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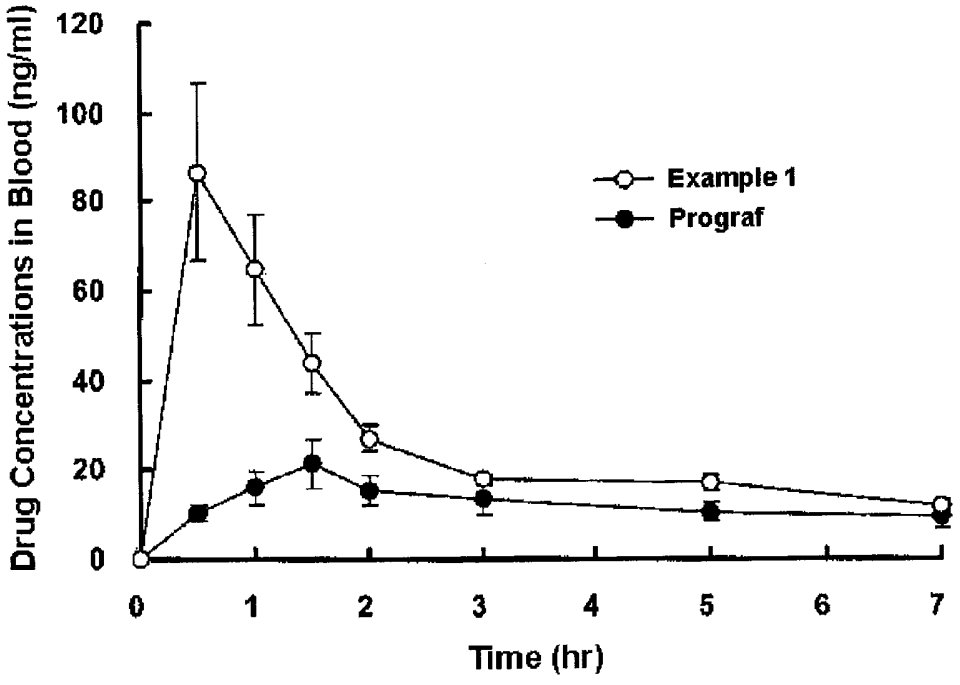
(54) Title: ORAL MICRO-EMULSION COMPOSITION COMPRISING TACROLIMUS



(57) Abstract: A microemulsion composition comprising tacrolimus as an active ingredient, a co-surfactant, a surfactant, an oil and an organic acid provides improved stability as well as high bioavailability of tacrolimus when orally administered.

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ORAL MICRO-EMULSION COMPOSITION COMPRISING TACROLIMUS

FIELD OF THE INVENTION

The present invention relates to a microemulsion composition for oral administration of tacrolimus, which provides improved bioavailability of the poorly water-soluble drug.

BACKGROUND OF THE INVENTION

Tacrolimus (FK506) found in a fermentation broth of *Streptomyces tsukubaensis* is one of the macrolide antibiotics having immuno-suppressive activity, and it has been known to inhibit T cell activation by binding with FKBP 12 (FK506 binding protein 12) to form FK506-FKBP complex, to block the serine/threonine phosphatase activity. Accordingly, tacrolimus has been used for alleviating chronic or acute tissue rejection that follows kidney or liver transplantation, and the effect of tacrolimus was reported to be higher than that of cyclosporin A when employed in first-line therapy for preventing acute tissue rejection or for reducing the use of corticosteroid.

However, the bioavailability of orally administered tacrolimus is unsatisfactorily low due to its low solubility in water (about 3.6 μg/ml at 25°C water), and accordingly, there have been numerous attempts to improve its solubility.

For example, Korean Patent Publication No. 1995-7210 discloses a method for preparing a tacrolimus solid dispersion using a water-soluble polymer such as hydroxypropyl methylcellulose. However, the manufacturing process of the dispersion is very complicated. US Patent No. 5,260,301 discloses a solution preparation of tacrolimus comprising ethanol as a solvent. However, this preparation has the problems of tacrolimus precipitation and ethanol loss due to volatilization.

