components include lecithin; MONTANOL-68, EPICURON 120 (Lucas Meyer, Germany) which is a mixture of about 70% of phosphatidylcholine, 12% phosphatidylethanolamine and about 15% other phospholipids; OVOTHIN 160 (Lucas Meyer, Germany) which is a mixture comprising about 60% phosphatidylcholine, 18% phosphatidylethanolamine and 12% other phospholipids; a purified phospholipid mixture; LIPOID E-75 or LIPOID E-80 (Lipoid, Germany) which is a phospholipid mixture comprising about 80% phosphatidylcholine, 8% phosphatidylethanolamine, 3.6% non-polar lipids and about 2% sphingomyelin. Purified egg yolk phospholipids, soybean oil phospholipids or other purified phospholipid mixtures are useful as this component. This listing is representative and not limiting, as other phospholipid materials which are known to those skilled in the art can be used.

The surfactant chosen should preferably be non-ionic to minimize irritation, and one skilled in the art can conduct tests to routinely select specific surfactants for this purpose. Generally, the surfactant is a non-ionic alkylene oxide condensate of an organic compound which contains one or more hydroxyl groups. For example, ethoxylated and/or propoxylated alcohol or ester compounds or mixtures thereof are commonly available and are well known to those skilled in the art. Suitable surfactants include, but are not limited to, TYLOXAPOL; POLOXAMER 4070; POLOXAMER 188; POLYOXYL 40 Stearate; EMULFOR EL-620, POLYSORBATE 80, and POLYSORBATE 20, as well as various compounds sold under the trade name TWEEN (ICI American Inc., Wilmington, Delaware, U.S.A.), PLURONIC F-68 (trade name of BASF, Ludwigshafen, Germany for a copolymer of polyoxyethylene and polyoxypropylene). At this time, PLURONIC F-68 and the POLOXAMER 188 are preferred. The TYLOXAPOL and TWEEN surfactants are also preferred because they are FDA approved for human use.

The aqueous component will be the continuous phase of the emulsion and may be water, saline or any other

suitable aqueous solution which can yield an isotonic and pH controlled preparation.

In addition, the compositions of the invention may also comprise conventional additives such as preservatives and antioxidants. Typical preservatives include Thimerosal, chlorbutanol, and methyl, ethyl, propyl or butyl parabens. The preferred oil phase antioxidant is α-tocopherol or α-tocopherol succinate. The aqueous phase may also include an antioxidant or a chelating agent of a polyamine carboxylic acid such as ethylene diamine tetraacetic acid ("EDTA"), or a pharmaceutically acceptable salt thereof.

The drug, cosmetic, or active ingredient, alone or with the oily excipients, are mixed with a sufficient amount of surfactants and/or dispersing and suspending agents to allow dispersibility within the desired size range in aqueous medium. The surfactant(s) may be any pharmaceutically acceptable one(s) that enable(s) adequate dispersibility and stability of the droplets in aqueous medium, in a form of stable submicron size-range droplets. The drug, with or without oily excipients, is vigorously mixed with an aqueous solution that may contain surfactants, to result in submicron droplets of the drug and excipients. If needed, a high shear mixer and a high pressure homogenizer are employed to achieve the desired droplet size. Sonication is an alternative method to achieve the desired submicron droplet size.

Highly efficient delivery of the submicron droplets to the skin is obtained with a dosage form which is semi-solid. To produce a semi-solid composition, many methods may be applied; addition of gelling agents, such as carbopols and adjusting to a pH, organic thickening agents such as polyvinyl pyrrolidone (PVP) or a hydroxypropyl methyl cellulose (HPMC) polymer, or cetostearyl alcohol and other waxes that may rigidify, solidify or increase the viscosity of the aqueous dispersion to the desired consistency level. Inorganic thickening agents such as

fumed silica (AEROSIL or CABOSIL), alumina, clay or other similar colloidal particles can be used to increase the viscosity of the formulation. It is also possible to use oil concentrations on the higher end of the disclosed range to achieve higher viscosity compositions. However, use of greater than 30% oil causes difficulty in achieving the desired droplet size.

Chemical skin penetration enhancers may be incorporated into the formulation to enhance penetration of the active ingredient through the skin. In this regard, DMSO, decyl methyl sulfoxide, N-dodecyl pyrrolidone, decanol, dodecanol, an organic acid such as oleic acid, or the like can be used. Overall pharmacological effects achieved with the combination of chemical enhancers and submicron droplets are greater than for either component used by itself.

This invention provides submicron spheres (or droplets) that are an insoluble assembly of unique entities dispersed in an aqueous phase with the aid of appropriate surfactants or emulsifying agents. The emulsifying agent and surfactant form a protective layer around the droplets thus enabling efficient dispersion and suspension of the oily phase in water. This layer is a monolayer, polar by virtue of the surfactants. The present droplets are neither vesicles nor liposomes since no bilayers resembling the bilayer forming the living cell wall is formed. Micelles may be formed and be present, but may account for only a very small fraction of the surfactants and insoluble matter of the formula and in negligible quantities, usually less than about 1% of the total mass of insoluble matter and surfactants or dispersing agents.

Experiments carried out and measurements by means of photon correlation spectroscopy (Coulter N4MD) and laser diffraction (Coulter LS130) indicated that the droplet size in the compositions of the invention is in the size range of about 0.02 to about 0.5 microns. Preferably, the

size range is mainly in the 0.1 to 0.3 micron (i.e., 100 to 300 nm) range.

Depending on the inherent activity of the active ingredient its quantity has to be adjusted for each specific drug.

Compositions according to the invention for topical application to obtain a topical or systemic effect, contain, for example as active ingredient: steroids or non-steroidal anti-inflammatory drugs, antibiotics, antifungals, antivirals, antihistamines, antineoplastics or local anesthetics. Specific examples would include substances such as clotrimazole, bifonazole, tetracycline, miconazole, triamcinolone, amphotericin gentamicin, hydrocortisone, iodoxuridine, diphenhydramine, minoxidil, lidocaine, tetracaine and clindamycin.

For systemic effects, the following categories of drugs are suitable: hypnotics, sedatives, anxiolytics, antidepressants, anticonvulsants, anti-inflammatory drugs, anti-fungals, prostanoids, prostanoid agonists, prostanoid antagonists, analgesics, hormones and vitamins. Specific examples would include lipophilic peptides, barbiturates, benzodiazepines, phenothiazines, cyclosporin, diphenoxylate, physotigmine, tacrine, diclofenac, dexamethasone, prostaglandins, nifedipine, nitroglycerine, atropine, verapamil, fentanyl, lipophilic peptides, ketotifen, phenytoin, miconazole and ketoconazole.

For cosmetic effects, the active ingredient might be for example Vitamin A, Vitamin E, a polyunsaturated fatty acid such as eicosapentanoic acid, retinoids, carotenes and benzoyl peroxide.

Instead of a viscous composition, the droplets of the invention can be topically and transdermally applied by an article which includes the droplets, an active ingredient and a support for retaining the composition thereon. The support would include an adhesive for securing the article to the skin of a subject. A wide variety of active ingredients, including steroids such as estradiol,

nicotine or nitroglycerine, can be administered by this article, which would generally be in the form of an occlusive dressing or an adhesive patch.

In the following description, concentrations will be indicated by % which denotes the concentration by weight of the component per 100 units volume of entire composition. All indicated concentrations should be understood as standing each by itself, and not cumulative. It should be appreciated by the artisan, however, that there is some dependency between the concentrations of the components, e.g., higher concentrations of the oil will generally require higher concentrations of the emulsifier and surfactant.

The emulsion used in the compositions of the present invention may comprise about 0.5 to 30% oil, about 0.1 to 10% emulsifier and about 0.05 to 5% surfactants. Generally, increasing the concentration of the non-aqueous phase, i.e., the combined concentration of the oily and the amphiphilic phase, increases viscosity of the composition. In order to obtain a viscous composition, the concentration of the oil could be increased to about 20 to 30%. As noted above, another way to increase the viscosity is to add a pharmaceutically acceptable gelling or thickening agent, such as Carbopol or the like. These viscous compositions are useful as creams or ointments.

Preferred concentrations of the components are as follows: about 5 to 20% oil; about 0.2 to 5% of the emulsifier, with about 0.2 to 1% being particularly preferred; and about 0.2 to 5% for the surfactant, with about 0.2 to 1% being particularly preferred. For a viscous composition, about 0.2 to 15% of the gelling or thickening agent can be included.

The drug or cosmetic agent (the active ingredient) is present in an amount of about 0.05 to 5% by weight of the composition, preferably about 0.1 to 2.5%. Depending upon whether the active ingredient is hydrophilic or hydrophobic, it will be physically present in the oily

phase or the aqueous component. Also, the pH of these compositions should be in a range which is suitable for the stability of the active ingredient, but silghtly acidic or as close to neutral as possible for compatibility with the skin.

The invention is illustrated with reference to the above-mentioned examples, which are to be construed in a strictly non-limitative manner.

**EXAMPLES**

The enhanced topical and transdermal effects of drugs administered in emulsions comprised of submicron size droplets in comparison to standard cream formulations and commercial preparations was established in several test systems. Antiinflammatory agents were tested utilizing the carrageenan induced paw edema in guinea pigs. Tranquilizers were assessed in guinea pigs utilizing behavioral tests indicative of sedation. Local anesthetics were tested in healthy human volunteers on the basis of loss of local sensation following application of various preparations.

The following summarizes the systems used and results obtained with the formulations tested. The following cases are to be construed as examples in a strictly non-limitative manner.

EXAMPLE 1: A diazepam submicron cream preparation was made as follows: 0.5 g of diazepam are mixed with 9 g of medium chain triglyceride (MCT) oil and 1 g of lecithin until an homogeneous oily phase is achieved. The oily phase is then dispersed into 90 ml of an aqueous phase which includes 2 g of PLURONIC F-68 and 0.1 g of a mixture of methyl and propyl parabens by initial mixing with a magnetic stirrer followed by a high shear mixer (Polytron K3000) for 5 minutes at 20,000 RPM to form an emulsion. Further treatment of the emulsion is conducted in a high pressure homogenizer (APV - Gaulin) at 800 bar for 6

minutes (about 10 cycles) at 45-55°C. Thereafter, the emulsion was cooled to room temperature and the mean droplet size was measured size to be 120 nanometers having a very narrow distribution with practically no droplets above one micron (less than 0.5%) being detected. CARBOPOL is added to a final concentration of 0.3%. Finally, the pH is elevated with sodium hydroxide to 7 and a semi-solid submicron droplet preparation is achieved.

EXAMPLE 2: Example 1 was repeated using 6 g MCT oil and 3 g oleic acid. The mean droplet size was found to be 150 nanometers.

EXAMPLE 3: (Comparative) A formulation was made in the same manner as Example 2 but without the procedure to reduce the droplet size. The final droplet size was between 5 and 50 microns.

EXAMPLE 4: (Comparative) A conventional diazepam cream was prepared as follows: diazepam 0.5 g, MCT oil 9 g, emulsifying wax 9 g, hot water 81 ml. A classical technique was used whereby the wax was melted, the oil and drug were added, and then the hot water was added with vigorous stirring. The mean droplet size of the cream was between 5 and 50 microns.

EXAMPLE 5: The systemic tranquilizing effect of topically applied diazepam creams of the first four examples were investigated and compared to the systemic administration of diazepam, as follows.

Materials and Methods

Guinea pigs, males and females, having a body weight of about 250 g were shaved 24 hours before application of the creams. The following formulations were applied: (a) diazepam 0.5% - small drops (Example 1); (b) diazepam 0.5% - small drops with oleic acid (Example 2);

(c) diazepam 0.5% - large drops with oleic acid (Example 3); (d) diazepam 0.5% in a conventional cream of large droplet size (Example 4). Five grams of each preparation was applied on the shaved area, i.e., about 20 $cm_2$ of each guinea pig.

Commercially available parenteral preparations were also used as controls, as follows: (e) diazepam 5 mg/ml (vials of 2 ml), 10 mg/kg administered intramuscularly, and (f) the same preparation administered subcutaneously (10 mg/kg).

Clinical appearance, following application or injection, was checked and recorded. The onset and termination times of the effects were recorded.

Three basic behavioral tests, indicating level of sedation, were used

(a) Righting reflex: animals are positioned on their back and the time that is required to return to normal position was recorded. Three levels of sedation are scored: low (score 1) - animal returns immediately to normal position; moderate (score 2) - up to 30 seconds are needed to return to normal position; severe-deep (score 3) - more than 30 seconds are needed to regain normal position.

(b) Step test: animals are positioned on a 5 cm high step, with the forelegs on the step. The time interval for changing this position was measured for each animal. The same course of time that was used for scoring of righting reflex was used here.

(c) Animals were positioned on their hind legs, their forelegs put on the top of their cage (20 cm high). The time interval for changing this position was measured for each animal. The same scoring methodology as above was used here.

(d) A total aggregate score for each animal was calculated to show the state of sedation for this study.

The results are shown in Table 1. It was found that topically applied diazepam is very effective when delivered in submicron droplets. A systemic-like effect

may be achieved with this preparation, but the same dose in large droplet formulation was not effective. Also, the inclusion of oleic acid in the formulation reduces the time for onset of activity and duration.

**Table 1: Efficacy of Different Topical and Systemic Diazepam Formulations in Guinea Pigs.**

| Treatment | No. of Animals | Score | Time of Activity (min) |
|---|---|---|---|
| Diazepam, i.m., 10 mg/kg | 4 | 39.0 | 15-120 |
| Diazepam, s.c., 10 mg/kg | 4 | 52.8 | 15-120 |
| Diazepam 0.5% cream (5 g) submicron drops | 5 | 47.5 | 45-240 |
| Diazepam 0.5% cream (5 g) submicron drops with oleic acid | 6 | 43.7 | 30-120 |
| Diazepam 0.5% cream (5 g) large drops with oleic acid | 5 | 3.0 | -- |
| Classical diazepam 0.5% cream (5 g) | 5 | -- | -- |

EXAMPLE 6: Example 1 was repeated using TWEEN-80 instead of PLURONIC F-68. The mean droplet size was 170 nanometers and an enhanced tranquilizing effect substantially equivalent to that of Example 1 was detected.

EXAMPLE 7: Example 1 was repeated using EMULFOR EL-620 instead of PLURONIC F-68. The mean droplet size was found to be 100 nanometers and the activity was comparable to that of Example 1.

EXAMPLE 8: Example 1 was again repeated except that the formulation contained 20 g MCT oil. The mean droplet size was found to be 210 nanometers, but the activity was significantly increased in comparison to Comparative Example 4 and was as good as that of Example 1.

EXAMPLE 9: Example 1 was repeated except that 20 g MCT oil and 1 g diazepam were used. The mean droplet size was 250 nanometers and the preparation exhibited increased activity compared to that of Comparative Example 4 which was at least as good as that of Example 1.

EXAMPLE 10: Example 1 was again repeated but 1 g oleic acid was included. The mean droplet size was 100 nanometers and the composition was found to be as active as that of Example 1.

EXAMPLE 11: Example 1 was repeated using TWEEN-65 instead of lecithin. The mean droplet size was found to be 250 nanometers and the formulation was much more active (a score of 35) than that of Example 4.

EXAMPLE 12: Example 1 was repeated using MONTANOL-68 instead of lecithin. The mean droplet size was found to be 300 nanometers and the formulation was much more active (a score of 30) than that of Example 4.

EXAMPLE 13: Example 1 was repeated using soybean oil instead of MCT oil. The mean droplet size was found to be 180 nanometers and the formulation was as active as that of Example 1 (a score of 45).

EXAMPLE 14: Example 1 was repeated with the addition of α-tocopherol as an antioxidant. The mean droplet size was found to be 100 nanometers and the formulation was as active as that of Example 1. This formulation was also found to be suitable for administering oxidation sensitive drugs such as nifedipine.

EXAMPLES 15-16: Example 1 was again repeated but 2 g of AEROSIL silica and hydroxypropyl cellulose, respectively, were included instead of CARBOPOL, and the pH was adjusted to 5.5. The mean droplet size for each example was found

to be 180 nanometers and the compositions were found to be as active as that of Example 1.

EXAMPLE 17: An indomethacin submicron cream preparation was made a follows: indomethacin 0.5 g, MCT oil 17 g, lecithin 0.8 g, EMULFOR EL-620 1.6 g, CARBOPOL 1.7 g and water 78 ml. The procedure of Example 1 was followed to obtain a mean droplet size of 130 nanometers.

EXAMPLE 18: (Comparative) A conventional, large droplet size indomethacin cream was prepared as follows: indomethacin 0.5 g, MCT oil 15 g, emulsifying wax 9 g, water 75 ml. The composition was prepared as in Example 2. The mean droplet size was found to be between 5-50 μm.

EXAMPLE 19: The topical anti-inflammatory effect of topically-applied indomethacin creams of Examples 17-18 were investigated and compared for their anti-inflammatory effect versus systemic administration.

Animals and Materials

(a) Guinea pigs (250 g).

(b) Indomethacin 0.5% in submicron cream (Example 17).

(c) Indomethacin 0.5% in conventional cream (Example 18).

(d) Indomethacin 0.5% in solution.

Study Procedure

(a) All animals received an injection of 0.1 ml carrageenan 0.1% into the hind paw. Measurements were taken from the area of injection and followed for up to 5 hours.

(b) The above creams were administered at carrageenan administration site and the solution of indomethacin was administered intramuscularly 15 minutes prior to carrageenan administration.

(c) The circumference of the paw was again measured and the change in size was compared for the different treatments. The volume changes were measured by a plethysmometer (Ugo, Basel).

The results presented in Table 2 demonstrate that a local application of indomethacin in submicron droplet cream was the most effective in reducing the edema caused by the carrageenan injection, and was more effective than large droplets of indomethacin cream or the same dose administered intramuscularly.

**Table 2: Performance of Different Indomethacin Formulations in Paw Edema Model in Guinea Pigs**

| Treatment | No. of Animals | Average change of circumference, percent — Hours after carrageenan injection: 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| Control (Carrageenan) | 4 | 17 | 32 | 61 | 80 | 83 |
| Indomethacin 0.5%, in cream small droplets | 4 | 0 | 7.3 | 24 | 32 | 36 |
| Indomethacin in cream, Large droplets | 4 | 16 | 55 | 67 | 47 | 39 |
| Indomethacin 10 mg/kg i.m. in solution | 4 | 19 | 22 | 25 | 36 | 33 |

EXAMPLE 20: A lidocaine submicron cream preparation was made as follows: lidocaine 4 g, MCT oil 6.5 mg, lecithin 0.8 g, EMULFOR EL-620 1.5 g, water 78 ml and CARBOPOL 1.7 g. Again, the procedures were the same as in Examples 1 and 17. The mean droplet size was found to be 160 nm.

EXAMPLE 21: (Comparative) A conventional, large droplet size lidocaine cream was prepared as per Example 3 except with lidocaine 4 g, MCT oil 5.5 g, emulsifying wax 8 g, petroleum 14 g, water 69 ml. The mean droplet size was greater than 50 microns.

EXAMPLE 22: A small droplet size eutectic local anesthetic was prepared as follows. 2.2 g lidocaine,

2.2 g tetracaine, 2 g PLURONIC F-68, 89 g water, and carbopol 4.5 g. The preparation procedure was as per Example 1, the pH was adjusted to 7.5 and the mean droplet size was found to be 250 nanometers.

EXAMPLE 23: (Comparative) A conventional, large droplet size eutectic local anesthetic was prepared as follows. The same formulation as in Example 22 was prepared but without the procedure to reduce the droplet size. The final droplet size was found to be between 20-100 μm.

EXAMPLE 24: The local anesthetic effect of topically applied lidocaine creams of Examples 20-23 were investigated and compared. Each preparation was applied to the forearm of 4 male human volunteers and the degree of local anesthesia with time was monitored. A gentle touch was made with a sharp needle and the sensitivity of an adjacent (untreated) area was compared to the application site to estimate the effectiveness of the tested preparation. The experiment was blind for the volunteers. The sensitivity at the site of application was given a score of intensity of 1 to 4 and an average dosage form performance was calculated. The results are shown in Table 3.

**Table 3: Average Score (Effectiveness) of Small vs. Large Droplet Size Lidocaine Creams**

| Droplets | Small | Large |
|---|---|---|
| Example # | 19 | 20 |
| Drug Conc., % | 4 | 4 |
| Droplet size, um | 0.25 | 10-50 |
| Delay, hours | 0.5 | 1 |
| Duration, hours | 4.5 | 3 |
| Effectiveness (Average Score) | 28 | 17 |

These data show that lidocaine alone in oleaginous base or in regular cream of emulsifying wax (i.e., one having a droplet size of greater than 50 microns), was not effective as local anesthetic. However, the small droplet size preparation of lidocaine provided local anesthesia and performed better than larger droplet size which was very poor. Moreover, the small droplet size eutectic mixture performed better than the same formulation but with large droplet size, as shown in Table 4.

**Table 4: Average Score (Effectiveness) of Small vs. Large Droplet Size Eutectic Local Anesthetic Mixture Creams**

| Droplets | Small | Large |
|---|---|---|
| Example # | 21 | 22 |
| Drug Conc., % | 4.4 | 4.4 |
| Droplet size, μm | 0.295 | 20-100 |
| Delay, hours | 0.3 | 0.5 |
| Duration, hours | 6 | 4.5 |
| Effectiveness (Average Score) | 58 | 40 |

EXAMPLE 25: A diclofenac submicron cream was prepared as follows: Oil phase - diclofenac diethylammonium 12.2 g, MCT oil 170 g, LIPOID E-80 30 g, α-tocopherol succinate 0.4 g; Aqueous phase - EDTA disodium salt 1 g, EMULFOR EL-620 25 g, glycerol 17.5 g, preservatives (methyl and propyl parabens) 0.5 g, reverse osmosis purified water to 1000 g.

The composition was prepared as follows. The emulsion was prepared by combining the oil and aqueous phases together with a magnetic stirrer for 5 minutes, followed by a high-speed, high-shear mixer (Polytron K3000) for 5 minutes at 3000 RPM. The emulsion which was obtained was treated by a high pressure homogenizer (APV-Gaulin) at 800 bar (6 minutes, about 10 cycles) at

45-55 °C. After homogenization, the emulsion was allowed to cool to room temperature, the particle size distribution was determined and the emulsion was then filtered through a 0.45 micron pore size filter (Unimodal) size after 8 cycles/800 bar is 120 ± 30 nm, with the dust before filtration being in the range of 2-4%.

The cream formulation was prepared as follows: To 1000 g of the emulsion, 50 g of 10% CARBOPOL 940, which was pre-swollen in purified water, was added and mixed thoroughly with the Polytron K3000 device at 5-10,000 RPM for 2-3 minutes. Pure triethanolamine was added dropwise with mixing to adjust the pH to 6-6.5. A final mixing with the Polytron K3000 device at the same conditions produces a cream which contains 1.16% Diclofenac DEA (which is equal to a 1% solution of sodium diclofenac). After pH, viscosity and drug content testing, the cream is packed into aluminum tubes.

EXAMPLE 26: A topical edema treatment by diclofenac in different droplet size formulations was evaluated. A formulation containing submicron droplets of diclofenac (Example 25) was compared to standard preparation using the carrageenan paw edema model (guinea pigs). Carrageenan (0-1 ml of 0.1% solution) was injected into hind paw (at time=o). Start size of edema at time zero was taken as 100% level. Surface of edema was treated immediately after carrageenan injection by test preparations:

a) 1.16% diclofenac diethylammonia (equivalent to 1.0% Diclofenac sodium) in submicron emulsion (90-150 nm droplets) (Example 25).

b) VOLTAREN EMULGEL (Ciba-Geigy) - as a reference composition with known activity. c) 1.16% diclofenac diethylammonia in large droplets (5-10 μm).

Changes in volume were made using a plethysmometer (Ugo, Basel), and the results are shown in Fig. 1.

EXAMPLE 27: A piroxicam small droplet cream was prepared from the following components: piroxicam 0.25 g, MCT oil 9.5 g, lecithin 0.5 g, Tween-80 0.5 g, water 38.4 g, carbopol 0.2 g, triethylamine 0.2 g. The composition was prepared as in Example 1. The mean droplet size was found to be 127 nm.

EXAMPLE 28: (Comparative) A conventional piroxicam (large droplet) cream was prepared as follows: piroxicam 0.178 g, MCT oil 5 g, cetosteryl alcohol 2.7 g, sodium dodecylsulfate 0.3 g, water 27 g. After melting together the cetostearyl alcohol with sodium dodecylsulfate, the MCT oil was added. Piroxicam was mixed with ready hot oil phase, and then 27 ml of boiling water was added and mixed thoroughly. After cooling to room temperature, the cream was obtained.

EXAMPLE 29: A topical edema treatment by piroxicam in different emulsion formulations was studied. The submicron droplets of piroxicam (Example 27) was compared to standard cream (Example 28) using the carrageenan paw edema model (guinea pigs) of Example 26. As shown in Fig. 3, piroxicam in the cream of Example 27 demonstrates relatively low antiinflammatory activity, while the formulation of Example 26 was found to be much more effective.

EXAMPLE 30: A topical naproxen submicron cream was prepared from the following components: naproxen 1g; Miglyol 810 17g; LIPOID E-80 3g; α-tocopherol succinate 0.04g; EMULFOR EL-620 2.5g; glycerol 1.75g; EDTA disodium dihydrate 0.1g; CARBOPOL 940 0.5g; triethanolamine 0.5g; and pure water to 100g. The naproxen, MIGLYOL 810, LIPOID E-80 and α-tocopherol succinate were mixed together at 45°C until completely dissolved to form an oil phase. The EMULFOR, glycerol and EDTA were dissolved in water and mixed thoroughly with the oil phase in a high shear mixer

(Polytron K3000) for 5 minutes at about 20,000 RPM to form an emulsion. Further treatment of the emulsion is conducted in a high pressure homogenizer (APV - Gaulin) at 800 bar for 8 cycles to a droplet size of about 100-150 nm. After filtration through a 0.45 micron filter, CARBOPOL in the form of a preswollen gel (10% in water) was added and mixed in the Polytron device for 2 minutes at 5000 RPM. The triethanolamine was added to a final pH of 5.5-6.5 and the formulation was mixed in the Polytron device until a homogeneous cream was obtained.

EXAMPLE 31: A topical edema treatment by naproxen in different formulations was studied. A submicron droplet cream of naproxen (Example 30) was compared to a standard cream using the carrageenan paw edema model (guinea pigs) of Examples 26 and 29 for the following formulations:

a) Naproxen in a submicron emulsion (100-150 nm droplets as per Example 30) applied topically.

b) Naproxen in a conventional cream (droplets larger than 20 microns) applied topically.

The results are illustrated in Fig. 3

## THE CLAIMS

What is claimed is:

1. A composition for topical application of pharmaceuticals or cosmetics comprising submicron size droplets comprising about 0.5 to 30% of a first component of an oily liquid, about 0.1 to 10% of a second component of an emulsifier and about 0.05 to 5% of a non-ionic surfactant, said droplets having a mean droplet size in the range of 0.05 to 0.5 μm, wherein said composition provides an enhanced topical and/or transdermal systemic effect compared to the same compositions which have larger size droplets.

2. The composition of claim 1 wherein the mean droplet size is between about 0.1 and 0.3 μm.

3. The composition of claim 1 wherein the first component comprises a medium chain triglyceride oil having a chain length of about 8 to 12 carbons, a vegetable oil, a mineral oil, an oil of animal source, a synthetic derivative thereof, or mixtures thereof.

4. The composition of claim 3 wherein the first component is present in an amount of about 20 to 30% to form a viscous composition.

5. The composition of claim 1 wherein the emulsifier is a phospholipid compound or a mixture of phospholipids.

6. The composition of claim 5 wherein the phospholipid is lecithin, phosphatidylcholine, phosphatidylethanolamine or mixtures thereof.

7. The composition of claim 5 wherein the emulsifier is present in an amount of about 0.2 to 5%.

8. The composition of claim 1 wherein the surfactant is a non-ionic alkylene oxide condensate of an organic compound which contains one or more hydroxyl groups.

9. The composition of claim 8 wherein the surfactant is an ethoxylated alcohol or ester compound.

10. The composition of claim 9 wherein the non-ionic surfactant is present in an amount of about 0.2 to 5%.

11. The composition of claim 1 which further comprises an active ingredient in an amount of 0.5 to 5%.

12. The composition of claim 1 wherein the first component comprises an active ingredient in the form of an essentially water-insoluble oily liquid.

13. The composition of claim 12 wherein the active ingredient is present with another oily liquid.

14. The composition of claim 1 wherein the first component comprises an active ingredient in the form of a solid, essentially water-insoluble or slightly water-soluble substance which is at last partially dissolved or dispersed in the oily liquid.

15. The composition of claim 1, further comprising an aqueous component which forms the continuous phase of an oil-in-water emulsion, with the droplets forming the oil phase of the emulsion.

16. The composition of claim 1, further comprising a dispersion enhancer in an amount sufficient to promote the homogeneity of the composition.

17. The composition of claim 1 further comprising a viscosity enhancing agent in an amount sufficient to impart a semi-solid form to the composition.

18. The composition of claim 17, wherein the viscosity enhancing agent is a physiologically acceptable organic or inorganic thickening agent

19. The composition of claim 18, wherein the viscosity enhacing agent is an organic thickening agent comprising a high molecular weight organic compound or an inorganic thichening agent comprising colloidal particles.

20. The composition of claim 1 further comprising a skin penetration enhancer in an amount sufficient to enhance the penetration of the composition through skin after the composition is topically applied thereto.

21. The composition of claim 20, wherein the skin penetration enhancer is DMSO, decyl methyl sulfoxide,

N-dodecyl pyrrolidone, decanol, dodecanol or an organic acid.

22. The composition of claim 11, wherein the active ingredient is at least one lipophilic peptide.

23. The composition of claim 11, wherein the active ingredient is at least one steroid, non-steroidal anti-inflammatory drug, antibiotic, tranquilizer, sedative, anti-histaminic, antifungal, antibacterial, antiviral, disinfectant, antipsoriasis, immunosuppressant, vasodilator or vasoconstrictor agent or a local anesthetic.

24. The composition of claim 23 where the active ingredient is clotrimazole, bifonazole, tetracycline, miconazole, triamcinolone, amphotericin B, gentamicin, hydrocortisone, iodoxuridine, diphenhydramine, minoxidil, lidocaine, tetracaine and clindamycin.

25. A method for enhanced topical and/or transdermal, systemic effects which comprises formulating the composition of claim 11 and topically applying the composition to the skin of a subject, wherein the composition provides enhanced topical and/or transdermal, systemic effects compared to the same compositions which have larger size droplets.

26. The method of claim 25, which further comprises selecting the active ingredient to be a lipophilic peptide, a prostanoid, a prostanoid agonist, a prostanoid antagonist, a polyunsaturated fatty acid or an anti-fungal agent prior to formulating the composition.

27. The method of claim 25, which further comprises selecting the active ingredient to be a barbiturate, benzodiazepine, ketotifen, phenytoin, phenothiazines, cyclosporin, physotigmine, tacrine, diphenoxylate, diclofenac, dexamethasone, prostaglandin, nifedipine, nitroglycerine, atropine, verapamil, fentanyl, miconazole or ketoconazole prior to formulating the composition.

28. The method of claim 25, which further comprises selecting the active ingredient to be Vitamin A, Vitamin

E, eicosapentanoic acid, a retinoid, a carotene or benzoyl peroxide.

29. A method for treating the skin of a subject which comprises formulating the composition of claim 11 and topically applying the composition to the skin of a subject, wherein the composition provides enhanced topical and/or transdermal systemic effects compared to the same compositions which have larger size droplets to alleviate, reduce or prevent dermatological conditions and diseases, including atopic dermatitis, psoriasis, acne and other types of skin inflammations or viral, fungal or bacterial skin infections.

30. A method for reducing local irritation produced by pharmaceuticals which induce local inflammatory reactions which comprises formulating the composition of claim 11 and topically applying the composition to the skin of a subject, wherein the composition provides enhanced topical and/or transdermal systemic effects compared to the same compositions which have larger size droplets.

31. A method for achieving local anesthesia or analgesia, or for providing general analgesia which comprises formulating the composition of claim 11 and topically applying the composition to a subject.

32. An article for topically and transdermally applying an active ingredient which comprises the composition of claim 11 and a support for retaining the composition thereon, said support including an adhesive for securing the article to the skin of a subject.

