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☑ Description : paged ..... 1 ... to paged ..... 18 .....
☐ Claim(s) : paged ..... to paged .....
☐ Drawing(s) : paged ..... to paged .....
☑ Abstract : paged ..... to paged .....
DATE OF RECEIPT .....

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CYCLOSPORIN-CONTAINING SOFT CAPSULE PREPARATIONS

The present invention relates to an, e.g. soft capsule preparation containing cyclosporin as an active ingredient. More specifically, the present invention relates to a soft capsule preparation containing a stable cyclosporin composition in a gelatin capsule shell containing a certain plasticizer and a process for preparing thereof.

Cyclosporin is a specific macromolecular (molecular weight 1202.64) cyclic peptide compound consisting of 11 amino acids, which has broad spectrum of useful pharmacological activities, particularly immuno-suppressive activity and anti-inflammatory activity. Therefore, cyclosporin has been used for suppression of inherent immunological responses of the living body, which are caused by tissue and organ transplantation, for example, transplantation of the heart, lung, liver, kidney, pancreas, bone marrow, skin and cornea, and especially the transplantation of foreign tissues and organs. In addition, cyclosporin is useful for the suppression of hematological disorders such as anemia, various autoimmune diseases such as systemic lupus erythematosus, idiopathic malabsorption syndrome, etc., and inflammatory diseases such as arthritis, rheumatoid disorders, etc. Cyclosporin is useful in treatment of protozoal diseases such as malaria, schistosomiasis, etc. , and furthermore, recently it is also used in chemotherapy.

Cyclosporin is highly lipophilic and hydrophobic. Therefore, cyclosporin is sparingly soluble in water, and as well dissolved in an organic solvent such as methanol, ethanol, acetone, ether, chloroform and the like. Due to low water-solubility of cyclosporin having above-mentioned properties, when cyclosporin is administered orally, its bioavailability is extremely low and may be greatly influenced by the conditions of each individual patient. Accordingly, it is very difficult to retain an effective therapeutic concentration. Moreover, cyclosporin may show considerable side effects such as nephrotoxicity. Thus, cyclosporin is very difficult to formulate into a preparation for oral administration due to its

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low water solubility. Accordingly, numerous studies have been extensively conducted to discover a preparation suitable for the effective oral administration of cyclosporin, which can provide a suitable uniform dosage and appropriate bioavailability.

In the prior art, the preparations suitable for oral administration of sparingly water-soluble cyclosporin have been usually formulated in the form of a emulsion pre-concentrate.

One typical method using this combination is taught in U.S. Patent No. 4,388,307 which issued on June 14, 1983. This patent discloses a liquid formulation of cyclosporin using ethanol. According to the method disclosed in this US Patent Specification, cyclosporin is combined with a carrier consisting of ethanol as a co-surfactant; olive oil as a vegetable oil, and a transesterification product of a natural vegetable oil triglyceride and a polyalkylene polyol as a surfactant to form the liquid formulation.

However, the resulting liquid formulation is administered as an aqueous dilution which makes it very difficult to adapt the subject to its administration and to provide a uniform dosage for oral administration.

In order to mitigate the inconvenience of diluting the cyclosporin liquid composition in water prior to oral administration, a liquid composition in the form of an emulsion pre-concentrate has been formulated into a soft capsule preparation, which is now commercially available as Sandimmune (registered trademark). In this case the cyclosporin soft capsule contains ethanol due to the solubility requirements of cyclosporin. However, since ethanol may permeate the gelatin shell of the capsule as it is volatile even at normal temperature, to prevent the volatilization of ethanol from the soft capsule preparations during storage and distribution, the soft capsule preparations may be wrapped in a special packing material, such as an aluminium-aluminum blister package.

Recently it has been possible to develop a cyclosporin preparation which has a stability during the storage period and further provides substantially no change in biological availability and its difference between individual subjects, so that the biological effect of cyclosporin can be uniformly maintained. One of the preparations developed for this purpose is disclosed in Korean Laid-open Patent

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Publication No. 93-113. This preparation is commercialized under the registered trademark Sandimmun Neoral. However, since this preparation also uses ethanol, it may have some disadvantages as in the prior ethanol-containing preparations, in storage stability, and changes in the ethanol content.

Accordingly, the present inventors have studied numerous combinations of various surfactants, oil components, co-surfactants etc. to find a cyclosporin composition which is stable, and provides higher bioavailability and lower difference in blood levels between individual subjects than those of the prior cyclosporin preparations in view of their pharmacokinetic properties. As a result, we have identified that a certain cyclosporin composition consisting of the components as defined below can satisfy the above-mentioned requirements, and then completed the present invention.

Therefore, it is an aspect of the present invention to provide a composition suitable for formulation into soft capsules, which comprises cyclosporin as an active ingredient; a hydrophilic substance polyethylene glycol or a non-hydrophilic substance propylene carbonate or their mixture; an oil component as defined below, and a surfactant.

It is a further aspect of the present invention to provide a soft capsule preparation comprising a composition which contains cyclosporin as an active ingredient; a hydrophilic substance polyethylene glycol or a non-hydrophilic substance propylene carbonate or their mixture; a mixture of an esterified compound of fatty acid and primary alcohol, medium chain fatty acid triglyceride (if desired) and fatty acid monoglyceride as an oil component; and a surfactant having an HLB (Hydrophilic Lipophilic Balance) value of 8 to 17.

Further it is another aspect of the present invention to provide a process for preparing the soft gelatin capsule preparation as defined above.

Even though the present invention is described herein particularly with respect to soft gelatine capsules, it is to be appreciated that the invention covers the composition itself which may be used as such e.g. as a drink solution, e.g. as Sandimmun Neoral, or be in other unit dosage forms.

In one aspect, the present invention relates to a cyclosporin-containing capsule which has a high storage stability such that there is little variation of the

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composition over time, and has an increased bioavailability, and which contains a composition comprising cyclosporin as an active ingredient; a hydrophilic substance polyethylene glycol or a non-hydrophilic substance propylene carbonate or their mixture as a second component; an oil component as defined below; and a surfactant.

To formulate such cyclosporin-containing composition into the soft capsule preparation, a gelatin shell must be used. However, when the soft capsule is formulated with the general capsule shell containing glycerine as plasticizer, the soft capsule preparation has some disadvantages in that the emulsified state of the emulsion pre-concentrate may be changed due to the inflow of glycerine into the emulsion and, therefore, the solubility of cyclosporin is significantly lower to result in the precipitation of cyclosporin from the emulsion.

Accordingly, in the present invention preferably a gelatin shell using a mixture of propylene glycol and polyethylene glycol, not glycerine, as a plasticizer is selected for the soft capsule shell, which can solve the problem related with inflow of glycerine.

However, when the capsule shell band containing propylene glycol and polyethylene glycol according to the present invention is prepared by means of a water-cooling method which is conventionally used for a cooling drum, it is not easily removed from the drum. Such removability of the capsule shell band from the cooling drum may be improved by over-cooling the cooling drum by continuously circulating a cooling water to reduce temperature of the band to about 17°C. However, the capsule shell band which is cooled to lower temperature may provide a low extent of seal during the encapsulation process and may cause lowering of productivity.

Therefore, the process for preparing the gelatin shell band not containing glycerine plasticizer according to the present invention adopts an air-cooling method, instead of the prior water-cooling method, in which the capsule shell band can be cooled down to the optimum temperature by providing an air flow from a fan and therefore, can be readily removed from the cooling drum and further, it is maintained at the optimum temperature of about 21°C to increase the extent of seal in the encapsulation process and ensure a high productivity.

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As mentioned above, the present products can be produced by using the glycerine-free gelatin capsule shell and applying the air-cooling method to the composition which does not contain ethanol as a low boiling volatile solvent and therefore, has a high storage stability such that there is little variation of the composition over time, and has an increase bioavailability.

More specifically, the present invention relates to a cyclosporin preparation, which comprises a composition containing

1) cyclosporin as an active ingredient;
2) polyethylene glycol or propylene carbonate or their mixture;
3) a mixture of an esterified compound of fatty acid and primary alcohol, and fatty acid monoglyceride, and optionally a medium chain fatty acid triglyceride, as an oil component and
4) a surfactant having an HLB (Hydrophilic Lipophilic Balance) value of 8 to 17,

e.g. in a gelatin shell containing polyethylene glycol and propylene glycol as a plasticizer. In another aspect the present invention provides a cyclosporin preparation, which comprises a composition containing

1) cyclosporin as an active ingredient; and
2) propylene carbonate.