Accordingly, the present inventors have endeavored to develop a microemulsion composition for oral administration of tacrolimus that is free from the above problems, and have found that a microemulsion composition for oral administration of tacrolimus comprising tacrolimus, a co-surfactant, a surfactant, an oil and an organic acid exhibits improved thermodynamic stability as well as high bioavailability of tacrolimus.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a microemulsion composition for oral administration of tacrolimus having improved bioavailability.

In accordance with one aspect of the present invention, there is provided a microemulsion composition for oral administration of tacrolimus comprising tacrolimus, a co-surfactant, a surfactant, an oil and an organic acid.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and other objects and features of the present invention will become apparent from the following description of the invention, when taken in conjunction with the accompanying drawings, which respectively show:

Fig. 1: the particle-size distribution of the inventive tacrolimus preparation of Example 1 in distilled water; and

Fig. 2: the dissolution rates (time-dependent drug concentrations in blood) of the inventive tacrolimus preparation of Example 1 and a commercially available tacrolimus preparation (Prograf®, Fujisawa Ireland), respectively, when orally administered.

DETAILED DESCRIPTION OF THE INVENTION

The composition of the present invention is a microemulsion in which tacrolimus is completely dissolved. It is stable without forming any precipitate

for a long period of time, and is spontaneously and easily emulsified in biological fluids to exhibit a high tacrolimus dissolution rate, and therefore it can be advantageously used for *in vivo* absorption of tacrolimus through oral administration.

The respective components employed for the preparation of the inventive microemulsion composition are described in detail as follows.

1. Active ingredient

In the present invention, tacrolimus is used as an active ingredient.

2. Co-surfactant

In the present invention, the co-surfactant serves to dissolve tacrolimus and to aid the emulsification of the preparation. Representative examples thereof include a non-toxic transcutol (diethyleneglycol monoethylether), polyethyleneglycol (preferably having a molecular weight of 200 to 600), triacetin or a mixture thereof.

The LD_{50} for acute oral toxicity of transcutol is 7.95 ml (specific gravity, 0.989)/kg (Gattefosse product profile), and that of polyethyleneglycol is 28.9 g/kg (Handbook of pharmaceutical excipients, p570~571, 3rd Ed., American pharmaceutical association, Washington D.C.). Also, the inventive composition comprising polyethyleneglycol can be formulated into a stable soft capsule because it does not degrade a gelatin film unlike other hydrophilic co-surfactants such as propylene glycol, ethanol or propylene glycol monoacetate. Triacetin may be used as a coating polymer for capsules, tablets or granules.

3. Surfactant

The surfactant used in the present invention may be any one of the known pharmaceutically acceptable surfactants, which can be used for forming a stable emulsion of oils and hydrophilic ingredients such as the co-surfactant in

water. Representative examples of the surfactant include:

(1) reaction products of a natural or hydrogenated vegetable oil with polyethylene glycol, i.e., polyoxyethylene glycolated natural or hydrogenated vegetable oils such as polyoxyethylene glycolated natural or hydrogenated castor oil (Cremophor®, BASF; and HCO®, Nikkol),

(2) polyoxyethylene-sorbitan-fatty acid esters, the fatty acid being mono- or tri-lauric, palmitic, stearic or oleic acid (Tween®, ICI),

(3) polyoxyethylene fatty acid esters such as polyoxyethylene stearic acid ester (Myrj®, ICI),

(4) polyoxyethylene-polyoxypropylene block copolymer (Poloxamer®, Pluronic® and Lutrol®, BASF),

(5) mono-, di- or mono/di-glycerides such as caprylic/capric acid mono- and di-glycerides (Imwitor®, Hûls),

(6) sorbitan fatty acid esters such as sorbitan monolauryl, sorbitan monopalmityl and sorbitan monostearyl esters (Span®, ICI), and

(7) trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols (Labrafil® and Labrasol®, Gattefosse) etc.

