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US 5504068 A**

(58) Field of Search by ISA  
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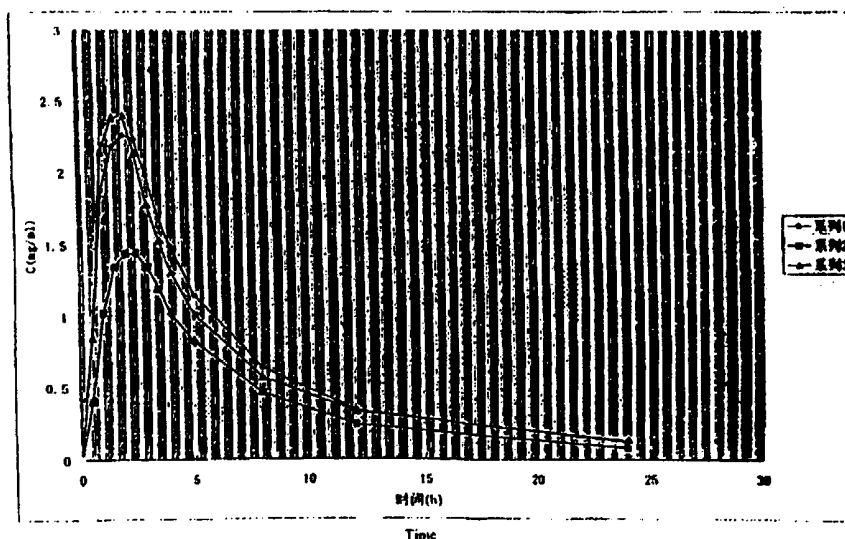
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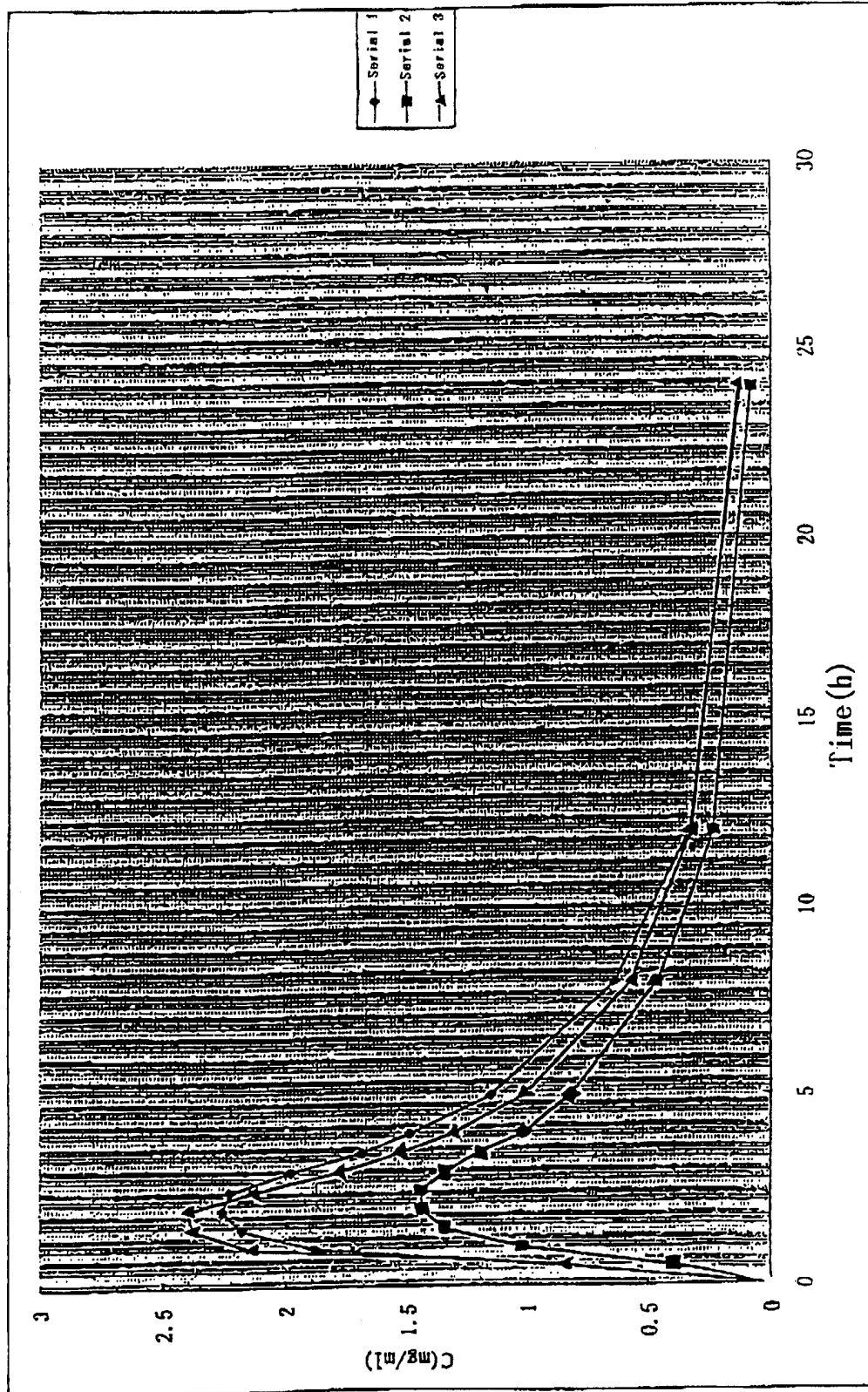
(54) Abstract Title  
**Pharmaceutical composition containing cyclosporin**