Such a composition, which is also a composition of the invention, may optionally additionally comprise any other component as described herein, if desired in the amounts described herein.

Cyclosporin, which is used as the pharmaceutically active ingredient in the composition according to the present invention, is a cyclic peptide compound having useful immuno-suppressive activity and anti-inflammatory activity as described above. Although cyclosporin A, B, C, D, G and the like can be used as the cyclosporin component in the present invention. Cyclosporin A is mostly preferred since its clinical effectiveness and pharmacological properties are well established in the art.

As the second component in the composition according to the present invention, and which may act as a co-surfactant polyethylene glycol which has a high boiling point, is non-volatile, does not permeate the gelatin shell of the soft

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capsule, and has a high solubility for cyclosporin, may be used as the hydrophilic substance. In the composition according to the present invention, although any polyethylene glycol which can be liquified can be used, polyethylene glycol (PEG) having molecular weight of 200 to 600, particularly PEG 200, can be preferably used.

Alternatively, propylene carbonate (b.p. about 242°C) can also be used as the non-hydrophilic component. In the present invention, the mixture of non-hydrophilic substance and hydrophilic substance as defined above can also be used. When the mixture of polyethylene glycol and propylene carbonate is used as the component in the present invention, they can be generally combined in the ratio of 1:0.1-5, preferably 1:0.1-3, most preferably 1:0.2-2, on the basis of weight.

In the present invention, the use of polyethylene glycol and propylene carbonate provides certain advantages. That is, the stability of the cyclosporin-containing composition during storage is improved and therefore the contents of the components contained therein are substantially uniformly maintained. Furthermore, the use of propylene carbonate can even increase the solubility of the active ingredient cyclosporin and inhibit the inflow of water from the gelatin capsule shell into the composition to provide a more stable composition.

In the composition of the present invention, the second component is used preferably in the ratio of 0.1 to 10 parts by weight, more preferably 0.5 to 8 parts by weight, and most preferably 1 to 5 parts by weight, per 1 part by weight of cyclosporin.

The third component used in the emulsion pre-concentrate according to the present invention is an oil component. As the oil component in the present invention, the mixture of esterified compounds of fatty acid and primary alcohol, medium chain fatty acid triglycerides (when present) and fatty acid monoglycerides can be used. The esterified compound of fatty acid and primary alcohol which can be used in the present invention may include an esterified compound of fatty acid having 8 to 20 carbon atoms and primary alcohol having 2 to 3 carbon atoms, for example, isopropyl myristate, isopropyl palmitate, ethyl linoleate, ethyl oleate, etc., with an esterified compound of linoleic acid and

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ethanol being particularly preferably. In addition, as the medium chain fatty acid triglyceride (when present) a triglyceride of saturated fatty acid having 8 to 10 carbon atoms can be used with caprylic /capric acid triglyceride as a vegetable oil triglyceride of saturated fatty acid being most preferably used. The fatty acid monoglyceride which can also be used as the oil component in the present invention includes a monoglyceride of fatty acid having 18 to 20 carbon atoms, particularly monoglyceride of oleic acid.

In a microemulsion pre-concentrate according to the present invention, the oil component may be used in the ratio of 1 to 10 parts by weight, preferably 2 to 6 parts by weight, per 1 part by weight of cyclosporin.

Preferably fatty acid monoglyceride and fatty acid ester are present as oil component, e.g. in the ratio 1:1 to 1:2, e.g. 1:1 to 1:1.2.

Optionally caprylic/capric acid triglyceride is also present e.g. in a ratio to ethyl linoleate of from 1:0.1 to 0.2.

In the oil mixture used as the oil component according to the present invention, the mixing ratio of fatty acid monoglyceride: an esterified compound of fatty acid and primary alcohol: medium chain fatty acid triglyceride (when present) may be generally in the range of 1:0.1-5; 0.1-10 preferably in the range of 1:0.1-3.0:0.1-3.0, on the basis of weight.

The fourth component used in the composition according to the present invention is a surfactant. The suitable surfactants for use in the present invention include any of pharmaceutically acceptable surfactants having an HLB (Hydrophilic Lipophilic Balance) value of 8 to 17, which are capable of stably emulsifying the lipophilic portion of the composition comprising the cyclosporin-containing oil component and the hydrophilic portion comprising the co-surfactant in water to form a stable microemulsion. Examples of the preferred surfactant according to the present invention include polyoxyethylene products of hydrogenated vegetable oils, polyoxyethylene-sorbitan-fatty acid esters, and the like, for example, NIKKOL HCO-50, NIKKOL HCO_40, NIKKOL HCO-60, TWEEN 20, TWEEN 21, TWEEN 40, TWEEN 60, TWEEN 80, TWEEN 81, etc. Particularly, a polyoxyethylene (50) hydrogenated castor oil which is commercialised under the trade mark NIKKOL HCO-50

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(NIKKO Chemical Co., Ltd.) and a polyoxyethlyene (20) sorbitan monolaurate which is commercialised under the trade mark TWEEN 20 (ICI Chemicals), having an acid value below 1, a saponification value of about 48-56, a hydroxyl value of about 45-55 and pH value (5%) of 4.5-7.0, can be preferably used.

The surfactant can include any one of the above-mentioned surfactants alone or, preferably, in a combination of two or more surfactants selected from the above surfactants. In the composition according to the present invention, the surfactants can be used in the ratio of 1 to 10 parts by weight, preferably in the ratio of 2 to 8 parts by weight, per 1 part by weight of cyclosporin.

In addition, when the mixture of two surfactants, i.e. polyoxyethylene (50) hydrogenated castor oil and polyoxyethylene (20) sorbitan monolaurate is used in the composition of the present invention, the constitutional ratio of polyoxyethylene (50) hydrogenated castor oil; polyoxyethylene (20) sorbitan monolaurate is preferably in the range of 1:0.1-5, more preferably in the range of 1:0.5-4, on the basis of weight.

In the composition according to the present invention, the four components are present preferably in the ratio of cyclosporin: second component; oil component; surfactant = 1 : 0.1- 10 : 1-10 : 1-10, and more preferably in the ratio of cyclosporin: second component: oil component : surfactant = 1 : 0.5-8: 2-6 : 2-8, by weight.

In addition to this composition, the composition illustrated in the following examples can be mentioned as further preferred compositions according to the present invention.

For oral administration, the composition of the present invention containing the above-mentioned components can be formulated into the form of a soft capsule.

Since the soft capsule preparation according to the present invention does not use ethanol as the low-boiling volatile solvent, it is pharmaceutically stable and can establish the desired improvements including improvement of bioavailability.

However, it may be difficult to reproductively prepare as a conventional soft capsule shell by means of a conventional method for preparation of soft capsules. When the soft capsule is formulated with the conventional capsule

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shell containing glycerine as plasticizer, the soft capsule thus prepared may have some disadvantages in that the emulsified state of the emulsion pre-concentrate may be changed due to the inflow of glycerine into the emulsion and therefore, the solubility of cyclosporin is significantly lowered which may result in the precipitation of cyclosporin from the emulsion.

Accordingly, in another aspect the present invention it is found that when the capsule shell is formulated by using a mixture of polyethylene glycol and propylene glycol, not glycerine, as a plasticizer, the soft capsule preparation which is stable for a long period can be obtained. Although any polyethylene glycol which can be liquified may be used as a plasticizer, it is preferable to use polyethylene glycol having molecular weight of 200 to 600.

Particularly, polyethylene glycol 200 is preferably used. In the soft capsule shell according to the present invention, the mixture of polyethyene glycol and propylene glycol is preferably used in the ratio of 0.1 to 0.5 parts by weight, more preferably 0.1 to 0.4 parts by weight and most preferably 0.2 to 0.3 parts by weight, with respect to one part by weight of gelatin used for preparing the capsule shell. In the mixture of polyethylene glycol and propylene glycol as the plasticizer, propylene glycol is combined preferably in the ratio of 1 to 10 parts by weight, more preferably 3 to 8 parts by weight and most preferably 3 to 6 parts by weight, with respect to one part by weight of polyethylene glycol.

In order to increase the removability of the soft capsule shell band from the cooling drum, the process for preparing the gelatin capsule shell band according to the present invention adopts the air-cooling method, instead of the water-cooling method. According to this air-cooling method, since the capsule shell band is not overheated and can be readily removed from the cooling drum while maintaining the optimum temperature of about 21°C, the extent of seal in the encapsulation process is high to ensure a high productivity and therefore, the process can be efficiently conducted.