The above-mentioned surfactants can be used separately or as a mixture, and polypolyoxyethylene glycolated hydrogenated vegetable oils such as Cremophor®; polyoxyethylene-sorbitan-fatty acid esters such as Tween®; and trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols such as Labrafil® are preferred.

4. Oil

The oil may be any one of the known pharmaceutically acceptable oils which are compatible with the surfactant used and it becomes emulsified together with other ingredients in water to form a stable microemulsion. Representative examples of the oil include:

(1) fatty acid triglycerides, preferably medium chain fatty acid triglycerides, such as fractionated coconut oil (Miglyol®, Huls; and Captex®, Abitec),

(2) mono-, di- or mono/di-glycerides, preferably mono- or di-glycerides of oleic acid,

(3) esters of fatty acids and monovalent alkanols, preferably esters of C_{8-20} fatty acids and C_{2-3} monovalent alkanols, such as isopropyl myristate, isopropyl palmitate, ethyl linoleate and ethyl oleate,

(4) propyleneglycol mono- or di-fatty acid esters such as propyleneglycol dicaprylate, propyleneglycol monocaprylate, propyleneglycol dilaurate, propyleneglycol isostearate, propyleneglycol monolaurate and propyleneglycol ricinolate,

(5) carbohydrates such as squalene and squalane, and

(6) tocopherols such as tocopherol, tocopherol acetate, tocopherol succinate and polyethyleneglycol-1000-tocopherol succinate (TPGS).

The above-mentioned oils can be used separately or as a mixture, and esters of fatty acids and monovalent alkanols such as ethyl linoleate; fatty acid triglycerides such as Miglyol® and Captex®; mono-, di- or mono/di-glycerides; and tocopherols are preferred.

5. Organic acid

The organic acid may be any one of the known pharmaceutically acceptable organic acids, which is used to stabilize tacrolimus. Representative examples of the organic acid include erythorbic acid, citric acid, tartaric acid, ascorbic acid, lactic acid, malic acid, succinic acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, dimethyl triaminepenta-acetic acid, pyruvic acid, malonic acid, myristic acid, picric acid, methanesulfonic acid, ethanesulfonic acid, p-aminobenzoic acid, benzenesulfonic acid, benzoic acid, edetic acid, sorbic acid, adipic acid, gluconic acid, aminocaproic acid, glycyrrhizinic acid, isostearic acid, dodecylbenzenesulfonic acid, fumaric acid, maleic acid, oxalic acid, butyric acid, palmitic acid, sulfonic acid, sulfinic acid, formic acid, propionic acid, tannic acid, pantothenic acid, aspartic acid, aminoacetic acid and DL-α-aminopropionic acid.

The above-mentioned organic acids can be used separately or as a mixture, and erythorbic acid and citric acid are preferred.

In the preparation of the inventive microemulsion composition, the active ingredient (tacrolimus), the co-surfactant, the surfactant, the oil and the organic acid are used in amounts corresponding to a weight ratio in the range of 1 : 5~200 : 5~400 : 1~100 : 0.01~50, preferably, 1 : 10~150 : 10~300 : 2~80 : 0.1~20.

The inventive microemulsion composition for oral administration may be prepared by uniformly dissolving tacrolimus in the co-surfactant, and adding the surfactant, oil and organic acid thereto. The resulting mixture forms emulsified microparticles having an average diameter of below 1 μm on contacting an aqueous medium.

The microemulsion composition of the present invention may be formulated into a soft or hard capsule, in accordance with any of the conventional procedures.

The following Examples are intended to further illustrate the present invention without limiting its scope.

Example 1

A soft capsule was prepared using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	20
Cremophor® RH40 (BASF)	27
Glyceryl monooleate	7
Labrafil® M1944CS (Gattefosse)	6
Ethyl linoleate	10
Erythorbic acid	1
Citric acid	1

Tacrolimus was uniformly dissolved in transcutol, and other ingredients were successively added and dissolved therein to obtain a microemulsion pre-concentrate. Then, the resulting pre-concentrate was filled into a soft capsule

in accordance with the conventional method described in the General Preparation Rule of the Korean Pharmacopoeia.