33. The article of claim 32 wherein the active ingredient is a steroid, nicotine or nitroglycerine.

34. The article of claim 32 in the form of an occlusive dressing or an adhesive patch.

# DICLOFENAC ANTIINFLAMMATORY ACTIVITY IN VOLTAREN EMULGEL AND SME CREAM (Carrageenan paw edema model)

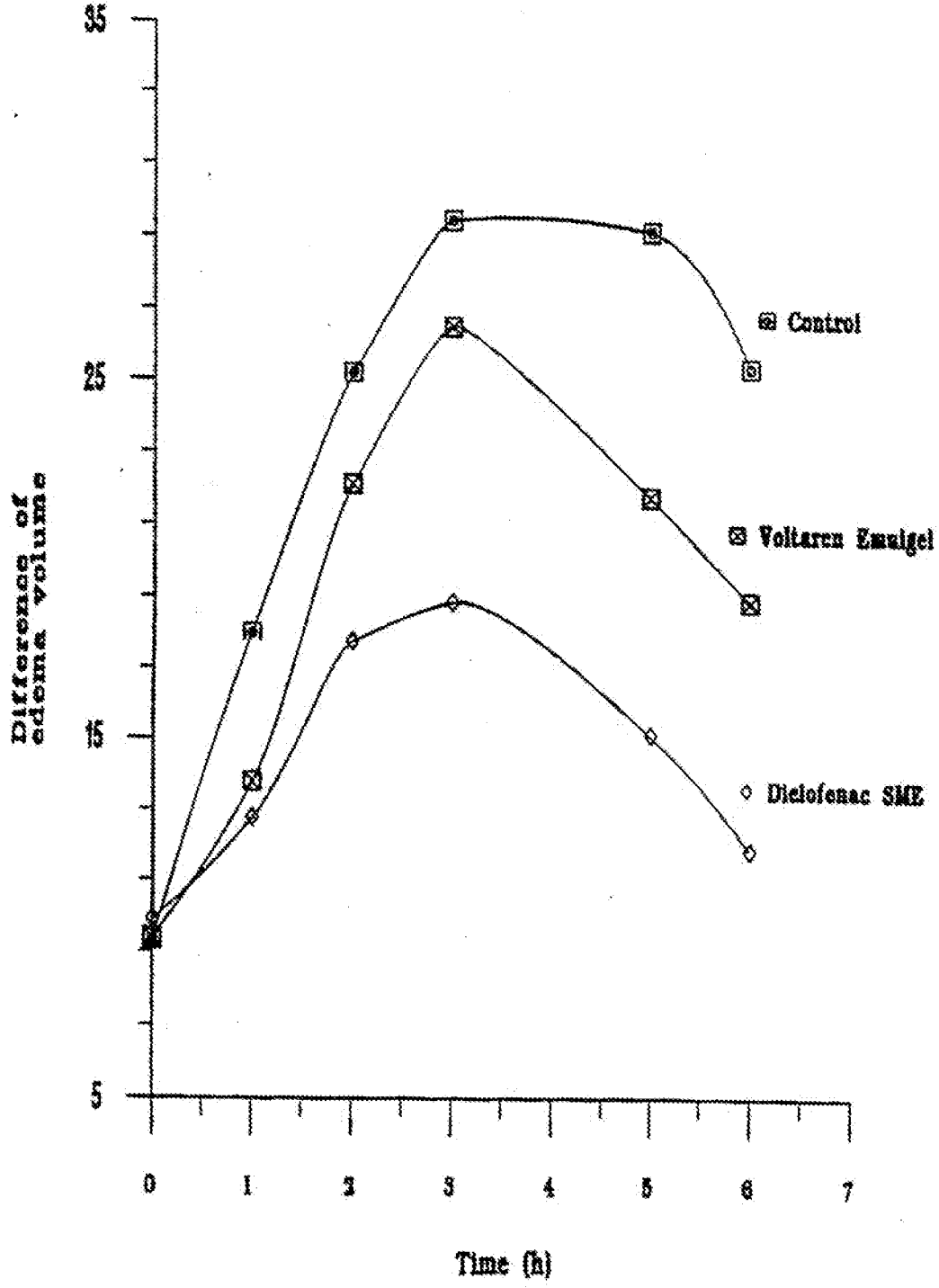



FIG. 1

# PIROXICAM ANTIINFLAMMATORY ACTIVITY IN REGULAR CREAM AND SME CREAM (Carrageenan paw edema model)

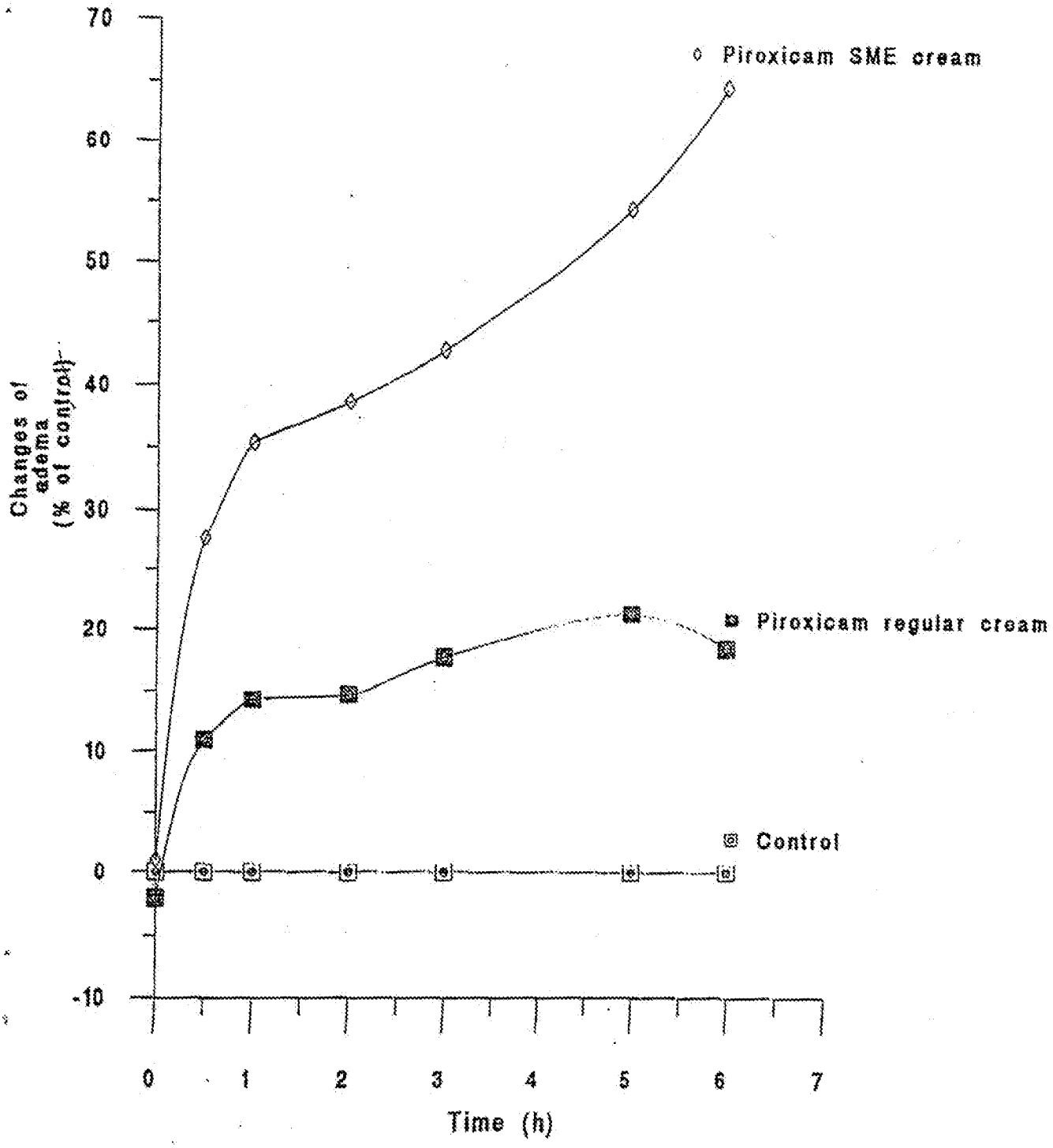
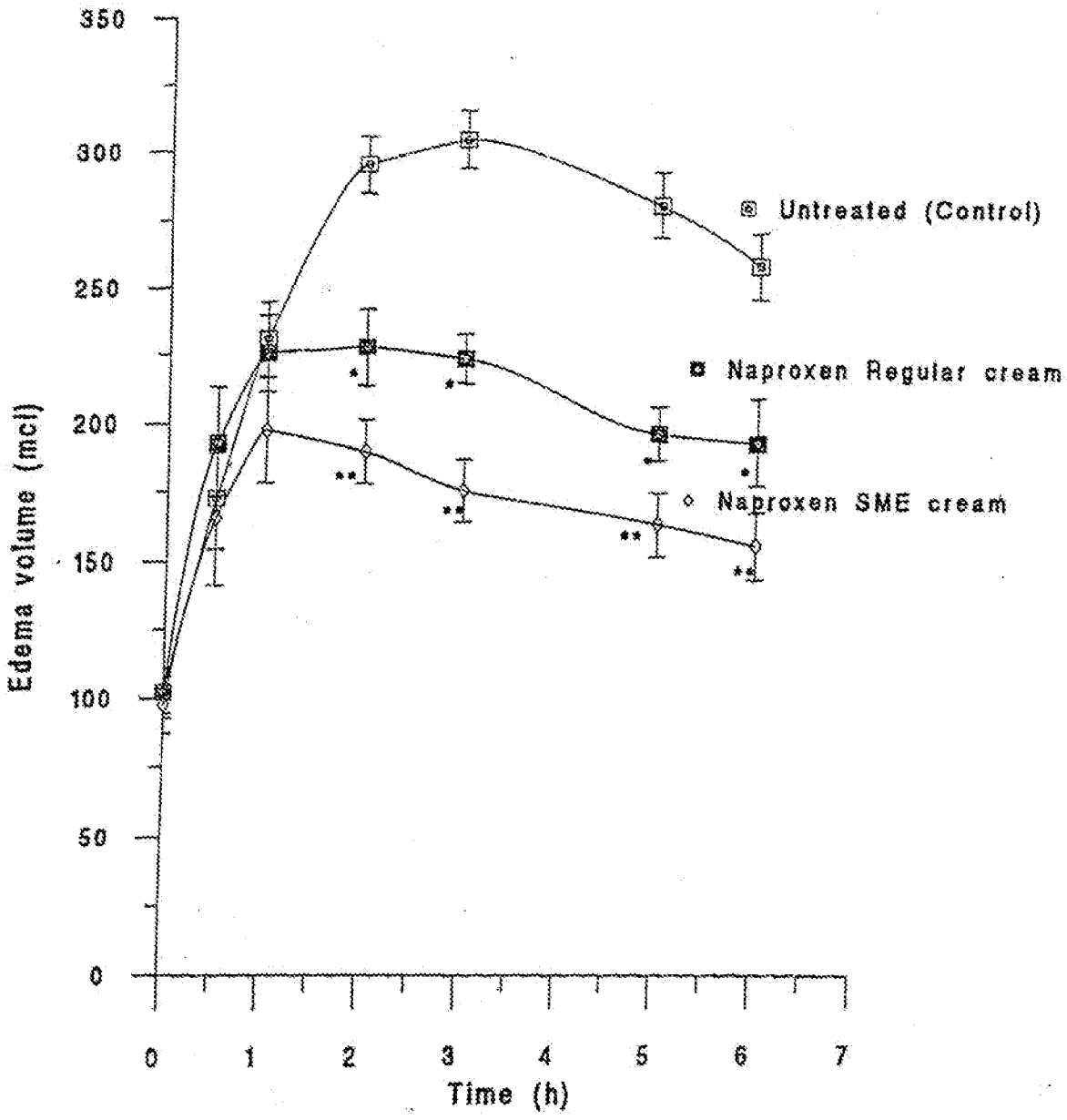



FIG. 2

NAPROXEN ANTIINFLAMMATORY ACTIVITY A COMPARISON OF REGULAR CREAM AND PHARMOS SME CREAM (1%)
Carrageenan paw edema model, edema volume-+S.D.
N=8 Rats




* Naproxen regular cream is different from Untreated (P<0.01)

** Naproxen SME cream is different from Untreated(P<0.01) and Naproxen regular cream(P<0.05)

FIG. 3

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/02800

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61K 9/127; A61F 13/02
US CL :424/450
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)
U.S. : 424/450, 447, 448; 514/859, 861, 863, 864, 886, 887, 938, 941, 943

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS: Microemulsions; Transdermal; Topical

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>Y | US, A, 4,647,586 (MIZUSHIMA)<br>03 MARCH 1987; See column 3, line 61 through column 6, line 49. | 1-7,10-13, 20-23,8-9, 14-15,24 |
| Y | US, A, 4,963,367 (ECANOW) 16 OCTOBER 1990<br>See the Abstract, column 7, line 25 through column 14, line 54; column 15, lines 58-68. | 16-19,25-32 |
| Y | US, A, 4,613,330 (MICHELSON)<br>23 SEPTEMBER 1986. See column 5, line 6 through column 6, line 4. | 29-34 |

☐ 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 part of particular relevance
"E" earlier document 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 another 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 |
|---|---|
| 28 JUNE 1993 | 29 JUL 1993 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. NOT APPLICABLE | Authorized officer<br>G. S. KISHORE<br>Telephone No. (703) 308-2351 |

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| 47/14 | G | 7329－4C | | |
| 47/34 | G | 7329－4C | | |

【公開番号】 特開平５－５８９０６

審査請求 未請求 請求項の数 2（全 4 頁） 最終頁に続く

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【発明の名称】

シクロスポリン点眼製剤

(54)【発明の名称】 シクロスポリン点眼製剤

【国際特許分類第５版】

(57)【要約】

【構成】

A61K 37/021）シクロスポリンと２）ポリソルベート、ポリオキシエチレン硬化ヒマシ油およびポリオキシエチレン脂肪酸
9/08エステルから選ばれた一種または二種以上の界面活性剤からなる点眼用水溶液製剤、および
9/141）シクロスポリンと２）ポリソルベート、ポリオキシエチレン硬化ヒマシ油およびポリオキシエチレン脂肪酸
47/14エステルから選ばれた一種または二種以上の界面活性剤からなる水溶液を凍結乾燥した点眼用製剤。
47/34【効果】本発明のシクロスポリン水溶液製剤および凍結乾燥製剤は、点眼用として優れた効果を示す。
47/44 G 7329-4C

【審査請求】未請求

【請求項の数】２

【全頁数】４

【特許請求の範囲】
【請求項１】
１）シクロスポリンと２）ポリソルベート、ポリオキシエチレン硬化ヒマシ油およびポリオキシエチレン脂肪酸エステルから選ばれた一種または二種以上の界面活性剤からなる点眼用水溶液製剤。
【請求項２】
１）シクロスポリンと２）ポリソルベート、ポリオキシエチレン硬化ヒマシ油およびポリオキシエチレン脂肪酸エステルから選ばれた一種または二種以上の界面活性剤からなる水溶液を凍結乾燥した点眼用製剤。
【発明の詳細な説明】
【０００１】
【産業上の利用分野】本発明は安全且つ使用時刺激を与えないシクロスポリン（Cyclosporin ）を含有する点眼製剤に関する。
【０００２】
【従来の技術】シクロスポリンは現在までＡ乃至Ｉまでの 9 種類が知られている。これらはいずれも分子量が約 1200 の、11 個のアミノ酸からなる環状ペプチドであり、（以下、本発明でいう「シクロスポリン」には、これらの各ペプチドおよびこれらの各ペプチドの混合物を含む。）医療上有用な免疫抑制、抗真菌、抗炎症作用等を有する（メルクインデックス、2748、396 頁、10 版： Helv.Chim.Acta 、60巻、1568-1578 頁（1977 年）： Helv.Chim.Acta 、65 巻、1655-1677 頁（1982 年）等）。
【０００３】そして現在、シクロスポリン製剤（シクロスポリンＡを主成分とする）は市販されており、免疫抑制剤として経口投与剤および注射剤の形態で使用されている（商品名「サンディミュン」；「最近の新薬」139-144 頁、38 集、1987年版）。しかし、シクロスポリンの水に対する溶解度が 20 ～30 μg ／ml と極めて低いため、上記注射剤はエタノールを含む界面活性剤溶液、経口投与剤は油性溶液製剤として調製されている。
【０００４】そして最近特に眼科領域で、免疫抑制剤として有用であることが、金井ら（第93 回日本眼科学会総会講演抄録、239 頁、「シクロスポリン点眼液の角膜移植後免疫抑制効果について」日本眼科学会雑誌、第93 巻臨時増刊号、平成元年 4月 5 日発行）により確認されるに至った。
【０００５】シクロスポリン点眼製剤としては、例えばシクロスポリンをα－サイクロデキストリンを用いる方法（特開昭 64 －85921 号）、中級脂肪酸モノおよび／またはジグリセリドを用いる方法（特開平 2－49733 号）、植物油または鉱物油を用いる方法（特公表平 3－503159号）などが知られている。
【０００６】
【発明が解決しようとする課題】本発明者らは、刺激や視野の曇りが発生しないシクロスポリン点眼製剤を見出し、本発明を完成した。
【０００７】
【課題を解決するための手段】本発明は、
（Ｉ）　１）シクロスポリンと２）ポリソルベート、ポリオキシエチレン硬化ヒマシ油およびポリオキシエチレン脂肪酸エステルから選ばれた一種または二種以上の界面活性剤からなる点眼用水溶液製剤、および（ＩＩ）１）シクロスポリンと２）ポリソルベート、ポリオキシエチレン硬化ヒマシ油およびポリオキシエチレン脂肪酸エステルから選ばれた一種または二種以上の界面活性剤からなる水溶液を凍結乾燥した点眼用製剤、からなる。
【０００８】即ち、以下の条件
（１）　シクロスポリンを界面活性剤のみで可溶化する目的で界面活性剤への溶解性、（２）可溶化したシクロスポリン液に緩衝剤、浸透圧調整剤、防腐剤、等を加えた場合の経時後の外観変化、（３）可溶化後、点眼濃度まで水で希釈した場合のウサギ点眼による目刺激試験、を満足する界面活性剤について、種々検討した結果、ポリソルベート、ポリオキシエチレン硬化ヒマシ油、ポリオキシエチレン脂肪酸エステル、が意外にも他の界面活性剤に比べて優れた効果を示した。
【０００９】本発明において使用されるポリソルベートとしては、例えば　ポリソルベート20 、 40 、 80 などを挙げることができる。好適にはポリソルベート 80 である。
【００１０】本発明において使用されるポリオキシエチレン硬化ヒマシ油としては、例えばポリオキシエチレン硬化ヒマシ油 40 、60、80、100 などを挙げることができる。好適にはポリオキシエチレン硬化ヒマシ油 60 である。
【００１１】本発明において使用されるポリオキシエチレン脂肪酸エステルとしては、例えばポリオキシエチレン脂肪酸モノステアレート（40）、モノラウレート（10）、モノオレエート（10）などを挙げることができる。好適にはポリオキシエチレン脂肪酸モノステアレート（40）である。
【００１２】本発明のシクロスポリンと界面活性剤との使用割合（重量比）は好ましくは 1：5 ないし 1：200 であり、更に好ましくは 1：20 ないし 1：100 である。
【００１３】本発明の水に対するシクロスポリンの濃度は、好ましくは 0.1～2.0 mg／ml、更に好ましくは 0.2～1.5 mg／mlである本発明の凍結乾燥した点眼用製剤は、可溶化した溶液に必要に応じて賦形剤として多価アルコール、例えば、グルコース、フラクトース、マルトース、スクロース、ソルビトール、キシリトール、マンニトールなどの糖類の一種または二種以上の混合物；ポリエチレングリコール 500 からポリエチレングリコール 30000；などを添加する。シクロスポリンと多価アルコール類との使用割合（重量比）は好ましくは 1：5 な

いし 1：200 であり、更に好ましくは 1：20 ないし 1：100 である。

【００１４】本発明において、これらの基本形に浸透圧調整剤として塩化ナトリウム，塩化カリウムのような無機塩類またはグルコース，マンニトール，ソルビトールのような糖類；防黴剤として塩化ベンザルコニウム，クロロブタノールなど；その他に緩衝剤としてクエン酸ナトリウム、リン酸ナトリウム等を加えて製剤上の改善を図ることは当業界の技術水準内のことであり、本発明に包含されるものである。

【００１５】本発明の点眼用水溶液製剤は、シクロスポリンを上記界面活性剤に溶解し、次いで水を加えて点眼濃度まで希釈することによって製造できる。このようにして得られた水溶液製剤は、必要に応じて緩衝剤を用いてｐＨを約 6.0 に調整後，無菌的な条件下で点眼容器に分別し使用に供しうる。

【００１６】また、本発明の凍結乾燥した点眼用製剤は、上記の可溶化した溶液に必要に応じて多価アルコールを添加し溶解する。次いで、バイアルに分注し、凍結乾燥機中で－40 ℃に凍結後、10 ℃の棚温で約 48時間真空乾燥することによって製造できる。このようにして得られた凍結乾燥剤は、使用時に防黴剤、浸透圧調整剤を添加した溶液で溶解し、点眼容器に移し使用に供しうる。

【００１７】

【実施例】以下に実施例、試験例を挙げるが、これらは本発明の説明のためのものであって、これによって本発明が限定されるものではない。

【００１８】なお、実施例、試験例で用いられるシクロスポリンはスイス国 Sandoz Ltd.から供給されたものであり、市販されている「サンディミュン」（商品名）の主剤と同じである。

【００１９】実施例　１．シクロスポリン 0.5ｇ をポリオキシエチレン硬化ヒマシ油（60） 20ｇに加温しつつ溶解した。溶解確認後、注射用水を徐々に添加しシクロスポリン・活性剤を可溶化した。さらに浸透圧調整剤として塩化ナトリウム８ｇ 、防黴剤を適量添加後、全量を 1000 ml とした。メンブランフィルターにて無菌的に沪過し、点眼容器に分注後、使用に供した。

【００２０】実施例　２．シクロスポリン 0.5 ｇを 20 gのポリソルベート 80 に溶解した。注射用水1000 ｍl を徐々に添加し、シクロスポリン均一水溶液を得た。次いで賦形剤としてグルコース 20ｇを添加溶解、通常の方法で凍結乾燥を行なった。使用時には無菌注用水にて溶解し、使用に供した。

【００２１】実施例　３．シクロスポリン 0.5ｇ を 20 gのポリソルベート８０中に溶解した。防黴剤を添加し非水の状態で保存した。使用時に浸透圧調整剤として塩化ナトリウム 9gを溶解した注射用水 1000 ml で使用濃度まで溶解希釈し点眼に供した。

【００２２】実施例　４．シクロスポリン 0.5ｇ をポリオキシエチレン脂肪酸モノステアレート（40）20ｇに溶解後、注射用水 100 ml を添加し均一溶液を得た。別に、マルトース10ｇを注射用水 100 ml で溶解し，シクロスポリン均一溶液に加え、注射用水にて全量 1000 ml とした。これをバイアルに分注後、凍結乾燥機中で －40℃に凍結した。さらに凍結乾燥を 10℃の棚温で 48 時間、30 ℃で 10 時間行ないシクロスポリン凍結乾燥製剤を得た。使用時には無菌注用水にて溶解し、使用に供した。

【００２３】実施例　５．シクロスポリン 1.0ｇ をポリオキシエチレン硬化ヒマシ油（６０）20ｇ に加温しつつ溶解した。これに注射用水 900 ml を徐々に添加し均一溶液を得た。40ｇのポリエチレングリコール 4000 を均一溶液に添加溶解し、注射用水にて全量を 1000 ml とした。これをバイアルに分注後、凍結乾燥機中で －50 ℃に凍結した。さらに、凍結乾燥を 0 ℃の棚温で 48 時間、30 ℃の棚温で行ないシクロスポリン凍結乾燥製剤を得た。使用時に防黴剤として塩化ベンザルコニウム、浸透圧調整剤として塩化カリウムを溶解した液にて溶解後、点眼容器に移し使用に供した。

【００２４】試験例　１．各種界面活性剤に対するシクロスポリンの溶解性、経時安定性および目刺激性を常法に従って調べた。結果を表に示す。

【００２５】

【表】

| 界面活性剤 | シクロスポリンの溶解性 | 経時安定性 | 目刺激性 |
|---|---|---|---|
| ポリソルベート 80 | ○ | ○ | ○ |
| ＰＯＥ硬化ヒマシ油 (60) | ○ | ○ | ○ |
| ＰＯＥ脂肪酸モノステアレート (40) | ○ | ○ | ○ |
| ＰＯＥ脂肪酸エーテル (25) | ○ | ○ | △ |
| プルロニックＦ68（商品名） | ○ | × | — |
| 精製卵黄レシチン | × | × | — |
| 庶糖脂肪酸ラウリルエステル | × | × | — |
| ポリグリセリンラウリルエステル | ○ | × | — |

【００２６】

【実施例の効果】シクロスポリン水溶液製剤はシクロスポリンを、選択した界面活性剤のみで溶解後、注射用水を可溶化の要領で徐々に添加し、使用濃度まで 25 ～500 倍に希釈すると澄明な水溶液として得られた。希釈した液は室温にて 6　カ月以上保存したが、析出や沈澱等は発生せず十分に点眼用に供するに可能な事がわかった。シクロスポリン凍結乾燥製剤は、水溶液の状態に比べ経時安定性に優れ、シクロスポリンの含量低下がほとんどない事を確認した。再溶解性は多価アルコール類を添加した場合、再溶解時の溶解性や外観が特によく凍結乾燥前の溶液状態となんら差は認められなかった。

ＰＯＥ＝ポリオキシエチレン

【００２７】

【発明の効果】本発明のシクロスポリン水溶液製剤および凍結乾燥製剤は、点眼用として優れた効果を示す。

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UK CL (Edition J) A5B BKA BKS
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(54) **Cyclosporin emulsion compositions**

(57) Pharmaceutical compositions comprising a cyclosporin, e.g. Ciclosporin or [Nva]²–Ciclosporin, in "microemulsion pre-concentrate" and microemulsion form. The compositions typically comprise (1.1) a $C_{1-6}$ alkyl or tetrahydrofurfuryl di– or partial-ether of a low molecular weight mono– or poly-oxy-alkane diol, as hydrophilic component. Compositions are also provided comprising a cyclosporin and (1.1) and, suitably, also a saccharide monoester, e.g. raffinose or saccharose monolaurate. Dosage forms include topical formulations and, in particular, oral dosage forms.

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At least one drawing originally filed was informal and the print reproduced here is taken from a later filed formal copy.