In preparing the soft capsule according to the present invention, a suitable air volume flow for the cooling drum to cool the capsule shell is preferably 5 to 15m^3/min., most preferably about 10m^3/min.

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In formulating the composition according to the present invention into soft capsules, the capsule preparation can further contain, if necessary, pharmaceutically acceptable additives which are conventionally utilized in the preparation of soft capsules. Such additives include, for example, lecithin, viscosity regulator, perfume (e.g. peppermint oil, etc.), anti-oxidant (e.g. tocopherol, Vitamin E etc.), preservative (e.g. parabene, etc.), coloring agent, amino acids, etc.

The soft capsule preparation according to the present invention can be prepared by uniformly mixing the co-surfactant, the oil component and the surfactant, dissolving cyclosporin therein while stirring and gently warming to the temperature of approximately 60°C, and then formulating the resulting concentrate, with or without the above-mentioned pharmaceutically acceptable additives conventionally utilized in preparation of soft capsules, with the gelatin shell containing polyethylene glycol and propylene glycol as the plasticizer in a machine for preparing soft capsules by means of the air-cooled method into the desired suitable cyclosporin soft capsule.

The compositions and preparations of the present invention are useful for the same indications and may be administered in the same way and dosage range as known cyclosporin compositions, if necessary adjusting the dose on the basis of standard bioavailability trials in animals, e.g. dogs, or humans, e.g. as described hereinafter.

Insofar as details of the compositions of any excipients or components are not specifically described herein, these are described in the literature, e.g. H.P. Fiedler, Lexikon der Hilfsstoffe, Edito Cantor Verlag, Aulendorf, Germany, 4th Edition 1996, Handbook of Pharmaceutical Excipients, American Pharmaceutical Association, Washington, and The Pharmaceutical Society, London, 2nd Edition, 1994 and Korean Patent Application 94-29208 filed 9.11.94.

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.

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EXAMPLE 1:

Component	Content (mg/Cap.)
Cyclosporin	25
polyethylene glycol 200	45
propylene carbonate	25
polyoxyethylene (50) hydrogenated castor oil	35
polyoxyethylene (20) sorbitan monolaurate	85
ethyl linoleate	40
caprylic/capric acid triglyceride	5
oleic acid monoglyceride	35
total	295 mg

EXAMPLE 2:

Component	Content /mg/Cap.)
Cyclosporin	25
polyethylene glycol 200	70
polyoxyethylene (50) hydrogenated castor oil	35
polyoxyethylene (20) sorbitan monolaurate	85
ethyl linoleate	40
caprylic /capric acid triglyceride	5
oleic acid monoglyceride	35
total	295 mg

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EXAMPLE 3:

Component	Content (mg/Cap.)
Cyclosporin	25
polyethylene glycol 200	100
propylene carbonate	50
polyoxyethylene (50) hydrogenated castor oil	35
polyoxyethylene (20) sorbitan monolaurate	85
ethyl linoleate	40
caprylic /capric acid triglyceride	5
oleic acid monoglyceride	35
total	375 mg

EXAMPLE 4:

Component	Content (mg/Cap.)
Cyclosporin	25
polyethylene glycol 200	45
propylene carbonate	25
polyoxyethylene (50) hydrogenated castor oil	50
polyoxyethylene (20) sorbitan monolaurate	100
ethyl linoleate	40
caprylic /capric acid triglyceride	5
oleic acid monoglyceride	35
total	325 mg

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EXAMPLE 5:

Component	Content (mg/Cap.)
Cyclosporin	25
polyethylene glycol 200	45
propylene carbonate	25
polyoxyethylene (50) hydrogenated castor oil	35
polyoxyethylene (20) sorbitan monolaurate	85
ethyl linoleate	80
caprylic /capric acid triglyceride	10
oleic acid monoglyceride	70
total	375 mg

EXAMPLE 6:

The soft capsule preparation was prepared from the composition of Example 1 using the following composition for capsule shell and then the change in the property and condition of the content due to the inflow of glycerine was visually observed.

6.1 (control group)

Component	Weight ratio
gelatin	20
purified water	16
glycerine	9

6.2 (test group)

Component	Weight ratio
gelatin	20
purified water	16
propylene glycol	4
polyethylene glycol 200	1

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The results as observed are described in the following Table 1.

Table 1: Stability of the content of the capsule preparation according to the capsule shell

Composition of Capsule	Just after formulation	After 1 day	After 2 days	After 5 days	After 10 days	After 30 days
Control group	0	+	+	++	+++	+++
Test group	0	0	0	0	0	0

Note: 0 = the content is stable
\+ = poor emulsification
++ = slight precipitation
+++ = precipitation

As can be seen from the result described in table 1, the capsule preparation prepared using the composition of 6.1 control group containing glycerine as the plasticizer causes some problems including the formation of precipitation due to the inflow of glycerine, whereas the capsule preparation prepared using the composition of 6.2 test group containing polyethylene glycol and propylene glycol as the plasticizer maintains the stable condition.

EXAMPLE 7:

The soft capsule preparation having the composition of Example 1 was prepared using the composition of the capsule shell of 6.2 test group used in the above Example 6 by means of the water-cooling method (water temperature about 12°C) and the air-cooling method (air volume flow about 10 m^3/min), respectively.

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In each case, the removability of the capsule shell band from the cooling drum was observed and compared. The result as observed is described in the following Table 2.

Table 2: Removability of the gelatin shell band from the cooling drum depending on the cooling method

(Unit: degree of angle)

Shell Composition	Water-cooling Method	Air-cooling Method
Example 6.2	> 100 degree (poor removability)	< 50 degree (good removability)

As can be seen from the result described in the Table 2 above, the soft capsule preparation prepared by the air-cooling method according to the present invention shows a far better removability from the cooling drum in comparisoin with that prepared by the water-cooling method. Specifically, it is generally considered that if the degree of angle for removing the gelatin shell band from the cooling drum is about 70 or more, the removability is poor, and if the degree of angle for removing the shell band is below about 70, the removability is good. The soft capsule preparation prepared by the water-cooling method is not satisfactorily removed from the cooling drum even when the preparation is removed at the angle of 100 degrees or more.

Contrary to this, the soft capsule preparation prepared by the air-cooling ethod according to the present invention can be easily removed from the cooling drum at the angle of 50 degree and below and therefore, can provide a good sealing strength and productivity.

EXAMPLE 8:

The bioavailability of the preparation prepared by encapsulating the composition of Example 1 with the gelatin shell having the composition of Example 6.2 as the test preparation was compared with the bioavailability of the commercial product containing ethanol, SANDIMMUN Capsule, as the control preparation

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to estimate the influence of the cyclosporin preparation according to the present invention on the bioavailability of cyclosporin and its difference between respective subjects.

In this experiment, both of the test preparation and the control preparation were administered in an amount of 300 mg as cyclosporin per kg of rabbit.

Rabbits were uniformly fed with the conventional rabbit solid feed composition for 4 days or more under the same condition in wire cages. When the oral preparation were administered, rabbits were fasted for 48 hours in a restraint cage made of steel, during which rabbits were allowed to freely take water.

Levin's tube having a diameter of 5 mm was interposed by the depth of 30 cm through the esophagus after the surface of the Levin's tube was coated with vaseline in order to reduce friction. Each of the test preparations and the control preparation was emulsified with 50 ml of water and then introduced into a syringe which is attached to the Levin's tube. Ear veins of rabbit were dilated using xylene and then blood was taken from each rabbit's ear vein before the test and after 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 24 hours by means of heparin-treated disposable syringe. To 1 ml of blood thus obtained were added 0.5 ml of aqueous saturated sodium chloride solution and 2 ml of ether, and then the mixture was shaken for 5 minutes and centrifuged with 5000 rpm for 10 minutes to separate the supernatant (ether layer). 1 ml of the supernatant was collected and then developed in an activated silica sep-pak^{R} (Waters). The developed sep-pak was washed with 5 ml of n-hexane and eluated with 2 ml of methanol. The eluate was evaporated to dryness in nitrogen gas under reduced pressure. The residue was analysed by means of HPLC (High Performance Liquid Chromatography) [HPLC condition: column μ-Bondapak^{R} C_{18} (Waters), mobile phase CH_3CN: MeOH; H_2O - 55: 15 : 30, detection 210 nm, flow rate 1.0 ml /min., column temperature 70°C, sensitivity 0.01 Aufs. injection volume 100 μl].