Comparative Example 1

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	20
Cremophor® RH40 (BASF)	27
Glyceryl monooleate	7
Labrafil® M1944CS (Gattefosse)	6
Ethyl linoleate	10

Comparative Example 2

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	70
Cremophor® RH40 (BASF)	94.5
Glyceryl monooleate	24.5
Labrafil® M1944CS (Gattefosse)	21
Ethyl linoleate	35
BHT	1

Example 2

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	20
Labrasol® (Gattefosse)	13
Cremophor® RH40 (BASF)	27
D-α-tocopherol	10
Erythorbic acid	2

Example 3

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	20
Labrasol® (Gattefosse)	20
Cremophor® RH40 (BASF)	13
Glyceryl monooleate	7
Ethyl linoleate	10
Erythorbic acid	2

Example 4

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	20
Labrasol® (Gattefosse)	27
Cremophor® RH40 (BASF)	13
Miglyol® 812N (Abitec)	10
Erythorbic acid	2

Example 5

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	20
Cremophor® RH40 (BASF)	27
Labrafil® M1944CS (Gattefosse)	13
Ethyl linoleate	10
Erythorbic acid	2

Example 6

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	70
Cremophor® RH40 (BASF)	94.5
Glyceryl monooleate	24.5
Labrafil® M1944CS (Gattefosse)	21

Ethyl linoleate	35
Erythorbic acid	1

Example 7

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	70
Cremophor® RH40 (BASF)	94.5
Glyceryl monooleate	24.5
Labrafil® M1944CS (Gattefosse)	21
Ethyl linoleate	35
Erythorbic acid	1
Citric acid	2

Example 8

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	70
Cremophor® RH40 (BASF)	94.5
Glyceryl monooleate	24.5
Labrafil® M1944CS (Gattefosse)	21
Ethyl linoleate	35
Citric acid	3

Example 9

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	70
Cremophor® RH40 (BASF)	94.5
Glyceryl monooleate	24.5
Labrafil® M1944CS (Gattefosse)	21
Ethyl linoleate	35
Erythorbic acid	0.5
Citric acid	5

Example 10

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	20
Tween® 20 (ICI)	40
Glyceryl monooleate	7
Labrafil® M1944CS (Gattefosse)	6
Miglyol® 812N (Abitec)	10
Citric acid	5

Example 11

A soft capsule was prepared by the procedure of Example 1 using the

following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	20
Polyethylene glycol 400	50
Cremophor® RH40 (BASF)	27
Glyceryl monooleate	7
Labrafil® M1944CS (Gattefosse)	6
Ethyl linoleate	10
Citric acid	5

Example 12

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	20
Polyethylene glycol 200	50
Cremophor® RH40 (BASF)	27
Glyceryl monooleate	7
Labrafil® M1944CS (Gattefosse)	6
Ethyl linoleate	10
Erythorbic acid	1
Citric acid	1

Example 13

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Polyethylene glycol 200	200
Cremophor® RH40 (BASF)	270
Glyceryl monooleate	40
Labrafil® M1944CS (Gattefosse)	30
Ethyl linoleate	50
Erythorbic acid	1
Citric acid	1

Example 14

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	50
Polyethylene glycol 400	50
Cremophor® RH40 (BASF)	135
Labrafil® M1944CS (Gattefosse)	65
D-α-tocopherol	50
Erythorbic acid	1
Citric acid	1

Example 15

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)

Tacrolimus	1.02
Polyethylene glycol 400	200
Tween® 20 (ICI)	200
Glyceryl monooleate	70
Miglyol® 812N (Abitec)	50
Erythorbic acid	1
Citric acid	1

Example 16

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	50
Polyethylene glycol 400	50
Cremophor® RH40 (BASF)	135
Labrafil® M1944CS (Gattefosse)	65
Ethyl linoleate	35
Erythorbic acid	0.5
Citric acid	5

