredient and a carrier comprising the following components:–

a) a trans-esterification product of a natural or hydrogenated vegetable oil triglyceride and a polyakylene polyol;

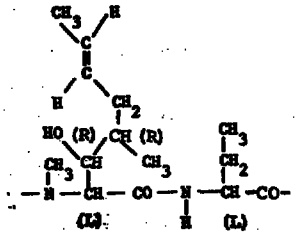
b) ethanol; and

c) a vegetable oil.

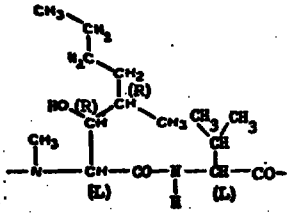
The compositions of the invention are particularly suitable for the cyclosporins of formula:–



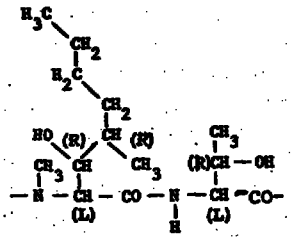
wherein A is:–



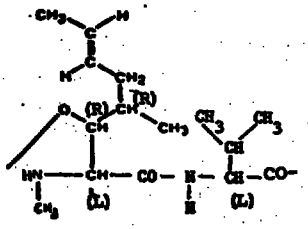
(cyclosporin A)



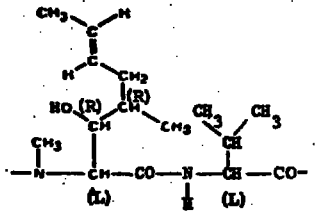
(dihydrocyclosporin D), or



(dihydrocyclosporin C)



(iso-cyclosporin D)



(cyclosporin D)

Cyclosporin A is preferred.

Component a) may be prepared in conventional manner, e.g. as described in U.S. Patent Specification No. 3,288,824. The ester may be a transesterification product of two molar parts of a natural oil, such as corn oil, almond oil, groundnut oil, olive oil and/or palm oil, with one molar part of a

polyethylene glycol of MW 200 to 800. Such esters are commercially available under the trade name LABRAFIL) see Fiedler, Lexicon der Hilstoffe, p.320, 1971), from Etablissement Gattefossé, Boulogne-sur-Siene, France. A preferred ester is derived from an unsaturated natural oil, e.g. LABRAFIL M 1944 CS, a triglyceride oleate polyethylene mixture. (The word "LABRAFIL" is a Registered Trade Mark).

It will be appreciated that the compositions according to the invention may also include one or more additional components such as e.g. d) a saturated fatty acid triglyceride. Such components d) may be obtained in conventional manner using, for example, fatty acids having a chain length of from 8 to 12 carbon atoms. Generally these glycerides will have an iodine number of less than 2. Examples of such glycerides are commercially available under the trade name MIGLYOL from Dynamit Nobel Witten/Ruhr Germany, especially MIGLYOL 812, or MYRITOL 318 from Henkel Düsseldorf, Germany. (The words "MIGLYOL" and "MYRITOL" are Registered Trade Marks).

Naturally when components present are solid, these should be chosen such that they can be melted at temperatures at which the cyclosporin is stable.

The preferred total concentration of the components present in the pharmaceutical compositions according to the invention, as well as the weight ratio of individual components will naturally depend, *inter alia*, on the particular components used, and in particular on the solvent/solubilizing effect thereof, the particular cyclosporin used, the concentration of cyclosporin desired in the final composition and the solvent/solubilizing effect of any further pharmaceutical excipients present. In general the preferred weight ratio of component a) [and d) when present] to peptide is 10 parts in total of the component (or components) to 0.2 to 10 parts of peptide, or more preferably 1 to 10 parts by weight of peptide, and conveniently from 1 to 7 parts by weight of peptide.

When component a) and optional component d) are both present, the weight ratio of component a) to component d) is from 1:1 to 1:2.

The pharmaceutical compositions of the invention may be made by mixing a pharmacologically active cyclosporin with a liquid carrier comprising component a), b) and c) [and optional additional components such as d)] as defined above. If one of the components is solid, temperatures up to about 70°C may be used, to produce a liquid melt in which the active agent may be dissolved in. The composition may be cooled and then, for example, ground.

The pharmaceutical compositions according to the invention may be formulated in conventional manner, if desired with further pharmaceutical excipients, into forms suitable for oral or parenteral administration. Preferably they are in liquid form. Examples of preferred compositions are:

i)Solutions for drinking, e.g. Example 1 hereinafter,
ii) Emulsions for drinking,
iii) Injection solutions,
iv) Solutions contained in capsules.

The modes of administration are preferably intramuscular and subcutaneous administration or more preferably oral administration. In particular when component d) is present, the pharmaceutical composition is preferably used for parenteral administration.

The pharmaceutical compositions according to the invention may be formulated with or without further excipients.

Components b) and c) together may be present in a concentration of up to 60% of the total composition. The content of component b), ethanol, may be for example 2 to 5% by weight for parenteral compositions and 1 to 20% by weight for oral compositions, based on the total weight of the composition. The content of component c), a vegetable oil, such as olive oil or corn oil in both oral and parenteral compositions may be for example from 35 to 60% by weight, based on the total weight of the composition.

The properties of the compositions according to the invention may be determined in conventional manner. The stability of solutions particularly against crystallization-out of the active agent may be determined using known tests. Tolerability of injection forms may be determined by observing the extent of bleeding and inflammations after injection, e.g. into thighs of rabbits and rhesus monkeys, and the time taken for these to heal, as well as by using other usual tolerability tests.