The results obtained from the test preparation and the control preparation are illustrated in the following Table 3:

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Table 3: Bioavailability of the test preparation of the present invention and the commercial product (SANDIMMUN^R)

Parameter	Control Prep. (A)		Test Prep. (B)		P (B/A)
	M ± S.D. (n=6)	CV % (S.D./M)	M ± S.D. (n=6)	CV % (S.D./M)	
AUC (μg.hr/ml)	13.5±10.0	74.0 %	57.0±17.0	29.8 %	4.1
C_{max} (μg.hr/ml)	0.8±0.3	37.5 %	6.0±1.5	25.0 %	7.5

Note: AUC = Area under the blood concentration curve

C_{max} = Maximum blood concentration of cyclosporin

M± S.D.= Mean value ± Standard deviation

CV = Ratio of standard deviation to mean value

P(B/A) = Ratio of mean value of the test preparation to mean value of the control preparation

As can be seen from the above table, the test preparation shows the increased AUC and C_{max} values which are about 4 times or more and about 7 times or more, respectively, as high as those of the control preparation. Accordingly, it can be identified that the bioavailability of the test preparation is significantly increased in comparison with that of the control preparation. In addition, the test preparation of the present invention exhibits an effect of decreasing the difference between respective test subjects (CV %) by about 2 times or more in AUC value and by about 1.5 times in C_{max} value, in comparison with the control preparation.

Accordingly, it could be determined that when the soft capsule preparation according to the present invention is administered per oral, it shows the increased bioavailability of cyclosporin about 4 times as high as that of the prior commercial product containing ethanol, SANDIMMUN^R Capsule and also a decrease of the difference between cyclosporin bioavailabilities in respective subjects, and at the same time, remains stable without any change during the long term storage. Thus, it is apparent that the soft capsule preparation

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according to the present invention provides a significant improvement in the field of preparation of cyclosporin soft capsules.

EXAMPLE 9:

Soft gels are made up containing:

	I	II
Cyclosporin A	25 mg	100 mg
Polyethylene glycol 200	45 mg	180 mg
Propylene carbonate	25 mg	100 mg
Polyoxyethylene 50-hydrogenated castor oil	40 mg	160 mg
Polysorbate 20	85 mg	340 mg
Ethyl linoleate	40 mg	160 mg
Glyceryl mono-oleate	40 mg	160 mg
Vitamin E	1 mg	4 mg
Total	301 mg	1204 mg

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WHAT IS CLAIMED IS:

1. A cyclosporin-containing preparation which comprises a composition containing:
(1) cyclosporin as an active ingredient,
(2) polyethylene glycol or propylene carbonate or their mixture,
(3) a mixture of an esterified compound of fatty acid and primary alcohol, and fatty acid monoglyceride as an oil component, and
(4) a surfactant having HLB (Hydrophilic-lipophilic balance) value of 8 to 17.

2. The cyclosporin-containing preparation of claim 1 wherein said cyclosporin is cyclosporin A and is in a gelatin shell containing polyethylene glycol and propylene glycol as a plasticizer.

3. The cyclosporin-containing preparation of claim 1 or 2 wherein said polyethylene glycol is a polyethylene glycol having molecular weight of 200 to 600.

4. The cyclosporin-containing preparation of claim 1, 2 or 3 wherein said polyethylene glycol is polyethylene glycol having molecular weight of 200.

5. The cyclosporin-containing preparation of 1, 2, 3 or 4 wherein the component (2) is a mixture of polyethylene glycol and propylene carbonate which are combined in the ratio of 1:0.1-5.

6. The cyclosporin-containing preparation of claim 5 wherein the component (2) is a mixture of polyethylene glycol and propylene carbonate which are combined in the ratio of 1:0.2-2.

7. The cyclosporin-containing preparation of any preceding claim wherein said esterified compound of fatty acid and primary alcohol in the oil mixture is ethyl linoleate.

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8. The cyclosporin-containing composition of any preceding claim comprising further a medium chain fatty acid triglyceride in the oil mixture which is optionally caprylic/capric acid triglyceride.

9. The cyclosporin-containing preparation of any preceding claim wherein said fatty acid monoglyceride is a monoglyceride of oleic acid.

10. The cyclosporin-containing preparation of any preceding claim wherein the mixing ratio of fatty acid monoglyceride, and the esterified compound of fatty acid and primary alcohol in the oil mixture is 1: 0.1-5 on the basis of weight.

11. The cyclosporin-containing preparation of any preceding claim wherein said surfactant is a polyoxyethylene product of hydrogenated vegetable oil or a polyoxethylene-sorbitan-fatty acid ester.

12. The cyclosporin-containing soft capsule preparation of claim 11 wherein said surfactant is a mixed surfactant consisting of a polyoxyethylene(50) hydrogenated castor oil : a polyoxyethylene(20) sorbitan monolaurate in the mixing ratio of 1:0.1-5.

13. The cyclosporin-containing soft capsule preparation of any preceding claim wherein said cyclosporin, said component (2), said oil component and said surfactant are present in the ratio of 1:0.1-10 : 1-10 : 1-10 on the basis of weight.

14. The cyclosporin-containing preparation of claim 13 wherein said cyclosporin, said component (2), said oil component and said surfactant are present in the ratio of 1:0.5-8 : 2-6 : 2-8 on the basis of weight.

15. The cyclosporin-containing preparation of any preceding claim wherein the mixture of polyethylene glycol and propylene glycol as the plasticizer is used in

the ratio of 0.1 to 0.5 part by weight with respect to one part by weight of gelatin.

16. The cyclosporin-containing preparation of any preceding claim wherein in the plasticizer propylene glycol is combined in the ratio of 1-10 part by weight with respect to one part by weight of polyethylene glycol.

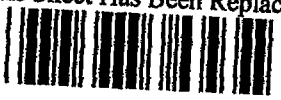
17. A process for preparing the cyclosporin-containing preparation according to any one of claims 1 to 16 which comprises uniformly mixing the component (2), the oil component and the surfactant, dissolving cyclosporin therein while stirring and gently warming to the temperature of approximately 60°C, and if desired encapusulating the resulting concentrate into a gelatin shell containing polyethylene glycol and propylene glycol as the plasticizer in a machine for preparing soft capsules and then cooling the produced soft capsule in the cooling drum by means of an air-cooling method.

18. The process of claim 17 wherein the cooling according to the air-cooling method is carried out at the air volume flow of 5 to 15m^3/min.

19. A cyclosporin preparation, which comprises a composition containing
    1) cyclosporin as an active ingredient; and
    2) propylene carbonate.

20. A composition according to claim 19 containing one or more further components as defined in any one of claims 1 to 16.

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WHAT IS CLAIMED IS:

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1. A soft gelatin capsule preparation containing a pharmaceutical composition comprising

(i) cyclosporin as an active agent,

(ii) propylene carbonate,

(iii) a mixture of a medium chain fatty acid triglyceride and a fatty acid monoglyceride as an oil component, and

(iv) a surfactant having an HLB value from 8 to 17 which comprises a polyoxyethylene hydrogenated vegetable oil, wherein

the ratio of cyclosporin : component (ii) : oil component : surfactant is 1:0.5-8 : 2-6 : 2-8, on the basis of weight.

2. A preparation according to claim 1 wherein said cyclosporin is cyclosporin A.

3. A preparation according to any preceding claim wherein the medium chain fatty acid triglyceride comprises caprylic/capric acid triglyceride.

4. A preparation according to any preceding claim wherein the fatty acid monoglyceride is a monoglyceride of oleic acid.

5. A preparation according to any preceding claim wherein an esterified compound of fatty acid and primary alcohol is additionally present.

6. A preparation according to claim 5 wherein the esterified compound of fatty acid and primary alcohol is ethyl linoleate.

7. A preparation according to claim 5 or 6 wherein the ratio of fatty acid monoglyceride : esterified compound of fatty acid and primary alcohol : medium chain fatty acid triglyceride is 1:0.1-3.0 : 0.1-3.0, on the basis of weight.

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8. A preparation according to any preceding claim wherein a mixture of a polyoxyethylene hydrogenated vegetable oil and polyoxethylene sorbitan fatty acid ester is present.

9. A preparation according to claim 8 wherein said surfactant is a mixed surfactant consisting of polyoxyethylene(50) hydrogenated castor oil : polyoxyethylene(20) sorbitan monolaurate in the ratio of 1 : 0.5-4, on the basis of weight.