FIG. 1

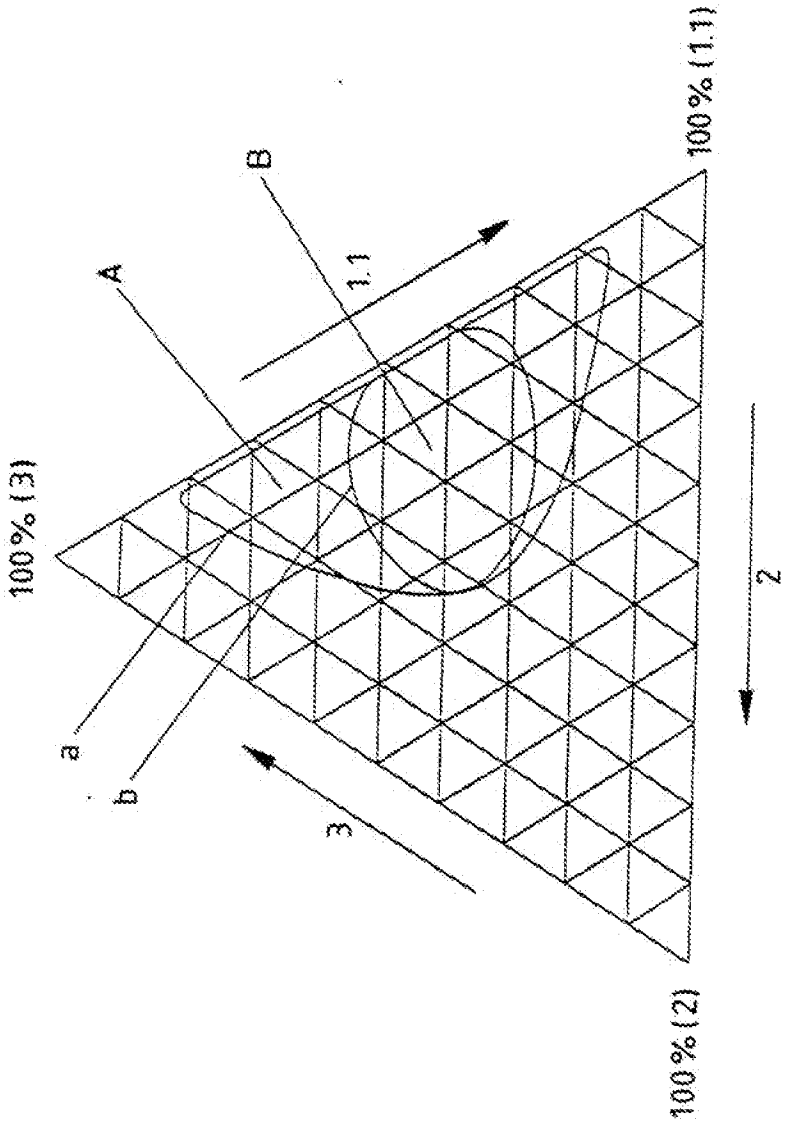


FIG. 2

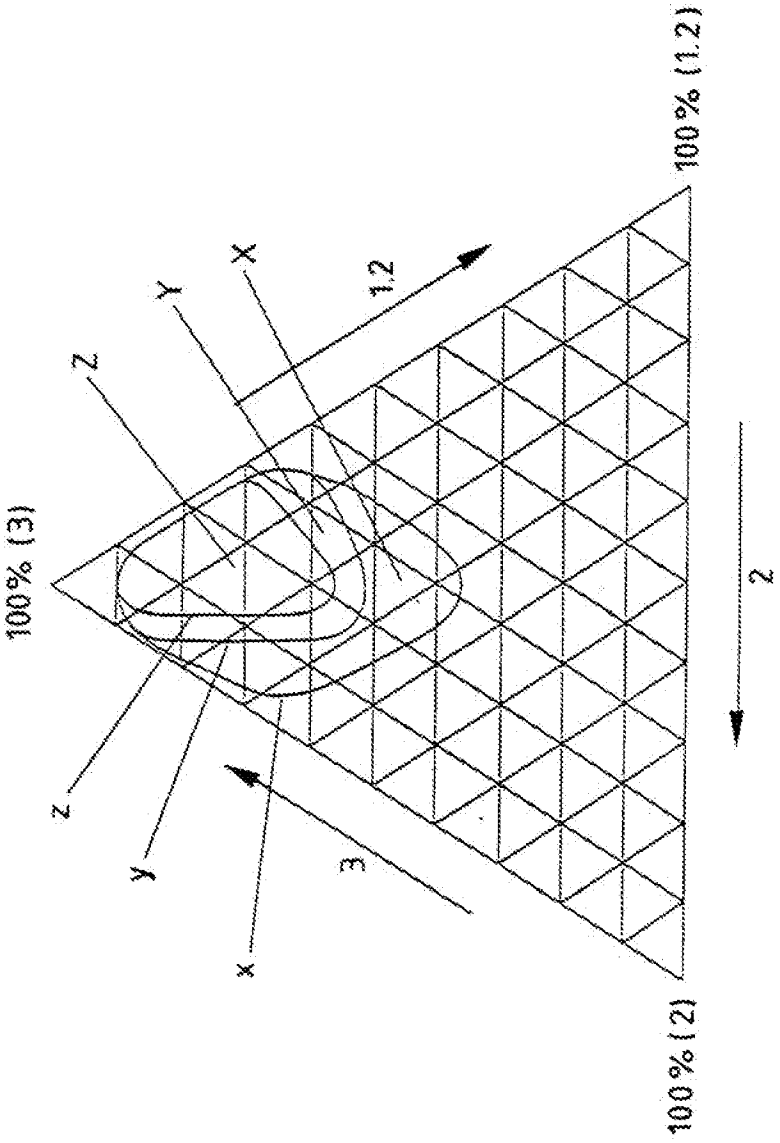


FIG. 3

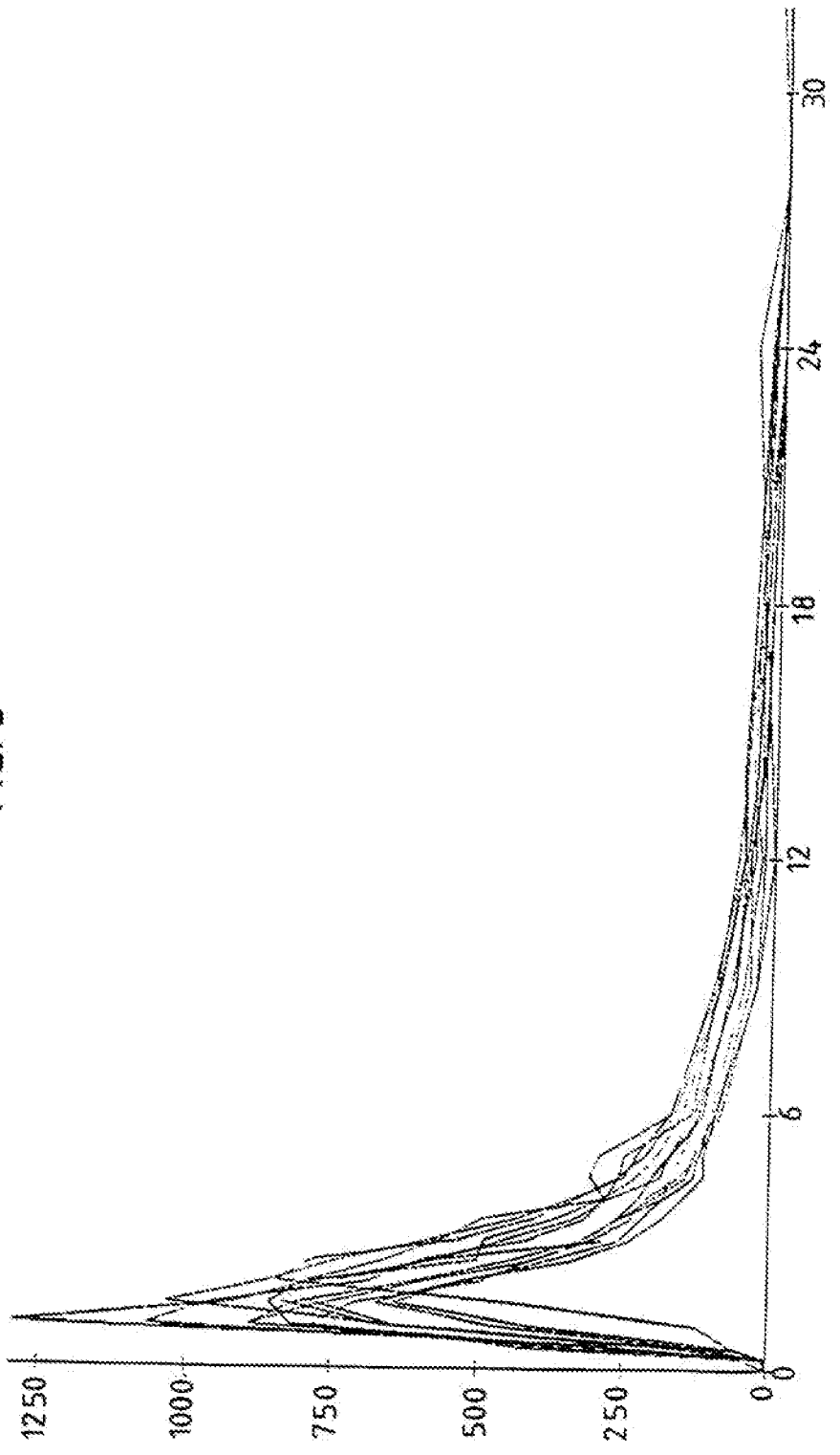
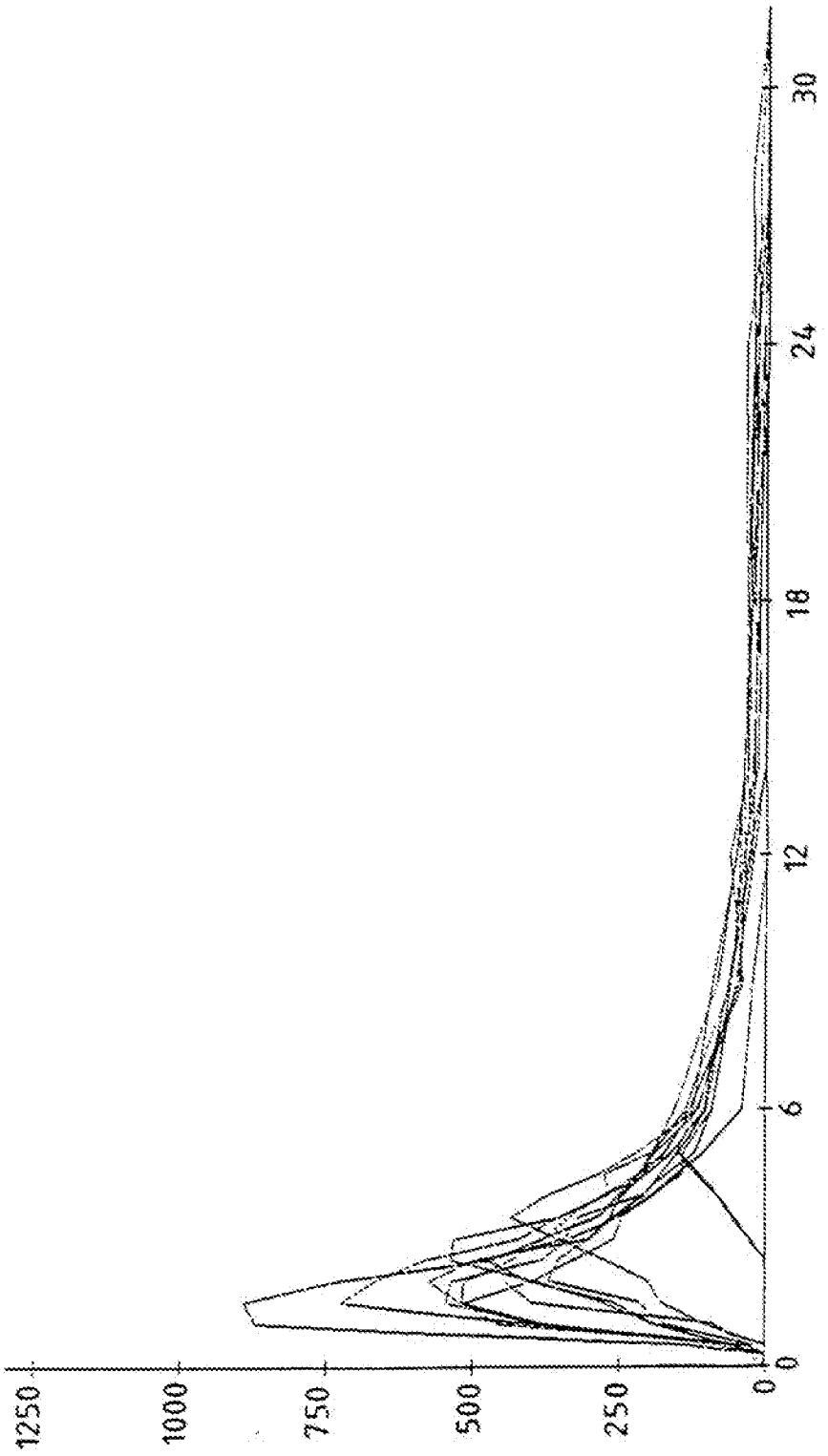


FIG. 4



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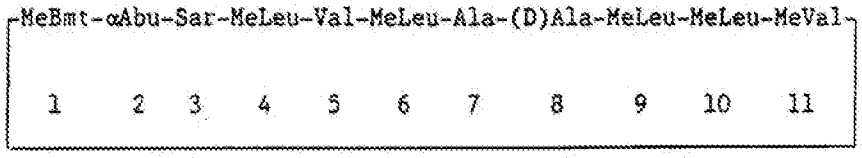
# PHARMACEUTICAL COMPOSITIONS COMPRISING CYCLOSPORINS

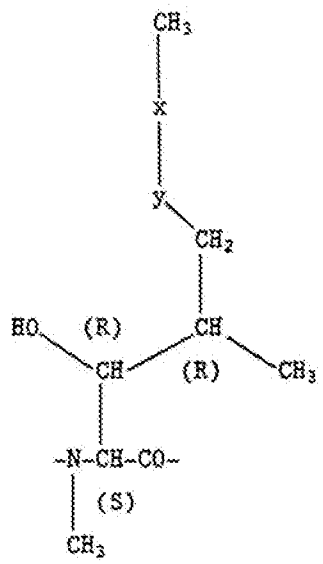
The present invention relates to novel galenic formulations comprising a cyclosporin as active ingredient.

The cyclosporins comprise a class of structurally distinctive, cyclic, poly-N-methylated endecapeptides, commonly possessing pharmacological, in particular immunosuppressive, anti-inflammatory and/or anti-parasitic activity. The first of the cyclosporins to be isolated was the naturally occurring fungal metabolite Ciclosporin or Cyclosporine, also known as cyclosporin A and commercially available under the Registered Trade Mark SANDIMMUN$^{R}$ or SANDIMMUNE$^{R}$. Ciclosporin is the cyclosporin of formula A.




(A)

wherein -MeBmt- represents the N-methyl-(4R)-4-but-2E-en-1-yl-4-methyl-(L)threonyl residue of formula B



(B)

in which -x-y- is -CH=CH- (trans).

As the parent of the class Ciclosporin has so far received the most attention. The primary area of clinical investigation for Ciclosporin has been as an immunosuppressive agent, in particular in relation to its application to recipients of organ transplants, e.g. heart, lung, combined heart-lung, liver, kidney, pancreatic, bone-marrow, skin and corneal transplants and, in particular, allogenic organ transplants. In this field Ciclosporin has achieved a remarkable success and reputation.

At the same time, applicability of Ciclosporin to various autoimmune diseases and to inflammatory conditions, in particular inflammatory conditions with an aetiology including an autoimmune component such as arthritis (for example rheumatoid arthritis, arthritis chronica progrediente and arthritis deformans) and rheumatic diseases, has been intensive and reports and results in vitro, in animal models and in clinical trials are wide-spread in the literature. Specific

auto-immune diseases for which Ciclosporin therapy has been proposed or applied include, autoimmune hematological disorder (including e.g. hemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopaenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease) endocrine opthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy).

Further areas of investigation have been potential applicability as an anti-parasitic, in particular anti-protozoal agent, with possible uses suggested including treatment of malaria, coccidiomycosis and schistosomiasis and, yet more recently, use as an agent for reversing or abrogating anti-neoplastic agent resistance in tumours and the like.

Since the original discovery of ciclosporin, a wide variety of naturally occurring cyclosporins have been isolated and identified and many further non-natural cyclosporins have been prepared by total- or semi-synthetic means or by the application of modified culture techniques. The class comprised by the cyclosporins is thus now substantial and includes, for example, the naturally occurring cyclosporins A through Z [c.f. Traber et al. 1, Helv. Chim. Acta. 60, 1247-1255 (1977); Traber et al. 2, Helv. Chim. Acta. 65 no. 162, 1655-1667 (1982); Kobel et al., Europ. J. Applied Microbiology and Biotechnology 14, 273-240 (1982); and von Wartburg et al., Progress in Allergy, 38, 28-45 (1986)], as well as various non-natural cyclosporin derivatives and artificial or synthetic cyclosporins including the so called

dihydro-cyclosporins [in which the moiety -x-y- of the -MeBmt- residue (Formula B above) is saturated to give -x-y- = $-CH_2-CH_2-$; derivatised cyclosporins (e.g. in which a further substituent is introduced at the α-carbon atom of the sarcosyl residue at the 3-position of the cyclosporin molecule); cyclosporins in which the -MeBmt- residue is present in isomeric form (e.g. in which the configuration across positions 6' and 7' of the -MeBmt- residue is cis rather than trans); and cyclosporins wherein variant amino acids are incorporated at specific positions within the peptide sequence, employing e.g. the total synthetic method for the production of cyclosporins developed by R. Wenger - see e.g. Traber 1, Traber 2 and Kobel loc. cit.; U.S. Patents Nos. 4 108 985, 4 210 581 and 4 220 641; European Patent Publication Nos. 0 034 567 and 0 056 782; International Patent Publication No. WO 86/02080; Wenger 1, Transp. Proc. 15, Suppl. 1:2230 (1983); Wenger 2, Angew. Chem. Int. Ed., 24, 77 (1985); and Wenger 3, Progress in the Chemistry of Organic Natural Products 50, 123 (1986).

The class comprised by the cyclosporins is thus now very large indeed and includes, for example, $[Thr]^2$-, $[Val]^2$-, $[Nva]^2$- and $[Nva]^2$-$[Nva]^5$-Ciclosporin (also known as cyclosporins C,D, G and H respectively), $[3\text{-}O\text{-acyl-MeBmt}]^1$-Ciclosporin (also known as cyclosporin A acetate), $[Dihydro\text{-}MeBmt]^1$-$[Val]^2$-Ciclosporin (also known as dihydro-cyclosporin D), $[(D)Fluoromethyl\text{-}Sar]^3$-Ciclosporin, $[(D)Ser]^8$-Ciclosporin, $[MeIle]^{11}$-Ciclosporin, $[(D)MeVal]^{11}$-Ciclosporin (also known as cyclosporin H), $[MeAla]^6$-Ciclosporin, $[(D)Pro]^3$-Ciclosporin and so on.

[In accordance with now conventional nomenclature for cyclosporins, these are defined by reference to the structure of Ciclosporin (i.e. Cyclosporin A). This is done by first indicating the amino acid residues present which differ from those present in Ciclosporin (e.g. "$[(D)Pro]^3$" to indicate that the cyclosporin in question has a -(D)Pro- rather than -Sar- residue at the 3-position) and then applying the term "Ciclosporin" to characterise remaining residues

which are identical to those present in Ciclosporin. Individual residues are numbered starting with the residue -MeBmt- or -dihydroMeBmt- in position 1.]

Very many of these further cyclosporins exhibit comparable pharmaceutical utility to Ciclosporin or more specific utility, for example activity particularly in reversing tumor resistance to cytostatic therapy, and proposals for their application as therapeutic agents abound in the literature.

Despite the very major contribution which Ciclosporin has made, in particular to the areas of organ transplant and the therapy of autoimmune diseases, difficulties encountered in providing more effective and convenient means of administration as well as the reported occurrence of undesirable side reactions, in particular nephrotoxic reaction, have been obvious serious impediments to its wider use or application. The cyclosporins are characteristically highly hydrophobic. Proposed liquid formulations, e.g. for oral administration of cyclosporins, have hitherto been based primarily on the use of ethanol and oils or similar excipients as carrier media. Thus the commercially available Ciclosporin drink-solution employs ethanol and olive oil as carrier medium in conjunction with labrafil as a surfactant - see e.g. US patent no. 4,388,307. Use of the drink-solution and similar compositions as proposed in the art is however accompanied by a variety of difficulties.

First, the necessity to use oils or oil based carriers may lend the preparations an unpleasant taste or otherwise reduce palatability, in particular for the purposes of long-term therapy. These effects can be masked by presentation in gelatin capsule form. However, in order to maintain the cyclosporin in solution, the ethanol content has to be kept high. Evaporation of the ethanol, e.g. from capsules or from other forms, e.g. when opened, results in the development of a cyclosporin precipitate. Where such compositions are presented in e.g.

soft gelatin encapsulated form, this particular difficulty necessitates packaging of the encapsulated product in an air-tight compartment, for example an air-tight blister or aluminium-foil blister-package. This in turn renders the product both bulky and more expensive to produce. The storage characteristics of formulations as aforesaid are far from ideal.

Bioavailability levels achieved using existing oral cyclosporin dosage systems are also low and exhibit wide variation between individuals, individual patient types and even for single individuals at different times during the course of therapy. Thus reports in the literature indicate that currently available therapy employing the commercially available Ciclosporin drink solution provides an average absolute bioavailability of ca. 30% only, with marked variation between individual groups, e.g. between liver (relatively low bioavailability) and bone-marrow (relatively high bioavailability) transplant recipients. Reported variation in bioavailability between subjects has varied from anything between one or a few percent for some patients to as much as 90% or more for others. And as already noted, marked change in bioavailability for individuals with time is frequently observed.

To achieve effective immunosuppressive therapy, cyclosporin blood or blood serum levels have to be maintained within in a specified range. The required range can in turn vary, depending on the particular condition being treated, e.g. whether therapy is to prevent transplant rejection or for the control of an autoimmune disease, and on whether or not alternative immunosuppressive therapy is employed concomitantly with cyclosporin therapy. Because of the wide variations in bioavailability levels achieved with conventional dosage forms, daily dosages needed to achieve required blood serum levels will also vary considerably from individual to individual and even for a single individual. For this reason it is necessary to monitor blood/blood-serum levels of patients receiving cyclosporin therapy at regular and frequent intervals. Monitoring of blood/blood-serum

levels, which is generally performed by RIA or equivalent immunoassay technique, e.g. employing monoclonal antibody based technology, has to be carried out on a regular basis. This is inevitably time consuming and inconvenient and adds substantially to the overall cost of therapy.

Beyond all these very evident practical difficulties lies the occurrence of undesirable side reactions already alluded to, observed employing available oral dosage forms.

Several proposals to meet these various problems have been suggested in the art, including both solid and liquid oral dosage forms. An overriding difficulty which has however remained is the inherent insolubility of the cyclosporins, e.g. Ciclosporin, in aqueous media and hence provision of a dosage from which can contain cyclosporins in sufficiently high concentration to permit convenient use and yet meet the required criteria in terms of bioavailability, e.g. enabling effective resorption from the stomach or gut lumen and achievement of consistent and appropriately high blood/blood-serum levels.

The particular difficulties encountered in relation to oral dosaging with cyclosporins have inevitably led to restrictions in the use of cyclosporin therapy for the treatment of relatively less severe or endangering disease conditions. A particular area of difficulty in this respect has been the adoption of cyclosporin therapy in the treatment of autoimmune diseases and other conditions affecting the skin, for example for the treatment of atopic dermatitis and psoriasis and, as also widely proposed in the art, for hair growth stimulation, e.g. in the treatment of alopecia due to ageing or disease.

Thus while oral Ciclosporin therapy has shown that the drug is of considerable potential benefit to patients suffering e.g. from psoriasis, the risk of side-reaction following oral therapy has prevented common use. Various proposals have been made in the art for

application of cyclosporins, e.g. Ciclosporin, in topical form and a number of topical delivery systems have been described. Attempts at topical application have however failed to provide any demonstrably effective therapy. A means of topical application providing effective dermal delivery and useful, e.g. for the treatment of psoriasis, would effectively make cyclosporin therapy available to, what is, a major patient population at need.

By the present invention there are provided novel cyclosporin galenic formulations in the form of a micro-emulsion pre-concentrate and/or based on the use of particular solvent media as hereinafter defined, which meet or substantially reduce difficulties in cyclosporin, e.g Ciclosporin, therapy hitherto encountered in the art. In particular it has been found that the compositions of the invention permit the preparation of solid, semi-solid and liquid compositions containing a cyclosporin in sufficiently high concentration to permit, e.g. convenient oral administration, while at the same time achieving improved efficacy, e.g. in terms of bioavailability characteristics.

More particularly it has been found that compositons in accordance with the present invention enable effective cyclosporin dosaging with concomitant enhancement of resorption/bioavailability levels, as well as reduced variability in resorption/bioavailability levels achieved both for individual patients receiving cyclosporin therapy as well as between individuals. By application of the teachings of the present invention cyclosporin dosage forms are obtainable providing reduced variablility in achieved cyclosporin blood/blood serum levels between dosages for individual patients as well as between individuals/ individual patient groups. The invention thus enables reduction of cyclosporin dosage levels required to achieve effective therapy. In addition it permits closer standardisation as well as optimisation of on-going daily dosage requirements for individual subjects receiving cyclosporin therapy as well as for groups of patients undergoing equivalent therapy.

By closer standardisation of individual patient dosaging rate and blood/blood-serum level response, as well as dosaging and response parameters for patient groups, monitoring requirements may be reduced, thus substantially reducing the cost of therapy.

By reduction of required cyclosporin dosaging/standardisation of achieved bio-availability characteristics, the present invention also offers a means permitting reduction in the occurrence of undesirable side-effects, in particular nephrotoxic reaction, in patients undergoing cyclosporin therapy.

In addition, the present invention enables the preparation of compositions which are non-alkanol based, e.g. which may be free or substantially free of ethanol. Such compositions avoid stability and related processing difficulties as hereinbefore discussed, inherent to known alkanolic compositions. The invention thus provides inter al. compositions which are better adapted, e.g. for presentation in capsule, e.g. hard or soft gelatin capsule form and/or which eliminate or substantially reduce packaging difficulties, for example as hereinbefore discussed, e.g. for soft gelatin encapsulated forms.

In relation to topical application, the present invention further enables the preparation of novel galenical formulations comprising a cyclosporin, e.g. Ciclosporin, as active ingredient and permitting improved treatment for autoimmune diseases affecting the skin, in particular, of dermatological disease involving morbid proliferation and/or keratinisation of the epidermis, especially of psoriasis and atopic dermatosis. Topically applicable compositions in accordance with the invention are also of use in the treatment of alopecia, e.g. for use in the promotion of hair growth.

In a first aspect, the present invention specifically provides pharmaceutical compositions comprising a cyclosporin as active ingredient, which compositions are in the form of a "microemulsion

pre-concentrate".

By the term "microemulsion pre-concentrate" as used herein is meant a system capable on contacting with, e.g. addition to, water of providing a microemulsion. The term microemulsion as used herein is used in its conventionally accepted sense as a non-opaque or substantially non-opaque colloidal dispersion comprising water and organic components including hydrophobic (lipophilic) organic components. Microemulsions are identifiable as possessing one or more of the following characteristics. They are formed spontaneously or substantially spontaneously when their components are brought into contact, that is without substantial energy supply, e.g. in the absence of heating or the use of high shear equipment or other substantial agitation. They exhibit thermodynamic stability. They are monophasic. They are substantially non-opaque, i.e. are transparent or opalescent when viewed by optical microscopic means. In their undisturbed state they are optically isotropic, though an anisotropic structure may be observable using e.g. x-ray technique.

Microemulsions comprise a dispersed or particulate (droplet) phase, the particles of which are of a size less than 2,000 Å, hence their optical transparency. The particles of a microemulsion may be spherical, though other structures are feasible, e.g. liquid crystals with lamellar, hexagonal or isotropic symmetries. Generally, micro-emulsions comprise droplets or particles having a maximum dimension (e.g. diameter) of less than 1,500 Å, e.g. typically from 100 to 1,000 Å.

[For further discussion of the characteristics of microemulsions see, e.g. Rosof, Progress in Surface and Membrane Science, 12, 405 et seq. Academic Press (1975); Friberg, Dispersion Science and Technology, 6 (3), 317 et seq. (1985); and Müller et al. Pharm. Ind., 50 (3), 370 et seq. (1988)].

From the foregoing it will be understood that the "microemulsion pre-concentrates" of the invention are galenic systems comprising a cyclosporin as active ingredient capable of forming a microemulsion, spontaneously or substantially spontaneously on contact with water alone.

Pharmaceutical "microemulsion pre-concentrate" compositions comprising cyclosporins as active ingredient are novel. Accordingly in one aspect the present invention provides:

A) A pharmaceutical composition comprising a cyclosporin as active ingredient, which composition is a "microemulsion pre-concentrate".

(The term "pharmaceutical composition" as used herein and in the accompanying claims is to be understood as defining compositions of which the individual components or ingredients are themselves pharmaceutically acceptable, e.g. where oral administration is foreseen, acceptable for oral use and, where topical administration is foreseen, topically acceptable.)

In addition to the cyclosporin active ingredient, the "microemulsion pre-concentrate" compositions of the invention will appropriately comprise:

1) a hydrophilic phase;
2) a lipophilic phase; and
3) a surfactant.

The cyclosporin is carried in the lipophilic phase. Suitably both the hydrophilic and lipophilic phases will serve as carrier medium.

"Microemulsion pre-concentrates" of the invention are of a type providing o/w (oil-in-water) microemulsions. As will be appreciated

however, compositions in accordance with (A) may contain minor quantities of water or otherwise exhibit fine structural features characteristic of microemulsions, e.g. of o/w or w/o (water-in-oil) type. The term "microemulsion pre-concentrate" as used herein is accordingly to be understood as embracing such possibilities.

Microemulsions obtained on contacting the "microemulsion pre-concentrate" compositions of the invention with water or other aqueous medium exhibit thermodynamic stability, that is they will remain stable at ambient temperatures, e.g. without clouding or regular emulsion size droplet formation or precipitation, over prolonged periods of time. [It will of course be understood that, to obtain a microemulsion, adequate water will be required. While the upper limit of dilution is not critical, a dilution of 1:1, e.g. 1:5 "p.p.w. ("microemulsion pre-concentrate": $H_2O$) or more will generally be appropriate.] Preferably, on contacting with water, the "microemulsion pre-concentrate" compositions of the invention are capable of providing microemulsions which remain stable at ambient temperatures, e.g. as evidenced by absence of any optically observable clouding or precipitation, over periods of at least 2 hours, more preferably at least 4 hours, most preferably at least 12 to 24 hours. Microemulsions obtainable from "microemulsion pre-concentrates" of the invention, e.g. at dilutions as indicated above, will preferably have an average particle size of less than about 1,500Å, more preferably of less than about 1,000 or 1,100Å, e.g. down to about 150 or 200Å.

Especially preferred in accordance with the present invention are compositions as defined under (A) in which the hydrophilic phase comprises:

1.1. A pharmaceutically acceptable $C_{1-5}$alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or poly-oxy-alkanediol; or

1.2. 1,2-propyleneglycol.

Suitable components (1.1.) are, e.g. di- or partial-, especially partial-, -ethers of mono- or poly-, especially mono- or di-, -oxy-alkanediols comprising from 2 to 12, especially 4 carbon atoms. Preferably the mono- or poly-oxy-alkanediol moiety is straight-chained. Especially suitable for use in accordance with the invention are di- or partial-ethers of formula I

$$R_1 - [O-(CH_2)_2]_x-OR_2 \qquad (I)$$

wherein $R_1$ is $C_{1-5}$ alkyl or tetrahydrofurfuryl,

$R_2$ is hydrogen, $C_{1-5}$alkyl or tetrahydrofurfuryl, and

x is an integer of from 1 to 6, especially from 1 to 4, most especially about 2.

Particularly preferred for use in accordance with the invention are partial ethers as defined above, e.g. products of formula I, wherein $R_2$ is hydrogen.

$C_{1-5}$alkyl moieties in the above defined ethers may be branched or straight chain, e.g. including methyl, ethyl, n-propyl, i-propyl, n-butyl and t-butyl groups.

Such ethers are known products and commercially available or may be produced analogously to the known products. Especially preferred products of formula I for use in relation to the present invention are those known and commercially available under the trade names Transcutol and Glycofurol.

Transcutol is the compound diethyleneglycol monoethyl ether of formula I, wherein $R_1 = C_2H_5$, $R_2 = H$ and $x = 2$.

Glycofurol, also known as tetrahydrofurfuryl alcohol polyethylene

glycol ether or α-(tetrahydrofuranyl)-ω-hydroxypoly(oxy-1,2-ethanediyl) has the formula I wherein $R_1$ =  , $R_2$ = H and x has an average value of from 1 to 2. It has an average molecular weight of ca. 190; a b.p. of from ca. 80-100°C (at 40N/m²), a density of ca. 1.070 - 1.090 g/cm³ (at 20°C); a hydroxy value of ca. 300-400; a refractive index of ca. 1.4545 (sodium D line, 589mm) (at 40°C); and a viscosity of ca. 8-18 mN s/m² (at 20°). [c.f. "Handbook of Pharmaceutical Excipients, published by American Pharmaceutical Association/ The Pharmaceutical Society of Great Briatin (1986), p. 127 and Fiedler, "Lexikon der Hilfstoffe", 3rd edition (1989), p. 577.]

The precise properties of Glycofurol vary according to relative purity. Thus lower quality grades contain significant amounts of tetrahydrofurfuryl alcohol and other impurities. For the purposes of the present invention Glycofurol 75, designating a product meeting the above physical data and for which the fraction having the formula I above in which x = 1-2 amounts to a minimum of 95%, is preferred.

Use of components defined under (1.1.) and (1.2.) above has in particular been found to provide compositions in accordance with (A) in which the hydrophilic phase is especially well suited as cyclosporin carrier medium, e.g. in which the hydrophilic phase enables cyclosporin-loading of the composition, adequate for convenient therapeutic dosaging, e.g. for oral administration.

Compositions in accordance with (A) comprising components as defined under (1.1.) and/or (1.2.) as hydrophilic phase may of course additionally include one or more further ingredients as hydrophilic phase component. Preferably however any additional components will comprise materials in which the cyclosporin active ingredient is sufficiently soluble, such that the efficacy of the hydrophilic phase as cyclosporin carrier medium is not materially impaired. Examples of possible additional hydrophilic phase components are lower (e.g. $C_{1-5}$)

alkanols, in particular ethanol.

While, however, use of alkanols, e.g. ethanol, as hydrophilic phase component is contemplated by the present invention, for reasons hereinbefore discussed, this will be generally less preferred. Preferably, compositions as defined under (A) will be non-alkanol-based, i.e. will not comprise an alkanol as a predominant hydrophilic phase component. Suitably the hydrophilic phase comprises less than 50%, more preferably less than 25%, most preferably less than 10% by weight alkanolic components. Most suitably, the hydrophilic phase will be free or substantially free of alkanolic components, i.e. comprise less than 5%, preferably less than 2%, e.g. from 0 to 1% alkanolic components. By "alkanol" is meant, in particular, $C_{1-5}$alkanols, especially ethanol.

In an especially preferred embodiment the hydrophilic phase of compositions defined under (A) will consist or consist essentially of components as defined under (1.1.) or (1.2.) above, in particular Transcutol, Glycofurol and/or 1,2-propylene glycol. Most suitably they will consist or consist essentially of either components (1.1.) or component (1.2.).

Compositions in accordance with (A) comprising a component (1.1), especially Glycofurol, are of particular interest in that they are well adapted for presentation in soft gelatin encapsulated form. Such compositions have, in accordance with the invention, also been found to exhibit surprisingly advantageous stability, e.g. as evidenced in long-term stability tests at normal and elevated temperatures. Such compositions are thus particularly well suited to meet difficulties commonly encountered in transport and storage of drug products, including long term storage at the user end, e.g. in hospitals, clinics and like facilities.

Compositions defined under (A) additionally comprise a lipophilic phase (2).

Suitable components for use as lipophilic phase include any pharmaceutically acceptable solvent which is non-miscible with the selected hydrophilic phase, e.g. as defined under (1.1.) or (1.2.). Such solvents will appropriately be devoid or substantially devoid of surfactant function. Especially suitable components for use as lipophilic phase components (2) are, e.g.:

Fatty acid triglycerides, preferably medium chain fatty acid triglycerides. Especially suitable are neutral oils, e.g. neutral plant oils, in particular fractionated coconut oils such as known and commercially available under the trade name Miglyol (c.f. Fiedler, loc. cit. pp. 808-809), including the products:

Miglyol 810: a fractionated coconut oil comprising caprylic-capric acid triglycerides and having a molecular weight : ca. 520. Fatty acid composition = $C_6$ max. 2%, $C_8$ ca. 65-75%, $C_{10}$ ca. 25-35%, $C_{12}$ max. 2%; acid no. = ca. 0.1; saponification no. = ca. 340-360; iodine no. = max. 1;

Miglyol 812: a fractionated coconut oil comprising caprylic-capric acid triglycerides and having a molecular weight = ca. 520. Fatty acid composition = $C_6$ max. ca. 3%, $C_8$ ca. 50-65%, $C_{10}$ ca. 30-45%, $C_{12}$ max. 5%; acid no. = ca. 0.1; saponification no. = ca. 330-345; iodine no. = max. 1;

Miglyol 818: a caprylic-capric-linoleic acid triglyceride having a molecular weight = ca. 510. Fatty acid composition = $C_6$ max. 3, $C_8$ ca. 45-60, $C_{10}$ ca. 25-40, $C_{12}$ ca. 2-5, $C_{18:2}$ ca. 4-6; acid no. = max. 0.2; saponification no. = ca. 315-335, iodine no. = max. 10; and

Captex 355([1]) a caprylic-capric acid triglyceride. Fatty acid content

= caproic ca. 2%, caprylic ca. 55%, capric ca. 42%. Acid no. = max. 0.1; saponification no. = ca. 325-340; iodine no. = max. 0.5.

Also suitable are caprylic-capric acid triglycerides such as known and commercially available under the trade name Myritol (c.f. Fiedler loc. cit., p. 834) including the product Myritol 813 which has an acid no. = max. 1, a saponification no. = ca. 340-350 and an iodine no. = ca. 0.5.

Further suitable products of this class are Capmul MCT(1), Captex 300(1) and Captex 800(1), Neobee M5(2) and Mazol 1400(3).

[(1) = Capital City Products, PO.Box 569, Columbus, OH, USA. (2) = Stepan, PVO Dept., 100 West Hunter Ave., Maywood, NJ 07607, USA. (3) = Mazer Chemicals, 3938 Porett Drive, Gurnee, IL, USA).]

Especially preferred as lipophilic phase component is the product Miglyol 812.

Compositions in accordance with the invention defined under (A) further comprise a pharmaceutically acceptable surfactant (3). The surfactant component may comprise (3.1.) hydrophilic or (3.2.) lipophilic surfactants, or mixtures thereof. Especially preferred are non-ionic hydrophilic and non-ionic lipophilic surfactants. Examples of suitable hydrophilic surfactants for use as surfactant components are e.g.:

3.1.1. Reaction products of natural or hydrogenated vegetable oils and ethylene glycol, i.e. polyoxyethylene glycolated natural or hydrogenated vegetable oils, for example polyoxyethylene glycolated natural or hydrogenated castor oils. Such products may be obtained in known manner, e.g. by reaction of a natural or hydrogenated castor oil or fractions thereof with ethylene oxide, e.g. in a molar ratio of from about 1:35 to about 1:60,

with optional removal of free polyethyleneglycol components from the product, e.g. in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819. Especially suitable are the various tensides available under the trade name Cremophor. Particularly suitable are the products Cremophor RH 40 having a saponification no. ca. 50-60, an acid no. = <1, an iodine no. = <1, a water content (Fischer) = <2%, an $n_D^{60}$ = ca. 1,453 - 1,457 and an HLB = ca. 14 - 16; Cremophor RH 60 having a saponification no. = ca. 40 - 50, an acid No. = <1, an iodine no. = <1, a water content (Fischer) = ca. 4.5-5.5%, an $n_D^{25}$ = ca. 1.453 - 1,457 and an HLB = ca. 15 - 17; and Cremophor EL having a molecular weight (by steam osmometry) = ca. 1630, a saponification no. = ca. 65-70, an acid no. = ca. 2, an iodine no. = ca. 28 - 32 and an $n_D^{25}$ = ca. 1.471 (c.f. Fiedler loc. cit. pp. 326-327). Also suitable for use in this category are the various tensides available under the trade name Nikkol, e.g. Nikkol HCO-60. The said product Nikkol HCO-60 is a reaction product of hydrogenated castor oil and ethylene oxide exhibiting the following characteristics: Acid no. = ca. 0.3; Saponification no. = ca. 47.4; Hydroxy value = ca. 42.5; pH (5%) = ca. 4.6; Color APHA = ca. 40; m.p. = ca. 36.0°C; Freezing point = ca. 32.4°C; $H_2O$ content (%, KF) = ca. 0.03;

3.1.2. Polyoxyethylene-sorbitan-fatty acid esters e.g. mono- and trilauryl, palmityl, stearyl and oleyl esters e.g. of the type known and commercially available under the trade name Tween (c.f. Fiedler, loc. cit. pp. 1300-1304) including the products Tween

20 [polyoxyethylene(20)sorbitanmonolaurate],
40 [polyoxyethylene(20)sorbitanmonopalmitate],
60 [polyoxyethylene(20)sorbitanmonostearate],
80 [polyoxyethylene(20)sorbitanmonooleate],
65 [polyoxyethylene(20)sorbitantristearate],

85 [polyoxyethylene(20)sorbitantrioleate],
21 [polyoxyethylene(4)sorbitanmonolaurate],
61 [polyoxyethylene(4)sorbitanmonostearate], and
81 [polyoxyethylene(5)sorbitanmonooleate].