Example 17

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	70
Tween® 20 (ICI)	150

Labrafil® M1944CS (Gattefosse)	21
Ethyl linoleate	35
D-α-tocopherol	20
Erythorbic acid	0.5
Citric acid	1

Example 18

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	70
Labrasol® (Gattefosse)	100
Tween® 20 (ICI)	50
Labrafil® M1944CS (Gattefosse)	20
Miglyol® 812N (Abitec)	30
D-α-tocopherol	20
Citric acid	2

Example 19

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Transcutol	20
Polyethylene glycol 400	70
Cremophor® RH40 (BASF)	50
Tween® 20 (ICI)	50

Glyceryl monooleate	30
Ethyl linoleate	40
Erythorbic acid	2

Example 20

A soft capsule was prepared by the procedure of Example 1 using the following ingredients:

	Quantity(mg/capsule)
Tacrolimus	1.02
Triacetin	50
Cremophor® RH40 (BASF)	75
Miglyol® 812N (Abitec)	25
Citric acid	2

Test Example 1: Analysis of the emulsified drug microparticles

In order to examine whether the inventive preparation would spontaneously emulsify to form microparticles upon contact with an aqueous solution, particle size distribution analysis was carried out, as follows.

0.1 g of the preparation of Example 1 was diluted with 10 ml of distilled water, and then, the particle size distribution of the emulsified preparation was determined with a particle analyzer (Shimadzu, SALD-2002 model, Japan). The result is shown in Fig. 1.

As shown in Fig. 1, the inventive microemulsion composition forms emulsified microparticles having an average particle size of below 1 μm upon contact with an aqueous solution, to form a microemulsion.

Test Example 2: Precipitation Formation Test

In order to examine whether the inventive preparation forms

precipitations upon contact with an aqueous solution, 0.1 g of the preparation of Example 1 was diluted to 10 ml of distilled water, artificial gastric juice or artificial intestinal juice, and then, the formation of precipitate was observed.

The result of the precipitation test is shown in Table 1 (precipitation: +, no precipitation: -).

<Table 1>

	Distilled water	Artificial gastric juice	Artificial intestinal juice
Example 1	-	-	-

As shown in Table 1, the inventive microemulsion preparation does not form precipitates upon contact with an aqueous solution.

Test Example 3: Stability Test

1 mg each of the preparations prepared in Example 1, and Comparative Examples 1 and 2; and 1 mg of the commercially available hard capsule, Prograf® (Fujisawa Ireland) as a comparative preparation were kept at 60°C, and the time-dependent change of the tacrolimus content ((measured content / initial content) x 100) of each capsule was analyzed by HPLC under the following conditions. The results are shown in Table 2:

- Column: Inertsil ODS2 (250 mm × 4.6 mm)
- Mobile phase: a mixture of acetonitrile, distilled water and phosphoric acid (60:40:1)
- Injection volume: 10 μl
- Oven temperature: 50°C
- Detector: UV 210 nm

<Table 2>

Incubation time	Changes of tacrolimus contents (%)			
	Comparative Example 1	Comparative Example 2	Example 1	Comparative preparation
0	100.0	100.0	100.0	100.0
7 days	39.7	38.1	95.7	92.6
14 days	-	-	93.7	88.8

As shown in Table 2, the microemulsion composition of Example 1 has an improved stability as compared to the composition of Comparative Examples 1 and 2 which do not contain an organic acid, under the accelerate test condition. Further, the microemulsion composition of Example 1 was more stable than the comparative preparation, Prograf® which is a solid preparation (a hard capsule), owing to the use of an organic acid as a stabilizer.

Test Example 4: Absorption Test

In order to investigate the bioavailability of the drug contained in the inventive preparation, an in vivo absorption test was carried out as follows employing the preparation of Example 1 (Experimental preparation) and the commercially available preparation (Prograf®; Fujisawa Ireland) as a comparative preparation.