(57) The present invention relates to a pharmaceutical composition containing cyclosporin, the active ingredient of which is cyclosporin, which characterized in that choosing a pharmaceutical organic acid such as medium or long chain saturated or unsaturated fatty acid, substituted carboxylic acid etc., or an admixture of one or more acids or fish oil as a hydrophobic ingredient, depending on the need of various dosage form, not adding water or adding appropriate amount water to made a hydrophilic medium, the formulation of the composition is suitable in preparation of dosage forms such as soft capsule, paste, eye dops, oral liquid and injection etc.



**GB 2 363 572 A**

Fig. 1



**Title****Pharmaceutical Composition containing cyclosporin****Field of the invention**

The present invention relates to a pharmaceutical composition comprising a cyclosporin as an active ingredient; a solvent or co-surfactant such as ethanol or propylene glycol or mixture thereof; as solubilizer a hydrophilic surfactant having HLB value of 10-19; as lipophilic component one or a mixture of two or more selected from the group consisting of pharmaceutical organic acids such as medium/long chain saturated or unsaturated fatty acid and substituted carboxylic acid, or fish oil; and where appropriated, water for making hydrophilic substrate being present or absent. The composition may be formulated into soft capsule, ointment, eye-drop, oral solution, injection and so on.

More particularly, the invention relates to a composition comprising cyclosporin which is insoluble in water. The composition may be formulated into many formulations, such as soft capsule, ointment, eye-drop, oral solution, injection and so on. In accordance with the present invention, here is provided information about the each component.

**Background**

The active ingredient is cyclosporin, also known as cyclosporin A or ciclosporine. It is a cyclic polypeptide consisting of 11 amino acids. Cyclosporin has now been as a novel and efficient immunosuppressive agent in the clinic field, especially in the prevention of organ rejection following