Especially preferred products of this class for use in the compositions of the invention are the above products Tween 40 and Tween 80;

3.1.3. Polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters of the type known and commercially available under the trade name Myrj (c.f. Fiedler, loc. cit., p. 834) as well as polyoxyethylene fatty acid esters known and commercially available under the trade name Cetiol HE. (c.f. Fiedler, loc. cit., p. 284); an especially preferred product of this class for use in the compositions of the invention is the product Myrj 52 having a $D^{25}$ = ca. 1.1., m.p. = ca. 40-44°C, an HLB = ca. 16.9., an acid no. = ca. 0-1 and a saponification no. = ca. 25-35;

3.1.4. Polyoxyethylene-polyoxypropylene co-polymers, e.g. of the type known and commercially available under the trade names Pluronic and Emkalyx (c.f. Fiedler, loc. cit., pp. 956-958). An especially preferred product of this class for use in the compositions of the invention is the product Pluronic F68;

3.1.5. Polyoxyethylene-polyoxypropylene block co-polymers, e.g. of the type known and commercially available under the trade name Poloxamer (c.f. Fiedler, loc. cit., pp. 959). An especially suitable product of this class for use in the compositions of the invention is the product Poloxamer 188;

3.1.6. Dioctylsuccinate, dioctylsodiumsulfosuccinate, di-[2-ethylhexyl]-succinate or sodium lauryl sulfate;

3.1.7. Phospholipids, in particular lecithins (c.f. Fiedler, loc. cit., pp. 731-733). Lecithins suitable for use in the compositions of the invention include, in particular, soya bean lecithins;

3.1.8. Propylene glycol mono- and di-fatty acid esters such as propylene glycol dicaprylate, propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, propylene glycol stearate and so forth (c.f. Fiedler, loc. cit., pp. 1013 et seq.). Especially preferred is propylene glycol caprylic-capric acid diester as known and commercially available under the trade name Miglyol 840 (c.f. Fiedler, loc. cit., p. 809). Miglyol 840 has a fatty acid content = $C_6$ max. ca. 3%, $C_8$ ca. 65-80%, $C_{10}$ ca. 15-30%, $C_{12}$ max. 3%. Acid no. = max. 0.1, iodine no. = ca. 320-340, iodine no. = max. 1; and

3.1.9. Bile salts, e.g. alkali metal salts, for example sodium taurocholate.

Examples of suitable lipophilic surfactants for use as surfactant component are, e.g.:

3.2.1. Trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols. Such trans-esterification products are known from the art and may be obtained e.g. in accordance with the general procedures

described in US Patent No. 3,288,824. They include transesterification products of various natural (e.g. non-hydrogenated) vegetable oils for example, maize oil, kernel oil, almond oil, ground nut oil, olive oil and palm oil and mixtures thereof with polyethylene glycols, in particular polyethylene glycols having an average molecular weight of from 200 to 800. Preferred are products obtained by trans-esterification of 2 molar parts of a natural vegetable oil triglyceride with one molar part of polyethylene glycol (e.g. having an average molecular weight of from 200 to 800). Various forms of trans-esterification product of the class defined are known and commercially available under the trade name Labrafil [see Fiedler, loc. cit., 707]. Especially useful as components of the compositions of the invention are the products: Labrafil M 1944 CS, a trans-esterification product of kernel oil and polyethylene glycol having an acid no. = ca. 2, a saponification no. ca. 145 - 175 and an iodine no. = ca. 60 - 90; and Labrafil M 2130 CS, a trans-esterification product of a $C_{12}$- to $C_{18}$- glyceride and polyethylene glycol having a melting point = ca. 35 - 40°C., an acid no. = <2, a saponification no. = ca. 185 - 200 and an iodine no. = <3;

3.2.2. Mono-, di- and mono/di-glycerides, especially esterification products of caprylic or capric acid with glycerol. Preferred products of this class are e.g. those comprising or consisting mainly or essentially of caprylic/capric acid mono- and di-glycerides such as are commercially available under the trade name Imwitor (c.f. loc. cit., pp. 645). A particularly suitable product of this class for use in the compositions of the invention is the product Imwitor 742, which is the esterification product of a mixture of ca. 60 p.p.w. caprylic acid and ca. 40 p.p.w. capric acid with glycerol. Imwitor 742 is typically a yellowish crystalline mass, liquid at ca. 26°C;

acid no. = max. 2; iodine no. = max. 1; saponification no. = ca. 235 - 275; % monoglycerides = ca. 40-50%; free glycerol = max. 2%; m.p. = ca. 24 - 26°C; unsaponifiables = 0.3% max.; peroxide no. = max. 1;

3.2.3. Sorbitan fatty acid esters e.g. of the type known and commercially available under the trade name Span, for example including sorbitan-monolauryl, -monopalmityl, -monostearyl, -tristearyl, -monooleyl and -trioleyl esters - (c.f. Fiedler, loc. cit., pp. 1139-1140);

3.2.4. Pentaerythritol fatty acid esters and polyalkylene glycol ethers, for example pentaerythrite- -dioleate, -distearate, -monolaurate, -polyglycol ether and -monostearate as well as pentaerythrite-fatty acid esters (c.f. Fiedler, loc. cit. pp. 923-924);

3.2.5. Monoglycerides, e.g. glycerol monooleate, glycerol monopalmitate and glycerol monostearate, for example as known and commercially available under the trade names Myvatex, Myvaplex and Myverol (c.f. Fiedler, loc. cit., pp. 836), and acetylated, e.g. mono-and di-acetylated monoglycerides, for example as known and commercially available under the trade name Myvacet (c.f. Fiedler, loc. cit., pp. 835);

3.2.6. Glycerol triacetate or (1,2,3)-triacetin (c.f. Fiedler, loc. cit., pp. 952); and

3.2.7. Sterols and derivatives thereof, for example cholesterols and derivatives thereof, in particular phytosterols, e.g. products comprising sitosterol, campesterol or stigmasterol, and ethylene oxide adducts thereof, for example soya sterols and derivatives thereof, such as known under the trade name Generol (c.f. Fiedler loc. cit., p.p. 554 and 555) in particular the products Generol 122, 122 E5, 122 E10, and 122 E25.

Compositions as defined under (A) above include systems comprising either a single surfactant or mixture of surfactants, e.g. comprising a first surfactant and one or more co-surfactants. Surfactant and co-surfactant combinations may be selected, e.g. from any of the surfactant types indicated under (3.1.1.) to (3.2.7.) above.

When the hydrophilic phase comprises a di- or partial-ether as defined under (1.1) above, in particular Transcutol or Glycofurol, use of a single surfactant will generally be sufficient, though co-surfactants may be added if desired, e.g. to further improve stability characteristics. When 1,2-propylene glycol is employed as sole or principle hydrophilic phase component, the use of at least two surfactants, i.e. a surfactant and co-surfactant, will generally be required. Compositions as defined under (A) comprising 1,2-propylene glycol as hydrophilic phase thus suitably comprise both a surfactant and a co-surfactant.

Surfactants as defined under (3.1.1.), (3.1.3.), (3.1.7), (3.2.2.) and (3.2.5.) above are of particular interest for use in compositions as defined under (A). Especially suitable surfactant/co-surfactant combinations are hydrophilic/lipophilic surfactant combinations, e.g. combinations of surfactants in accordance with (3.1.1.) with surfactants in accordance with (3.2.5.).

When the surfactant comprises an effective solvent for the cyclosporin active ingredient, as in the case e.g. of surfactants or mixtures of

surfactants under (3.1.1.) to (3.2.7.) above, it may be incorporated into compositions as defined under (A), not only as surfactant, but in excess as an additional carrier or co-solvent phase, i.e. as part of the hydrophilic or lipophilic phase.

Compositions in accordance with (A) above may also comprise:

4. A thickening agent.

Suitable thickening agents may be of those known and employed in the art, including, e.g. pharmaceutically acceptable polymeric materials and inorganic thickening agents, for example of the following types:

4.1. Polyacrylate and polyacrylate co-polymer resins, for example poly-acrylic acid and poly-acrylic acid/methacrylic acid resins, such as known and commercially available under the trade name Carbopol (c.f. Fiedler, loc. cit., pp. 254-256), in particular the products Carbopol 934, 940 and 941, and Eudragit (c.f. Fiedler, loc. cit., pp. 486-487), in particular the products Eudragit E, L, S, RL and RS and, most especially, the products Eudragit E, L and S;

4.2. Celluloses and cellulose derivatives including: alkyl celluloses, e.g. methyl-, ethyl- and propyl-celluloses; hydroxyalkyl-celluloses, e.g. hydroxypropyl-celluloses and hydroxypropylalkyl-celluloses such as hydroxypropyl-methyl-celluloses; acylated celluloses, e.g. cellulose-acetates, cellulose-acetatephthallates, cellulose-acetatesuccinates and hydroxypropylmethyl-cellulose phthallates; and salts thereof such as sodium-carboxymethyl--celluloses. Examples of such products suitable for use in accordance with the present invention are those known and

commercially available, e.g. under the trade names Klucel and Methocel (c.f. Fiedler, loc. cit., pp. 688 and 790), in particular the products Klucel LF, MF, GF and HF and Methocel K 100, K 15M, K 100M, E 5M, E 15, E 15M and E 100M;

4.3. Polyvinylpyrrolidones, including for example poly-N-vinylpyrrolidones and vinylpyrrolidone co-polymers such as vinylpyrrolidone-vinylacetate co-polymers. Examples of such compounds suitable for use in accordance with the present invention are those known and commercially available, e.g. under the trade name Kollidon (or, in the USA, Povidone) (c.f. Fiedler, loc. cit., pp. 694-696), in particular the products Kollidon 30 and 90;

4.4. Polyvinyl resins, e.g. including polyvinylacetates and alcohols, as well as other polymeric materials including gum traganth, gum arabicum, alginates, e.g. alginic acid, and salts thereof, e.g. sodium alginates;

4.5. Inorganic thickening agents such as atapulgite, bentonite and silicates including hydrophilic silicon dioxide products, e.g. alkylated (for example methylated) silica gels, in particular colloidal silicon dioxide products as known and commercially available under the trade name Aerosil [c.f. Handbook of Pharmaceutical Excipients, loc. cit., p.p. 253-256] in particular the products Aerosil 130, 200, 300, 380, 0, OX 50, TT 600, MOX 80, MOX 170, LK 84 and the methylated Aerosil R 972.

In the case of compositions in accordance with (A) which are intended for oral administration, such thickening agents may be included, e.g.

to provide a sustained release effect. However, where oral administration is intended, the use of thickening agents as aforesaid will generally not be required and is generally less preferred. Use of thickening agents is, on the other hand, indicated, e.g. where topical application is foreseen.

Compositions in accordance with (A) above may also include one or more further ingredients in particular diluents, anti-oxidants [e.g. ascorbyl palmitate, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT) and tocopherols, e.g. α-tocopherol (vitamin E)], flavouring agents and so forth. Use of an anti-oxidant, in particular a tocopherol, is particularly advantageous.

While it is foreseen, especially where oral administration is contemplated, that compositions in accordance with the invention as defined under (A) should comprise end dosage forms for administration as such, the present invention also provides pharmaceutical compositions comprising a cyclosporin as active ingredient and which are themselves microemulsions. Thus where oral administration is practiced, microemulsions obtained, e.g. by diluting a "microemulsion pre-concentrate" as defined under (A) with water or other aqueous medium may be employed as formulations for drinking. Similarly, where topical application is foreseen, compositions comprising a hydrocolloid thickening agent, e.g. as set forth under (4.2.) or (4.4.) above will suitably also comprise water, thus providing an aqueous microemulsion in gel, paste, cream or like form. Such compositions are also new. Accordingly in a yet further aspect the present invention provides:

B) A pharmaceutical composition which is a microemulsion and comprises a cyclosporin as active ingredient.

Compositions as defined under (B) may comprise any of components (1) to (3) as hereinbefore described in relation to compositions as

defined under (A) and water. Compositions (B) are o/w microemulsions. Preferably they will exhibit stability characteristics as hereinbefore described in relation to microemulsions obtainable from compositions defined under (A).

In accordance with the present invention it has further been found that use of di- or partial-ethers as defined under (1.1.) as carrier media is quite generally advantageous for the preparation of pharmaceutical compositions comprising cyclosporins, not only in relation to the preparation of "microemulsion pre-concentrate" and microemulsion formulations as hereinbefore described. Thus use of such ethers as components of other oral and, in particular, topical delivery systems is surprisingly found of itself to meet difficulties hitherto encountered in the art as hereinbefore described. Such compositions are also new. Accordingly in a yet further embodiment the present invention also provides:

C) A pharmaceutical composition comprising a cyclosporin as active ingredient, together with a pharmaceutically acceptable $C_{1-5}$alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or poly-oxy-alkane diol.

Preferred ether components for use in compositions as defined under (C) above are as hereinbefore described in relation to (1.1.), the products Transcutol and Glycofurol being especially preferred. Compositions in accordance with (C) suitably contain one or more further ingredients, e.g. surfactants, co-solvents or thickening agents.

In particular, compositions as defined under (C) will suitably also comprise a pharmaceutically acceptable hydrophilic surfactant especially a non-ionic hydrophilic surfactant. Suitable hydrophilic surfactant components are any of those hereinbefore described under (3.1.1.) to (3.1.9.).

Compositions as defined under (C) also suitably comprise a pharmaceutically acceptable lipophilic surfactant either as a surfactant or as a co-solvent, or a pharmaceutically acceptable co-solvent. Suitable co-solvent/lipophilic surfactant components are any of those hereinbefore described under (2) and (3.2.1.) to (3.2.7.).

Compositions in accordance with (C) include forms other than as defined under (A) and (B), for example solutions, suspensions, dispersions regular emulsions and the like. In partiuclar compositions in accordance with (C) which additionally comprise a surfactant or both a surfactant and a co-solvent include, for example, emulsion pre-concentrates (i.e. compositions which, on contacting with water, provide regular emulsions - as opposed to microemulsions - of the o/w or w/o type), and regular emulsions of both hydrophilic/lipophilic and lipophilic/hydrophilic type. In the case of formulations, e.g. for drinking or for topical application, they will in particular also include aqueous emulsions of o/w or w/o type. In general emulsion pre-concentrates giving o/w emulsions and (ii) o/w emulsions as such will be preferred, in particular where oral administration is contemplated.

Compositions as defined under (C) may further comprise a pharmaceutically acceptable thickening agent, suitable thickening agents being any of those hereinbefore described under (4.1.) to (4.5.).

Compositions in accordance with (C) may also comprise further additives, e.g. preserving and flavouring agents etc... as hereinbefore described in relation to compositions (A). In particular they will preferably also include an anti-oxidant, e.g. any of the specific anti-oxidants hereinbefore described in relation to compositions (A).

Of particular interest in accordance with the present invention are:

D) Compositions as defined under (C) additionally comprising: (5) a fatty acid saccharide monoester.

Compositions as defined under (D) will generally comprise the cyclosporin in a carrier medium comprising components (1.1.), e.g. Glycofurol or Transcutol, and component (5). Commonly, the cyclosporin and component (5) will each be present in compositions in accordance with (D) in molecular dispersion or solution including, where appropriate, solid solution. Component (5) will generally act in compositions in accordance with (D) as solubilizor for the cyclosporin. Compositions in accordance with (D) have the particular advantage of meeting stability and related difficulties otherwise associated with components (5) resulting from their inherent strongly hygroscopic properties.

Preferred components (5) for use in compositions in accordance with (D) are water soluble fatty acid saccharide monoesters, e.g. fatty acid monoesters of saccharides having a solubility in water of at least 3.3% at ambient temperature, e.g. at ca. 20°C, i.e. which are soluble in water at ambient temperature in an amount of at least 1g monoester per 30 ml water.

The fatty acid moiety of components (5) may comprise saturated or unsaturated fatty acids or mixtures thereof. Particularly suitable components (5) are $C_{6-18}$-fatty acid saccharide monoesters, in particular water soluble $C_{6-18}$-fatty acid saccharide monoesters. Especially suitable components (5) are caproic ($C_6$), caprylic ($C_8$), capric ($C_{10}$), lauric ($C_{12}$), myristic ($C_{14}$), palmitic ($C_{16}$), oleic ($C_{18}$), ricinoleic ($C_{18}$) and 12-hydroxystearic ($C_{18}$) acid saccharide monoesters, especially lauric acid saccharide monoesters.

The saccharide moiety of component (5) may comprise any appropriate

sugar residue, e.g. mono-, di- or tri-saccharide residue. Suitably, the saccharide moiety will comprise a di- or tri-saccharide residue. Preferred components (5) comprise $C_{6-14}$-fatty acid di-saccharide monoesters and $C_{8-18}$-fatty acid tri-saccharide monoesters. Especially suitable saccharide moieties are saccharose and raffinose residues.

Particularly suitable components (5) are thus: saccharose monocaproate, saccharose monolaurate, saccharose monomyristate, saccharose monooleate, saccharose monoricinoleate, raffinose monocaproate, raffinose monolaurate, raffinose monomyristate, raffinose monopalmitate and raffinose monooleate. Most preferred components (5) are raffinose monolaurate and, especially, saccharose monolaurate.

Components (5) will suitably have a hydrophilic-lipophilic balance (HLB) of at least 10.

Components (5) suitably have an ester residue purity of at least 80%, more preferably at least 90%, most preferably at least 95%. Components (5) suitably have a melting point of from about 15° to about 60°C, more preferably from about 25° to about 50°C.

Compositions in accordance with (D) may also contain further ingredients, e.g. as hereinbefore described in relation to compositions (C).

In particular, they may include a component capable of modifying the release characteristics of the composition with respect to the cyclosporin, for example thickening agents, e.g. such as hereinbefore described under (4.1.) to (4.5.).

Compositions in accordance with (D) will in particular also suitably comprise one or more anti-oxidants, e.g. as hereinbefore specified in relation to compositions (A).

Compositions in accordance with (D) will also suitably comprise one or more stabilizors or buffering agents, in particular to prevent hydrolysis of component (5) during processing or on storage. Such stabilizors may include acid stabilizors such as citric acid, acetic acid, tartaric acid or fumaric acid as well as basic stabilizors such as potassium hydrogen phosphate.

Such stabilizors or buffer agents will appropriately be added in an amount sufficient to achieve or maintain a pH within the range of from about 3 to 8, more preferably about 5 to 6, compositions in accordance with (D) having a pH within the above indicated ranges being generally preferred.

Compositions in accordance with (D) will in particular also preferably comprise a polyoxyalkylene-free hydrophilic surfactant, such as set forth under (3.1.6.) or (3.1.7.) above.

Compositions in accordance with the present invention may be employed for administration in any appropriate manner, e.g. orally, e.g. in unit dosage form, for example in hard or soft gelatin encapsulated form, parenterally or topically e.g. for application to the skin, for example in the form of a cream, paste, lotion, gel, ointment, poultice, cataplasm, plaster, dermal patch or the like, or for ophthalmic application, for example in the form of an eye-drop, -lotion or -gel formulation. Readily flowable forms, for example solutions and microemulsions, may also be employed e.g. for intralesional injection for the treatment of psoriasis, or may be administered rectally, e.g. as an enema for the treatment of inflammatory bowel disease or Crohn's disease. Compositions in accordance with the invention are however primarily intended for oral or topical application, in particular application to the skin.

The relative proportion of ingredients in the compositions of the invention will, of course, vary considerably depending on the

particular type of composition concerned, e.g. whether it is a "microemulsion pre-concentrate", microemulsion, regular emulsion, solution and so forth. The relative proportions will also vary, depending on the particular function of ingredients in the composition, for example, in the case of a surfactant component of a "microemulsion pre-concentrate", on whether this is employed as a surfactant only or both a surfactant and a co-solvent. The relative proportions will also vary depending on the particular ingredients employed and the desired physical characteristics of the product composition, e.g. in the case of a composition for topical use, whether this is to be a free flowing liquid or a paste. Determination of workable proportions in any particular instance will generally be within the capability of the man skilled on the art. All indicated proportions and relative weight ranges described below are accordingly to be understood as being indicative of preferred or individually inventive teachings only and not as not limiting the invention in its broadest aspect.

The amount of cyclosporin in compositions of the invention will of course vary, e.g. depending on the intended route of administration and to what extent other components, in particular components (2) to (5) as hereinbefore described, are present. In general however the cyclosporin will be present in an amount within the range of from 0.05 especially about 0.1 to about 35% by weight based on the total weight of the composition.

Components (1) will suitably be present in the compositions of the invention in an amount of from about 0.5 to about 90% by weight based on the total weight of the composition. In the case of compositions in accordance with the invention comprising a component (1.1.) (e.g. Glycofurol or Transcutol), (1.1.) will generally be present in an amount of from about 1 to about 90% by weight, more commonly from about 5 or 10 to about 70% by weight based on the total weight of the composition. In the case of compositions in accordance with (A) or (B)

above comprising a component (1.2.), (1.2.) will generally be present in an amount of from about 2 to about 50% by weight based on the total weight of the composition. In the case of compositions in accordance with the invention comprising a component (2) or (3), these will each be generally present in an amount of from about 0.5 to about 90% by weight based on the total weight of the composition. In an especially preferred aspect the present invention relates to:

E) Compositions as defined under (A) or (C) above for oral administration, e.g. in a form suitable or convenient for oral administration.

For compositions as defined under (A) to (C) intended for non-topical administration and, in particular, for oral dosage forms (E):

a) The cyclosporin will generally be present in an amount of from about 1 or 2 to about 30%, suitably from about 4 to about 25% by weight based on the total weight of the composition. More suitably the cyclosporin will be present in an amount of from about 5 to about 25, especially to about 20%, e.g. from about 5 to 15% by weight based on the total weight of the composition;

b) Component (1.1) when present will generally be present in an amount of from about 15 to about 85, suitably from about 20 to about 80, more suitably from about 25 to about 70, e.g. from about 30 to about 50 or 60% by weight based on the total weight of the composition;

c) Cyclosporin and component (1.1.) when present will generally be present in a ratio of about 1:0.75 to 20, suitably about 1:1 to 15, more suitably about 1:1 to 5, e.g. about 1:1 or 1:1.5 to 4 p.p.w. [Cyclosporin: (1.1.)];

d) Component (1.2.) when present will generally be present in an amount of from about 3 to about 45, suitably about 5 to about 30% by weight based on the total weight of the composition;

e) Cyclosporin and component (1.2.) when present will generally be present in a ratio of about 1:0.1 to 20, suitably about 1:0.2 to 10 p.p.w.. More suitably they will be present in a ratio of about 1:0.3 to 6, e.g. about 1:0.5 to 3 p.p.w. [Cyclosporin: (1.1)].

f) Component (2) when present will generally be present in an amount up to about 45%, suitably up to about 40% by weight based on the total weight of the composition. More suitably component (2) will be present in an amount of from about 2 to about 45, yet more suitably from about 3 to about 35, most suitably from about 5 or 10 to about 30% by weight based on the total weight of the composition.

g) Components (2) and (1.1) when present will generally be present in a ratio of about 1:0.5 to 40, suitably about 1:0.5 to 20, more suitably about 1:0.75 to 10, e.g. about 1:0.75 to 4 p.p.w. [(2):(1)].

h) Components (2) and (1.2) when present will suitably be present in a ratio of about 1:0.075 to 22, suitably about 1:0.1 to 15, most suitably about 1:0.15 to 6 p.p.w., e.g. about 1:0.5 to 3 p.p.w. [(2):(1.2)].

i) Components (3) when present [including both components of type (3.1.) and (3.2.)], will generally be present in an amount of up to about 90, e.g. from about 20 to about 90% by weight based on the total weight of the composition. More suitably components (3) will be present in an amount of from about 20 or 25 to about 80 or 90% by weight based on the total weight of the composition, e.g. from about 25 to about 55% when a component (1.1) is employed or

from about 40 to 75% when a component (1.2) is employed.

j) Cyclosporin and component (3) [including both components of type (3.1.) and (3.2.)] when present will generally be present in a ratio of about 1:0.5 to 20, more suitably to 12 p.p.w.. Appropriately they will be present in a ratio of about 1:1 to 10 p.p.w., e.g. about 1:1 to 5 p.p.w. when a component (1.1) is present or about 1:3 to 8 p.p.w. when a component (1.2) is present. [Cyclosporin: (3)].

For compositions as defined under (A) and (B) ["microemulsion pre-concentrates" and microemulsions] the relative proportions of ingredients comprising (1) the hydrophilic phase, (2) the lipophilic phase and (3) the surfactant will vary with the concentration of cyclosporin present. They will also vary in relative proportion to each other.

Compositions according to (A) may thus be defined as comprising a cyclosporin together with (1) a hydrophilic phase [e.g. as defined under (1.1) or (1.2) above], (2) a lipophilic phase [e.g. as defined under (2.1) or (2.2) above] and a surfactant [e.g. as defined under (3.1) or (3.2) above], the relative proportions of cyclosporin: (1):(2):(3) being such that on contact with water, e.g. as hereinbefore indicated in relative proportions of 1:1 p.p.w. [cyclosporin+(1)+(2)+(3)):$H_2O$] or more, a microemulsion [e.g. of o/w type] is obtainable.

Similarly compositions according to (B) may be defined as comprising a cyclosporin together with components (1), (2) and (3) as aforesaid and water in relative proportions, e.g. as hereinbefore indicated, required to provide a microemulsion [e.g. of o/w type].

Compositions in accordance with (A) and (B) preferably comprise from about 2 to about 30, more preferably from about 5 to about 20, most

preferably from about 10 to about 15% by weight of cyclosporin based on the total weight of cyclosporin plus components (1) + (2) + (3).

When (1) of compositions (A) or (B) is as defined under (1.1) above, e.g. comprises Transcutol or Glycofurol, components (1.1), (2) and (3) will preferably be present in amounts of from about 15 to about 85%, more preferably from about 25 to about 65% of (1.1), from about 2 to about 40, more preferably from about 3 to about 35 most preferably from about 3 to about 30% of (2) and from about 15 to about 85, more preferably from about 25 to about 55 or 60% of (3), all %ages being by weight based on the total of (1.1) + (2) + (3). Use of Glycofurol is of particular interest.

When (1) of compositions (A) or (B) is 1,2-propylene glycol [(1.2) above], components (1.2.), (2) and (3) will suitably be present in amounts of from about 3 to about 35%, more preferably from about 3 to about 25% of (1.2), from about 2 to about 35%, more preferably from about 3 to about 30% of (2) and from about 45 to about 90%, more preferably from about 50 to about 90%, e.g. from about 55 to about 80% of (3), all %ages being by weight based on the total of (1.2) + (2) + (3). As previously indicated, when (1) is 1,2-propylene glycol component (3) will generally comprise both a surfactant and a co-surfactant. When a co-surfactant is employed, surfactant and co-surfactant will suitably be present in a ratio of up to about 50:1, preferably up to 20:1, more preferably up to 15:1, e.g. from 2 to 15:1 p.p.w. (surfactant: co-surfactant).

Fig. I attached, represents a three-way plot for relative concentrations of components (1.1) (e.g. Glycofurol), (2) (e.g. Miglyol 812), and (3) (e.g. Cremophore RH40) in compositions according to (A) and comprising ca. 10% cyclosporin (e.g. Ciclosporin) by weight. Relative concentration of component (1.1) increases from 0% along the left hand margin of the plot to 100% at the lower right corner, as indicated by the arrow "1.1". Concentration of component

(2) increases from 0% at the right hand margin of the plot to 100% at the lower left corner, as indicated by the arrow "2". Thus a composition comprising 50% of (1.1) and 50% of (2) only, is designated at the mid-point of the base-line of the plot. Relative concentration of component (3) increases from 0% at the base-line of the plot to 100% at the apex, as indicated by the arrow "3". Lines within the plot represent increments of 10%, from 0% at each margin to 100% at the apex opposite.

For compositions as defined under (A) and (B) the relative proportion of components (1.1), (2) and (3) will suitably lie within the area A defined by the line a of Fig. I. More suitably the relative proportion of components (1.1), (2) and (3) will lie within the area B defined by the line b of Fig. I, microemulsions based on these proportions being found to have greatest stability, e.g. of >24 hrs./an average particle size of less than 1,000Å. Compositions in accordance with the invention comprising the components (1.1), (2) and (3) in relative proportion as defined above with reference to Fig. I accordingly represent especially preferred embodiments.

Fig. II attached, represents a three-way plot for relative concentrations of components (1.2), (2) e.g. Miglyol 812 and (3) in compositions according to (A) and comprising ca. 10% cyclosporin (e.g. Ciclosporin) by weight. In this case (3) comprises an appropriate surfactant/co-surfactant mixture, e.g. in a ratio of 11:1 p.p.w., for example comprising 11 p.p.w. Cremophor RH40 and 1 p.p.w. Glycerinmonooleate. Relative amounts of components (1.2), (2) and (3) are indicated, as for Fig. I, by arrows "1.2", "2" and "3" respectively.

For compositions as defined under (A) and (B) the relative proportions of components (1.2), (2) and (3) will suitably lie within the area X defined by the line x of Fig. II. More suitably the relative proportion of components (1.2), (2) and (3) will lie within the area Y

defined by line y of Fig. II. Most suitably the relative proportion of components (1.2), (2) and (3) will lie within the area Z of Fig. I defined by line z, microemulsions based on proportions within the areas Y and Z having an average particle size of the order of 1,100Å and <200Å respectively and a stability, e.g. of >24 hrs..

Compositions in accordance with (E) above may additionally include a thickening agent, though, as previously indicated, this will generally be less preferred. Suitable thickening agents include any of those hereinbefore described under (4) above. The amount of thickening agent present may vary e.g. depending on the required consistency of the end product, e.g. whether it is to be in a thickened flowable form, for example for filling into a capsule or the like, or sufficiently resilient to be mouldable or formable, e.g. for use in the manufacture of tablets or the like. The amount will of course also depend on the nature of the thickening agent chosen. In general components (4), when present will be present in an amount of up to about 25% by weight based on the total weight of the composition, more suitably in an amount of up to about 15 or 20% by weight, e.g. in an amount of from 0.5 or 5 up to 15 or 20% by weight based on the total weight of the composition.

Compositions in accordance with (E) may also include further additives or ingredients, e.g. as hereinbefore described with reference to compositions (A) and (C). In particular they may comprise antioxidants, e.g. in an amount of up to about 0.5 or 1% by weight based on the total weight of the composition, and sweetening or flavouring agents, e.g. in an amount of up to about 2.5 or 5% by weight based on the total weight of the composition.

Compositions (E) in accordance with definition (A) have been found to exhibit especially advantageous properties when administered orally, e.g. in terms of both the consistancy and high level of bioavailability achieved. In particular, and in contrast with other

galenic systems, e.g. as known from the art, it has been found that such compositions are compatible with tenside materials, e.g bile salts, present in the gastro-intestinal tract. That is, they are fully dispersible in aqueous systems comprising such natural tensides and are thus capable of providing microemulsion systems in situ which are stable and do not exhibit precipitation or other disruption of fine particulate structure. Function of such systems on oral administration remains independent of and/or unimpaired by the relative presence or absence of bile salts at any particular time or for any given individual. Such compositions accordingly represent an especially preferred embodiment of the invention.

Compositions in accordance with (E) above will preferably be compounded in unit dosage form, e.g. by filling into orally administerable capsule shells, e.g. soft or hard gelatine capsule shells or by tabletting or other moulding process. Where compositions (E) are in unit dosage form, each unit dosage will suitably contain between about 5 or 10 and about 200mg cyclosporin, more suitably between about 15 or 25 and about 150mg, e.g. 25, 50 or 100mg cyclosporin. Thus unit dosage forms in accordance with the invention, suitable for administration 1x, 2x or 3x up to 5x daily (e.g. depending on the particular purpose of therapy, the phase of therapy etc...) will appropriately comprise e.g. about 50mg or about 100mg cyclosporin per unit dosage.

Compositions in accordance with (B) above for oral administration may be prepared, by addition of compositions as described in relation to (A) or (E) above to water or any other aqueous system, e.g. in relative proportions (composition:$H_2O$) as hereinbefore indicated, for example a sweetened or flavoured preparation for drinking. Such compositions may thus comprise any system as hereinabove defined or described in relation to compositions (A) or (E), plus sufficient water to form a microemulsion.

Compositions as defined under (D) above are, in particular, intended for oral administration, though use in form suitable, e.g. for topical, including dermal and topical ophthalmic, parenteral or rectal administration, as well as for intralesional injection, is also embraced.