Six 14 to 15-week old male Sprague-Dawley rats (weight: 250 g) were acclimated for more than 4 days while allowing free access to the feed and water. The rats were then put on a 48-hour fast, while they were allowed free access to water.

The rats were divided into two groups each consisting of three rats, and were orally administered with the experimental and comparative preparations, respectively, in an amount corresponding to 10 mg/kg weight of tacrolimus. Blood samples were taken from the rats before the administration, and 0.5, 1, 1.5, 2, 3, 4, 5, 7 and 24 hours after the administration.

400 μl of a mixture of methanol and 0.2 M zinc sulfate (MeOH : 0.2 M

$ZnSO_4$ = 2 : 8) was added to 200 μl of each blood sample, and the mixture was shaken. Each mixture was centrifuged at 3,000 rpm for 10 minutes to obtain a supernatant, which was then filtered through a 0.22 μm filter and the filtrate was analyzed by LC-MS, under the following condition:

- Column: Waters MS C18 (2.1×150 mm with guard column)
- Mobile phase: 65% methanol, 95% methanol
- Injection volume: 30 μl
- Flow rate: 0.3 ml /min.
- Detector: SIR mode m/z : 826.7 (Na adduct)

The results are shown in Table 3 and Fig. 2.

<Table 3>

Preparation	AUC (ng·hr/ml)	C_{max} (ng/ml)	T_{max} (hour)
Example 1	190.4±27.2	86.6±19.9	0.5±0.0
Comparative Preparation	85.7±17.2	21.3±5.3	1.5±0.0

AUC: Area under the plasma concentration versus time curve integrated for 0 to 24 hours

C_{max}: Maximum blood concentration

T_{max}: Time at the maximum blood concentration

As shown in Table 3 and Fig. 2, the bioavailability of the inventive preparation of Example 1 was improved over that of Prograf® by a factor of more than 2 times.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes

may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

WHAT IS CLAIMED IS:

1. A microemulsion composition for oral administration of tacrolimus comprising tacrolimus, a co-surfactant, a surfactant, an oil and an organic acid.

2. The composition of claim 1, wherein the tacrolimus : co-surfactant : surfactant : oil : organic acid weight ratio is in the range of 1 : 5~200 : 5~400 : 1~100 : 0.01~50.

3. The composition of claim 1, wherein the co-surfactant is selected from the group consisting of transcutol, polyethyleneglycol, triacetin and a mixture thereof.