10. A preparation according to any preceding claim which is ethanol-free.

11. A preparation according to any preceding claim wherein the soft gelatin capsule contains polyethylene glycol and propylene glycol as a plasticizer.

12. A preparation according to claim 11 wherein the ratio of polyethylene glycol and propylene glycol : gelatin is 0.2-0.3 : 1, on the basis of weight.

13. A preparation according to claim 11 or 12 wherein the ratio of the plasticizer polyethylene glycol : propylene glycol is 1 : 3-6, on the basis of weight.

14. A process for preparing the cyclosporin-containing preparation according to any one of claims 1 to 13 which comprises uniformly mixing the component (ii), the oil component and the surfactant, dissolving cyclosporin therein while stirring and gently warming to the temperature of approximately 60°C, and if desired encapsulating the resulting concentrate into a gelatin shell containing polyethylene glycol and propylene glycol as the plasticizer in a machine for preparing soft capsules and then cooling the produced soft capsule in the cooling drum by means of an air-cooling method.

15. The process of claim 14 wherein the cooling according to the air-cooling method is carried out at the air volume flow of 5 to 15m^3/min.

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REPLACEMENT SHEETS SG
☑ Description : paged 1.. to page 1 18..
☑ Claim(s) : paged 19. to page 1 20.....
☐ Drawing(s) : paged ..... to paged .....
☑ Abstract : paged 21 to paged .....
06 APR 1998
DATE OF RECEIPT .....

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CYCLOSPORIN-CONTAINING SOFT CAPSULE PREPARATIONS

The present invention relates to an, e.g. soft capsule preparation containing cyclosporin as an active ingredient. More specifically, the present invention relates to a soft capsule preparation containing a stable cyclosporin composition in a gelatin capsule shell containing a certain plasticizer and a process for preparing thereof.

Cyclosporin is a specific macromolecular (molecular weight 1202.64) cyclic peptide compound consisting of 11 amino acids, which has broad spectrum of useful pharmacological activities, particularly immuno-suppressive activity and anti-inflammatory activity. Therefore, cyclosporin has been used for suppression of inherent immunological responses of the living body, which are caused by tissue and organ transplantation, for example, transplantation of the heart, lung, liver, kidney, pancreas, bone marrow, skin and cornea, and especially the transplantation of foreign tissues and organs. In addition, cyclosporin is useful for the suppression of hematological disorders such as anemia, various autoimmune diseases such as systemic lupus erythematosus, idiopathic malabsorption syndrome, etc., and inflammatory diseases such as arthritis, rheumatoid disorders, etc. Cyclosporin is useful in treatment of protozoal diseases such as malaria, schistosomiasis, etc. , and furthermore, recently it is also used in chemotherapy.

Cyclosporin is highly lipophilic and hydrophobic. Therefore, cyclosporin is sparingly soluble in water, and as well dissolved in an organic solvent such as methanol, ethanol, acetone, ether, chloroform and the like. Due to low water-solubility of cyclosporin having above-mentioned properties, when cyclosporin is administered orally, its bioavailability is extremely low and may be greatly influenced by the conditions of each individual patient. Accordingly, it is very difficult to retain an effective therapeutic concentration. Moreover, cyclosporin may show considerable side effects such as nephrotoxicity. Thus, cyclosporin is very difficult to formulate into a preparation for oral administration due to its low water solubility. Accordingly, numerous studies have been extensively

REPLACEMENT SHEE
06 APR 1999

conducted to discover a preparation suitable for the effective oral administration of cyclosporin, which can provide a suitable uniform dosage and appropriate bioavailability.

In the prior art, the preparations suitable for oral administration of sparingly water-soluble cyclosporin have been usually formulated in the form of a emulsion pre-concentrate.

One typical method using this combination is taught in U.S. Patent No. 4,388,307 which issued on June 14, 1983. This patent discloses a liquid formulation of cyclosporin using ethanol. According to the method disclosed in this US Patent Specification, cyclosporin is combined with a carrier consisting of ethanol as a co-surfactant; olive oil as a vegetable oil, and a transesterification product of a natural vegetable oil triglyceride and a polyalkylene polyol as a surfactant to form the liquid formulation.

However, the resulting liquid formulation is administered as an aqueous dilution which makes it very difficult to adapt the subject to its administration and to provide a uniform dosage for oral administration.

In order to mitigate the inconvenience of diluting the cyclosporin liquid composition in water prior to oral administration, a liquid composition in the form of an emulsion pre-concentrate has been formulated into a soft capsule preparation, which is now commercially available as Sandimmune (registered trademark). In this case the cyclosporin soft capsule contains ethanol due to the solubility requirements of cyclosporin. However, since ethanol may permeate the gelatin shell of the capsule as it is volatile even at normal temperature, to prevent the volatilization of ethanol from the soft capsule preparations during storage and distribution, the soft capsule preparations may be wrapped in a special packing material, such as an aluminium-aluminum blister package.

Recently it has been possible to develop a cyclosporin preparation which has a stability during the storage period and further provides substantially no change in biological availability and its difference between individual subjects, so that the biological effect of cyclosporin can be uniformly maintained. One of the preparations developed for this purpose is disclosed in Korean Laid-open Patent Publication No. 93-113. This preparation is commercialized under the registered trademark Sandimmun Neoral. However, since this preparation also uses

REPLACEMENT SHEET
0 3 APR 1998

ethanol, it may have some disadvantages as in the prior ethanol-containing preparations, in storage stability, and changes in the ethanol content.

Accordingly, the present inventors have studied numerous combinations of various surfactants, oil components, co-surfactants etc. to find a cyclosporin composition which is stable, and provides higher bioavailability and lower difference in blood levels between individual subjects than those of the prior cyclosporin preparations in view of their pharmacokinetic properties. As a result, we have identified that a certain cyclosporin composition consisting of the components as defined below can satisfy the above-mentioned requirements, and then completed the present invention.

Therefore, it is an aspect of the present invention to provide a composition suitable for formulation into soft capsules, which comprises cyclosporin as an active ingredient; a hydrophilic substance polyethylene glycol or a non-hydrophilic substance propylene carbonate or their mixture; an oil component as defined below, and a surfactant.

It is a further aspect of the present invention to provide a soft capsule preparation comprising a composition which contains cyclosporin as an active ingredient; a hydrophilic substance polyethylene glycol or a non-hydrophilic substance propylene carbonate or their mixture; a mixture of an esterified compound of fatty acid and primary alcohol, medium chain fatty acid triglyceride (if desired) and fatty acid monoglyceride as an oil component; and a surfactant having an HLB (Hydrophilic Lipophilic Balance) value of 8 to 17.

Further it is another aspect of the present invention to provide a process for preparing the soft gelatin capsule preparation as defined above.

Even though the present invention is described herein particularly with respect to soft gelatine capsules, it is to be appreciated that the invention covers the composition itself which may be used as such e.g. as a drink solution, e.g. as Sandimmun Neoral, or be in other unit dosage forms.

In one aspect, the present invention relates to a cyclosporin-containing capsule which has a high storage stability such that there is little variation of the composition over time, and has an increased bioavailability, and which contains a composition comprising cyclosporin as an active ingredient; a hydrophilic substance polyethylene glycol or a non-hydrophilic substance propylene

REPLACEMENT SHEET
06 APR 1998

carbonate or their mixture as a second component; an oil component as defined below; and a surfactant.

To formulate such cyclosporin-containing composition into the soft capsule preparation, a gelatin shell must be used. However, when the soft capsule is formulated with the general capsule shell containing glycerine as plasticizer, the soft capsule preparation has some disadvantages in that the emulsified state of the emulsion pre-concentrate may be changed due to the inflow of glycerine into the emulsion and, therefore, the solubility of cyclosporin is significantly lower to result in the precipitation of cyclosporin from the emulsion.

Accordingly, in the present invention preferably a gelatin shell using a mixture of propylene glycol and polyethylene glycol, not glycerine, as a plasticizer is selected for the soft capsule shell, which can solve the problem related with inflow of glycerine.

However, when the capsule shell band containing propylene glycol and polyethylene glycol according to the present invention is prepared by means of a water-cooling method which is conventionally used for a cooling drum, it is not easily removed from the drum. Such removability of the capsule shell band from the cooling drum may be improved by over-cooling the cooling drum by continuously circulating a cooling water to reduce temperature of the band to about 17°C. However, the capsule shell band which is cooled to lower temperature may provide a low extent of seal during the encapsulation process and may cause lowering of productivity.