The absorption of the pharmacologically active peptide, e.g. rapid onset of a satisfactory concentration of the peptide in the blood, and a high total absorption of the peptide over 24 hours, is indicated in standard tests.

In one test a pharmaceutical composition according to the invention is administered to rabbits, rats, dogs or rhesus monkeys orally, intramuscularly or subcutaneously, at a dose of from 2 to 600 mg/kg animal body weight of active cyclosporin. Blood serium samples and urine samples are taken at regular intervals thereafter, e.g. every hour, and are analysed for the concentration of cyclosporin therein in conventional manner.

For example the pharmacological activity in a sample may be ascertained in conventional manner according to known tests. In the case of cyclosporin A the effect of the peptide present in inhibiting lymphocyte proliferation may be ascertained. Thus the blood serum is collected at regular intervals after administration, and is added at a concentration of from 0.3 to 10% to a mouse *in vitro* spleen cell suspension in which lymphocyte proliferation is induced by Concavalin A over a 72 hour culture period. ^{3}H-thymidine is then added and the thymidine incorporation after 24 hours is measured to indicate the lymphocyte proliferation.

If desired, the cyclosporin may be administered in radio-active form. For example in one experiment 100 mg of ^{3}H-labelled cyclosporin A (prepared by cultivation of the known strain Tolypocladium inflatum Gams NRRL 8044 in the presence of methionine marked with tritium in the SCH_3 group thereof) contained in a pharmaceutical composition according to the invention in the form of a drinking solution, or in a capsule, is administered perorally, or in the form of an injection solution is administered intramuscularly, to male beagle dogs. Blood sam-

ples are obtained from each dog every 15 minutes after administration up to 1 hour after administration and thereafter every hour thereafter up to 8 hours after administration. The urine is collected also. Determination of the radio-activity in the blood and in the urine indicates the peptide absorption.

The amount of cyclosporin to be administered in the pharmaceutical compositions according to the invention will naturally depend upon the mode of administration, the effect desired and the condition to be treated.

For the cyclosporins, the amounts to be administered for a therapeutic effect are well-known. When using compositions according to the invention a daily dose of from about 3 mg/kg to about 50 mg/kg is indicated in order to treat chronic inflammations or to provoke an immunosuppressive effect.

The following examples illustrate the invention. All temperatures are in degrees Centigrade.

EXAMPLE 1: Drink Solution

200 mg of cyclosporin A are dissolved on stirring in 1 ml of a mixture of Labrafil M 1944 CS and ethanol (parts by weight 40:15) at 25°. 0.4 ml of olive oil or corn oil are added. The resultant mixture is filtered and filled into a small vial.

The final solution contains for every 10 parts by weight of Labrafil; 3 parts by weight of cyclosporin A, 3 parts by weight of ethanol and 5 parts by weight of olive oil or corn oil.

EXAMPLE 2: parenteral forms for i.m. and s.c. administration

100 mg of cyclosporin A are dissolved on stirring in a mixture of 40 mg ethanol, 100 mg Labrafil M 1944 CS and 200 mg Miglyol 812 at 25°. The resulting mixture is made up to 1 ml with olive oil and filled under sterile conditions into an ampoule.

The final solution contains for every 10 parts by weight of Miglyol 812, 5 parts by weight each of cyclosporin A and Labrafil and 25 parts by weight of olive oil.

CLAIMS

1. A pharmaceutical composition comprising a pharmacologically active cyclosporin as active ingredient and a carrier comprising the followning components:
a) a trans-esterification product of a natural or hydrogenated vegetable oil triglyceride and a polyalkylene polyol;
b) ethanol; and
c) a vegetable oil.

2. A pharmaceutical composition according to claim 1, wherein the active ingredient is selected from the group consisting of cyclosporin A, dihydrocyclosporin C, cyclosporin D and dihydrocyclosporin D.

3. A pharmaceutical composition according to claim 2, wherein the active ingredient is cyclosporin A.

4. A pharmaceutical composition according to any one of claims 1 to 3, wherein component a) is a trans-esterification product of two molar parts of a natural vegetable oil triglyceride and one molar part of a polyethylene glycol of MW 200 to 800.

5. A pharmaceutical composition according to any one of claims 1 to 4, wherein component c) is olive oil or corn oil.

6. A pharmaceutical composition according to claim 5, wherein component c) is olive oil.

7. A pharmaceutical composition according to any one of claims 1 to 6, wherein the ratio of component a) to cyclosporin is 10:0.2 to 10 parts by weight.

8. A pharmaceutical composition according to claim 7, wherein the ratio of component a) to cyclosporin is 10:1 to 10 parts by weight.

9. A pharmaceutical composition according to claim 8, wherein the ratio of component a) to cyclosporin is 10:1 to 7 parts by weight.

10. A pharmaceutical composition according to any one of claims 1 to 9, wherein components b) and c) together are present in an amount of up to 60% by weight based based on the total weight of the composition.

11. A pharmaceutical composition according to any one of claims 1 to 10, comprising from 1 to 20% by weight of component b), based on the total weight of the composition.

12. A composition according to any one of claims 1 to 11, comprising from 35 to 60% by weight of component c), based on the total weight of the composition.

13. A composition according to any one of claims 1 to 12, formulated as a solution for oral administration.

14. A composition according to any one of claims 1 to 12, formulated as a solution for parenteral administration and containing from 2 to 5% by weight of component b), based on the total weight of the composition.

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