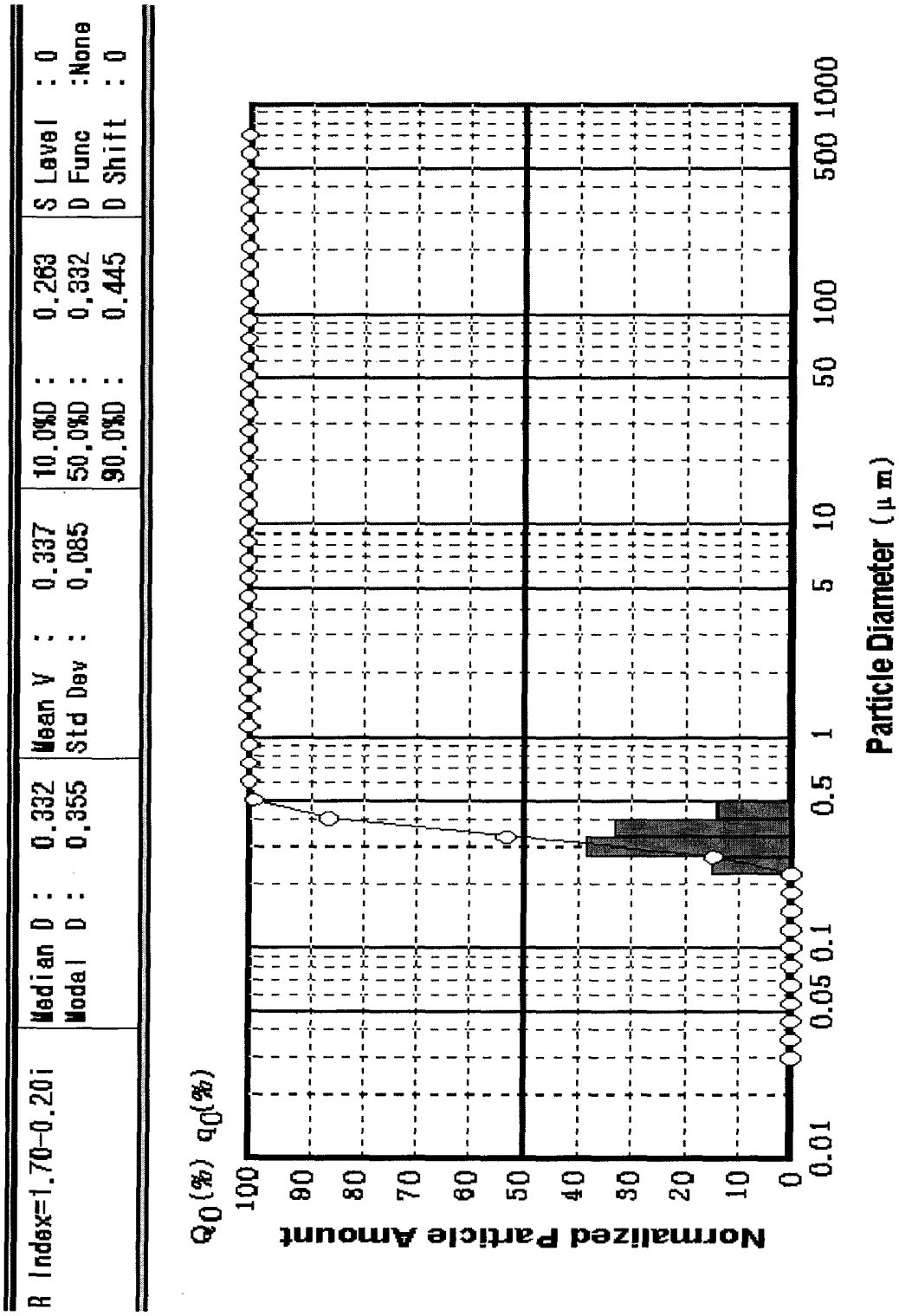
4. The composition of claim 1, wherein the surfactant is selected from the group consisting of polyoxyethylene glycolated hydrogenated vegetable oils; polyoxyethylene-sorbitan-fatty acid esters; trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols; and a mixture thereof.

5. The composition of claim 1, wherein the oil is selected from the group consisting of esters of fatty acids and monovalent alkanols; fatty acid tri-, mono-, di- or mono/di-glycerides; tocopherols; and a mixture thereof.

6. The composition of claim 1, wherein the organic acid is selected from the group consisting of erythorbic acid, citric acid, tartaric acid, ascorbic acid, lactic acid, malic acid, succinic acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, dimethyl triaminepenta-acetic acid, pyruvic acid, malonic acid, myristic acid, picric acid, methanesulfonic acid, ethanesulfonic acid, p-aminobenzoic acid, benzenesulfonic acid, benzoic acid, edetic acid, sorbic acid, adipic acid, gluconic acid, aminocaproic acid, glycyrrhizinic acid, isostearic acid, dodecylbenzenesulfonic acid, fumaric acid, maleic acid, oxalic acid, butyric acid, palmitic acid, sulfonic acid, sulfinic acid, formic acid, propionic acid, tannic acid, pantothenic acid, aspartic acid, aminoacetic acid, DL-α-aminopropionic acid and a

mixture thereof.