organ and bone marrow transplantation and the therapy of various autoimmune diseases. It acts in the early lymphocyte proliferation phase and the action of inhibition for cell is reversible. In addition, It doesn't affect hematopoietic function of bone marrow and not cause to decrease of amount of WBC and RBC. Cyclosporin is white crystal powder which has molecular weight of 1202.64. It's highly hydrophobic and sparingly water-soluble, and as well dissolved in an organic solvent such as methanol, ethanol, acetone, ether, chloroform and the like. Due to above-mentioned reasons, cyclosporine oral solution is poor absorbed and has low bioavailability. In the 1980's, the scientists of Sandoz Company dissolved cyclosporin with ethanol, then formulated an oil form in junction with vegetable oil and Labrafil M 1944CS having HLB value of 3. After added some water in the formulation, the composition become unstable and turbid. The sandoz's formulation containing cyclosporin is thus generally administered with dilution of milk or fruit juice. The bioavailability of said formulation depends on the patient's body condition, individual difference etc. The variation of bioavailability is in the range of about 4-60%. Therefore, it is very difficult for said formulation to retain an effective therapeutic concentration of Cyclosporin. Further, the primary side effects of cyclosporin are hepatotoxic and nephrotoxic. With the dosage increasing, said side effect become more serious. Furthermore, the evaporation of ethanol during the preparation process and the storage of the soft capsule over time may also result in the precipitation of cyclosporin contained in the formulation, whereby bioavailability levels and stability of cyclosporin are decreased.

In order to improve the bioavailability of Cyclosporin, reduce the marked difference in the individual and the inconvenience of diluting with milk or juice before the oral cyclosporine solution is administered, numerous studies have been extensively conducted to discover an novel preparation suitable for cyclosporin well -distribution in the water with molecular state, which make

absorption of cyclosporin not be affected by bile and the fat in food. Accordingly, Sandoz Company has marketed a preparation of cycloprine in the form of a emulsion pre-concentrate which trademark as SANDIMUN NEORAL and Korea-America Pharmaceutical Company has also marketed a preparation of cycloprine in the form of a emulsion pre-concentrade which trademark as IMPLANTA.

#### Object of the invention

The object of the present invention is to develop a liquid composition which enable the stability of cycloprine more higher.

The inventors of the present invention have studied about various surfactant, co-surfactaaant, solubilizar, and oil ingredient based on the research of solubilization for insoluble drugs and find a new liquid composition comprising cyclosporin, which is never disclosed in the prior art. The present composition has many advantages such as improvement stability and no-influence with co-surfactant migration during the preparation process and the storage period , even when exposed or opened or in water-existing condition, it may still exhibit more stability than the known preparation. The ratio of cyclosporin as an active ingredient is in the range of 0.5-15% by weight based on the weight of composition.

Within the range , the composition is in the best emulsified state. Thus, the new oral preparation containing cyclosporine in the present invention has great improvement on bioavailability than those of the prior art, and has the same bioequivalence with said Sandimmun Neoral on the market.

#### Summary of the present invnetion

The present invention relates to a pharmaceutical composition containing cyclosporin which comprises:

- (1) cyclosporin as active ingredient;

(2) as solvent or co-surfactant ethanol, propylene glycol or mixture thereof;  
(3) as solubilizer hydrophilic surfactant having HLB value from 10 to 19;  
(4) as lipophilic component a pharmaceutical organic acid selected from the group consisting of saturated or unsaturated fatty acid having medium/long chain, substituted carboxylic acid or mixture thereof, or fish oil;

(5) where appropriated, presence or absence of water or hydrophilic base containing water.

The composition may be formulated into various form such as soft capsule, soft cream, eye-drop, oral solution and injection etc.

#### Detailed description of the present invention.

The present invention relates to a pharmaceutical composition containing cyclosporin which comprises:

(1) cyclosporin as active ingredient;  
(2) as solvent or co-surfactant ethanol, propylene glycol or mixture thereof;  
(3) as solubilizer hydrophilic surfactant having HLB value from 10 to 19;  
(4) as lipophilic component a pharmaceutical organic acid selected from the group consisting of saturated or unsaturated fatty acid having medium/long chain, substituted carboxylic acid or mixture thereof, or fish oil;

(5) where appropriated, presence or absence of water or hydrophilic base containing water.

The composition may be formulated into various form such as soft capsule, soft cream, eye-drop, oral solution and injection etc.

According to the present invention, the solvent or co-surfactant for dissolving an insoluble drug is selected from the group consisting of ethanol, propylene glycol and the mixture thereof. The ratio of ethanol: propylene glycol is 1: 0.1-10(w/w), more preferably 1: 0.5-5(w/w) and most preferably 1: 1-3(w/w).