In the case of compositions as defined under (D) the cyclosporin and required component (1.1) may be present in a ratio of about 1:0.5 to 200, preferably about 1:0.5 to 100, more preferably about 1:0.5 to 50 p.p.w.. Yet more suitably they will be present in a ratio of about 1:1 to 10, more preferably 1:1 to 5, most preferably about 1:1.5 to 2.5, e.g. about 1:1.6 or 1:2 p.p.w. [Cyclosporin: (1.1)]. Cyclosporin and required component (5) will suitably present in a ratio of about 1:3 to 200, preferably about 1:3 to 100, more preferably about 1:3 to 50 p.p.w.. Yet more suitably they will be present in a ratio of about 1:5 to 20, preferably about 1:5 to to 10, most preferably about 1:6.0 to 6.5, e.g. about 1:6.25 p.p.w. [Cyclosporin:(1.1)].

Suitably compositions in accordance with (D) will be made up in unit dosage form, whether for oral administration or otherwise.

The amount of cyclosporin present in such unit dosage forms will of course vary depending on e.g. the condition to be treated, the intended mode of administration and the effect desired. In general however, unit dosage forms in accordance with (D) will suitably comprise from about 2 to about 200mg cyclosporin, per unit dosage.

Suitable dosage forms for oral administration include e.g. liquids, granulates and the like. Preferred dosage forms are however unit dosage forms, for example tabletted or encapsulated forms, in particular hard or soft gelatin encapsulated forms.

Unit dosage forms for oral administration in accordance with (D) will suitably comprise from about 5 or 10 to about 200mg, more suitably

from about 15 or 20 to about 100mg, e.g. 25, 50 or 100mg cyclosporin per unit dosage.

Compositions (D) have the further advantage that they are able to provide the basis for compositions exhibiting modified release characteristics, for example delayed release of cyclosporin or release of cyclosporin over prolonged periods of time, e.g. following oral administration. Such compositions additionally comprise a component capable of modifying the release characteristics of the composition with respect to the cyclosporin. Such components include, for example, (4), a thickening agent, e.g. in accordance with any of (4.1) to (4.5) above.

When compositions (D) comprise a component (4), this is suitably present in an amount of from about 0.5 to 50%, more preferably from about 1 to 20%, most preferably from about 2 to 10% by weight based on the total weight of Cyclosporin plus (1.1) + (4) + (5).

As previously indicated, compositions in accordance with (D) will advantageously include one or more stabilizors or buffering agents or polyoxyalkylene-free surfactants. Such stabilizors and/or buffering agents will suitably be present in an amount of up to 5% by weight or, when citric or acetic acid are employed, up to 10% by weight based on the weight of cyclosporin plus (1.1) + (5). When a surfactant as aforesaid is present, this is suitably present in an amount of from about 5 to about 50, more preferably from about 10 to about 25% by weight based on the weight of component (5).

Compositions in accordance with (D) will also suitably comprise further additives in particular flavouring agents or, in particular, anti-oxidants. Suitable anti-oxidants and quantities employed are as hereinbefore described in relation to compositions (E).

Compositions in accordance with (D) will also preferably be free or

substantially free of lower alkanols, in particular ethanol, e.g. comprise less than 5%, more preferably less then 2%, e.g. from 0 to 1%, lower alkanolic components based on the total weight of the composition.

Compositions as defined under (A) to (C) are also of particular interest for topical administration. Accordingly in a yet further aspect the present invention provides:

F) Compositions as defined under any one of (A) to (C) above for topical, especially for dermal application, i.e. in a form suitable or convenient for topical application.

Where topical administration is contemplated, the cyclosporin will suitably be present in an amount of from about 0.05, more preferably from about 0.1, to about 15% by weight based on the total weight of the composition. More preferably the cyclosporin will be present in an amount of from about 0.1 to about 10% by weight.

In the case of compsitions (F) which are compositions in accordance with (A) or (B), the relative proportion of components (1), (2) and (3) will be as hereinbefore described for such compositions, e.g. with reference to Figs. I and II.

Compositions (F) in accordance with (C) the other hand may take any suitable form, e.g. comprise solutions, suspensions, dispersions and regular emulsions. Component (1.1) may suitably be present in such compositions in an amount of from about 1 to about 70%, preferably from about 5 to about 50%, more preferably from about 7 to about 25% by weight based on the total weight of the composition.

Compositions (F) will suitably comprise one or more carriers or diluents and/or other ingredients providing a carrier system, e.g. thickening agents, emulsifying agents, preserving agents, moisturising

agents, colourants and so forth.

Compositions (F) may be in any form suitable for topical application, e.g. application to the skin surface, for example flowable, e.g. liquid or semi-liquid form, in the form of a powder or in the form of a topically applicable spray. Examples of suitable flowable forms include e.g. gels, including oil-in-water and water-in-oil emulsions or microemulsions, creams, pastes amd ointments and the like as well as lotions, and tinctures, etc.. Such compositions also include, e.g. cataplasms and poultices as well as transdermal patch systems.

Selection of excipients for the preparation of such formulations will, of course, be determined by the type of formulation desired as well as the particular condition to be treated, the status of the condition, area to be treated, skin condition and effect desired. Thus chronic psoriatic plaques will more suitably be treated with hydrophobic, e.g. fat-based compositions, for example compositions in accordance with the invention comprising a petrolatum based ointment or cream as carrier medium. In contrast, compositions for use in the treatment of disease conditions involving acute phase inflammatory processes will more appropriately be treated with more hydrophilic compositions, e.g. compositions in accordance with the invention in the form of an oil-in-water emulsion or gel. Although, compositions (F) may comprise, e.g. lower alkanols, for example ethanol, for example as diluent or diluent component, use of these will preferably be avoided, e.g. where compromised skin is to be treated, as in the case of psoriasis. Preferred compositions (F) are thus free or substantially alkanol free, e.g. contain less than 5%, more preferably less than 2%, e.g. from about 0 to 1% by weight alkanolic components, in particular of ethanol.

Especially preferred compositions (F) are compositions in accordance with (A), (B) or (C) additionally comprising: (6) a (further) pharmaceutically acceptable diluent or carrier which is non-miscible

with component (1.1.). Compositions as aforesaid will preferably take the form of a water-free or substantially water-free emulsion, i.e. comprise less than 10%, preferably less than 5%, most preferably less than 1% water. Such emulsions include both emulsions comprising component (1.1.) in (6), and emulsions comprising (6) in (1.1.). Preferably they will comprise an emulsion of (1.1.) in (6).

Suitable components (6) include, for example:

6.1. Solid hydrocarbons, for example petroleum jellies, e.g. white petrolatum or Vaseline®, ceresin and solid paraffins, as well as waxes including animal, vegetable and synthetic waxes such as, for example, spermaceti, carnauba and bees wax;

6.2. Liquid hydrocarbons, e.g. liquid paraffins and fatty acid esters such as isopropylmyristate and cetyl palmitate;

6.3. Non-volatile silicones including silicone oils and pastes, and silicone-polyalkyleneoxide co-polylymers [c.f. Fiedler, loc.cit., pp. 1109 and 1110] for example such as known and commercially available under the trade name Piroethicon.

Components (6) will suitably be present in compositions (F) in an amount of up to about 80%, e.g. from about 5 to about 70%, preferably from about 25 to about 60% by weight based on the total weight of the composition.

By use of individual ingredients (6) or mixtures thereof, emulsions may be obtained in liquid or semi-solid form depending on, e.g., desired requirements for topical application.

Compositions (F) will suitably also comprise a surfactant. Suitable

surfactants include, in particular, lipophilic surfactants, including any of those listed under (3.2.1.) to (3.2.7.) above, especially surfactants having an HLB of ca. 5-7. Examples of surfactants of particular utility in relation to compositions (F) include for example, surfactants as described under (3.1.2.), and (3.2.3.) above as well as glycerol monstearate, propyleneglycol monostearate, diethyleneglycol monostearate and glycerol ricinoleate.

Surfactants as aforesaid will suitably be present in compositions (F) in an amount of up to about 60%, e.g. from about 2 to about 50%, preferably from about 10 to about 40% by weight based on the total weight of the composition.

Compositions (F) may further comprise one or more consistency promoting agents, for example microcrystalline waxes, vegetable oils such as olive oils, corn oils and kernel oils, and vegetable oil derivatives including hydrogenated vegetable oils and vegetable oil partial-glycerides, e.g. in an amount of from about 0.1 to about 10%, preferably from about 1 to about 5% weight based on the total weight of the composition.

Compositions (F) will also suitably comprise:

- an anti-oxidant, e.g. any of the antioxidants hereinbefore described in relation to compositions (A), for example in an amount of from about 0.01 to about 0.5% by weight based on the total weight of the composition;

- an anti-bacterial agent, e.g. benzyl alcohol, methyl- or propyl-paraben, benzalkonium chloride, benzoic acid, sorbic acid or chlorobutanol, for example in an amount of from about 0.05 to about 2% by weight based on the total weight of the composition;

- a stabilizor such as microcrystalline starch, sodium EDTA or magnesium sulfate, e.g. in an amount of from about 0.1 to about 10% by weight based on the total weight of the composition; and/or

- a skin penetration enhancer, for example a $C_{12-24}$ mono- or poly-unsaturated fatty acid or alcohol (e.g. vaccenic, cis-vaccenic, linoleic, linolenic, elaidic oleic, petroselinic, erucic or nervonic acid or any of their corresponding alcohols, especially oleic acid or oleyl alcohol), or 1-dodecylazacycloheptan-2-one also known as Azone (c.f. Fiedler, loc. cit., p. 190), e.g. in an amount of from about 1 to about 20, suitably from about 3 to about 15% by weight based on the total weight of the composition.

In addition to the foregoing the present invention also provides a process for the production of a pharmaceutical composition as hereinbefore defined, e.g. as hereinbefore defined under anyone of (A) to (F) above, which process comprises bringing the individual components thereof into intimate admixture and, when required compounding the obtained composition in unit dosage form, for example filling said composition into gelatin, e.g. soft or hard gelatin, capsules.

In a more particular embodiment the invention provides a process for the preparation of a composition as defined under any one of (A) to (D) above, which process comprises bringing a cyclosporin, e.g. Ciclosporin, into inimite admixture with a component (1.1) as hereinbefore defined to obtain a composition as defined under (C) and, optionally, a component (5) as hereinbefore defined to obtain a composition as defined under (D), or with a component (1.2) as hereinbefore defined, whereby optionally when a component (1.1) is employed, or necessarily when a component (1.2) is employed, said aforesaid ingredients are further combined with a component (2) and a component (3) as hereinbefore defined, the relative proportions of

component (1.1) or (1.2), (2) and (3) being chosen such that a composition as defined under (A) is obtained and further, when required, contacting said obtained composition (A) with water, so as to obtain a composition as defined under (B) and when required, compounding an obtained composition (A), (C) or (D) in unit dosage form, e.g. soft or hard gelatin capsule form.

In a specific embodiment the present invention provides a process for producing a composition as defined under (A) above, which process comprises intimately admixing a cyclosporin, e.g Ciclosporin, with a component (1.1) or (1.2) as hereinbefore defined, and a component (2) and a component (3) as hereinbefore defined, the relative proportion of the components (1.1) or (1.2), (2) and (3) being selected relative to the quantity of cyclosporin employed such that a "microemulsion pre-concentrate", e.g. composition capable on addition to water, e.g. in a ratio of at least 1:1 p.p.w. (composition:$H_2O$) of providing a system comprising a dispersed or particle phase of which the individual particles have a size of less than 2,000 Å, preferably of from about 100 to about 1,000 Å is obtained.

The preferred cyclosporin in relation to the compositions of the invention is Ciclosporin. A further preferred cyclosporin to which the teachings of the present invention are applicable is [Nva]$^2$-Ciclosporin, also known as cyclosporin G.

The following examples are illustrative of compositions in accordance with the present invention. Examples 1,2,4,5 and 7 illustrate the preparation of compositions in oral unit dosage form, suitable for use, e.g. in the prevention of transplant rejection or for the treatment of autoimmune disease, e.g. any of the autoimmune diseases or conditions hereinbefore described, on administration of from 1 to 5 unit dosages/day. Examples 3 and 6 illustrate the preparation of compositions for topical application, suitable for treatment, e.g. of atopic or contact dermatitis, psoriasis or hair loss, on application

at the desired site of therapy, e.g. dermatitidic reaction or psoriatic lesion or to the scalp, at regular intervals, e.g. once, twice or three times per day.

The examples are described with particular reference to Ciclosporin. However, equivalent compositions may be obtained employing any other appropriate cyclosporin. In particular equivalent compositions may in all cases be obtained on replacement of Ciclosporin with [Nva]$^2$-Ciclosporin in the same amount as indicated for Ciclosporin.

EXAMPLE 1

Preparation of oral dosage forms: "microemulsion pre-concentrate" type:

| 1.1. | COMPONENT | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| (1.1) | Glycofurol 75 | 180.0 |
| (2.1) | Miglyol 812 | 90.0 |
| (3.1.1) | Cremophor RH 40 | 180.0 |
| | TOTAL | 500.0 |

The cyclosporin is dissolved in (1.1) with stirring at room temperature and (2.1) and (3.1.1) are added to the obtained solution, again with stirring. The obtained mixture is filled into a size 1 hard gelatin capsule and sealed using Quali-Seal technique.

The following compositions may be prepared analogously for filling into size 1 or 2 hard gelatin capsules:

| 1.2. | COMPONENT | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| (1.1) | Glycofurol 75 | 180.0 |
| (2.1) | Miglyol 812 | 78.0 |
| (3.1.1) | Cremophor RH 40 | 192.0 |
| | TOTAL | 500.0 |

1.3.

| COMPONENT | | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| (1.1) | Glycofurol 75 | 200.0 |
| (2.1) | Miglyol 812 | 60.0 |
| (3.1.1) | Nikkol HCO-40 | 120.0 |
| | Ethanol* | 19.0 |
| | Ascorbylpalmitate** | 1.0 |
| | TOTAL | 450.0 |

*Co-solvent (hydrophilic phase)

**Antioxidant

1.4.

| COMPONENT | | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| (1) | Glycofurol 75 | 100.0 |
| (2.1) | Miglyol 812 | 75.0 |
| (3.1.7) | Lecithin | 75.0 |
| | TOTAL | 300.0 |

1.5.

| COMPONENT | | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 100.0 |
| (1.1) | Glycofurol 75 | 260.0 |
| (1.2) | Propyleneglycol | 50.0 |
| (2.1) | Myritol 318 | 100.0 |
| (3.1.1) | Cremophor RH 40 | 340.0 |
| | BHA* | 5.0 |
| | TOTAL | 855.0 |

*Anti-oxidant

| 1.6. | COMPONENT | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| (1.2) | 1,2-Propyleneglycol | 68.0 |
| (2.1) | Miglyol 812 | 68.0 |
| (3.1.1) | Cremophor RH 40 | 250.0 |
| (3.2.5) | Glycerol monooleate* | 24.0 |
| | TOTAL | 460.0 |

| 1.7. | COMPONENT | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| (1.2) | 1,2-Propyleneglycol | 68.0 |
| (2.1) | Miglyol 812 | 24.0 |
| (3.1.1) | Cremophor RH 40 | 250.0 |
| (3.2.5) | Glycerol monooleate* | 68.0 |
| | TOTAL | 460.0 |

| 1.8. | COMPONENT | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 100 .0 |
| (1.2) | 1,2-Propyleneglycol | 75.0 |
| (2.1) | Miglyol 812 | 25.0 |
| (3.1.1) | Cremophor RH 40 | 150.0 |
| (3.2.5) | Glycerol monooleate* | 150.0 |
| | TOTAL | 500.0 |

| 1.9. | COMPONENT | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| (1.2) | 1,2-Propyleneglycol | 200.0 |
| (2.1) | Miglyol 812 | 50.0 |
| (3.1.1) | Cremophor RH 40 | 150.0 |
| (3.2.7) | Generol 122 E16* | 50.0 |
| | TOTAL | 500.0 |

| 1.10. | COMPONENT | | QUANTITY (mg/capsule) |
|---|---|---|---|
| | | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| | (1.2) | 1,2-Propyleneglycol | 75.0 |
| | (2.1) | Miglyol 812 | 75.0 |
| | (3.1.1) | Cremophor RH 40 | 250.0 |
| | (3.2.7) | Generol 122 E25* | 50.0 |
| | | TOTAL | 500.0 |

*Co-surfactant

Compositions 1.1, 1.2, 1.6 and 1.7 are especially preferred. Equivalent compositions to 1.1 to 1.5 can in all cases be prepared replacing the Glycofurol component with Transcutol in the same or equivalent amount.

Equivalent compositions to 1.1 to 1.5 may be prepared but replacing the 50mg amount of cyclosporin with 15, 20 or 100mg cyclosporin (e.g. Ciclosporin) the quantities of the remaining components for each composition remaining as indicated.

EXAMPLE 2

Preparation of oral dosage forms: thickened "microemulsion pre-concentrate" type:

| 2.1. | COMPONENT | | QUANTITY (mg/capsule) |
|---|---|---|---|
| | | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| | (1.1) | Glycofurol 75 | 180.0 |
| | (2.1) | Miglyol 812 | 90.0 |
| | (3.1.1) | Cremophor RH 40 | 180.0 |
| | (4.2) | Methocel K100 | 100.0 |
| | | TOTAL | 600.0 |

Ciclosporin and (1.1) to (3.1.1) are combined as in example 1 and the obtained mixture mixed homogeneously with (4.2). The product is filled into size 2 hard gelatin capsules.

The following composition may be obtained analogously:

| 2.2. | COMPONENT | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin | 50.0 |
| (1.1) | Glycofurol 75 | 180.0 |
| (2.1) | Miglyol 812 | 90.0 |
| (3.1.1) | Cremophor RH 40 | 180.0 |
| (4.6) | Aerosil 200 | 9.0 |
| (4.2) | Methocel K100 | 100.0 |
| | TOTAL | 609.0 |

| 2.3. | COMPONENT | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 100.0 |
| (1.1) | Glycofurol | 210.0 |
| (2.1) | Myritol 318 | 90.0 |
| (3.1.1) | Nikkol HCO-60 | 170.0 |
| (4.2) | Klucel EF | 30.0 |
| | TOTAL | 600.0 |

Equivalent compositions to 2.1 to 2.3 can be prepared replacing the Glycofurol component with Transcutol in the same or equivalent amount.

EXAMPLE 3

Preparation of topically applicable form: "microemulsion pre-concentrate" type:

| COMPONENT | | % BY WEIGHT |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 0.1 |
| (1.1) | Glycofurol | 50.0 |
| (2.1) | Miglyol 812 | 16.6 |
| (3.1.1) | Cremophor RH 40 | 33.3 |

The above composition is prepared analogously to example 1. An equivalent composition is obtained on replacement of the Glycofurol component with Transcutol. The composition may be made the basis of a cream, gel or the like by combination with further additives, e.g. hydrocolloid thickening agents, paraffins etc... as hereinbefore described.

**EXAMPLE 4**

**Preparation of oral dosage forms: regular emulsion pre-concentrate type:**

| 4.1. | COMPONENT | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g.Ciclosporin) | 100.0 |
| (1.1) | Transcutol | 154.0 |
| (3.1.1) | Cremophor RH 40 | 146.0 |
| (3.2.1) | Labrafil M 1944 CS | 50.0 |
| | TOTAL | 450.0 |

Cyclosporin is dissolved in (1.1) with stirring at room temperature and (3.1.1) and (3.2.1) added to the obtained solution, again with stirring. The obtained mixture is filled into size 1 hard gelatin capsules and sealed employing Quali-Seal technique.

The following compositions may be prepared analogously for filling into size 1 or 2 hard gelatin capsules as appropriate.

| 4.2. | COMPONENT | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| (1.1) | Transcutol | 80.0 |
| (3.1.1) | Cremophor RH 40 | 75.0 |
| (3.2.1) | Labrafil M 2130 CS | 25.0 |
| | TOTAL | 230.0 |

| 4.3. | COMPONENT | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 100.0 |
| (1.1) | Glycofurol 75 | 150.0 |
| (3.1.1) | Nikkol HCO-40 | 200.0 |
| | TOTAL | 450.0 |

| 4.4. | COMPONENT | QUANTITY (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| (1.1) | Transcutol | 100.0 |
| (3.1.1) | Cremophor RH 40 | 94.0 |
| (3.2.1) | Labrafil M 1944 | 31.0 |
| | TOTAL | 275.0 |

Equivalent compositions may be prepared by replacing Transcutol in 4.1, 4.2 or 4.4 with the same or equivalent amount of Glycofurol, or the Glycofurol in 4.3 with the same or equivalent amount of Transcutol.

**EXAMPLE 5**

**Preparation of oral dosage forms: thickened emulsion pre-concentrate type:**

| 5.1. | COMPONENT | | QUANTITY (mg/capsule) |
|---|---|---|---|
| | | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| | (1.1) | Transcutol | 80.0 |
| | (3.1.1) | Cremophor RH 40 | 75.0 |
| | (3.2.1) | Labrafil M 1944 CS | 25.0 |
| | (4.1) | Eudragit E | 50.0 |
| | | TOTAL | 280.0 |

(3.1.1), (3.2.1) and (4.1) are combined with and dissolved in (1.1) with stirring and light warming. Cyclosporin is then added with light warming and further stirring and the product filled into size 2 hard-gelatin capsules and sealed.

The following compositions can be prepared analogously for filling into size 1 or 2 hard gelatin capsules as appropriate:

| 5.2. | COMPONENT | | QUANTITY (mg/capsule) |
|---|---|---|---|
| | | Cyclosporin (e.g. Ciclosporin) | 100.0 |
| | (1.1) | Transcutol | 180.0 |
| | (3.1.4) | Pluronic F68 | 140.0 |
| | (3.1.6) | Sodium laurylsulphate | 5.0 |
| | (4.2) | Sodium carboxymethylcellulose | 25.0 |
| | | TOTAL | 350.0 |

| 5.3. | COMPONENT | | QUANTITY (mg/capsule) |
|---|---|---|---|
| | | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| | (1.1) | Transcutol | 163.0 |
| | (3.1.1) | Cremophor RH 40 | 100.0 |
| | (3.2.1) | Labrafil M 1944 CS | 35.0 |
| | (4.3) | Kollidon 30 | 72.0 |
| | | TOTAL | 420.0 |

Equivalent compositions may be prepared by replacing the Transcutol

component with Glycofurol in the same or equivalent amount.

EXAMPLE 6

**Preparation of topical dosage forms: emulsion type:**

The following are prepared by intimate admixture of the indicated ingredients analogously to examples 2 and 5 above, to provide ointment preparations suitable for topical application:

| 6.1. | COMPONENT | % BY WEIGHT |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 0.1 |
| (1.1) | Transcutol | 15.0 |
| (3.1.1) | Cremophor RH 40 | 5.0 |
| (3.2.1) | Labrafil M 2l3 | 15.0 |
| (3.2.5) | Glycerolmonostearate | 10.0 |
| (6.2) | White petrolatum | 54.9 |

| 6.2. | COMPONENT | % BY WEIGHT |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 0.1 |
| (1.2) | Glycofurol | 15.0 |
| (3.2.5) | Glycerolmonostearate | 8.0 |
| (6.1) | Mineral oil | 39.0 |
| (6.1) | White petrolatum | 37.9 |

EXAMPLE 7

**Preparation of oral dosage forms: sugar ester type:**

| 7.1. | INGREDIENT | AMOUNT (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| (1.1) | Glycofurol | 100.0 |
| (5) | Saccharose monolaurate L-1695* | 312.5 |
| | TOTAL | 462.0 |

| 7.2. | INGREDIENT | AMOUNT (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| (1.1) | Transcutol | 80.0 |
| (5) | Saccharose monolaurate L-1695* | 312.5 |
| | TOTAL | 442.5 |

| 7.3. | INGREDIENT | AMOUNT (mg/capsule) |
|---|---|---|
| | Cyclosporin (e.g. Ciclosporin) | 50.0 |
| (1.1) | Glycofurol | 100.0 |
| (5) | Saccharose monolaurate L-1695* | 312.5 |
| (4.2) | Klucel LF | 50.0 |
| | TOTAL | 512.5 |

(* Product commercially available from Mitsubishi-Kasei Food Corp., Tokyo 104, Japan: HLB-value = at least 12.3: lauryl ester residue purity = at least 95%: M.P. = ca. 35°C: decomposition at ca. 235°C: surface tension of 0.1% by weight aqueous solution = ca. 72.0 dyn/cm at 25°C.)

The composition of example 7.1 is prepared by dissolving cyclosporin and (5) with stirring and warming over an oil bath at 100°C in component (1.1). The composition of examples 7.2 and 7.3 are prepared analogously.

The obtained compositions are filled, with warming, into hard gelatin capsules size 1 (compositions 7.1 and 7.2) or 0 (composition 7.3).

Utility of compositions in accordance with the invention may be shown in animal or clinical trials, for example performed as follows:

BIOAVAILABILITY STUDY FOR COMPOSITIONS IN ACCORDANCE WITH THE INVENTION IN THE DOG

a) Test compositions

| | | |
|---|---|---|
| COMPOSITION I | as per example | 1.1 |
| COMPOSITION II | " | 1.2 |
| COMPOSITION III | " | 1.6 |
| COMPOSITION IV | " | 2.1 |
| COMPOSITION V | " | 2.2 |
| COMPOSITION VI | " | 4.4 |
| COMPOSITION VII | " | 5.3 |

b) Test method

Groups of 8 beagle dogs (male, ca. 11-13kg) are used. Animals receive no food within 16 hours of administration of test composition but are allowed free access to water until administration. Test compositions are administered by gavage, followed by 20ml NaCl 0.9% solution. The animals are allowed free access to food and water three hours after administration of test composition.

2ml blood samples (or 5ml for the blank) are taken from the vena saphena and collected in 5ml plastic tubes containing EDTA at

-15min. (blank), 30min., and 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post administration. Blood samples are stored at -18°C pending assay.

Blood samples are analysed by RIA. Areas under the blood drug concentration versus time curves are calculated by the trapezoidal rule. Analysis of variance is performed with respect to AUC (area under curve), Cmax (maximum concentation) and Tmax (time of maximum).

c) Results

Calculated average AUC (in ng hr./ml$^{-1}$) and Cmax (in ng/ml$^{-1}$) values from typical trial runs are shown in the following table, together with calculated variation in response between test animals receiving the same composition (CV).

| COMPOSITION | AUC (0-24h) | CV (%) | Cmax | CV% |
|---|---|---|---|---|
| I | 2969 | 46.1 | 655 | 42.4 |
| II | 3315 | 35.9 | 606 | 29.0 |
| III | 3392 | 33.0 | 623 | 25.0 |
| IV | 4010 | 35.1 | 756 | 30.0 |
| V | 2769 | 27.8 | 469 | 21.7 |
| VI | 2375 | 40.3 | 518 | 29.2 |
| VII | 2329 | 23.1 | 470 | 36.1 |

As will be seen from the above table, compositions in accordance with the invention exhibit high bioavailability (AUC and Cmax.) coupled with relatively low variability in subject response both for AUC and Cmax.

Comparable advantageous results may be obtained employing other compositions in accordance with examples 1,2,4,5 and 7 herein, in particular the compositions of example 1.

The advantageous properties of the compositions of the invention on oral administration may also be demonstrated in clinical trials, e.g. performed as follows:

Trial subjects are adult volunteers, e.g. professionally educated males of from 30 to 55 years. Trial groups suitably comprise 12 subjects.

The following inclusion/exclusion criteria are applied:
Inclusion: Normal screening ECG; normal blood-pressure and heart rate; body weight = 50-95kg.
Exclusion: Clinically significant intercurrent medical condition which might interfere with drug absorption, distribution, metabolism, excretion or safety; symptoms of a significant clinical illness in the two-week pre-trial period; clinically relevant abnormal laboratory values or electrocardiogram; need for concomitant medication during the entire course of the study; administration of any drug known to have a well-defined potential toxicity to a major organ system within the previous 3 months; administration of any investigational drug within 6 weeks prior to entry into the trial; history of drug or alcohol abuse; loss of 500ml or more blood within the past 3 month period; adverse drug reaction or hypersensitivity; history of allergy requiring drug therapy; Hep.-B/HIV-positive.

Complete physical examination and ECG is performed pre- and post-trial. The following parameters are evaluated within 1-month periods pre- and post-trial:
Blood: - red blood cell count, haemoglobin, hematocrit, erythrocyte sedimentation, white blood cell count, smear, platelet count and fasting glucose;

Serum/plasma - total protein and electrophoresis, cholesterol, triglycerides, $Na^+$, $K^+$, $Fe^{++}$, $Ca^{++}$, $Cl^-$ creatinine, urea, uric acid, SGOT, SGPT, -GT, alkaline phosphatase, total bilirubin, α-amylase; Urine - pH, microalbumin, glucose, erythrocytes, ketone bodies, sediment.
Creatinine clearance is also determined 1-month prior to trial entry.

Subjects each receive trial compositions in randomised sequence. Compositions are administered orally, once to a total dose of 150mg cyclosporin, e.g. Ciclosporin, and at least 14 days are allowed between each administration.

Administration is performed in the morning after an overnight fast of 10hrs. with only water allowed. Only caffein-free beverages are permitted within the 24hr. period following administration. Subjects are not allowed to smoke within the 12hr. period following administration. Subjects receive a standardised lunch 4 hrs. following administration.

Blood samples (2ml) are taken 1 hr. prior to administration and post-administration at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 9, 12, 14, 24, 28 and 32 hrs.. For determination of creatinine 2ml blood samples are taken immediately prior to administration and at 12, 24 and 48 hrs. post-administration. Samples for cyclosporin determination are collected in two EDTA coated polystyrene tubes (1ml each) at each time point and are deep frozen at -20°C after gentle agitation. Cyclosporin is assayed in whole blood using RIA with specific and/or non-specific MAB assay - detection limit in both cases = ca. 10ng/ml.

In one such trial COMPOSTION I above in accordance with the invention (hard gelatin encapsulated form) is compared with COMPOSITION X.

COMPOSITION X [COMPARATIVE (ART) COMPOSITION]

Unit dosage form (soft gelatin capsule) comprising

| | |
|---|---|
| Ciclosporin | 50mg |
| Labrafil | 150mg |
| Ethanol | 50mg |
| Maize oil | 213mg |
| Total | 463mg/dosage. |

(* current Sandimmun oral, drink solution)

In a trial performed in this manner a bioavailability level of 149.0% (±48) is recorded for COMPOSITION I as compared with COMPOSITION X (for which bioavailability achieved is set as 100%). AUC values (0-32 hrs. ng.h/ml) and Cmax. values (ng/ml) established for COMPOSITION I are 2992 (±627) and 882 (±18) respectively as compared with 2137 (±606) and 515 (±180) for COMPOSITION X.

Figs. III and IV attached provide superimposed graphical representations from such a trial of whole blood Ciclosporin concentrations recorded for all 12 trial participants following single oral administrations of COMPOSITION I (Fig. III) and COMPOSITION X (Fig. IV), each in an amount providing a Ciclosporin dosage of 150mg, as determined by specific monoclonal RIA. Blood concentration (in ng/ml) is recorded vertically, and time (in hrs.) horizontally.

Comparison of Figs. III and IV clearly demonstrates the marked reduction in variability of inter-subject response with respect to bioavailability parameters recorded, on administration of COMPOSITION I as compared with COMPOSITION X. The determined coefficient of variation [(standard deviation/mean value) x 100] with respect to Cmax. for COMPOSITION X is 35% as compared with a value of only 20%

for COMPOSITION I.

Similar or equivalent results may be obtained following oral administration of other compositions in accordance with the invention, e.g. as herein described in the examples, in particular the compositions of example 1.

IN VIVO TESTING FOR TOPICAL FORMS

ALLERGIC CONTACT DERMATITIS TEST IN THE GUINEA PIG

Guinea pigs (Hartley, male, 400-500g) are sensitised by application of 50µl, 0.5% DNFB in acetone/olive oil (4:1) applied to marked areas on the shaven, left and right flank. This second challenge exposure induces an allergic inflammation, leading to reddening and cellular infiltration (thickening) of the skin. Test composition (e.g. in accordance with example 3,6.1 or 6.2 above) in an amount of from 200-250mg is applied with a spatula to the DNFB treated area of the right flank. The left flank is similarly treated with placebo as control. Application of test composition/placebo is effected 5x at intrvals of 20 mins., 8 hrs., 24 hrs., 32 hrs., and 48 hrs., after the challenge. Skin thickness at the site of application is determined before each application, and again 8 hrs. after the last application, by raising the skin into a fold and measuring the thickness of this. Degree of reddening or inflammation is also estimated visually on a scale of from 0 to 4. Efficacy of test preparation in preventing inflammatory response is determined by comparison with results recorded for placebo treated flanks.

In the above test method substantial reduction in skin thickening as compared with placebo are achieved following first application of test composition, e.g. in accordance with examples 3,6.1 or 6.2, continuing throught treatment until completion of the experiment.

The following results are recorded for the composition of example 3

| TIME APTER CHALLENGE (HRS) | 8 | 24 | 32 | 48 | 56 |
|---|---|---|---|---|---|
| % INHIBITION OF SKIN THICKNESS / US PLACEBO CONTROL | 56 | 68 | 76 | 75 | 73 |

Claims

1. A pharmaceutical composition comprising a cyclosporin as active ingredient, which composition is a "microemulsion pre-concentrate".