FIG. 1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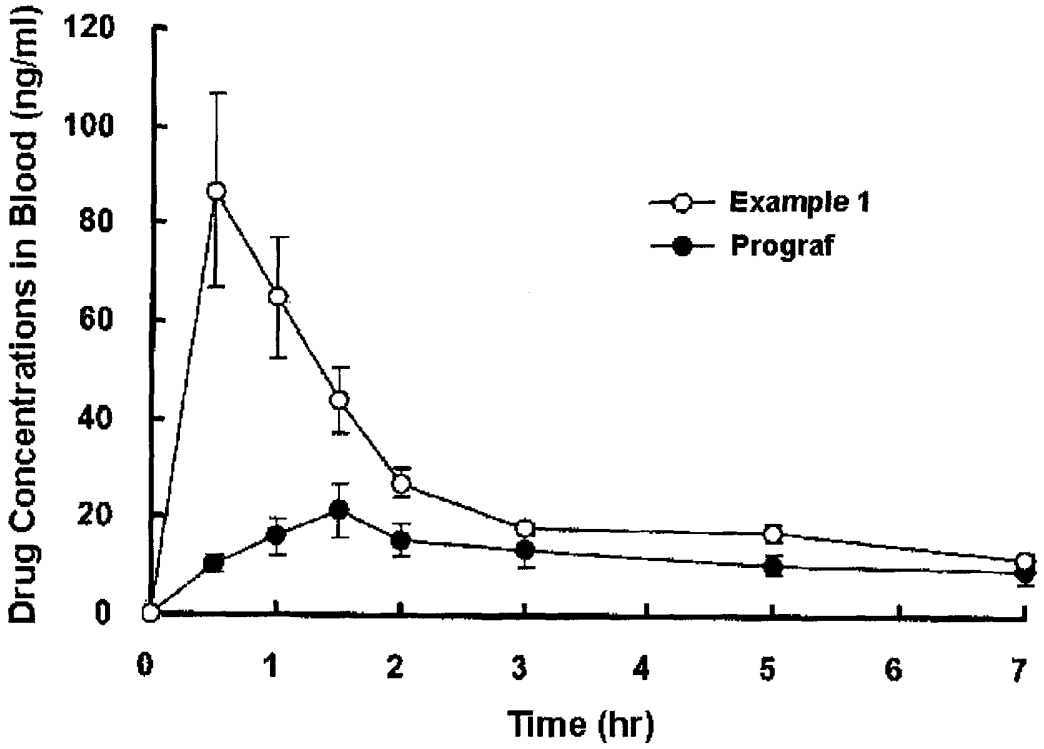
Median D : 0.332
Modal D : 0.355
Mean V : 0.337
Std Dev : 0.085
10.0%D : 0.263
50.0%D : 0.332
90.0%D : 0.445
S Level : 0
D Func :None
D Shift : 0
Normalized Particle Amount
Particle Diameter (μm)
Q0(%) q0(%)
100
80
80
70
60
50
40
30
20
10
0
0.01
0.05
0.1
0.5
1
5
10
50
100
500
1000

FIG. 2


Drug Concentrations in Blood (ng/ml)
120
100
80
60
40
20
0
0
1
2
3
4
5
6
7
Time (hr)
Example 1
Prograf

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2005/004152

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/113(2006.01)i, A61K 9/107(2006.01)i

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 8 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
KOREAN PATENTS AND APPLICATIONS FOR INVENTIONS SINCE 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)
CAS(ONLINE), MEDLINE, DELPHION

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/012771 A1(Smyth, Gyles, Darren) 12.Feb.2004 See the whole document	1-6
Y	Uno et al., "Pharmacokinetic advantages of a newly developed tacrolimus oil-in-water-type emulsion via the enteral route", Lipids, (1999), Vol.34(3) , pp249-254 See the paragraph of "Preparation of emulsion" in page 249	1-6
Y	WO 00/53212 A1(Hangzhou Zhongmeihuadong Pharm. Co. Ltd.) 14.Sept.2000 See the whole document	1-6
A	Uno et al., "Pharmacokinetics of water-in-oil-in-water-type multiple emulsion of a new tacrolimus formulation", Lipids, (1997), Vol.32(5), pp543-548 See the whole document	1-6
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☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"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
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 MARCH 2006 (09.03.2006)	**10 MARCH 2006 (10.03.2006)**

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2005/004152

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