According to the composition of present invention, the hydrophilic pharmaceutical surfactant having HLB from 10 to 19 is used as solubilizers for liposoluble drugs to achieve the balance between the hydrophilic component and the lipophilic component and form a steady emulsion. These surfactants involve, for example, the derivatives of polyoxyethylene castor oil, such as Cremophor EL, Cremophor RH40, Cremophor 60, or Tween type, such as Tween 80, Tween 65, Tween 20, and the Myrj such as Myrj 52. The derivatives of polyoxyethylene castor oil are preferred.

According to the composition of the present invention, said composition characterizes by using a pharmaceutical organic acids or fish oil as lipophilic component, wherein an organic acid is selected from the group consisting of saturated or unsaturated fatty acid having medium/long chain and substituted carboxylic acid or mixture thereof. The lipophilic component make the composition of the present invention more stable and simple than that of prior art. In the present invention, the above-mentioned carboxylic acid may be in esterified or free form. Among the all components, the lipophilic component may be the saturated acids having medium/long chain are C<sub>8-28</sub> carboxylic acid; the unsaturated acids having medium/long chain are C<sub>10-24</sub> mono-, di-, or tri-olefine acid; the substituted carboxylic lactic; or the fish oil containing 70% DHA. As lipophilic component unsaturated fatty acids having the medium/long chain especially C<sub>14-22</sub> mono-, di-, or tri-olefine acid are preferred.

According to the present invention, the another character of the composition of present invention lies in that water is present or absent depending on different form of each composition. The ratio of the active

ingredient to the water is in the range of 1:0-1000 by weight. For example, adding certain water in to the oral solution containing cyclosporin can cut down the temperature of solidify or forming flocculation of a composition. Accordingly, the character can be applied for the preparation of hydrophilic ointment and eye-drop.

According to the present invention, to meet the different requirement in the clinic application, the composition which contain cyclosporin or other fat-soluble drugs is formulated into soft gelatin capsule, ointment, eye-drop, oral solution, injection and so on.

Further, depending on the different requirement of the formulation, excipient or adjuvant may also be used, e.g., anti-oxidant, flavoring agent, osmosis promoter, agent for adjusting pH, antiseptic and so on, and not limited to above-mentioned range. The method of preparation of various formulations can be taken under the conventional method in the art.

The present invention will be more specifically illustrated by the following examples. However, it should be understood that the present invention is not limited by these examples in any manner.

Example 1 The preparation of CsA oral solution

INGREDIENT	QUANTITY(mg)
Cyclosporin	100
Mixture of ethanol and propylene glycol	230
Polyoxyethylene castor oil	400
Oleate	220
Vitamin E	2
Purified water	a.q.

Total

1000ml



Example 2 The preparation of CsA capsule

INGREDIENT	QUANTITY(mg)
Cyclosporin	50
Mixture of ethanol and propylene glycol	100
Polyoxyethylene castor oil	200
Refined fish oil	130
<hr/>	
Total	1300 capsules

Example 3 The preparation of CsA eye-drop

INGREDIENT	QUANTITY(mg)
Cyclosporin	20
Mixture of ethanol and propylene glycol	50
Polyoxyethylene castor oil	90
Stearic magnesium	220
Vitamin E	1
Physiological saline	a.q.
<hr/>	
Total	1000ml

A study on relative bioavailability was carried out by comparing the oral solution preparation prepared by the example 1 (new cyclosporin oral solution, thereafter named as -New Cyspin) with the known cyclosporin soft capsule (named as Cyspinin below) and Sandimmun capsule.