2. A composition according to claim 1 comprising:
   1) a hydrophilic phase;
   2) a lipophilic phase, and
   3) a surfactant.

3. A composition according to claim 1 or 2 comprising:
   1.1) a pharmaceutically acceptable $C_{1-5}$alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or poly-oxy-alkanediol, or
   1.2) 1,2-propyleneglycol,
   as hydrophilic component.

4. A composition according to claim 3 comprising Transcutol or Glycofurol as hydrophilic component.

5. A composition according to claim 3 comprising 1,2-propyleneglycol as hydrophilic component.

6. A composition according to any one of claims 1 to 5 comprising a medium chain fatty acid triglyceride as lipophilic component.

7. A composition according to claim 6 comprising a caprylic-capric acid triglyceride as lipophilic component.

8. A composition according to any one of claims 1 to 7 comprising a polyoxyethylene glycolated natural or hydrogenated vegetable oil, a polyoxyethylene fatty acid ester, a phospholipid or a mono- or di-glyceride as surfactant.

9. A composition according to any one of claims 1 to 8 comprising 3a) a surfactant and 3b) a co-surfactant.

10. A composition according to any one of claims 1 to 9, capable on contacting with water of providing a microemulsion having an average particle size of <1,000A.

11. A pharmaceutical composition comprising a cyclosporin as active ingredient, which composition is a microemulsion.

12. A composition according to claim 11 comprising a composition as defined in any of claims 1 to 10 and water.

13. A pharmaceutical composition comprising a cyclosporin as active ingredient, together with (1.1) a pharmaceutically acceptable $C_{1-5}$alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or poly-oxy-alkanediol.

14. A composition according to claim 13, wherein (1.1) comprises Transcutol or Glycofurol.

15. A composition according to claim 13 or 14 additionally comprising:
2) a lipophilic co-solvent, or
3) a surfactant.

16. A composition according to claim 15, wherein (3) is a hydrophilic surfactant.

17. A composition according to claim 15 or 16, wherein (2) is a medium chain fatty acid triglyceride.

18. A composition according to any one of claims 13 to 17 additionally comprising:

5) a fatty acid saccharide monoester.

19. A composition according to claim 18, wherein (5) is raffinose or saccharose monolaurate.

20. A composition according to any one of claims 1 to 19 comprising from about 0.05 to about 35% by weight of cyclosporin based on the total weight of the composition.

21. A composition according to any one of claims 3, 4, 6 to 10 and 12 to 20, wherein (1.1) is present in an amount of from about 1 to about 90% by weight, based on the total weight of the composition.

22. A composition according to anyone of claims 3, 5 to 10 and 12, wherein (1.2) is present in an amount of from about 2 to about 50% by weight based on the total weight of the composition.

23. A composition according to any one of claims 2 to 10, 12 and 15 to 22, wherein (2) or (3) are each present in an amount of from about 0.5 to about 90% by weight based on the total weight of the composition.

24. A composition according to any one of claims 20 to 23 comprising from about 5 to about 25% by weight of cyclosporin.

25. A composition according to claim 24 comprising from about 5 to about 15% by weight of cyclosporin.

26. A composition according to any one of claims 21 and 23 to 25, wherein (1.1) is present in an amount of from about 20 to about 80% by weight.

27. A composition according to claim 26, wherein (1.1) is present in ana mount of from about 40 to about 70% by weight.

28. A composition according to any one of claims 22 to 25, wherein (1.2) is present in an amount of from about 3 to about 45% by weight.

29. A composition according to claim 28, wherein (1.2) is present in an amount of from about 5 to about 30% by weight.

30. A composition according to any one of claims 23 to 29, wherein (2) is present in an amount of from about 2 to about 45% by weight.

31. A composition according to claim 30, wherein (2) is present in an amount of from about 5 to about 25% by weight.

32. A composition according to any one of claims 23 to 31, wherein (3) is present in an amount of from about 20 to about 90% by weight.

33. A composition according to claim 32, wherein (3) is present in an amount of from about 25 to about 80% by weight.

34. A composition according to claim 33 comprising a component (1.1) and wherein (3) is present in an amount of from about 30 to about 50% by weight.

35. A composition according to claim 33 comprising a component (1.2) and wherein (3) is present in an amount of from about 40 to about 75% by weight.

36. A composition according to any one of claims 3, 4, 6 to 10 and 12, comprising from about 15 to about 85% of (1.1), from about 2

to about 40% of (2), and from about 15 to about 85% of (3), each by weight based on the total of (1.1)+(2)+(3).

37. A composition according to claim 36 comprising from about 25 to about 65% of (1.1), from about 3 to about 35% of (2), and from about 25 to about 60% of (3), each by weight based on the total of (1.1)+(2)+(3).

38. A composition according to any one of claims 3, 4, 6 to 10 and 12, wherein the relative proportion of components (1.1):(2):(3) lies within the area (A) defined by line (a) of accompanying Fig. I.

39. A composition according to claim 38, wherein the relative proportion lies within the area (B) defined by line (b) of Fig. I.

40. A composition according to any one of claims 3, 5 to 10 and 12, comprising from about 3 to about 35% of (1.2), from about 2 to about 35% of (2), and from about 45 to about 90% of (3), each by weight based on the total of (1.2)+(2)+(3).

41. A composition according to claim 40 comprising from about 3 to about 25% of (1.2), from about 3 to about 30% of (2), and from ab 55 to about 80% of (3), each by weight based on the total of (1.2)+(2)+(3).

42. A composition according to any one of claims 3, 5 to 10 and 12, wherein the relative proportion of components (1.2):(2):(3) lies within the area X defined by line x of accompanying Fig. II.

43. A composition according to claim 42, wherein the relative proportion lies within the area Y defined by line y of Fig. II.

44. A composition according to claim 43, wherein the relative proportion lies within the area Z defined by line z of Fig. II.

45. A composition according to any one of claims 40 to 44, wherein (3) comprises (3.1) a surfactant and (3.2) a co-surfactant.

46. A composition according to claim 45, wherein (3.1) and (3.2) are present in a ratio of about 1 to 50:1 p.p.w..

47. A composition according to claim 46, wherein the ratio is about 2 to 15:1 p.p.w..

48. A composition according to any one of claim 36 to 47, wherein the cyclosporin is present in an amount of from about 2 to about 30% by weight based on the total of [cyclosporin]+[(1.1) or (1.2)]+(2)+(3).

49. A composition according to claim 48, wherein the cyclosporin is present in an amount of from about 4 to about 25% by weight.

50. A composition according to claim 49, wherein the cyclosporin is present in an amount of from about 5 to about 20% by weight.

51. A composition according to claim 50, wherein the cyclosporin is present in an amount of from about 5 to about 15% by weight.

52. A composition according to any one of claims 18 to 21 and 23 to 25, wherein the cyclosporin and (1.1) are present in a ratio of about 1:0.5 to 200 p.p.w. [cyclosporin:(1.1)].

53. A composition according to claim 52, wherein the ratio is about 1:0.5 to 50 p.p.w..

54. A composition according to claim 53, wherein the ratio is about 1:1 to 10 p.p.w..

55. A composition according to claim 54, wherein the ratio is about 1:1 to 5 p.p.w..

56. A composition according to any one of claims 18 to 21, 23 to 25 and 52 to 55, wherein the cyclosporin and (5) are present in a ratio of about 1:3 to 200 p.p.w. [cyclosporin:(5)].

57. A composition according to claim 56, wherein the ratio is about 1:3 to 50 p.p.w..

58. A composition according to claim 57, wherein the ratio is about 1:5 to 10 p.p.w..

59. A composition according to any one of claims 1 to 12 and 36 to 51 which is non-alkanol-based.

60. A composition according to any one of claims 1 to 12 and 36 to 51 which is non-ethanol-based.

61. A composition according to any one of the preceding claims which is free or substantially free of ethanol.

62. A composition according to any one of the preceding claims in a form suitable or convenient for oral administration.

63. A composition according to any one of the preceding claims in unit dosage form.

64. A composition according to claim 63 in soft or hard gelatin encapsulated form.

65. A composition according to claim 63 or 64 comprising from about 5 to about 200mg cyclosporin/unit dosage.

66. A composition according to claim 65 comprising from about 15 to about 100mg cyclosporin/unit dosage.

67. A composition according to claim 66 comprising from about 20 to about 100mg cyclosporin/unit dosage.

68. A composition according to any one of claims 1 to 17 or 36 to 47 comprising from about 0.5 to about 50% by weight cyclosporin based on the total weight of the composition, in a form suitable or convenient for topical application.

69. A composition according to any one of claims 13 to 17 comprising from about 0.05 to about 50% by weight cyclosporin and from about 1 to about 70% by weight of (1.1) each based on the total weight of the composition, in a form suitable or convenient for topical application.

70. A composition according to claim 68 or 69 comprising from about 0.1 to about 10% by weight cyclosporin.

71. A composition according to claim 69 or 70 comprising from about 5 to about 50% by weight of (1.1).

72. A composition according to claim 71 comprising from about 7 to about 25% by weight of (1.1).

73. A composition according to any one of claims 68 to 72 comprising (6) a pharmaceutically acceptable solvent or carrier which is non-miscible with (1.1).

74. A composition according to claim 73, wherein (6) comprises a solid hydrocarbon, a wax, a liquid hydrocarbon, a fatty acid ester or a non-volatile silicone.

75. A composition according to claim 73 or 74, wherein (6) is present in an amount of up to about 80% by weight based on the total weight of the composition.

76. A composition according to claim 75, wherein (6) is present in an amount of from about 5 to about 70% by weight.

77. A composition according to claim 76, wherein (6) is present in an amount of from about 25 to about 60% by weight.

78. A composition according to any one of claims 68 to 77 comprising a surfactant.

79. A composition according to claim 78, wherein the surfactant has an HLB of ca. 5 to 7.

80. A composition according to claim 78 or 79, wherein the surfactant is present in an amount of up to about 60% by weight based on the total weight of the composition.

81. A composition according to claim 80, wherein (6) is present in an amount of from about 2 to about 40% by weight based on the total weight of the composition.

82. A composition according to claim 81, wherein the surfactant is present in an amount of from about 10 to about 40% by weight based on the total weight of the composition.

83. A composition according to any one of claims 68 to 82 additionally comprising a consistency promoting agent.

84. A composition according to claim 83, wherein the consistency promoting agent is a microcrystalline wax, a vegetable oil or a vegetable oil derivative.

85. A composition according to claim 83 or 84, wherein the consistency promoting agent is present in an amount of from about 0.1 to about 10% by weight based on the total weight of the composition.

86. A composition according to any one of claims 68 to 85 in flowable form, in the form of a powder, in the form of a topically applicable spray or in the form of a cataplasm, poultice or transdermal patch.

87. A composition according to claim 86 in the form of a gel, cream, paste, ointment or tincture.

88. A composition according to any of the preceding claims, wherein the cyclosporin is Ciclosporin.

89. A composition according to any of the proceding claims, wherein the cyclosporin is [Nva]$^2$-Ciclosporin.

90. A composition according to claim 1 or 2, substantially as hereinbefore described, in particular with reference to any one of examples 1.1 to 2.3.

91. A composition according to claim 13, substantially as hereinbefore described, in particular with reference to any one of examples 4.1 to 5.3.

92. A composition according to claim 68 or 69, substantially as hereinbefore described, in particular with reference to any one of examples 3 or 6.

93. A composition according to claim 18, substantially as hereinbefore described, in particular with reference to any one of examples 7.1 to 7.3.

Published 1990 at The Patent Office, State House, 66-71 High Holborn, London WC1R 4TP. Further copies may be obtained from The Patent Office, Sales Branch, St Mary Cray, Orpington, Kent BR5 3RD. Printed by Multiplex techniques ltd, St Mary Cray, Kent, Con. 1/87

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 14222478 |
| **Filing Date:** | 21-Mar-2014 |
| **Title of Invention:** | METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS |
| **First Named Inventor/Applicant Name:** | Andrew Acheampong |
| **Filer:** | Laura Lee Wine/Maria Stein |
| **Attorney Docket Number:** | 17618CON6CON1 (AP) |

Filed as Large Entity

## Utility under 35 USC 111(a) Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| Submission- Information Disclosure Stmt | 1806 | 1 | 180 | 180 |
| | | **Total in USD ($)** | | **180** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 19523368 |
| **Application Number:** | 14222478 |
| **International Application Number:** | |
| **Confirmation Number:** | 9616 |
| **Title of Invention:** | METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS |
| **First Named Inventor/Applicant Name:** | Andrew Acheampong |
| **Customer Number:** | 51957 |
| **Filer:** | Laura Lee Wine/Maria Stein |
| **Filer Authorized By:** | Laura Lee Wine |
| **Attorney Docket Number:** | 17618CON6CON1 (AP) |
| **Receipt Date:** | 08-JUL-2014 |
| **Filing Date:** | 21-MAR-2014 |
| **Time Stamp:** | 18:33:50 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

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|---|---|
| Submitted with Payment | yes |
| Payment Type | Deposit Account |
| Payment was successfully received in RAM | $180 |
| RAM confirmation Number | 4809 |
| Deposit Account | 010885 |
| Authorized User | |

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 17618CON6CON1_IDS.pdf | 19307634<br>c01c00293d3baaab4487be8b6a7ab893a871972c | yes | 171 |

**Multipart Description/PDF files in .zip description**

| Document Description | Start | End |
|---|---|---|
| Transmittal Letter | 1 | 2 |
| Information Disclosure Statement (IDS) Form (SB08) | 3 | 6 |
| Foreign Reference | 7 | 52 |
| Foreign Reference | 53 | 87 |
| Foreign Reference | 88 | 91 |
| Foreign Reference | 92 | 171 |

**Warnings:**

**Information:**

| | | | | | |
|---|---|---|---|---|---|
| 2 | Fee Worksheet (SB06) | fee-info.pdf | 30486<br>7c8a69f9dea2ab67e7c4e1fa42afd2ba666bb0a5 | no | 2 |

**Warnings:**

**Information:**

| | |
|---|---|
| **Total Files Size (in bytes):** | 19338120 |

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**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In the Patent Application of:<br><br>Andrew Acheampong, Andrew, et al.<br><br>Application No.: 14/222,478<br><br>Filing Date: March 21, 2014<br><br>Title: METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORING COMPONENTS | Examiner: Cordero Garcia, Marcela M.<br><br>Group Art Unit: 1676<br><br>Confirmation No.: 9616 |

**INFORMATION DISCLOSURE STATEMENT**
**UNDER 37 C.F.R. § 1.97 & § 1.98**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. § 1.97 & § 1.98, Applicants submit for consideration in the above-identified application the documents listed on the attached Form PTO/SB/08a.

Pursuant to the USPTO notice dated July 11, 2003, waiving the requirements under 37 C.F.R. § 1.98 (a)(2)(i) to provide copies of U.S. Patents and U.S. Published Applications, copies of these documents if cited are not submitted herewith. However, copies of any foreign patent documents and non-patent literature documents that may be cited on the attached Form PTO/SB/08a are submitted herewith. The Examiner is requested to make these documents of record.

This Information Disclosure Statement is submitted:

[ ] With the application; accordingly, no fee or separate requirements are required.

[ ] Before the mailing of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) is provided with the attached Form PTO/SB/08a.

[ ] Within three months of the application filing date or before mailing of a first Office Action on the merits; accordingly, no fee or separate requirements are required. However, if applicable, a certification under 37 C.F.R. § 1.97 (e)(1) is provided with the attached Form PTO/SB/08a.

[ X ] After receipt of a first Office Action on the merits but before mailing of a final Office Action or Notice of Allowance.

[ X ] A fee is required and submitted herewith.

[ ] A Certification under 37 C.F.R. § 1.97 (e) is provided with the attached Form PTO/SB/08a; accordingly; no fee is believed to be due.

[ ] After mailing of a final Office Action or Notice of Allowance, but before payment of the Issue Fee.

[ ] A fee is required and submitted herewith AND a Certification under 37 C.F.R. § 1.97 (e) is provided with the attached Form PTO/SB/08a.

Applicants would appreciate the Examiner initialing and returning the Form PTO/SB/08a indicating that the information has been considered and made of record herein.

If the Patent and Trademark Office determines that an extension and/or other relief (such as payment of a fee under 37 C.F.R. § 1.17 (p)) is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petition and/or other fees due in connection with the filing of this document to **Deposit Account No. 01-0885** referencing our docket number.

Respectfully submitted,

July 8, 2014 /Laura L. Wine/

Dated: By: Laura L. Wine, Reg. No. 68681

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 14/222,478 | 03/21/2014 | Andrew Acheampong | 17618CON6CON1 (AP) | 9616 |

51957 7590 06/25/2014

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

| EXAMINER | |
|---|---|
| CORDERO GARCIA, MARCELA M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1676 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 06/25/2014 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents_ip@allergan.com
pair_allergan@firsttofile.com

| Office Action Summary | Application No. 14/222,478 | Applicant(s) ACHEAMPONG ET AL. | |
|---|---|---|---|
| | Examiner MARCELA M. CORDERO GARCIA | Art Unit 1676 | AIA (First Inventor to File) Status No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *3/21/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5)☒ Claim(s) *37-63* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *37-63* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *3/28/2014*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

1. The present application is being examined under the pre-AIA first to invent provisions.

## DETAILED ACTION

### *Election/Restrictions*

2. Upon reconsideration, the election restriction requirement mailed on 5/9/2014 is herein vacated.

### *Status of the claims*

3. Claims 37-63 are pending. Claims 37-63 are presented for examination on the merits.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 37-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. Claims 37, 49 and 57 comprise the limitation "at a frequency of twice a day"

New Matter

6. The claims have been amended (cf. amendment 3/21/2014) to include new claims. Applicants state that the amendments add no new matter, and point out at least at page 4, line 25- page 5, line 14, page 14, line 28 -page 15, line 1, page 26, lines 5-19, and page 27, lines 4-31 of the application specification filed herewith as support for the amendments.

***Lack of Ipsis Verbis Support***

7. With respect to the limitation “at a frequency of twice a day”, such embodiment does not appear to be expressly disclosed.

***Lack of Inherent Support***

8. “While there is no in haec verba requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure.” See MPEP 2163. Example 1 of the instant disclosure, which has the embodiments with the concentrations as claimed, however it is silent with regards to the frequency of administration.

All other claims that depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, first paragraph for the reasons set forth above.

***Double Patenting***

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more

information about eTerminal Disclaimers, refer to

http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

10. Claims 37-63 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 8,629,111 (cited in the IDS dated 3/28/2014). Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in US '111 are drawn to a topical ophthalmic emulsion for treating an eye of a human comprising cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; wherein cyclosporin A is the only peptide present in the topical ophthalmic emulsion which encompasses and/or inherently discloses the instantly claimed method. Furthermore, the instantly claimed functional effects of the composition/method would necessarily be the same as all the structural/manipulative limitations of the instant claims are taught by the claims in '111.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

11. Claims 37-63 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 8,633,162 (cited in the IDS dated 3/28/2014). Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in US ‘162 are drawn to a method of treating dry eye disease, the method comprising topically administering to the eye of a human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion

comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is effective in treating dry eye disease which encompasses and/or inherently discloses the instantly claimed method. Furthermore, the instantly claimed functional effects of the composition/method would necessarily be the same as all the structural/manipulative limitations of the instant claims are taught by the claims in '162. With regards to the claimed frequency of administration, it is noted that "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such **concentration** or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."" (MPEP 2144.05). Thus one of ordinary skill in the art would have been able to adjust the dosage as to find an effective dosage and timing of administration.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

12. Claims 37-63 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 8,642,556 (cited in the IDS dated 3/28/2014). Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in US '556 are drawn to a first topical ophthalmic emulsion for treating an eye of a human, wherein the first topical ophthalmic

emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and wherein the first topical ophthalmic emulsion is therapeutically effective in treating dry eye disease; and wherein the first topical ophthalmic emulsion provides overall efficacy substantially equal to a second topical ophthalmic emulsion comprising cyclosporin A in an amount of about 0.1% by weight and castor oil in an amount of about 1.25% by weight which encompasses and/or inherently discloses the instantly claimed method. Furthermore, the instantly claimed functional effects of the composition/method would necessarily be the same as all the structural/manipulative limitations of the instant claims are taught by the claims in '556. With regards to the claimed frequency of administration, it is noted that "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such **concentration** or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."" (MPEP 2144.05). Thus one of ordinary skill in the art would have been able to adjust the dosage as to find an effective dosage and timing of administration.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

13. Claims 37-63 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 8,648,048 (cited in the IDS

dated 3/28/2014). Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in US '048 are drawn to a method of increasing tear production in the eye of a human, the method comprising topically administering to the eye of the human in need thereof an emulsion at a frequency of twice a day, wherein the emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is effective in increasing tear production which encompasses and/or inherently discloses the instantly claimed method. Furthermore, the instantly claimed functional effects of the composition/method would necessarily be the same as all the structural/manipulative limitations of the instant claims are taught by the claims in '048.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

14. Claims 37-63 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 8,685,930. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims in US '930 are drawn to an topical ophthalmic emulsion for treating an eye of a human having keratoconjunctivitis sicca, wherein the topical ophthalmic emulsion comprises cyclosporin A in an amount of about 0.05% by weight, polysorbate 80, acrylate/C10-30 alkyl acrylate cross-polymer, water, and castor oil in an amount of about 1.25% by weight; and wherein the topical ophthalmic emulsion is therapeutically

effective in treating keratoconjunctivitis sicca, which encompasses and/or inherently discloses the instantly claimed method. Furthermore, the instantly claimed functional effects of the composition/method would necessarily be the same as all the structural/manipulative limitations of the instant claims are taught by the claims in '930. With regards to the claimed frequency of administration, it is noted that "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such **concentration** or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."" (MPEP 2144.05). Thus one of ordinary skill in the art would have been able to adjust the dosage as to find an effective dosage and timing of administration.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

***Conclusion***

15. No claim is currently allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karlheinz R. Skowronek can be reached on (571)-272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCELA M CORDERO GARCIA/
Primary Examiner, Art Unit 1676

MMCG 06/2014

| Notice of References Cited | Application/Control No. 14/222,478 | Applicant(s)/Patent Under Reexamination ACHEAMPONG ET AL. | |
|---|---|---|---|
| | Examiner MARCELA M. CORDERO | Art Unit 1676 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
|---|---|---|---|---|---|
| * | A | US-8,685,930 | 04-2014 | Acheampong et al. | 514/20.5 |
| | B | US- | | | |
| | C | US- | | | |
| | D | US- | | | |
| | E | US- | | | |
| | F | US- | | | |
| | G | US- | | | |
| | H | US- | | | |
| | I | US- | | | |
| | J | US- | | | |
| | K | US- | | | |
| | L | US- | | | |
| | M | US- | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | Classification |
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| | N | | | | | |
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| | Q | | | | | |
| | R | | | | | |
| | S | | | | | |
| | T | | | | | |

**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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# BIB DATA SHEET

**CONFIRMATION NO. 9616**

| SERIAL NUMBER | FILING or 371(c) DATE<br>RULE | CLASS | GROUP ART UNIT | ATTORNEY DOCKET NO. |
|---|---|---|---|---|
| 14/222,478 | 03/21/2014 | 514 | 1676 | 17618CON6CON1 (AP) |

**APPLICANTS**

Allergan, Inc., Irvine, CA, Assignee (with 37 CFR 1.172 Interest);

**INVENTORS**

Andrew Acheampong, Irvine, CA;
Diane D. Tang-Liu, Las Vegas, CA;
James N. Chang, Newport Beach, CA;
David F. Power, San Clemente, CA;

**** CONTINUING DATA ***************************

This application is a CON of 13/961,828 08/07/2013 PAT 8685930
which is a CON of 11/897,177 08/28/2007 PAT 8618064
and is a CON of 10/927,857 08/27/2004 ABN
which claims benefit of 60/503,137 09/15/2003

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

04/15/2014

| Foreign Priority claimed ☐ Yes ☑ No<br>35 USC 119(a-d) conditions met ☐ Yes ☑ No<br>Verified and Acknowledged /MARCELA M CORDERO GARCIA/ Examiner's Signature | ☐ Met after Allowance<br>Initials | STATE OR COUNTRY | SHEETS DRAWINGS | TOTAL CLAIMS | INDEPENDENT CLAIMS |
|---|---|---|---|---|---|
| | | CA | 0 | 27 | 4 |

**ADDRESS**

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599
UNITED STATES

**TITLE**

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

| FILING FEE RECEIVED | | |
|---|---|---|
| 2580 | FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following: | ☐ All Fees<br>☐ 1.16 Fees (Filing)<br>☐ 1.17 Fees (Processing Ext. of time)<br>☐ 1.18 Fees (Issue)<br>☐ Other _____<br>☐ Credit |

| Search Notes | Application/Control No. | Applicant(s)/Patent Under Reexamination |
|---|---|---|
| | 14222478 | ACHEAMPONG ET AL. |
| | Examiner | Art Unit |
| | MARCELA M CORDERO GARCIA | 1676 |

| CPC- SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| CPC COMBINATION SETS - SEARCHED | | |
|---|---|---|
| Symbol | Date | Examiner |
| | | |

| US CLASSIFICATION SEARCHED | | | |
|---|---|---|---|
| Class | Subclass | Date | Examiner |
| none | none | 6/16/2014 | MMCG |

| SEARCH NOTES | | |
|---|---|---|
| Search Notes | Date | Examiner |
| EAST search (attached) | 6/14/2014 | MMCG |
| STN search (attached) | 6/16/2014 | MMCG |
| also ran PALM Inventor search | 6/16/2014 | MMCG |

| INTERFERENCE SEARCH | | | |
|---|---|---|---|
| US Class/ CPC Symbol | US Subclass / CPC Group | Date | Examiner |
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                  Information in CAS REGISTRY
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                  New on STN
 NEWS  5  JAN 09  Chinese Dissertations Added to CAplus
 NEWS  6  JAN 27  STN on the Web Now Compatible with Microsoft Windows 8.1 and
                  current Versions of Internet Explorer and Google Chrome
 NEWS  7  JAN 27  Annual MEDLINE Reload on STN Introduces New Searching
                  Capabilities and the Updated 2014 MeSH Thesaurus
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 NEWS  9  FEB 03  DWPI: New coverage of Singapore PCT-transfers and grants
 NEWS 10  FEB 24  INFULL and DEFULL databases Now Available via STN Viewer
 NEWS 11  MAR 28  New STN Platform Enhancements Available, Increase Efficiency
                  of Search Workflow.
 NEWS 12  APR 25  New Format Adopted for Taiwanese Granted Patent Numbers
                  in CAS Databases and INPADOC.
 NEWS 13  MAY 2   New STN Global Value Pricing Empowers You to Maximize the
                  Value of STN
 NEWS 14  MAY 9   STN AnaVist, Version 2.1, Improves Operating System
                  Compatibility and Performance
 NEWS 15  MAY 19  Availability of Digital Object Identifiers (DOIs) Enhanced in
                  STN Databases
 NEWS 16  MAY 20  New Cluster NPS available for all Databases with the Numeric
                  Property Search feature
 NEWS 17  MAY 29  CAS REGISTRY BLAST Upgrade Improves Search Capabilities and
                  Results Ranking
 NEWS 18  JUN 10  Additional Experimental Spectra Now Available in CAS REGISTRY
                  on STN
 NEWS 19  JUN 10  MEDLINE on STN Now Updated Daily
 NEWS 20  JUN 10  New Emtree Release Includes Changes in Cell Line Terminology

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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.54       0.78

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FILE 'MEDLINE' ENTERED AT 12:17:32 ON 16 JUN 2014

=> cyclosporin (10a) (twice or two) (10a) (castor oil) (10a) (emulsion)
L1           0 CYCLOSPORIN (10A) (TWICE OR TWO) (10A) (CASTOR OIL) (10A) (EMULS
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ION)

=> cyclosporin (10a) (castor oil) (10a) (emulsion)
L2 14 CYCLOSPORIN (10A) (CASTOR OIL) (10A) (EMULSION)

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L2 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:1840673 CAPLUS
DOCUMENT NUMBER: 158:87295
TITLE: Non-irritating eyedrop nano-emulsion composition comprising cyclosporin utilized as active ingredient, and method for manufacturing it
INVENTOR(S): Hwang, Seong Ju; Cha, Gwang Ho; Kang, Han; Sun, Bo Gyeong
PATENT ASSIGNEE(S): Huons Co., Ltd., S. Korea; Yonsei University, Industry-Academic Cooperation Foundation
SOURCE: Repub. Korea, 16pp.
CODEN: KRXXFC
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| KR 1211902 | B1 | 20121213 | KR 2012-45708 | 20120430 |
| WO 2013165074 | A1 | 20131107 | WO 2013-KR509 | 20130122 |

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

PRIORITY APPLN. INFO.: KR 2012-45708 A 20120430

AB The present invention relates to a non-irritating eyedrop nano-emulsion composition comprising cyclosporin utilized as an active ingredient, and a method for manufacturing the same. The composition comprises cyclosporine (0.01-1 weight%) as the active ingredient i.e. cyclosporine A; polyethoxylated castor oil or polyethoxylated hydrogenated castor oil (0.5-9.79 weight%); and phosphate buffer (90-99.29 weight%). The manufacturing method involves following step: (i) mixing and stirring the cyclosporine, polyethoxylated castor oil or polyethoxylated hydrogenated castor oil and water without utilizing a sep. emulsifier or high speed single machine to manufacture the non-irritating eyedrop nano-emulsion composition The composition has nano-emulsion with average particle size of less than or equal to 50nm. The composition further comprises a thickener (0.1-5 weight%) that is selected from hyaluronic acid or its salts, chitosan, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, polyvinylpyrrolidone, CM-cellulose, carbomer, glycerin and poly(ethylene oxide); and ethanol (0.1-3 weight%). According to the present invention, the eyedrop nano-emulsion composition has excellent non-irritating property and excellent phys. and chemical stabilities for long

term storage.

L2 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:974032 CAPLUS
DOCUMENT NUMBER: 157:209519
TITLE: Cyclosporin-containing ophthalmic emulsion gel and its preparation method
INVENTOR(S): Mao, Yufeng
PATENT ASSIGNEE(S): Wuxi Xinrentang Pharmaceutical Technology Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 12pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| CN 102525887 | A | 20120704 | CN 2012-10011033 | 20120116 |
| PRIORITY APPLN. INFO.: | | | CN 2012-10011033 | 20120116 |

AB The ophthalmic emulsion gel is composed of hydrophilic polymer(polyalkenyl alc. or non-ionic surfactant emulsifier) 0.01-10, higher fatty acid glyceride(one or more of olive oil, peanut oil, castor oil, mineral oil, etc.) 0.01-10, hydrophobic drug cyclosporin A 0.001-10, gel matrix(one or more of hydroxypropyl Me cellulose, hydroxypropyl Et cellulose, Me cellulose, etc.) 0.02-10, pH regulator(one or more of NaOH, sodium bicarbonate, HCl, etc.) 0-10, osmotic pressure regulator(glucose, glycerol, 0.7-0.9% NaCl solution, mannitol or sorbitol) 0-10, and purified water 10-12 weight parts. The preparation method comprises mixing higher fatty acid glyceride with hydrophobic drug cyclosporin, dissolving, regulating pH to 3-9, obtaining oil phase; dissolving hydrophilic polymer in 1-2 parts of water for injection to obtain water phase; adding oil phase into water phase, mixing to obtain emulsion; adding 9-10 parts of water for injection into beaker, sprinkling gel matrix on the surface of water for injection, standing and swelling; mixing emulsion with gel, stirring, regulating pH with pH regulator to 3-9, adding osmotic pressure regulator till the osmotic pressure of mixed solution is 200-350 Osmol/kg, subpackaging, and sterilizing at 115-125 and 0.05-0.15 MPa for 15-25 min. The ophthalmic emulsion gel directly acts on infected part, and can throughly and effectively play its role.

L2 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2011:1544834 CAPLUS
DOCUMENT NUMBER: 155:694448
TITLE: Cyclosporin emulsions
INVENTOR(S): Morgan, Aileen; Gore, Anuradha V.; Attar, Mayssa; Pujara, Chetan
PATENT ASSIGNEE(S): Allergan, Inc., USA
SOURCE: PCT Int. Appl., 23pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2011150102 | A1 | 20111201 | WO 2011-US37964 | 20110525 |
| W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, | | | | |

KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA,
MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE,
PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV,
SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,
HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS,
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MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL,
SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

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|---|---|---|---|---|
| US 20110294744 | A1 | 20111201 | US 2011-13115764 | 20110525 |
| EP 2575854 | A1 | 20130410 | EP 2011-726545 | 20110525 |

R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,
HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO,
RS, SE, SI, SK, SM, TR

PRIORITY APPLN. INFO.: US 2010-61347851 P 20100525
WO 2011-US37964 W 20110525

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB Disclosed herein is a composition comprising cyclosporin A at a concentration between about 0.001% (w/v) and about 1.0% (w/v), a plant oil at a concentration between about 0.01% (w/v) and about 10% (w/v), and macrogol 15 hydroxystearate at a concentration between about 0.01% (w/v) and about 10% (w/v).