Therefore, the process for preparing the gelatin shell band not containing glycerine plasticizer according to the present invention adopts an air-cooling method, instead of the prior water-cooling method, in which the capsule shell band can be cooled down to the optimum temperature by providing an air flow from a fan and therefore, can be readily removed from the cooling drum and further, it is maintained at the optimum temperature of about 21°C to increase the extent of seal in the encapsulation process and ensure a high productivity.

As mentioned above, the present products can be produced by using the glycerine-free gelatin capsule shell and applying the air-cooling method to the composition which does not contain ethanol as a low boiling volatile solvent and

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06 APR 1998

therefore, has a high storage stability such that there is little variation of the composition over time, and has an increase bioavailability.

More specifically, the present invention relates to a cyclosporin preparation, which comprises a composition containing

1) cyclosporin as an active ingredient;

2) polyethylene glycol or propylene carbonate or their mixture;

3) a mixture of an esterified compound of fatty acid and primary alcohol, and fatty acid monoglyceride, and optionally a medium chain fatty acid triglyceride, as an oil component and

4) a surfactant having an HLB (Hydrophilic Lipophilic Balance) value of 8 to 17,

e.g. in a gelatin shell containing polyethylene glycol and propylene glycol as a plasticizer. In another aspect the present invention provides a cyclosporin preparation, which comprises a composition containing

1) cyclosporin as an active ingredient; and

2) propylene carbonate.

Such a composition, which is also a composition of the invention, may optionally additionally comprise any other component as described herein, if desired in the amounts described herein.

Cyclosporin, which is used as the pharmaceutically active ingredient in the composition according to the present invention, is a cyclic peptide compound having useful immuno-suppressive activity and anti-inflammatory activity as described above. Although cyclosporin A, B, C, D, G and the like can be used as the cyclosporin component in the present invention. Cyclosporin A is mostly preferred since its clinical effectiveness and pharmacological properties are well established in the art.

As the second component in the composition according to the present invention, and which may act as a co-surfactant polyethylene glycol which has a high boiling point, is non-volatile, does not permeate the gelatin shell of the soft capsule, and has a high solubility for cyclosporin, may be used as the hydrophilic substance. In the composition according to the present invention, although any polyethylene glycol which can be liquified can be used, polyethylene glycol

REPLACEMENT SHEET
06 APR 1998

(PEG) having molecular weight of 200 to 600, particularly PEG 200, can be preferably used.

Alternatively, propylene carbonate (b.p. about 242°C) can also be used as the non-hydrophilic component. In the present invention, the mixture of non-hydrophilic substance and hydrophilic substance as defined above can also be used. When the mixture of polyethylene glycol and propylene carbonate is used as the component in the present invention, they can be generally combined in the ratio of 1:0.1-5, preferably 1:0.1-3, most preferably 1:0.2-2, on the basis of weight.

In the present invention, the use of polyethylene glycol and propylene carbonate provides certain advantages. That is, the stability of the cyclosporin-containing composition during storage is improved and therefore the contents of the components contained therein are substantially uniformly maintained. Furthermore, the use of propylene carbonate can even increase the solubility of the active ingredient cyclosporin and inhibit the inflow of water from the gelatin capsule shell into the composition to provide a more stable composition.

In the composition of the present invention, the second component is used preferably in the ratio of 0.1 to 10 parts by weight, more preferably 0.5 to 8 parts by weight, and most preferably 1 to 5 parts by weight, per 1 part by weight of cyclosporin.

The third component used in the emulsion pre-concentrate according to the present invention is an oil component. As the oil component in the present invention, the mixture of esterified compounds of fatty acid and primary alcohol, medium chain fatty acid triglycerides (when present) and fatty acid monoglycerides can be used. The esterified compound of fatty acid and primary alcohol which can be used in the present invention may include an esterified compound of fatty acid having 8 to 20 carbon atoms and primary alcohol having 2 to 3 carbon atoms, for example, isopropyl myristate, isopropyl palmitate, ethyl linoleate, ethyl oleate, etc., with an esterified compound of linoleic acid and ethanol being particularly preferably. In addition, as the medium chain fatty acid triglyceride (when present) a triglyceride of saturated fatty acid having 8 to 10 carbon atoms can be used with caprylic /capric acid triglyceride as a vegetable oil triglyceride of saturated fatty acid being most preferably used. The fatty acid

REPLACEMENT SHEET
06 APR 1998

monoglyceride which can also be used as the oil component in the present invention includes a monoglyceride of fatty acid having 18 to 20 carbon atoms, particularly monoglyceride of oleic acid.

In a microemulsion pre-concentrate according to the present invention, the oil component may be used in the ratio of 1 to 10 parts by weight, preferably 2 to 6 parts by weight, per 1 part by weight of cyclosporin.

Preferably fatty acid monoglyceride and fatty acid ester are present as oil component, e.g. in the ratio 1:1 to 1:2, e.g. 1:1 to 1:1.2.

Optionally caprylic/capric acid triglyceride is also present e.g. in a ratio to ethyl linoleate of from 1:0.1 to 0.2.

In the oil mixture used as the oil component according to the present invention, the mixing ratio of fatty acid monoglyceride: an esterified compound of fatty acid and primary alcohol: medium chain fatty acid triglyceride (when present) may be generally in the range of 1:0.1-5; 0.1-10 preferably in the range of 1:0.1-3.0:0.1-3.0, on the basis of weight.

The fourth component used in the composition according to the present invention is a surfactant. The suitable surfactants for use in the present invention include any of pharmaceutically acceptable surfactants having an HLB (Hydrophilic Lipophilic Balance) value of 8 to 17, which are capable of stably emulsifying the lipophilic portion of the composition comprising the cyclosporin-containing oil component and the hydrophilic portion comprising the co-surfactant in water to form a stable microemulsion. Examples of the preferred surfactant according to the present invention include polyoxyethylene products of hydrogenated vegetable oils, polyoxyethylene-sorbitan-fatty acid esters, and the like, for example, NIKKOL HCO-50, NIKKOL HCO_40, NIKKOL HCO-60, TWEEN 20, TWEEN 21, TWEEN 40, TWEEN 60, TWEEN 80, TWEEN 81, etc. Particularly, a polyoxyethylene (50) hydrogenated castor oil which is commercialised under the trade mark NIKKOL HCO-50 (NIKKO Chemical Co., Ltd.) and a polyoxyethlyene (20) sorbitan monolaurate which is commercialised under the trade mark TWEEN 20 (ICI Chemicals), having an acid value below 1, a saponification value of about 48-56, a hydroxyl value of about 45-55 and pH value (5%) of 4.5-7.0, can be preferably used.

REPLACEMENT SHEET
06 APR 1998

The surfactant can include any one of the above-mentioned surfactants alone or, preferably, in a combination of two or more surfactants selected from the above surfactants. In the composition according to the present invention, the surfactants can be used in the ratio of 1 to 10 parts by weight, preferably in the ratio of 2 to 8 parts by weight, per 1 part by weight of cyclosporin.

In addition, when the mixture of two surfactants, i.e. polyoxyethylene (50) hydrogenated castor oil and polyoxyethylene (20) sorbitan monolaurate is used in the composition of the present invention, the constitutional ratio of polyoxyethylene (50) hydrogenated castor oil; polyoxyethylene (20) sorbitan monolaurate is preferably in the range of 1:0.1-5, more preferably in the range of 1:0.5-4, on the basis of weight.

In the composition according to the present invention, the four components are present preferably in the ratio of cyclosporin: second component; oil component; surfactant = 1 : 0.1- 10 : 1-10 : 1-10, and more preferably in the ratio of cyclosporin: second component: oil component : surfactant = 1 : 0.5-8: 2-6 : 2-8, by weight.

In addition to this composition, the composition illustrated in the following examples can be mentioned as further preferred compositions according to the present invention.

For oral administration, the composition of the present invention containing the above-mentioned components can be formulated into the form of a soft capsule. Since the soft capsule preparation according to the present invention does not use ethanol as the low-boiling volatile solvent, it is pharmaceutically stable and can establish the desired improvements including improvement of bioavailability. However, it may be difficult to reproductively prepare as a conventional soft capsule shell by means of a conventional method for preparation of soft capsules. When the soft capsule is formulated with the conventional capsule shell containing glycerine as plasticizer, the soft capsule thus prepared may have some disadvantages in that the emulsified state of the emulsion pre-concentrate may be changed due to the inflow of glycerine into the emulsion and therefore, the solubility of cyclosporin is significantly lowered which may result in the precipitation of cyclosporin from the emulsion.