A result of pharmacokinetic parameters derived from above comparison is obtained from 12 male health volunteers who received cyclosporin soft capsule (Cyspinin commercial), New Cyclosporine Oral Solution ("New

Cyspin”) provided by Hangzhou Zhongmeihuadong Pharmaceutical Co. Ltd. and the Cyclosporine capsule named as Sandimmun Neoral (“Sandimmun Neoral” is commercial available). The obtained whole-blood concentration was detected by HPLC, followed by pharmacokinetical assay according to statistic matrix, by use of 3P87 and NDST computer programs. The results showed: after oral administration of the Cyspinin, New Cyspin and Sandimmun Neoral, respectively, AUC (AUC is an area under curve of concentration of blood-drug vs time and is a main parameter for determining bioavailability in the art) were  $11.43 \pm 2.49$ ,  $16.77 \pm 2.49$  and  $16.39 \pm 3.54$  mg/l\*h, respectively; Cmax (peak value of blood-drug concentration) were  $1.56 \pm 0.25$ ,  $2.38 \pm 0.38$  and  $2.47 \pm 0.42$  mg/l respectively; and Tmax (time for achieving peak value of blood-drug concentration) were  $2.04 \pm 0.54$ ,  $2.00 \pm 0.56$  and  $1.62 \pm 0.38$  h respectively. The major pharmacokinetic parameters AUC, Cmax and Tmax showed: remarkable difference existed between Cysipinin and New Cyspin, Sandimmun Neoral, but no remarkable difference existed between New Cyspin and Sandimmun Neoral. The relative bioavailability of Cyspin and New Cyspin Vs Sandimmun Neoral was  $73.4 \pm 25.2\%$ ,  $105.0 \pm 17.9\%$ . The results of the study confirmed the bioequivalence of New Cyspin and Sandimmun Neoral in human body.

12 male health adult volunteers were selected to voluntarily receive the administration under complying with the requirement of “ Guideline for Medical Preparation in Bioavailability Study Conducted on Human Body” issued by the Medical Administration Bureau of Health Ministry. Routine laboratory tests showed that their blood, urine, liver and kidney functions, electrocardiogram and related immunological indexes were normal. During the two weeks before the test and the period in test the testees were required to free from any drugs.

Cyclosporine Reference Standard, supplied by Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd. ( 9201C, Purity 0.976mg/mg)

Inside-label, Cyclosporin D (thereafter named as 'CSD'), purity 98.4%, supplied by *Sichuan Industrial Institute of Antibiotics* and prepared to 1.2mg/l solution for being ready.

The volunteers should not take any food from supper the day before to 4 hours after administration. There were totally 12 persons in the test, divided into 3 group, each group including 4 persons. The first group took orally CYSPIN IN 500mg, the second group took NEW CYSPIN 500mg, the third group took Sandimmun Neoral 500mg, all taking together with 300ml of juice. The volunteers were given standard food with little fat 4 hours after administration. Each volunteer undergo Cross-administration (Cyspin ,New Cyspin & Sandimmun Neoral) one time with the interval of 7 days. Collect venous blood respectively at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 8.0, 12 and 24 hours after orally administration. Put the blood sample in the heparin-anticoagulating test tube, stored at -40°C for determination after shaking vigorously.

The blood samples obtained were detected by direct injection method, through column conversion. 1ml of whole blood sample was transferred into a 5 ml plastic centrifugal tube with plug, followed by accurately adding 1.0 ml of CSD working solution, 1.0 ml of methanol and 1.0 ml of hexane, successively, the mixture was allowed to be vertically blended for 1 min, and then centrifuged for 10 min (1600r/min). The hexane phase in upper level was discarded while the clear solution in lower level was transferred into a 1.5 ml centrifugal tube and again centrifuged for 10min (1600r/min), 1.0 ml of the centrifuged solution was applied into the chromatography system for assay. An RP2 column (30x4.6mm, 25-40 $\mu$ m) was applied as the purifying column, self-filled according to homogenization method. The mobile phase for purification was a mixture of methanol and water (65:35), flow rate 1ml/min. The purification time was defined as 10min, tangential time 1min; a Shim-pack CLC-OB column (150 $\times$ 6mm, 5 $\mu$ m) together with a pre-