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2007:1175883 CAPLUS
DOCUMENT NUMBER: 147:455518
TITLE: Liquid crystal emulsion-type pharmaceutical compositions containing cyclosporin
INVENTOR(S): Akamatsu, Akira; Fujii, Masahiro; Sakaguchi, Tomonori; Horisawa, Eijiro
PATENT ASSIGNEE(S): Maruho Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 12pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| JP 2007269795 | A | 20071018 | JP 2007-60987 | 20070309 |
| JP 5026824 | B2 | 20120919 | | |
| CA 2697756 | A1 | 20090319 | CA 2007-2697756 | 20070910 |
| WO 2009034604 | A1 | 20090319 | WO 2007-JP67564 | 20070910 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,
KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,
PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
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BY, KG, KZ, MD, RU, TJ, TM

| | | | | |
|---|---|---|---|---|
| EP 2193798 | A1 | 20100609 | EP 2007-806996 | 20070910 |

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR,
AL, BA, HR, MK, RS

US 20100190695 A1 20100729 US 2010-676929 20100308
PRIORITY APPLN. INFO.: JP 2006-66545 A 20060310
WO 2007-JP67564 W 20070910
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The invention provides a liquid crystal emulsion-type pharmaceutical composition
characterized by containing cyclosporin and a nonionic surfactant, wherein the composition provides improved transdermal absorption property. For example, a liquid crystal emulsion-type composition containing cyclosporin A 0.1, squalane 1.4,
behenic acid 0.2, cetostearyl alc. 0.9, glycerin monostearate 0.6, polyoxyethylene polyoxypropylene cetyl ether 0.6, 1,3-butylene glycol 9, L-arginine 0.1, pH adjuster q.s., and water balance to 100 % was formulated.

L2 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2007:63260 CAPLUS
DOCUMENT NUMBER: 146:149038
TITLE: Opthalmic emulsion comprising cyclosporin
INVENTOR(S): Chang, James N.; Olejnik, Orest; Firestone, Bruce A.
PATENT ASSIGNEE(S): Allergan, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 24pp., Cont.-in-part of U.S. Ser. No. 181,409.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 20070015694 | A1 | 20070118 | US 2005-255821 | 20051019 |
| US 7288520 | B2 | 20071030 | | |
| US 20070015690 | A1 | 20070118 | US 2005-181178 | 20050713 |
| US 7297679 | B2 | 20071120 | | |
| US 20070015710 | A1 | 20070118 | US 2005-181187 | 20050713 |
| US 7276476 | B2 | 20071002 | | |
| US 20070015691 | A1 | 20070118 | US 2005-181409 | 20050713 |
| US 20070015692 | A1 | 20070118 | US 2005-181428 | 20050713 |
| US 7202209 | B2 | 20070410 | | |
| US 20070015693 | A1 | 20070118 | US 2005-181509 | 20050713 |
| US 20070149447 | A1 | 20070628 | US 2007-679934 | 20070228 |
| US 8536134 | B2 | 20130917 | | |
| US 20080009436 | A1 | 20080110 | US 2007-857223 | 20070918 |
| US 8211855 | B2 | 20120703 | | |
| US 20080070834 | A1 | 20080320 | US 2007-940652 | 20071115 |
| US 8575108 | B2 | 20131105 | | |
| US 20120270805 | A1 | 20121025 | US 2012-13536479 | 20120628 |
| US 8563518 | B2 | 20131022 | | |
| US 20140011753 | A1 | 20140109 | US 2013-14027006 | 20130913 |
| US 20140045772 | A1 | 20140213 | US 2013-14059025 | 20131021 |
| US 20140057855 | A1 | 20140227 | US 2013-14071427 | 20131104 |
| PRIORITY APPLN. INFO.: | | | US 2005-181178 | A2 20050713 |
| | | | US 2005-181187 | A2 20050713 |
| | | | US 2005-181409 | A2 20050713 |
| | | | US 2005-181428 | A2 20050713 |
| | | | US 2005-181509 | A2 20050713 |
| | | | US 2005-255821 | A3 20051019 |
| | | | US 2007-679934 | A1 20070228 |
| | | | US 2007-857223 | A1 20070918 |
| | | | US 2007-940652 | A1 20071115 |
| | | | US 2012-13536479 | A1 20120628 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A composition is disclosed herein comprising from about 0.001% to about 0.4% cyclosporin A, castor oil, and a surfactant selected from the group consisting of alc. ethoxylated, alcs., alkyl glycosides, alkyl polyglycosides, alkylphenol ethoxylates, amine oxides, block polymers, carboxylated alc. or alkylphenol ethoxylates, carboxylic adds/fatty acids, cellulose derivs., ethoxylated alcs., ethoxylated alkylphenols, ethoxylated aryl phenols, ethoxylated fatty acids, ethoxylated fatty acids, ethoxylated fatty esters and oils, fatty alcs., fatty esters, glycol esters, lanolin-based derivs., lecithin and lecithin derivs., lignin and lignin derivs., Me esters, monoglycerides and derivs., phospholipids, polyacrylic acids, polyethylene glycols, polyethylene oxide-polypropylene oxide copolymers, polyethylene oxides, polymeric surfactants, polypropylene oxides, propoxylated alcs., propoxylated alkyl phenols, propoxylated fatty acids, protein-based surfactants, sarcosine derivs., silicone-based surfactants, sorbitan derivs., stearates, sucrose and glucose esters and derivs., and combinations thereof. For example, emulsion was prepared containing cyclosporin A 0.1%, castor oil 1%, clove oil 0.7%, Polysorbate-80 1%, diglycerol 0.7%, glycerin 2%, CM-cellulose 0.5%, sodium hydroxide to adjust pH (7.2) and water as needed.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 89 THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2000:875740 CAPLUS

DOCUMENT NUMBER: 134:33000

TITLE: Emulsion preconcentrate comprising a cyclosporin, propylene carbonate, and glycerides

INVENTOR(S): Sherman, Bernard Charles

PATENT ASSIGNEE(S): Can.

SOURCE: U.S., 5 pp.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6159933 | A | 20001212 | US 1998-66712 | 19980427 |
| CA 2236131 | A1 | 19981029 | CA 1998-2236131 | 19980429 |
| PRIORITY APPLN. INFO.: | | | NZ 1997-314701 A | 19970429 |

AB Pharmaceutical compns. in the form of an emulsion preconc. or microemulsion preconc. which comprise a cyclosporin as active ingredient, propylene carbonate as hydrophilic solvent, glycerides as lipophilic solvent, and a surfactant. An emulsion preconc. containing cyclosporin 1, Maisine 3.2, propylene carbonate 1.4, Cremophor RH40 3.8, and polysorbate 20 1.2 g was prepared, and 1 g of the preconc. was combined with 20 mL of warm water to form an emulsion or microemulsion.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2000:283997 CAPLUS

DOCUMENT NUMBER: 132:298857

TITLE: Pharmaceutical composition comprising cyclosporin in association with a carrier in a self-emulsifying drug

delivery system
INVENTOR(S): Mulye, Nirmal
PATENT ASSIGNEE(S): Pharmasolutions, Inc., USA
SOURCE: U.S., 8 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6057289 | A | 20000502 | US 1999-303158 | 19990430 |
| WO 2000066140 | A1 | 20001109 | WO 2000-US11624 | 20000428 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2000046812 | A | 20001117 | AU 2000-46812 | 20000428 |

PRIORITY APPLN. INFO.: US 1999-303158 A 19990430
WO 2000-US11624 W 20000428
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB The present invention is directed to a pharmaceutical composition comprising a pharmaceutically effective amount of cyclosporin in association with a pharmaceutical carrier, said carrier comprising a drug solubilizing effective amount of a fatty acid having 6-22 carbon atoms and a nonionic surfactant. An emulsion ready for encapsulation into a capsule contained cyclosporin 100, oleic acid 200, and polyoxyl 35 castor oil 200 mg.
OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 1999:594969 CAPLUS
DOCUMENT NUMBER: 131:219189
TITLE: Emulsion preconcentrates comprising a cyclosporin and glycerides
INVENTOR(S): Sherman, Bernard Charles
PATENT ASSIGNEE(S): Can.
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9945946 | A1 | 19990916 | WO 1999-CA192 | 19990305 |
| W: CA, US | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |

PRIORITY APPLN. INFO.: NZ 1998-329929 A 19980309
AB Pharmaceutical compns. in the form of an ethanol-free emulsion preconcs. which comprises a cyclosporin as active ingredient, a lipophilic solvent selected from glycerides, a hydrophilic solvent selected from propylene

glycol and polyethylene glycol, a surfactant selected from polyoxyethylene glycolated natural or hydrogenated vegetable oil, and a co-surfactant preferably selected from polyoxyethylene-sorbitan-fatty acid esters. A pharmaceutical emulsion contained cyclosporin 1.0, maisine 2.1, propylene glycol 2.6, Cremophor RH40 3.6, Polysorbate-80 1.0, and water q.s. 100%.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 1999:44999 CAPLUS
DOCUMENT NUMBER: 130:100683
TITLE: Pharmaceutical emulsions containing cyclosporins and surfactants
INVENTOR(S): Bhalani, Vinayak T.; Patel, Satishchandra P.
PATENT ASSIGNEE(S): Sidmak Laboratories, Inc., USA
SOURCE: U.S., 4 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5858401 | A | 19990112 | US 1997-786314 | 19970122 |
| US 7070802 | B1 | 20060704 | US 2001-797912 | 20010305 |
| US 7988995 | B1 | 20110802 | US 2002-207146 | 20020730 |
| US 20060188561 | A1 | 20060824 | US 2006-400585 | 20060407 |
| US 8119157 | B2 | 20120221 | | |
| US 20070259810 | A1 | 20071108 | US 2007-686555 | 20070315 |
| US 7799340 | B2 | 20100921 | | |
| US 20120135940 | A1 | 20120531 | US 2012-13349138 | 20120112 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1996-60010410 | P | 19960122 |
| US 1997-786314 | A2 | 19970122 |
| US 1998-196353 | B1 | 19981119 |
| US 2001-797912 | A1 | 20010305 |
| US 2002-207146 | A1 | 20020730 |
| US 2006-400585 | A1 | 20060407 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A stable solution of cyclosporin forming a polar lipid self-emulsifying drug delivery system is disclosed. The composition typically consists of cyclosporin dissolved in a polar lipid, such as a medium chain monoglyceride of C6-12 fatty acids having a monoglyceride content of at least 50% and a surfactant. The composition provided here instantly forms a fine emulsion on exposure to water. The encapsulated dosage form of this composition needs neither a hydrophilic component nor air-tight blister packaging, and is particularly suitable for oral administration. Thus, 1.0 g of cyclosporin A was dissolved in 5.0 g of Capmul MCM at 25°-30°. Then 6.0 g of Tween 80 was added and mixed to achieve a homogeneous solution The mixture appeared as a clear solution to the naked eye, and a microscopic anal. revealed no crystals. The formulation was filled in a soft gelatin capsule such that each capsule contained 50 mg of cyclosporin.

OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 1998:719247 CAPLUS
DOCUMENT NUMBER: 129:347306
ORIGINAL REFERENCE NO.: 129:70613a,70616a

TITLE: Emulsion preconcentrate comprising a cyclosporin and acetylated monoglyceride
INVENTOR(S): Sherman, Bernard Charles
PATENT ASSIGNEE(S): Can.
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9848779 | A1 | 19981105 | WO 1998-CA408 | 19980429 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW | | | | |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| CA 2285983 | A1 | 19981105 | CA 1998-2285983 | 19980429 |
| ZA 9803596 | A | 19981105 | ZA 1998-3596 | 19980429 |
| AU 9870248 | A | 19981124 | AU 1998-70248 | 19980429 |
| EP 981329 | A1 | 20000301 | EP 1998-916755 | 19980429 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, FI | | | | |
| US 6258783 | B1 | 20010710 | US 1999-403660 | 19991027 |
| US 20010027178 | A1 | 20011004 | US 2001-783969 | 20010216 |

PRIORITY APPLN. INFO.:
NZ 1997-314702 A 19970429
WO 1998-CA408 W 19980429
US 1999-403660 A1 19991027

AB Pharmaceutical compns. in the form of an emulsion preconc. or microemulsion preconc. which comprise a cyclosporin as active ingredient, acetylated monoglyceride as lipophilic solvent, a surfactant, and optionally a hydrophilic solvent. One example contained cyclsporine 1.0, Myvacet 9-45 6.0, and Cremophor RH 40 3.7 parts.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 1996:38846 CAPLUS
DOCUMENT NUMBER: 124:66660
ORIGINAL REFERENCE NO.: 124:12317a,12320a
TITLE: Lacrimal gland-specific emulsions for topical application to ocular tissue
INVENTOR(S): Ding, Shulin; Tien, Walter L.; Olejnik, Orest
PATENT ASSIGNEE(S): Allergan, Inc., USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9531211 | A1 | 19951123 | WO 1995-US6302 | 19950517 |
| W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, | | | | |

MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

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|---|---|---|---|---|
| US 5474979 | A | 19951212 | US 1994-243279 | 19940517 |
| CA 2190485 | A1 | 19951123 | CA 1995-2190485 | 19950517 |
| CA 2190485 | C | 20030415 | | |
| CA 2309033 | A1 | 19951123 | CA 1995-2309033 | 19950517 |
| CA 2309033 | C | 20030826 | | |
| AU 9526409 | A | 19951205 | AU 1995-26409 | 19950517 |
| AU 693213 | B2 | 19980625 | | |
| EP 759773 | A1 | 19970305 | EP 1995-921294 | 19950517 |
| EP 759773 | B1 | 20010808 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| CN 1152876 | A | 19970625 | CN 1995-194078 | 19950517 |
| CN 1229136 | C | 20051130 | | |
| BR 9507664 | A | 19971007 | BR 1995-7664 | 19950517 |
| JP 10500414 | T | 19980113 | JP 1995-529895 | 19950517 |
| JP 3441462 | B2 | 20030902 | | |
| EP 1044678 | A1 | 20001018 | EP 2000-202069 | 19950517 |
| EP 1044678 | B1 | 20030312 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE | | | | |
| AT 203911 | T | 20010815 | AT 1995-921294 | 19950517 |
| ES 2161895 | T3 | 20011216 | ES 1995-921294 | 19950517 |
| PT 759773 | E | 20020228 | PT 1995-921294 | 19950517 |
| AT 234076 | T | 20030315 | AT 2000-202069 | 19950517 |
| PT 1044678 | E | 20030829 | PT 2000-202069 | 19950517 |
| ES 2194670 | T3 | 20031201 | ES 2000-202069 | 19950517 |
| MX 2002000724 | A | 20030425 | MX 2002-724 | 19961115 |
| CN 1288722 | A | 20010328 | CN 2000-120126 | 20000714 |
| CN 1198587 | C | 20050427 | | |
| HK 1034190 | A1 | 20051209 | HK 2001-104710 | 20010709 |
| GR 3036945 | T3 | 20020131 | GR 2001-401814 | 20011018 |
| KR 450703 | B1 | 20041001 | KR 2001-88637 | 20011229 |
| JP 2003231646 | A | 20030819 | JP 2003-63234 | 20030310 |
| JP 4119284 | B2 | 20080716 | | |

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|---|---|---|---|
| PRIORITY APPLN. INFO.: | US 1994-243279 | A | 19940517 |
| | CA 1995-2190485 | A3 | 19950517 |
| | EP 1995-921294 | A3 | 19950517 |
| | JP 1995-529895 | A3 | 19950517 |
| | WO 1995-US6302 | W | 19950517 |
| | KR 1996-706523 | A3 | 19961118 |

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB A pharmaceutical composition is disclosed in the form of a nonirritating emulsion which includes at least one cyclosporin in admixt. with a higher fatty acid glyceride and polysorbate 80. More particularly, the cyclosporin may be cyclosporine A and the higher fatty acid glyceride may be castor oil. The composition allows a high comfort level and low irritation potential suitable for delivery of medications to sensitive areas such as ocular tissues with enhanced absorption in the lacrimal gland. In addition, the composition has stability for up to 9 mo without crystallization of cyclosporin.

For example, an ophthalmic emulsion containing cyclosporin A 0.2, castor oil 2.5, Polysorbate-80 1.0, Pemulen 0.05, glycerol 2.2, NaOH q.s., and purified water to 100% was formulated to treat keratoconjunctivitis sicca.

| | | |
|---|---|---|
| OS.CITING REF COUNT: | 36 | THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (38 CITINGS) |
| REFERENCE COUNT: | 2 | THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT |

L2 ANSWER 12 OF 14 CAPLUS 

ACCESSION NUMBER: 1995:379416 CAPLUS
DOCUMENT NUMBER: 122:169924
ORIGINAL REFERENCE NO.: 122:31059a,31062a
TITLE: Cyclosporin A in fat emulsion carriers: experimental studies on pharmacokinetics and tissue distribution
AUTHOR(S): Tibell, A.; Lindholm, A.; Sawe, J.; Chen, G; Norrlind, B.
CORPORATE SOURCE: Department Transplantation Surgery, Karolinska Institute, Stockholm, Swed.
SOURCE: Pharmacology & Toxicology (Copenhagen) (1995), 76(2), 115-21
CODEN: PHTOEH; ISSN: 0901-9928
DIGITAL OBJECT ID: 10.1111/j.1600-0773.1995.tb00115.x
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the com. available i.v. formulation of cyclosporin A (Sandimmun), ethoxylated castor oil (Cremophor EL) is used as a solubilizing agent. The authors recently reported that the acute nephrotoxic effect of this drug was alleviated by replacing Cremophore EL with a soybean oil-based fat emulsion in a rat model. To further explore the potential of fat emulsions as carriers for cyclosporin A, data on the in vivo pharmacokinetics and tissue distribution are required. In this study in pigs, the pharmacokinetics of soybean oil-cyclosporin A was compared to that of Sandimmun. The 2 formulations seemed bioequivalent, as there were no significant differences in the systemic clearances, vols. of distribution or elimination half-lives. Moreover, the tissue distributions of soybean oil-cyclosporin A and Sandimmun were compared in rats. These studies also included two addnl. lipid-based carriers; one based on iodized ester of poppy seed oil and the other on a liposomal preparation The tissue distributions were similar regardless of the carriers used. Fat emulsion carriers seem to offer possibilities for preparing better tolerated i.v. formulations of cyclosporin A while maintaining the same characteristics concerning pharmacokinetics and tissue distribution.
OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)

L2 ANSWER 13 OF 14 EMBASE 
ACCESSION NUMBER: 1999105661 EMBASE
TITLE: Distribution of cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs.
AUTHOR: Acheampong, Andrew A., Dr. (correspondence); Shackleton, Martha; Tang-Liu, Diane D.-S.; Ding, Shulin; Stern, Mike E.; Decker, Robert
CORPORATE SOURCE: Allergan, Irvine, CA, United States. acheampong_andrew@Allergan.com
AUTHOR: Acheampong, Andrew A., Dr. (correspondence)
CORPORATE SOURCE: Allergan Inc., 2525 Dupont Drive, Irvine, CA 92715, United States. acheampong_andrew@Allergan.com
SOURCE: Current Eye Research, (Feb 1999) Vol. 18, No. 2, pp. 91-103.
Refs: 30
ISSN: 0271-3683 CODEN: CEYRDM
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 012 Ophthalmology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered Embase: 28 Apr 1999
Last Updated on Embase: 28 Apr 1999

AB Purpose. To determine the ocular pharmacokinetics of cyclosporin A after topical ophthalmic administration. Methods. Radiolabled cyclosporin A in either a castor oil-in-water emulsion or a corn oil ointment was applied to the eyes of beagle dogs or albino rabbits using the following paradigms: (i) single doses of 0.2% emulsion to rabbits and dogs, (ii) single doses of 0.05%, 0.2%, or 0.4% emulsion to rabbits, (iii) multiple doses of 0.2% emulsion to dogs, (iv) single and multiple doses of 0.2% ointment to rabbits. The distribution of cyclosporin A was determined by measuring the distribution of radioactivity. Results. After a single dose, cyclosporin A was rapidly absorbed into the conjunctiva (C(max): dogs, 1490 ng/g; rabbits, 1340 ng/g) and cornea (C(max): dogs, 311 ng/g; rabbits, 955 ng/g). High concentrations (> 300 ng/g) could be detected in the cornea up to 96 hours post-dose. Lower concentrations were found in the intraocular tissues, and systemic absorption was minimal. After multiple doses, there was some accumulation in the cornea, lens, lacrimal gland, and iris-cilliary body, but limited accumulation in the conjunctiva and sclera. Ocular tissue concentrations of cyclosporin A increased with increasing dose concentration; proportionally in lacrimal gland and intraocular tissues; less than proportionally in conjunctiva and cornea. The pharmacokinetic profile of the cyclosporin A corn oil ointment was similar to that of the emulsion. Conclusions. Topical ophthalmic cyclosporin A penetrated into extraocular tissues at concentrations adequate for local immunomodulation while penetration into intraocular tissues was much less and absorption into the blood was minimal.

L2 ANSWER 14 OF 14 MEDLINE ® on STN
ACCESSION NUMBER: 1999238168 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10223652
TITLE: Distribution of cyclosporin A in ocular tissues after topical administration to albino rabbits and beagle dogs.
AUTHOR: Acheampong A A
CORPORATE SOURCE: Allergan, Irvine, CA 92715, USA.
acheampong_andrew@Allergan.com
AUTHOR: Shackleton M; Tang-Liu D D; Ding S; Stern M E; Decker R
SOURCE: Current eye research, (1999 Feb) Vol. 18, No. 2, pp. 91-103.
Journal code: 8104312. ISSN: 0271-3683. L-ISSN: 0271-3683.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 14 Jun 1999
Last Updated on STN: 14 Jun 1999
Entered Medline: 2 Jun 1999
OS.CITING REF COUNT: 3 There are 3 MEDLINE records that cite this record

AB PURPOSE: To determine the ocular pharmacokinetics of cyclosporin A after topical ophthalmic administration.

METHODS: Radiolabled cyclosporin A in either a castor oil-in-water emulsion or a corn oil ointment was applied to the eyes of beagle dogs or albino rabbits using the following paradigms: (i) single doses of 0.2% emulsion to rabbits and dogs, (ii) single doses of 0.05%, 0.2%, or 0.4% emulsion to rabbits, (iii) multiple doses of 0.2% emulsion to dogs, (iv) single and multiple doses of 0.2% ointment to rabbits. The distribution of cyclosporin A was determined by measuring the distribution of radioactivity.

RESULTS: After a single dose, cyclosporin A was rapidly absorbed into the conjunctiva (Cmax: dogs, 1490 ng/g; rabbits, 1340 ng/g) and cornea (Cmax: dogs, 311 ng/g; rabbits, 955 ng/g). High concentrations (>300 ng/g) could be detected in the cornea up to 96 hours post-dose. Lower concentrations were found in the intraocular tissues, and systemic absorption was minimal. After multiple doses, there was some accumulation in the cornea, lens, lacrimal gland, and iris-cilliary body, but limited accumulation in the conjunctiva and sclera. Ocular tissue concentrations of cyclosporin A increased with increasing dose concentration; proportionally in lacrimal gland and intraocular tissues; less than proportionally in conjunctiva and cornea. The pharmacokinetic profile of the cyclosporin A corn oil ointment was similar to that of the emulsion.

CONCLUSIONS: Topical ophthalmic cyclosporin A penetrated into extraocular tissues at concentrations adequate for local immunomodulation while penetration into intraocular tissues was much less and absorption into the blood was minimal.

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(FILE 'HOME' ENTERED AT 12:17:16 ON 16 JUN 2014)

FILE 'REGISTRY' ENTERED AT 12:17:22 ON 16 JUN 2014

FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE' ENTERED AT 12:17:32 ON 16 JUN 2014
L1 0 CYCLOSPORIN (10A) (TWICE OR TWO) (10A) (CASTOR OIL) (10A) (EMUL
L2 14 CYCLOSPORIN (10A) (CASTOR OIL) (10A) (EMULSION)

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| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 79.00 | 79.78 |

SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 12:19:01 ON 16 JUN 2014

| INFORMATION DISCLOSURE STATEMENT BY APPLICANT ( **Not for submission under 37 CFR 1.99)** | | |
|---|---|---|
| | Application Number | 14222478 |
| | Filing Date | 2014-03-21 |
| | First Named Inventor | ANDREW ACHEAMPONG |
| | Art Unit | 1621 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| U.S.PATENTS | | | | | | |
|---|---|---|---|---|---|---|
| Examiner Initial* | Cite No | Patent Number | Kind Code[1] | Issue Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
| | 1 | 3278447 | | 1966-10-11 | Thomas McNicholas | |
| | 2 | 4388229 | | 1983-06-14 | Cherng-Chyi Fu | |
| | 3 | 4388307 | | 1983-06-14 | Thomas Cavanak | |
| | 4 | 4614736 | | 1986-09-30 | Delevallee et al | |
| | 5 | 4649047 | | 1987-03-10 | Renee Kaswan | |
| | 6 | 4764503 | | 1988-08-16 | Roland Wenger | |
| | 7 | 4814323 | | 1989-03-21 | Andrieu et al | |
| | 8 | 4839342 | | 1989-06-13 | Renee Kaswan | |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | Filing Date | 2014-03-21 |
| | First Named Inventor | ANDREW ACHEAMPONG |
| | Art Unit | 1621 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | | | | |
|---|---|---|---|---|---|---|
| | 9 | 4970076 | | 1990-11-13 | David Horrobin | |
| | 10 | 4990337 | | 1991-02-05 | Kurihara et al | |
| | 11 | 4996193 | | 1991-02-26 | Hewitt et al | |
| | 12 | 5011681 | | 1991-04-30 | Ciotti et al | |
| | 13 | 5047396 | | 1991-09-10 | Orban et al | |
| | 14 | 5051402 | | 1991-09-24 | Kurihara et al | |
| | 15 | 5053000 | | 1991-10-01 | Booth et al | |
| | 16 | 5075104 | | 1991-12-24 | Gressel et al | |
| | 17 | 5286730 | | 1994-02-15 | Caufield et al | |
| | 18 | 5286731 | | 1994-02-15 | Caufield et al | |
| | 19 | 5294604 | | 1994-03-15 | Nussenblatt et al | |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | Filing Date | 2014-03-21 |
| | First Named Inventor | ANDREW ACHEAMPONG |
| | Art Unit | 1621 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | | | | |
|---|---|---|---|---|---|---|
| | 20 | 5296158 | | 1994-03-22 | MacGilp et al | |
| | 21 | 5342625 | | 1994-08-30 | Hauer et al | |
| | 22 | 5364632 | | 1994-11-15 | Simon Benita | |
| | 23 | 5368854 | | 1994-11-29 | Donna Rennick | |
| | 24 | 5411952 | | 1995-05-02 | Renee Kaswan | |
| | 25 | 5424078 | | 1995-06-13 | Anthony Dziabo | |
| | 26 | 5441732 | | 1995-08-15 | Hoeg et al | |
| | 27 | 5474919 | | 1995-12-12 | Chartrain et al | |
| | 28 | 5474979 | | 1995-12-12 | Ding et al | U.S. Application No. 08/243,279 and its entire prosecution history** |
| | 29 | 5496811 | | 1996-03-05 | Aviv et al | |
| | 30 | 5504068 | | 1996-04-02 | Komiya et al | |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | Filing Date | 2014-03-21 |
| | First Named Inventor | ANDREW ACHEAMPONG |
| | Art Unit | 1621 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | | | | |
|---|---|---|---|---|---|---|
| | 31 | 5540931 | | 1996-07-30 | Hewitt et al | |
| | 32 | 5543393 | | 1996-08-06 | Kim et al | |
| | 33 | 5589455 | | 1996-12-31 | Jong Woo | |
| | 34 | 5591971 | | 1997-01-07 | Shahar et al | |
| | 35 | 5614491 | | 1997-03-25 | Walch et al | |
| | 36 | 5639724 | | 1997-06-17 | Thomas Cavanak | |
| | 37 | 5652212 | | 1997-07-29 | Cavanak et al | |
| | 38 | 5719123 | | 1998-02-17 | Morley et al | |
| | 39 | 5721273 | | 1998-02-24 | Sallee et al | |
| | 40 | 5739105 | | 1998-04-14 | Kim et al | |
| | 41 | 5753166 | | 1998-05-19 | Dalton et al | |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | Filing Date | 2014-03-21 |
| | First Named Inventor | ANDREW ACHEAMPONG |
| | Art Unit | 1621 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | | | | |
|---|---|---|---|---|---|---|
| | 42 | 5766629 | | 1998-06-16 | Cho et al | |
| | 43 | 5798333 | | 1998-08-25 | Bernard Sherman | |
| | 44 | 5807820 | | 1998-09-15 | Elias et al | |
| | 45 | 5827822 | | 1998-10-27 | Floch'h et al | |
| | 46 | 5827862 | | 1998-10-27 | Yoshitaka Yamamura | |
| | 47 | 5834017 | | 1998-11-10 | Cho et al | |
| | 48 | 5843452 | | 1998-12-01 | Wiedmann et al | |
| | 49 | 5843891 | | 1998-12-01 | Bernard Sherman | |
| | 50 | 5858401 | | 1999-01-12 | Bhalani et al | |
| | 51 | 5866159 | | 1999-02-02 | Hauer et al | |
| | 52 | 5891846 | | 1999-04-06 | Ishida et al | |

Receipt date: 03/28/2014

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
( **Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 14222478 14222478 - GAU: 1676 |
| Filing Date | 2014-03-21 |
| First Named Inventor | ANDREW ACHEAMPONG |
| Art Unit | 1621 |
| Examiner Name | TBD |
| Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | | | | |
|---|---|---|---|---|---|---|
| | 53 | 5916589 | | 1999-06-29 | Hauer et al | |
| | 54 | 5929030 | | 1999-07-27 | Hamied et al | |
| | 55 | 5951971 | | 1999-09-14 | Kawashima et al | |
| | 56 | 5962014 | | 1999-10-05 | Hauer et al | |
| | 57 | 5962017 | | 1999-10-05 | Hauer et al | |
| | 58 | 5962019 | | 1999-10-05 | Cho et al | |
| | 59 | 5977066 | | 1999-11-02 | Thomas Cavanak | |
| | 60 | 5981479 | | 1999-11-09 | Ko et al | |
| | 61 | 5981607 | | 1999-11-09 | Ding et al | U.S. Application No. 09/008,924 and its entire prosecution history** |
| | 62 | 5998365 | | 1999-12-07 | Bernard Sherman | |
| | 63 | 6004566 | | 1999-12-21 | Friedman et al | |

Receipt date: 03/28/2014

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
**( Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 14222478 14222478 - GAU: 1676 |
| Filing Date | 2014-03-21 |
| First Named Inventor | ANDREW ACHEAMPONG |
| Art Unit | 1621 |
| Examiner Name | TBD |
| Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | | | | |
|---|---|---|---|---|---|---|
| | 64 | 6007840 | | 1999-12-28 | Hauer et al | |
| | 65 | 6008191 | | 1999-12-28 | Amarjit Singh | |
| | 66 | 6008192 | | 1999-12-28 | Al-Razzak et al | |
| | 67 | 6022852 | | 2000-02-08 | Klokkers et al | |
| | 68 | 6024978 | | 2000-02-15 | Hauer et al | |
| | 69 | 6046163 | | 2000-04-04 | Stuchlik et al | |
| | 70 | 6057289 | | 2000-05-02 | Nirmal Mulye | |
| | 71 | 6159933 | | 2000-12-12 | Bernard Sherman | |
| | 72 | 6197335 | | 2001-03-06 | Bernard Sherman | |
| | 73 | 6254860 | | 2001-07-03 | Michael Garst | |
| | 74 | 6254885 | | 2001-07-03 | Cho et al | |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | Filing Date | 2014-03-21 |
| | First Named Inventor | ANDREW ACHEAMPONG |
| | Art Unit | 1621 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | | | | |
|---|---|---|---|---|---|---|
| | 75 | 6267985 | | 2001-07-31 | Chen et al | |
| | 76 | 6284268 | | 2001-09-04 | Mishra et al | |
| | 77 | 6294192 | | 2001-09-25 | Patel et al | |
| | 78 | 6306825 | | 2001-10-23 | Thomas Cavanak | |
| | 79 | 6323204 | | 2001-11-27 | James Burke | |
| | 80 | 6346511 | | 2002-02-12 | Singh et al | |
| | 81 | 6350442 | | 2002-02-26 | Michael Garst | |
| | 82 | 6413547 | | 2002-07-02 | Bennett et al | |
| | 83 | 6420355 | | 2002-07-16 | Richter et al | |
| | 84 | 6468968 | | 2002-10-22 | Cavanak et al | |
| | 85 | 6475519 | | 2002-11-05 | Meinzer et al | |