REPLACEMENT SHEET
06 APR 1998

Accordingly, in another aspect the present invention it is found that when the capsule shell is formulated by using a mixture of polyethylene glycol and propylene glycol, not glycerine, as a plasticizer, the soft capsule preparation which is stable for a long period can be obtained. Although any polyethylene glycol which can be liquified may be used as a plasticizer, it is preferable to use polyethylene glycol having molecular weight of 200 to 600.

Particularly, polyethylene glycol 200 is preferably used. In the soft capsule shell according to the present invention, the mixture of polyethyene glycol and propylene glycol is preferably used in the ratio of 0.1 to 0.5 parts by weight, more preferably 0.1 to 0.4 parts by weight and most preferably 0.2 to 0.3 parts by weight, with respect to one part by weight of gelatin used for preparing the capsule shell. In the mixture of polyethylene glycol and propylene glycol as the plasticizer, propylene glycol is combined preferably in the ratio of 1 to 10 parts by weight, more preferably 3 to 8 parts by weight and most preferably 3 to 6 parts by weight, with respect to one part by weight of polyethylene glycol.

In order to increase the removability of the soft capsule shell band from the cooling drum, the process for preparing the gelatin capsule shell band according to the present invention adopts the air-cooling method, instead of the water-cooling method. According to this air-cooling method, since the capsule shell band is not overheated and can be readily removed from the cooling drum while maintaining the optimum temperature of about 21°C, the extent of seal in the encapsulation process is high to ensure a high productivity and therefore, the process can be efficiently conducted.

In preparing the soft capsule according to the present invention, a suitable air volume flow for the cooling drum to cool the capsule shell is preferably 5 to 15m^3/min., most preferably about 10m^3/min.

In formulating the composition according to the present invention into soft capsules, the capsule preparation can further contain, if necessary, pharmaceutically acceptable additives which are conventionally utilized in the preparation of soft capsules. Such additives include, for example, lecithin, viscosity regulator, perfume (e.g. peppermint oil, etc.), anti-oxidant (e.g. tocopherol, Vitamin E etc.), preservative (e.g. parabene, etc.), coloring agent, amino acids, etc.

REPLACEMENT SHEET
0 APR 1998

The soft capsule preparation according to the present invention can be prepared by uniformly mixing the co-surfactant, the oil component and the surfactant, dissolving cyclosporin therein while stirring and gently warming to the temperature of approximately 60°C, and then formulating the resulting concentrate, with or without the above-mentioned pharmaceutically acceptable additives conventionally utilized in preparation of soft capsules, with the gelatin shell containing polyethylene glycol and propylene glycol as the plasticizer in a machine for preparing soft capsules by means of the air-cooled method into the desired suitable cyclosporin soft capsule.

The compositions and preparations of the present invention are useful for the same indications and may be administered in the same way and dosage range as known cyclosporin compositions, if necessary adjusting the dose on the basis of standard bioavailability trials in animals, e.g. dogs, or humans, e.g. as described hereinafter.

Insofar as details of the compositions of any excipients or components are not specifically described herein, these are described in the literature, e.g. H.P. Fiedler, Lexikon der Hilfsstoffe, Edito Cantor Verlag, Aulendorf, Germany, 4th Edition 1996, Handbook of Pharmaceutical Excipients, American Pharmaceutical Association, Washington, and The Pharmaceutical Society, London, 2nd Edition, 1994 and Korean Patent Application 94-29208 filed 9.11.94.

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.

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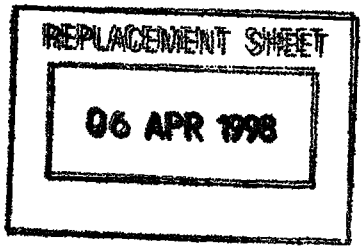
06 APR 1998

EXAMPLE 1:

Component	Content (mg/Cap.)
Cyclosporin	25
polyethylene glycol 200	45
propylene carbonate	25
polyoxyethylene (50) hydrogenated castor oil	35
polyoxyethylene (20) sorbitan monolaurate	85
ethyl linoleate	40
caprylic/capric acid triglyceride	5
oleic acid monoglyceride	35
total	295 mg

EXAMPLE 2:

Component	Content /mg/Cap.)
Cyclosporin	25
polyethylene glycol 200	70
polyoxyethylene (50) hydrogenated castor oil	35
polyoxyethylene (20) sorbitan monolaurate	85
ethyl linoleate	40
caprylic /capric acid triglyceride	5
oleic acid monoglyceride	35
total	295 mg



EXAMPLE 3:

Component	Content (mg/Cap.)
Cyclosporin	25
polyethylene glycol 200	100
propylene carbonate	50
polyoxyethylene (50) hydrogenated castor oil	35
polyoxyethylene (20) sorbitan monolaurate	85
ethyl linoleate	40
caprylic /capric acid triglyceride	5
oleic acid monoglyceride	35
total	375 mg

EXAMPLE 4:

Component	Content (mg/Cap.)
Cyclosporin	25
polyethylene glycol 200	45
propylene carbonate	25
polyoxyethylene (50) hydrogenated castor oil	50
polyoxyethylene (20) sorbitan monolaurate	100
ethyl linoleate	40
caprylic /capric acid triglyceride	5
oleic acid monoglyceride	35
total	325 mg

REPLACEMENT SHEET
06 APR 1998

EXAMPLE 5:

Component	Content (mg/Cap.)
Cyclosporin	25
polyethylene glycol 200	45
propylene carbonate	25
polyoxyethylene (50) hydrogenated castor oil	35
polyoxyethylene (20) sorbitan monolaurate	85
ethyl linoleate	80
caprylic /capric acid triglyceride	10
oleic acid monoglyceride	70
total	375 mg

EXAMPLE 6:

The soft capsule preparation was prepared from the composition of Example 1 using the following composition for capsule shell and then the change in the property and condition of the content due to the inflow of glycerine was visually observed.

6.1 (control group)

Component	Weight ratio
gelatin	20
purified water	16
glycerine	9

6.2 (test group)

Component	Weight ratio
gelatin	20
purified water	16
propylene glycol	4
polyethylene glycol 200	1

REPLACEMENT SHEET
06 APR 1998

The results as observed are described in the following Table 1.

Table 1: Stability of the content of the capsule preparation according to the capsule shell

Composition of Capsule	Just after formulation	After 1 day	After 2 days	After 5 days	After 10 days	After 30 days
Control group	0	+	+	++	+++	+++
Test group	0	0	0	0	0	0

Note: 0 = the content is stable
+ = poor emulsification
++ = slight precipitation
+++ = precipitation

As can be seen from the result described in table 1, the capsule preparation prepared using the composition of 6.1 control group containing glycerine as the plasticizer causes some problems including the formation of precipitation due to the inflow of glycerine, whereas the capsule preparation prepared using the composition of 6.2 test group containing polyethylene glycol and propylene glycol as the plasticizer maintains the stable condition.

EXAMPLE 7:

The soft capsule preparation having the composition of Example 1 was prepared using the composition of the capsule shell of 6.2 test group used in the above Example 6 by means of the water-cooling method (water temperature about 12°C) and the air-cooling method (air volume flow about 10 m^3/min), respectively.

REPLACEMENT SHEET
06 APR 1998

In each case, the removability of the capsule shell band from the cooling drum was observed and compared. The result as observed is described in the following Table 2.

Table 2: Removability of the gelatin shell band from the cooling drum depending on the cooling method

(Unit: degree of angle)

Shell Composition	Water-cooling Method	Air-cooling Method
Example 6.2	> 100 degree (poor removability)	< 50 degree (good removability)

As can be seen from the result described in the Table 2 above, the soft capsule preparation prepared by the air-cooling method according to the present invention shows a far better removability from the cooling drum in comparisoin with that prepared by the water-cooling method. Specifically, it is generally considered that if the degree of angle for removing the gelatin shell band from the cooling drum is about 70 or more, the removability is poor, and if the degree of angle for removing the shell band is below about 70, the removability is good. The soft capsule preparation prepared by the water-cooling method is not satisfactorily removed from the cooling drum even when the preparation is removed at the angle of 100 degrees or more.

Contrary to this, the soft capsule preparation prepared by the air-cooling ethod according to the present invention can be easily removed from the cooling drum at the angle of 50 degree and below and therefore, can provide a good sealing strength and productivity.