column (ODS, 10×4.6mm, 10μm) were applied for separation, column temperature 70°C; the mobile phase for assay was a mixture of acetonitrile and 0.025mol/l of Sulphonamide (82:18, pH 2.5), flow rate 1ml/min, the wave length for detection was at 210nm, and sensitivity of instrument was set at 0.02 AUFS. The detected retention time of CsA and CsD were 9.2 min and 11.2 min, respectively. Quantitative assay was conducted through measuring peak height by internal standard method, and a linear range existed from 0.025-3mg/l,  $y=1.04 \times 10^{-3}x-4.06 \times 10^{-3}$ ,  $R=0.9999$ , the signal-to-noise ratio was 3, the concentration limit of whole blood was 0.01mg/l. In this range, respectively took 1.0 ml standard CsA in high, middle and low concentration, followed by adding 1.0 ml of empty whole blood sample, 1.0 ml of CSD working solution, 1.0 ml of n-hexane, successively, the mixture was allowed to be vertically blended for 1 min. According to the above-mentioned method, detected the high of CsA (H). And then took 1.0 ml standard CsA with the same concentration, adding 1.0 ml of water, 1.0 ml of CsD working solution, after being vertically blended for 1 min, directly detected the high of CsA (H0). Treated the H/H0 as purification recovery, the average purification recovery was 98.5% (Table 1), the average method recovery was 99.3% (Table 2). Intra-day RSD was 2.3% and day-to-day RSD was 2.6% (Table 3). Figure 1 is the Curve of Mean Concentration vs. Time. In Figure 1, abscissa represents time after administration (hr), ordinate represents blood-drug concentration (mg/l), each point in triangle shows the curve of the average concentration after administration of sandimmun Neoral vs time, each point in square shows the curve of the average concentration after administration of cyspinin Neoral vs time, each point in rhomboid represents shows the curve of the average concentration after administration of New cyspin solution vs time.

#### Pharmacokinetic parameters and bioavailability F

- 1) The practical pharmacokinetic computer program which was used to

control 3 P87 and new medical statistic program NDST, formulated by the Chinese Society of Pharmacology, were adopted for statistic processing in a P-133 computer. 1,2 -dimensional analogue-curves of fit were conducted respectively based on variation of blood conc. The results declared: pharmacokinetic result of oral administration of New Cyspin met the 1-dimensional model. The calculation of AUC, MRT, etc. was conducted according to statistic matrix, Cmax and Tmax were obtained based on actual data of blood conc. vs time, T1/2 was calculated according to 1-dimensional model, and pair-t test was adopted for statistic processing, in which AUC of Cyspin , New Cyspin and Sandimmun Neoral were  $11.43 \pm 2.48$ ,  $16.77 \pm 2.49$  and  $16.39 \pm 3.54 \text{mg/l} \cdot \text{h}$ ; Cmax  $1.56 \pm 0.25$ ,  $2.38 \pm 0.388$  and  $2.47 \pm 0.42 \text{mg/l}$ ; Tmax  $2.04 \pm 0.54$ ,  $2.00 \pm 0.56$  and  $1.62 \pm 0.38 \text{h}$ .

## 2) Calculation of Bioavailability (F)

$$F = (\text{AUC of New Cyspin} / \text{AUC of Sandimmun Neoral}) \times 100\%$$

The relative bioavailability of Cysipinin and New Cyspin vs Sandimmun Neoral was  $73.4 \pm 25.2\%$ ,  $105.0 \pm 17.9\%$ , calculated by average, was  $69.7\%$  and  $102.3\%$ .

**Table 1. The Purification Recovery of CsA in the Whole Blood Samples (Tested by HPLC, N=5)**

CsA Conc. (mg/l)	H	HO	Purification Recovery (%)	RSD (%)	Average
0.101	729	740	98.51	2.01	
0.504	3566	3641	97.95	1.83	98.51
2.018	14456	14593	99.06	1.05	

**Table 2 The Method Recovery of CsA in the Whole Blood Samples  
(Tested by HPLC, N=5)**

Adding (mg/l)	Measurement (mg/l)	Recovery (%)	Average	SD (%)
0.101	0.101	99.81		
0.504	0.496	98.41	99.31	0.64
2.018	2.012	99.70		

**Table 3. The Precision of CsA in the Whole Blood Samples (Tested by HPLC)**

Concentration (mg/l)	RSD (Intra-day)	Times	RSD (Day-to-day)	Times
0.102	1.76	5	1.88	3
0.505	1.48	5	2.34	3
2.070	2.27	5	2.57	3

## Claim

What is claimed is:

1. A pharmaceutical composition comprising:

- 1) a cyclosporin as active ingredient;
- 2) a solvent or a co-surfactant such as ethanol, propylene glycol and the mixture of them
- 3) a hydrophilic surfactant having a hydrophilic-lipophilic balance (HLB) value of 10 to 19 as solubilizer;
- 4) lipophilic component which is one or a mixture of two or more selected from the group consisting of pharmaceutical organic acids such as medium/long chain saturated or unsaturated fatty acid and substitutive carboxylic acid, and fish oil as;
- 5) where appropriated, water for making the hydrophilic substrate is present or absent.

said composition is formulated into soft capsule, ointment, eye-drop, oral solution, injection, etc.

2. The composition according to claim 1 wherein said solvent or co-surfactant is ethanol, propylene glycol or a mixture of them.
3. The composition according to claim 1 wherein the ratio of said ethanol to propylene glycol is from 1:0.1 to 1:10 (w/w).
4. The composition according to claim 1 wherein the ratio of said ethanol to propylene glycol is from 1:0.5 to 1:5 (w/w).
5. The composition according to claim 1 wherein said the surfactant having the HLB value of 10 to 19 is the derivatives of polyoxyethylene castor oil, Tween, and Myrj.
6. The composition according to claim 1 wherein as the lipophilic component said medium/long chain saturated fatty acid is C<sub>8-28</sub> carboxylic acid.
7. The composition according to claim 1 wherein as the lipophilic component

said medium/long chain unsaturated fatty acid is C<sub>10-24</sub> mono-, di-, or tri-olefine acid.

8. The composition according to claim 1 wherein as the lipophilic component said medium/long chain unsaturated fatty acid is C<sub>14-22</sub> mono-, di-, or tri-olefine acid.
9. The composition according to claim 1 wherein said substituted carboxylic acid is lactic acid .
10. The composition according to claim 1 wherein as the lipophilic component said fish oil comprises 70% DHA (w/w).
11. The composition according to claim 1 wherein said oil component is one or a mixture of two or more selected from the group consisting of pharmaceutical organic acids, such as medium/long chain saturated or unsaturated fatty acid and substituted carboxylic acid.
12. The composition according to claim 1 wherein said ratio of cyclosporin to the puried water is 1:0-1000. (w/w).
13. The composition according to claim 1 wherein said composition is formulated into soft capsule, ointment, eye-drop, oral solution, injection and so on.



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CN00/00041

## A. CLASSIFICATION OF SUBJECT MATTER

IPC<sup>6</sup> : A61K38/13,A61K31/045,A61K31/20

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)

IPC<sup>6</sup> : A61K38/13,A61K31/045,A61K31/20

Documentation searched other than minimum documentation to the extent that such documents are included in the field searched

Electronic data base consulted during the international search(name of data base and, where practicable, search terms used)  
CNPAT, PAJ, EPOQUE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant claim No.
A	CN1079907A, 29. DEC. 1993 see the abstract and the claims.	1-13
A	CN1128671A, 14. AUG. 1996 see the abstract and the claims.	1-13
A	CN1204261A, 06. JAN. 1999 see the abstract and the claims.	1-13
A	US5504068, 02. APR. 1996 see the whole document.	1-13
A	US5589455, 31. DEC. 1996. see the whole document.	1-13

 Further documents are listed in the continuation of Box C.
  See patent family annex.

- \* Special categories of cited documents:
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- "P" document published prior to the international filing date but later than the priority date claimed
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- "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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Date of the actual completion of the international search

17.MAR.2000 ( 17.03.00 )

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INTERNATIONAL SEARCH REPORT  
Information on patent family members

International application No.  
PCT/CN00/00041

Patent document cited in search report	Publication date	Patent family members	Publication date
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