EXAMPLE 8:

The bioavailability of the preparation prepared by encapsulating the composition of Example 1 with the gelatin shell having the composition of Example 6.2 as the test preparation was compared with the bioavailability of the commercial product containing ethanol, SANDIMMUN Capsule, as the control preparation to

REPLACEMENT SHEET
06 APR 1998

estimate the influence of the cyclosporin preparation according to the present invention on the bioavailability of cyclosporin and its difference between respective subjects.

In this experiment, both of the test preparation and the control preparation were administered in an amount of 300 mg as cyclosporin per kg of rabbit.

Rabbits were uniformly fed with the conventional rabbit solid feed composition for 4 days or more under the same condition in wire cages. When the oral preparation were administered, rabbits were fasted for 48 hours in a restraint cage made of steel, during which rabbits were allowed to freely take water.

Levin's tube having a diameter of 5 mm was interposed by the depth of 30 cm through the esophagus after the surface of the Levin's tube was coated with vaseline in order to reduce friction. Each of the test preparations and the control preparation was emulsified with 50 ml of water and then introduced into a syringe which is attached to the Levin's tube. Ear veins of rabbit were dilated using xylene and then blood was taken from each rabbit's ear vein before the test and after 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 24 hours by means of heparin-treated disposable syringe. To 1 ml of blood thus obtained were added 0.5 ml of aqueous saturated sodium chloride solution and 2 ml of ether, and then the mixture was shaken for 5 minutes and centrifuged with 5000 rpm for 10 minutes to separate the supernatant (ether layer). 1 ml of the supernatant was collected and then developed in an activated silica sep-pak^{R} (Waters). The developed sep-pak was washed with 5 ml of n-hexane and eluated with 2 ml of methanol. The eluate was evaporated to dryness in nitrogen gas under reduced pressure. The residue was analysed by means of HPLC (High Performance Liquid Chromatography) [HPLC condition: column μ-Bondapak^{R} C_{18} (Waters), mobile phase CH_3CN: MeOH; H_2O - 55: 15 : 30, detection 210 nm, flow rate 1.0 ml /min., column temperature 70°C, sensitivity 0.01 Aufs. injection volume 100 μl].

The results obtained from the test preparation and the control preparation are illustrated in the following Table 3:

REPLACEMENT SHEET
06 APR 1998

Table 3: Bioavailability of the test preparation of the present invention and the commercial product (SANDIMMUN^R)

Parameter	Control Prep. (A)		Test Prep. (B)		P (B/A)
	M ± S.D. (n=6)	CV % (S.D./M)	M ± S.D. (n=6)	CV % (S.D./M)	
AUC (μg.hr/ml)	13.5±10.0	74.0 %	57.0±17.0	29.8 %	4.1
C_{max} (μg.hr/ml)	0.8±0.3	37.5 %	6.0±1.5	25.0 %	7.5

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06 APR 1998

Note: AUC = Area under the blood concentration curve

C_{max} = Maximum blood concentration of cyclosporin

M± S.D.= Mean value ± Standard deviation

CV = Ratio of standard deviation to mean value

P(B/A) = Ratio of mean value of the test preparation to mean value of the control preparation

As can be seen from the above table, the test preparation shows the increased AUC and C_{max} values which are about 4 times or more and about 7 times or more, respectively, as high as those of the control preparation. Accordingly, it can be identified that the bioavailability of the test preparation is significantly increased in comparison with that of the control preparation. In addition, the test preparation of the present invention exhibits an effect of decreasing the difference between respective test subjects (CV %) by about 2 times or more in AUC value and by about 1.5 times in C_{max} value, in comparison with the control preparation.

Accordingly, it could be determined that when the soft capsule preparation according to the present invention is administered per oral, it shows the increased bioavailability of cyclosporin about 4 times as high as that of the prior commercial product containing ethanol, SANDIMMUN^R Capsule and also a decrease of the difference between cyclosporin bioavailabilities in respective subjects, and at the same time, remains stable without any change during the long term storage. Thus, it is apparent that the soft capsule preparation according to

the present invention provides a significant improvement in the field of preparation of cyclosporin soft capsules.

EXAMPLE 9:

Soft gels are made up containing:

	I	II
Cyclosporin A	25 mg	100 mg
Polyethylene glycol 200	45 mg	180 mg
Propylene carbonate	25 mg	100 mg
Polyoxyethylene 50-hydrogenated castor oil	40 mg	160 mg
Polysorbate 20	85 mg	340 mg
Ethyl linoleate	40 mg	160 mg
Glyceryl mono-oleate	40 mg	160 mg
Vitamin E	1 mg	4 mg
Total	301 mg	1204 mg

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WHAT IS CLAIMED IS:

1. A soft gelatin capsule preparation containing a pharmaceutical composition comprising

(i) cyclosporin as an active agent,

(ii) propylene carbonate,

(iii) a mixture of a medium chain fatty acid triglyceride and a fatty acid monoglyceride as an oil component, and

(iv) a surfactant having an HLB value from 8 to 17 which comprises a polyoxyethylene hydrogenated vegetable oil.

2. A composition according to claim 1 wherein said cyclosporin is cyclosporin A.

3. A composition according to any preceding claim wherein the ratio of the component (ii) : cyclosporin is 1-5 : 1, on the basis of weight.

4. A composition according to any preceding claim wherein the medium chain fatty acid triglyceride comprises caprylic/capric acid triglyceride.

5. A composition according to any preceding claim wherein the fatty acid monoglyceride is a monoglyceride of oleic acid.

6. A composition according to any preceding claim wherein an esterified compound of fatty acid and primary alcohol is additionally present.

7. A composition according to claim 6 wherein the esterified compound of fatty acid and primary alcohol is ethyl linoleate.

8. A composition according to any preceding claim wherein the ratio of the oil component : cyclosporin is 2-6 : 1, on the basis of weight.

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06 APR 1998

9. A composition according to claim 6, 7 or 8 wherein the ratio of fatty acid monoglyceride : esterified compound of fatty acid and primary alcohol : medium chain fatty acid triglyceride is 1:0.1-3.0 : 0.1-3.0, on the basis of weight.

10. A composition according to any preceding claim wherein a mixture of a polyoxyethylene hydrogenated vegetable oil and polyoxethylene sorbitan fatty acid ester is present.

11. A composition according to any preceding claim wherein the ratio of the surfactant : cyclosporin is 2-8 : 1, on the basis of weight.

12. A composition according to claim 10 or 11 wherein said surfactant is a mixed surfactant consisting of polyoxyethylene(50) hydrogenated castor oil : polyoxyethylene(20) sorbitan monolaurate in the ratio of 1 : 0.5-4, on the basis of weight.

13. A composition according to any preceding claim wherein the ratio of cyclosporin : component (ii) : oil component : surfactant is 1:0.5-8 : 2-6 : 2-8, on the basis of weight.

14. A composition according to any preceding claim which is ethanol-free.

15. A composition according to any preceding claim wherein the soft gelatine capsule contains polyethylene glycol and propylene glycol as a plasticizer.

16. A composition according to claim 15 wherein the ratio of polyethylene glycol and propylene glycol : gelatin is 0.2-0.3 : 1, on the basis of weight.

17. A composition according to claim 15 or 16 wherein the ratio of the plasticizer polyethylene glycol : propylene glycol is 1 : 3-6, on the basis of weight.

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06 APR 1998

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ABSTRACT OF DISCLOSURE

The present invention relates to a cyclosporin-containing soft capsule preparation which comprises a composition containing cyclosporin as an active ingredient; a hydrophilic component polyethylene glycol or a non-hydrophilic component propylene carbonate or their mixture, a mixture of an esterified compound of fatty acid and primary alcohol, medium chain fatty acid triglyceride and fatty acid monoglyceride as an oil component; and a surfactant having an HLB (Hydrophilic Lipophilic Balance) value of 8 to 17, in a gelatin shell containing polyethylene glycol and propylene glycol as a plasticizer.

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(57) Abstract

The present invention relates to a cyclosporin-containing soft capsule preparation which comprises a composition containing cyclosporin as an active ingredient; a hydrophilic component polyethylene glycol or a non-hydrophilic component propylene carbonate or their mixture, a mixture of an esterified compound of fatty acid and primary alcohol, medium chain fatty acid triglyceride and fatty acid monoglyceride as an oil component; and a surfactant having an HLB (Hydrophilic Lipophilic Balance) value of 8 to 17, in a gelatin shell containing polyethylene glycol and propylene glycol as a plasticizer.