Receipt date: 03/28/2014

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
( **Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 14222478 14222478 - GAU: 1676 |
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| First Named Inventor | ANDREW ACHEAMPONG |
| Art Unit | 1621 |
| Examiner Name | TBD |
| Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | | | | |
|---|---|---|---|---|---|---|
| | 86 | 6486124 | | 2002-11-26 | Olbrich et al | |
| | 87 | 6544953 | | 2003-04-08 | Tsuzuki et al | |
| | 88 | 6555526 | | 2003-04-29 | Matsuo et al | |
| | 89 | 6562873 | | 2003-05-13 | Olejnik et al | |
| | 90 | 6569463 | | 2003-05-27 | Patel et al | |
| | 91 | 6582718 | | 2003-06-24 | Yoichi Kawashima | |
| | 92 | 6656460 | | 2003-12-02 | Benita et al | |
| | 93 | 6872705 | | 2005-03-29 | Robert Lyons | |
| | 94 | 6984628 | | 2006-01-10 | Bakhit et al | |
| | 95 | 7202209 | | 2007-04-10 | James N. Chang | U.S. Application No. 11/181,428 and its entire prosecution history** |
| | 96 | 7276476 | | 2007-10-02 | Chang et al | U.S. Application No. 11/181,187 and its entire prosecution history** |

| Receipt date: 03/28/2014 | Application Number | 14222478 | 14222478 - GAU: 1676 |
|---|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | Filing Date | 2014-03-21 | |
| | First Named Inventor | ANDREW ACHEAMPONG | |
| | Art Unit | 1621 | |
| | Examiner Name | TBD | |
| | Attorney Docket Number | 17618-US-CN6CN1-AP | |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | | | | |
|---|---|---|---|---|---|---|
| | 97 | 7288520 | | 2007-10-30 | Chang et al | U.S. Application No. 11/255,821 and its entire prosecution history** |
| | 98 | 7297679 | | 2007-11-20 | James Chang | U.S. Application No. 11/181,178 and its entire prosecution history** |
| | 99 | 7501393 | | 2009-03-10 | Tien et al | U.S. Application No. 11/161,218 and its entire prosecution history** |
| | 100 | 8211855 | | 2012-07-03 | Chang et al | U.S. Application No. 11/857,223 and its entire prosecution history** |
| | 101 | 8288348 | | 2012-10-16 | Chang et al | U.S. Application No. 11/917,448 and its entire prosecution history** |
| | 102 | 8618064 | | 2013-12-31 | Acheampong et al | U.S. Application No. 11/897,177 and its entire prosecution history** |
| | 103 | 8629111 | | 2014-01-14 | Acheampong et al | U.S. Application No. 13/967,163 and its entire prosecution history** |
| | 104 | 8633162 | | 2014-01-21 | Acheampong et al | U.S. Application No. 13/967,179 and its entire prosecution history** |
| | 105 | 8642556 | | 2014-02-04 | Acheampong et al | U.S. Application No. 13/967,189 and its entire prosecution history** |
| | 106 | 8648048 | | 2014-02-11 | Acheampong et al | U.S. Application No. 13/967,168 and its entire prosecution history** |

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**U.S.PATENT APPLICATION PUBLICATIONS**

Receipt date: 03/28/2014

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**

( **Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 14222478 14222478 - GAU: 1676 |
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| First Named Inventor | ANDREW ACHEAMPONG |
| Art Unit | 1621 |
| Examiner Name | TBD |
| Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| Examiner Initial* | Cite No | Publication Number | Kind Code[1] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear |
|---|---|---|---|---|---|---|
| | 1 | 20010003589 | | 2001-06-14 | Neuer et al | |
| | 2 | 20010014665 | | 2001-08-16 | Fischer et al | |
| | 3 | 20010036449 | | 2001-11-01 | Michael Garst | |
| | 4 | 20020012680 | | 2002-01-31 | Patel et al | |
| | 5 | 20020013272 | | 2002-01-31 | Cavanak et al | |
| | 6 | 20020016290 | | 2002-02-07 | Floc'h et al | |
| | 7 | 20020016292 | | 2002-02-07 | Richter et al | |
| | 8 | 20020025927 | | 2002-02-28 | Olbrich et al | |
| | 9 | 20020045601 | | 2002-04-18 | Yoichi Kawashima | |
| | 10 | 20020107183 | | 2002-08-08 | Petszulat et al | |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | Filing Date | 2014-03-21 |
| | First Named Inventor | ANDREW ACHEAMPONG |
| | Art Unit | 1621 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | | | | |
|---|---|---|---|---|---|---|
| | 11 | 20020119190 | | 2002-08-29 | Meinzer et al | |
| | 12 | 20020165134 | | 2002-11-07 | Richter et al | |
| | 13 | 20030021816 | | 2003-01-30 | Kang et al | |
| | 14 | 20030044452 | | 2003-03-06 | Ryuji Ueno | |
| | 15 | 20030055028 | | 2003-03-20 | Stergiopoulos et al | |
| | 16 | 20030059470 | | 2003-03-27 | Rainer Muller | |
| | 17 | 20030060402 | | 2003-03-27 | Cavanak et al | |
| | 18 | 20030087813 | | 2003-05-08 | Or et al | |
| | 19 | 20030104992 | | 2003-06-05 | Or et al | |
| | 20 | 20030108626 | | 2003-06-12 | Benita et al | |
| | 21 | 20030109425 | | 2003-06-12 | Or et al | |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | Filing Date | 2014-03-21 |
| | First Named Inventor | ANDREW ACHEAMPONG |
| | Art Unit | 1621 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | | | | |
|---|---|---|---|---|---|---|
| | 22 | 20030109426 | | 2003-06-12 | Or et al | |
| | 23 | 20030133984 | | 2003-07-17 | Ambuhl et al | |
| | 24 | 20030143250 | | 2003-07-31 | Hauer et al | |
| | 25 | 20030147954 | | 2003-08-07 | Yang et al | |
| | 26 | 20030166517 | | 2003-09-04 | Fricker et al | |
| | 27 | 20050014691 | | 2005-01-20 | Bakhit et al | |
| | 28 | 20050059583 | | 2005-03-17 | Andrew Acheampong | U.S. Application No. 10/927,857 and its entire prosecution history** |
| | 29 | 20070015691 | | 2007-01-18 | James Chang | U.S. Application No. 11/181,409 and its entire prosecution history** |
| | 30 | 20070027072 | | 2007-02-01 | Tien et al | |
| | 31 | 20070087962 | | 2007-04-19 | Tien et al | |
| | 32 | 20070149447 | | 2007-06-28 | Chang et al | U.S. Application No. 11/679,934 and its entire prosecution history** |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | Filing Date | 2014-03-21 |
| | First Named Inventor | ANDREW ACHEAMPONG |
| | Art Unit | 1621 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | | | | |
|---|---|---|---|---|---|---|
| | 33 | 20080039378 | | 2008-02-14 | Graham et al | U.S. Application No. 11/781,095 and its entire prosecution history** |
| | 34 | 20080070834 | | 2008-03-20 | Chang et al | U.S. Application No. 11/940,652 and its entire prosecution history** |
| | 35 | 20080146497 | | 2008-06-19 | Graham et al | U.S. Application No. 11/858,200 and its entire prosecution history** |
| | 36 | 20080207495 | | 2008-08-28 | Graham et al | U.S. Application No. 12/035,698 and its entire prosecution history** |
| | 37 | 20090131307 | | 2009-05-21 | Tien et al | U.S. Application No. 12/361,335 and its entire prosecution history** |
| | 38 | 20100279951 | | 2010-11-04 | Morgan et al | U.S. Application No. 12/771,952 and its entire prosecution history** |
| | 39 | 20110009339 | | 2011-01-13 | Rhett Schiffman | U.S. Application No. 12/759,431 and its entire prosecution history** |
| | 40 | 20110294744 | | 2011-12-01 | Morgan et al | U.S. Application No. 13/115,764 and its entire prosecution history** |
| | 41 | 20120270805 | | 2012-10-25 | Chang et al | U.S. Application No. 13/536,479 and its entire prosecution history** |
| | 42 | 20130059796 | | 2013-03-07 | Chang et al | U.S. Application No. 13/649,287 and its entire prosecution history** |

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**FOREIGN PATENT DOCUMENTS**

Receipt date: 03/28/2014

**INFORMATION DISCLOSURE STATEMENT BY APPLICANT**
( **Not for submission under 37 CFR 1.99)**

| | |
|---|---|
| Application Number | 14222478 14222478 - GAU: 1676 |
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| Examiner Name | TBD |
| Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| Examiner Initial* | Cite No | Foreign Document Number[3] | Country Code[2] ¡ | Kind Code[4] | Publication Date | Name of Patentee or Applicant of cited Document | Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear | T[5] |
|---|---|---|---|---|---|---|---|---|
| | 1 | 19810655 | DE | | 1999-09-16 | Eberhard-Karis-Universitat Tubingen Universitatskl | | ☐ |
| | 2 | 0448856 | EP | | 1991-10-02 | Chatfield Pharmaceuticals | | ☐ |
| | 3 | 0471293 | EP | | 1992-02-19 | ABBOTT LABORATORIES | | ☐ |
| | 4 | 0480690 | EP | | 1992-04-15 | IOLAB CORPORATION | | ☐ |
| | 5 | 0547229 | EP | | 1993-01-07 | LLT Institute Co., Ltd. | | ☐ |
| | 6 | 0760237 | EP | | 1997-03-05 | Cipla Limited | | ☐ |
| | 7 | 1995-031211 | WO | | 1995-11-23 | Allergan, Inc. | | ☐ |
| | 8 | 2000-000179 | WO | | 2000-01-06 | Won Jin Biopharma Co., Ltd | | ☐ |
| | 9 | 2001-032142 | WO | | 2001-05-10 | Cipla Limited | | ☐ |
| | 10 | 2001-041671 | WO | | 2001-06-14 | Transneuronix, Inc. | | ☐ |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | Filing Date | 2014-03-21 |
| | First Named Inventor | ANDREW ACHEAMPONG |
| | Art Unit | 1621 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 11 | 2002-009667 | WO | | 2002-02-07 | Pharmasol GMBH | | ☐ |
| | 12 | 2002-049603 | WO | | 2002-06-27 | LG Household & Health Care Ltd. | | ☐ |
| | 13 | 2003-030834 | WO | | 2003-04-17 | Enanta Pharmaceuticals, Inc. | | ☐ |
| | 14 | 2003-053405 | WO | | 2003-07-03 | Yissum Research Development Company of the Hebrew | | ☐ |

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**NON-PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published. | T[5] |
|---|---|---|---|
| | 1 | ABDULRAZIK, M. ET AL, Ocular Delivery of Cyclosporin A II. Effect of Submicron Emulsion's Surface Charge on Ocular Distribution of Topical Cyclosporin A, S.T.P. Pharma Sciences, Dec. 2001, 427-432, 11(6) | ☐ |
| | 2 | ACHEAMPONG, ANDREW ET AL, Cyclosporine Distribution into the Conjunctiva, Cornea, Lacrimal Gland and Systemic Blood Following Topical Dosing of Cyclosporine to Rabbit, Dog and Human eyes, 1996, 179 | ☐ |
| | 3 | ACHEAMPONG, ANDREW ET AL, Cyclosporine Distribution Into The Conjunctiva, Cornea, Lacrimal Gland, and Systemic Blood Following Topical Dosing of Cyclosporine to Rabbit, Dog, and Human Eyes, Adv. Exp. Med. Biol., 1998, 1001-1004, 438 | ☐ |
| | 4 | ACHEAMPONG, ANDREW ET AL, Distribution of Cyclosporin A in Ocular Tissues After Topical Administration to Albino Rabbits and Beagle Dogs, Current Eye Research, 1999, 91-103, 18(2) | ☐ |
| | 5 | AKPEK, ESEN KARAMURSEL ET AL, A Randomized Trial of Topical Cyclosporin 0.05% in Topical Steroid-Resistant Atopic Keratoconjunctivitis, Ophthalmology, 2004, 476-482, 111 | ☐ |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
|---|---|---|
| **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** ( **Not for submission under 37 CFR 1.99)** | Filing Date | 2014-03-21 |
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| | Art Unit | 1621 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | |
|---|---|---|---|
| | 6 | ANGELOV, O. ET AL, Preclinical Safety Studies of Cyclosporine Ophthalmic Emulsion, Adv Exp Med Biol, 1998, 991-995, 438 | ☐ |
| | 7 | ANGELOV, O. ET AL, Safety Assessment of Cyclosporine Ophthalmic Emulsion in Rabbits and Dogs, XIth Congress of the European Society of Ophthalmology, 1997, 25-28, 1-5, Soc. Ophthalmol Eur., HU | ☐ |
| | 8 | ARDIZZONE, SANDRO ET AL, A Practical Guide to the Management of Distal Ulcerative Colitis, Drugs, 1998, 519-542, 55(4) | ☐ |
| | 9 | BANIC, MARKO ET AL, Effect of Cyclosporine in a Murine Model of Experimental Colitis, Digestive Diseases and Sciences, June 2002, 1362-1368, 47(6) | ☐ |
| | 10 | BF GOODRICH, CARBOPOL 1342 A New Polymer Which Functions Both As a Thickener And An Emulsifier TDS-73, Carbopol High Performance Polymers, 1987, 25 Pages | ☐ |
| | 11 | BF GOODRICH, Carbopol, Pemulen and Noveon Polymers, 1995, 2 Pages | ☐ |
| | 12 | BF GOODRICH, Pemulen Polymeric Emulsifiers TDS-182, March 1993, 9 Pages | ☐ |
| | 13 | BONINI, S. ET AL, Vernal Keratoconjunctivitis, Eye, 2004, 345-351, 18 | ☐ |
| | 14 | BREWSTER, MARCUS ET AL, Enhanced Delivery of Ganciclovir to the Brain Through the Use of Redox Targeting, Antimicrobial Agents and Chemotherapy, Apr 1994, 817-823, 38(4) | ☐ |
| | 15 | BREWSTER, MARCUS ET AL, Intravenous and Oral Pharmacokinetic Evaluation of a 2-Hydroxypropyl-ß-cyclodextrin-Based Formulation of Carbamazepine in the Dog: Comparison with Commercially Available Tablets and Suspensions, Journal of Pharmaceutical Sciences, March 1997, 335-339, 86(3) | ☐ |
| | 16 | BREWSTER, MARCUS ET AL, Preparation, Characterization, and Anesthetic Properties of 2-Hydroxypropyl-ß-cyclodextrin Complexes of Pregnanolone and Pregnenolone in Rat and Mouse, Journal of Pharmaceutical Sciences, October 1995, 1154-1159, 84(10) | ☐ |

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|---|---|---|
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| | First Named Inventor | ANDREW ACHEAMPONG |
| | Art Unit | 1621 |
| | Examiner Name | TBD |
| | Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | |
|---|---|---|---|
| | 17 | BRINKMEIER, THOMAS ET AL, Pyodermatitis-Pyostomatitis Vegetans: A Clinical Course of Two Decades with Response to Cyclosporine and Low-Dose Prednisolone, Acta Derm Venereol, 2001, 134-136, 81 | ☐ |
| | 18 | CASTILLO, JOSE M. BENITEZ DEL ET AL, Influence of Topical Cyclosporine A and Dissolvent on Corneal Epithelium Permeability of Fluorescein, Documenta Ophthalmologica, 1995, 49-55, 91 | ☐ |
| | 19 | CHEEKS, LISA ET AL, Influence of Vehicle and Anterior Chamber Protein Concentration on Cyclosporine Penetration Through the Isolated Rabbit Cornea, Current Eye Research, 1992, 641-649, 11(7) | ☐ |
| | 20 | Database WPI Week 200044, Derwent Pub. Ltd., London, GB; An 2000-492678 & JP2000/143542, 2000, 2 Pages | ☐ |
| | 21 | DING, SHULIN ET AL, Cyclosporine Ophthalmic O/W emulsion: Formulation and Emulsion Characterization, Pharm Res, 1997, 1 page, 14 (11) | ☐ |
| | 22 | DONNENFELD, ERIC D., The Economics Of Using Restasis, Ophthalmology Management, 10/2003, 3 pages, US | ☐ |
| | 23 | DROSOS, A. A. ET AL, Efficacy and Safety of Cyclosporine-A Therapy for Primary Sjogren's Syndrome, Ter. Arkh., 1998, 77-80, 60(4) | ☐ |
| | 24 | DROSOS, A.A. ET AL, Cyclosporin A Therapy in Patients with Primary Sjogren's Syndrome: Results at One Year, Scand J Rheumatology, 1986, 246-249, 61 | ☐ |
| | 25 | DURRANI, A.M. ET AL, Pilocarpine Bioavailability From a Mucoadhesive Liposomal Ophthalmic Drug Delivery System, International Journal of Pharmaceutics, 1992, 409-415, 88 | ☐ |
| | 26 | EISEN, DRORE ET AL, Topical Cyclosporine for Oral Mucosal Disorders, J Am Acad Dermatol, Dec. 1990, 1259-1264, 23 | ☐ |
| | 27 | EPSTEIN, JOEL ET AL, Topical Cyclosporine in a Bioadhesive for Treatment of Oral Lichenoid Muscosal Reactions, Oral Surg Oral Med Oral Pathol Oral, 1996, 532-536, 82 | ☐ |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | |
|---|---|---|---|
| | 28 | ERDMANN, S. ET AL, Pemphigus Vulgaris Der Mund- Und Kehlkopfschleimhaut Pemphigus Vulgaris of the Oral Mucosa and the Larynx, H+G Zeitschrift Fuer Hautkrankheiten, 1997, 283-286, 72(4) | ☐ |
| | 29 | FDA Concludes Restasis (Cyclosporine) Not Effective for Dry Eye (6/18/1999). Accessed online at http://www.dryeyeinfo.org/Restasis_Cyclosporine.htm on 8/14/09. 1 Page | ☐ |
| | 30 | GAETA, G.M. ET AL, Cyclosporin Bioadhesive Gel in the Topical Treatment of Erosive Oral Lichen Planus, International Journal of Immunopathology and Pharmacology, 1994, 125-132, 7(2) | ☐ |
| | 31 | GIPSON, ILENE ET AL, Character of Ocular Surface Mucins and Their Alteration in Dry Eye Disease, The Ocular Surface, April 2004, 131-148, 2(2) | ☐ |
| | 32 | GREMSE, DAVID ET AL, Ulcerative Colitis in Children, Pediatr Drugs, 2002, 807-815, 4(12) | ☐ |
| | 33 | GUNDUZ, KAAN ET AL, Topical Cyclosporin Treatment of Keratoconjunctivitis Sicca in Secondary Sjogren's Syndrome, Acta Ophthalmologica, 1994, 438-442, 72 | ☐ |
| | 34 | http://web.archive.org/web/2001030625323/http://www.surfactant.co.kr/surfactants/pegester.html, 2001, 6 Pages, retrieved on 7/05/2008 | ☐ |
| | 35 | HUNTER, P.A. ET AL, Cyclosporin A Applied Topically to the Recipient Eye Inhibits Corneal Graft Rejection, Clin Exp Immunol, 1981, 173-177, 45 | ☐ |
| | 36 | JUMAA, MUHANNAD ET AL, Physicochemical Properties and Hemolytic Effect of Different Lipid Emulsion Formulations Using a Mixture of Emulsifiers, Pharmaceutica Acta Helvetiae, 1999, 293-301, 73 | ☐ |
| | 37 | KANAI, A. ET AL, The Effect on the Cornea of Alpha Cyclodextrin Vehicle for Eye Drops, Transplantation Proceedings, February 1989, 3150-3152, Vol. 21 | ☐ |
| | 38 | KANPOLAT, AYFER ET AL, Penetration of Cyclosporin A into the Rabbit Cornea and Aqueous Humor after Topical Drop and Collagen Shield Administration, Cornea/External Disease, April 1994, 119-122, 20(2) | ☐ |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | |
|---|---|---|---|
| | 39 | KAUR, RABINDER ET AL, Solid Dispersions of Drugs in Polyocyethylene 40 Stearate: Dissolution Rates and Physico-Chemical Interactions, Journal of Pharmacy and Pharmacology, December 1979, 48P | ☐ |
| | 40 | KUWANO, MITSUAKI ET AL, Cyclosporine A Formulation Affects Its Ocular Distribution in Rabbits, Pharmaceutical Research, January 2002, 108-111, 19(1) | ☐ |
| | 41 | Lambert Technologies Corp. Material Safety Data Sheet for LUMULSE ™ POE-40 MS KP, last revision 8/22/2003. 3 pages | ☐ |
| | 42 | LEIBOVITZ, Z. ET AL., Our Experience In Processing Maize (Corn) Germ Oil, Journal Of The American Oil Chemists Society, 02/1983, 395-399, 80 (2), US | ☐ |
| | 43 | LIXIN, XIE ET AL, Effect Of Cyclosporine A Delivery System in Corneal Transplantation, Chinese Medical Journal, 2002, 110-113, 115 (1), US | ☐ |
| | 44 | LOPATIN, D.E., Chemical Compositions and Functions of Saliva, 8/24/2001, 31 Pages | ☐ |
| | 45 | LYONS, R.T. ET AL, Influence of Three Emulsion Formulation Parameters on the Ocular Bioavailability of Cyclosporine A in Albino Rabbits, Am Assoc Pharm Sci, 2000, 1 Page, 2(4) | ☐ |
| | 46 | PEDERSEN, ANNE MARIE ET AL, Primary Sjogren's Syndrome: Oral Aspects on Pathogenesis, Diagnostic Criteria, Clinical Features and Approaches for Therapy, Expert Opin Pharma, 2001, 1415-1436, 2(9) | ☐ |
| | 47 | PHILLIPS, THOMAS ET AL, Cyclosporine Has a Direct Effect on the Differentiation of a Mucin-Secreting Cell Line, Journal of Cellular Physiology, 2000, 400-408, 184 | ☐ |
| | 48 | PRESENT, D.H. ET AL, Cyclosporine and Other Immunosuppressive Agents: Current and Future Role in the Treatment of Inflammatory Bowel Disease, American Journal of Gastroenterology, 1993, 627-630, 88(5) | ☐ |
| | 49 | Restasis ® Product Information Sheet, Allergan, Inc., 2009, 5 Pages | ☐ |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
|---|---|---|
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| | Attorney Docket Number | 17618-US-CN6CN1-AP |

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | |
|---|---|---|---|
| | 50 | Restasis® Increasing Tear Production, Retrieved on 08/14/2009, http://www.restasisprofessional.com/_clinical/clinical_increasing.htm 3 pages | ☐ |
| | 51 | ROBINSON, N.A. ET AL, Desquamative Gingivitis: A Sign of Mucocutaneous Disorders - a Review, Australian Dental Journal, 2003, 205-211, 48(4) | ☐ |
| | 52 | RUDINGER, J., Characteristics of the Amino Acids as Components of a Peptide Hormone Sequence, Peptide Hormones, 1976, 1-7 | ☐ |
| | 53 | SALL, KENNETH ET AL, Two Multicenter, Randomized Studies of the Efficacy and Safety of Cyclosporine Ophthalmic Emulsion in Moderate to Severe Dry Eye Disease, Ophthalmology, 2000, 631-639, 107 | ☐ |
| | 54 | SANDBORN, WILLIAM ET AL, A Placebo-Controlled Trial of Cyclosporine Enemas for Mildly to Moderately Active Left-Sided Ulcerative Colitis, Gastroenterology, 1994, 1429-1435, 106 | ☐ |
| | 55 | SANDBORN, WILLIAM ET AL, Cyclosporine Enemas for Treatment-Resistant, Mildly to Moderately Active, Left-Sided Ulcerative Colitis, American Journal of Gastroenterology, 1993, 640-645, 88(5) | ☐ |
| | 56 | SCHWAB, MATTHIAS ET AL, Pharmacokinetic Considerations in the Treatment of Inflammatory Bowel Disease, Clin Pharm, 2001, 723-751, 60(10) | ☐ |
| | 57 | SECCHI, ANTONIO ET AL, Topical Use of Cyclosporine in the Treatment of Vernal Keratoconjunctivitis, American Journal of Ophthalmology, December 1990, 641-645, 110 | ☐ |
| | 58 | SMALL, DAVE ET AL, The Ocular Pharmacokinetics of Cyclosporine in Albino Rabbits and Beagle Dogs, Ocular Drug Delivery and Metabolism, 1999, 54 | ☐ |
| | 59 | SMALL, DAVID ET AL, Blood Concentrations of Cyclosporin A During Long-Term Treatment With Cyclosporin A ophthalmic Emulsions in Patients with Moderate to Severe Dry Eye Disease, Journal of Ocular Pharmacology and Therapeutics, 2002, 411-418, 18(5) | ☐ |
| | 60 | SMILEK, DAWN ET AL, A Single Amino Acid Change in a Myelin Basic Protein Peptide Confers the Capacity to Prevent Rather Than Induce Experimental Autoimmune Encephalomyelitis, Proc. Natl. Acad. Sci., Nov 1991, 9633-9637, 88 | ☐ |

| Receipt date: 03/28/2014 | Application Number | 14222478 14222478 - GAU: 1676 |
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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.M.C.G./

| | | | |
|---|---|---|---|
| | 61 | STEPHENSON, MICHELLE, The Latest Uses Of Restasis, Review Of Ophthalmology, 12/30/2005, 7 Pages, US | ☐ |
| | 62 | STEVENSON, DARA ET AL, Efficacy and Safety of Cyclosporin A ophthalmic Emulsion in the Treatment of Moderate-to-Severe Dry Eye Disease, Ophthalmology, 2000, 967-974, 107 | ☐ |
| | 63 | TESAVIBUL, N. ET AL, Topical Cyclosporine A (CsA) for Ocular Surface Abnormalities in Graft Versus Host Disease Patients, Invest Ophthalmol Vis Sci, Feb 1996, S1026, 37(3) | ☐ |
| | 64 | The Online Medical Dictionary, Derivative, Analog, Analogue, Xerostomia, accessed 7/7/2005 and 7/13/2005, 6 Pages | ☐ |
| | 65 | The United States Pharmacopeia, USP XXII, January 1990, 8 Pages, 22 | ☐ |
| | 66 | TIBELL, A. ET AL., Cyclosporin A In Fat Emulsion Carriers: Experimental Studies On Pharmacokinetics And Tissue Distribution, Pharmacology & Toxicology, 1995, 115-121, 76, US | ☐ |
| | 67 | TSUBOTA, KAZUO ET AL, Use of Topical Cyclosporin A in a Primary Sjogren's Syndrome Mouse Model, Invest Ophthalmol Vis Sci, Aug. 1998, 1551-1559, 39(9) | ☐ |
| | 68 | VAN DER REIJDEN, WILLY ET AL, Treatment of Oral Dryness Related Complaints (Xerostomia) in Sjogren's Syndrome, Ann Rheum Dis, 1999, 465-473, 58 | ☐ |
| | 69 | WIEDERHOLT, MICHAEL ET AL, Pharmacokinetic of Topical Cyclosporin A in the Rabbit Eye, Invest Ophthalmol Vis Sci, 1986, 519-524, 27 | ☐ |
| | 70 | WINTER, T.A. ET AL, Cyclosporin A Retention Enemas in Refractory Distal Ulcerative Colitis and 'Pouchitis', Scand J Gastroenterol, 1993, 701-704, 28 | ☐ |
| | 71 | U.S. Pending Application: 13/961,828 and its entire prosecution history, Filed on August 07, 2013 | ☐ |

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|---|---|---|---|
| | 72 | U.S. Re-Examination Application: 90/009,944 and its entire prosecution history, Filed on August 27, 2011 | ☐ |

If you wish to add additional non-patent literature document citation information please click the Add button

**EXAMINER SIGNATURE**

| Examiner Signature | /Marcela Cordero Garcia/ | Date Considered | 06/14/2014 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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| | Attorney Docket Number | 17618-US-CN6CN1-AP |

**CERTIFICATION STATEMENT**

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

**OR**

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

**Signature indicates consideration of publication and file history. The Examiner has access to these materials through the PTO computer systems. If additional copies are desired, please notify the Applicants through their attorneys.

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

**SIGNATURE**

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

| Signature | /Laura L. Wine/ | Date (YYYY-MM-DD) | 2014-03-27 |
|---|---|---|---|
| Name/Print | Laura L. Wine | Registration Number | 68,681 |

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

## Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

**EAST Search History**

**EAST Search History (Prior Art)**

| Ref # | Hits | Search Query | DBs | Default Operator | Plurals | Time Stamp |
|---|---|---|---|---|---|---|
| S22 | 3690 | ding.inv. and dry | US-PGPUB; USPAT; EPO; JPO; DERWENT | ADJ | ON | 2014/06/14 11:45 |
| S23 | 41 | ding.inv. and keratoconjunctivitis | US-PGPUB; USPAT; EPO; JPO; DERWENT | ADJ | ON | 2014/06/14 11:46 |
| S24 | 19 | ding.inv. and cyclosporin.clm. | US-PGPUB; USPAT; EPO; JPO; DERWENT | ADJ | ON | 2014/06/14 11:46 |
| S25 | 118 | cyclosporin same polysorbate same "castor oil" | US-PGPUB; USPAT; EPO; JPO; DERWENT | ADJ | ON | 2014/06/14 15:44 |
| S26 | 24 | cyclosporin same polysorbate same "castor oil".clm. | US-PGPUB; USPAT; EPO; JPO; DERWENT | ADJ | ON | 2014/06/14 15:44 |

**EAST Search History (Interference)**

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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 14/222,478 | 03/21/2014 | Andrew Acheampong | 17618CON6CON1 (AP) | 9616 |

51957 7590 05/09/2014

ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

| EXAMINER | |
|---|---|
| CORDERO GARCIA, MARCELA M | |
| ART UNIT | PAPER NUMBER |
| 1676 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 05/09/2014 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. 14/222,478 | Applicant(s) ACHEAMPONG ET AL. | |
|---|---|---|---|
| | Examiner MARCELA M. CORDERO GARCIA | Art Unit 1676 | AIA (First Inventor to File) Status No |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *3/21/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims***

5)☒ Claim(s) *1-36* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☒ Claim(s) *1-36* are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

## DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

### *Election/Restrictions*

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-20, drawn to a method of treating an eye of a human or animal, classified, e.g., in class 514, subclass 20.5.

II. Claims 21-36, drawn to a composition, classified, e.g., in class 514, subclass 11.

The inventions are distinct, each from the other because of the following reasons:

Inventions II and I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, treating diseases such as corneal transplantation may be done with a cyclosporine solution in polymer or copolymer instead of an emulsion as instantly claimed (e.g., Lixin, Chinese Medical Journal 2002, cited in the IDS dated 3/28/2014).

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the following reasons apply:

A reference that would anticipate and/or make obvious one of the inventions would not necessarily anticipate and/or make obvious another invention.

**Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined** even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

This application contains claims directed to the following patentably distinct species: (A) the many and multiple diseases to be treated (e.g., dry eye syndrome,

phacoanaphylactic endophthalmitis, uveitis, vernal conjunctivitis, atopic keratoconjunctivitis, corneal graft rejection); (B) the many and multiple hydrophobic components (e.g., vegetable oils, animal oilds, mineral oils, synthetic oils and mixtures thereof); (C) the many and multiple active agents: cyclosporin A, derivatives and mixtures thereof; (D) the many and multiple additional components (e.g., emulsifier component, tonicity component and/or polyelectrolyte component). The species are independent or distinct because they are drawn to different diseases having different symptoms and patient population and/or compounds having different molecular and physical-chemical properties. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, or a single grouping of patentably indistinct species [i.e., for Group I: elect species for (A), (B), (C) and (D); for Group II: elect species of (B), (C) and (D)], for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-36 are generic.

There is a search and/or examination burden for the patentably distinct species as set forth above because at least the following reason(s) apply: A reference that would anticipate and/or make obvious one of the species would not necessarily anticipate and/or make obvious another species.

**Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined** even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing**

**the elected species or grouping of patentably indistinct species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species or grouping of patentably indistinct species.

Should applicant traverse on the ground that the species, or groupings of patentably indistinct species from which election is required, are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing them to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

The examiner has required restriction between product or apparatus claims and process claims. Where applicant elects claims directed to the product/apparatus, and all product/apparatus claims are subsequently found allowable, withdrawn process claims that include all the limitations of the allowable product/apparatus claims should be considered for rejoinder. All claims directed to a nonelected process invention must include all the limitations of an allowable product/apparatus claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product/apparatus claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product/apparatus are found allowable, an otherwise proper restriction requirement between product/apparatus claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an

allowable product/apparatus claim will not be rejoined. See MPEP § 821.04. Additionally, in order for rejoinder to occur, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product/apparatus claims. **Failure to do so may result in no rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karlheinz R. Skowronek can be reached on (571)-272-9047. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information

system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCELA M CORDERO GARCIA/
Primary Examiner, Art Unit 1676

MMCG 05/2014

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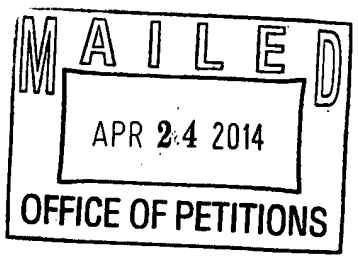


Doc Code: TRACK1.GRANT

| ***Decision Granting Request for Prioritized Examination (Track I or After RCE)*** | Application No.: 14/222,478 |
|---|---|

1. THE REQUEST FILED March 21, 2014 IS **GRANTED**.

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Irvin Dingle at (571)272-3210, Office of Petitions.

Irvin Dingle
/Irvin Dingle/
[*Signature*]

Paralegal Specialist
(Title)

## PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/222,478

### APPLICATION AS FILED - PART I

| FOR | (Column 1) NUMBER FILED | (Column 2) NUMBER EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY FEE($) |
|---|---|---|---|---|---|---|---|
| BASIC FEE (37 CFR 1.16(a), (b), or (c)) | N/A | N/A | N/A | | | N/A | 280 |
| SEARCH FEE (37 CFR 1.16(k), (i), or (m)) | N/A | N/A | N/A | | | N/A | 600 |
| EXAMINATION FEE (37 CFR 1.16(o), (p), or (q)) | N/A | N/A | N/A | | | N/A | 720 |
| TOTAL CLAIMS (37 CFR 1.16(i)) | 27 minus 20 = | * 7 | | | OR | x 80 = | 560 |
| INDEPENDENT CLAIMS (37 CFR 1.16(h)) | 4 minus 3 = | * 1 | | | | x 420 = | 420 |
| APPLICATION SIZE FEE (37 CFR 1.16(s)) | If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). | | | | | | 0.00 |
| MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j)) | | | | | | | 0.00 |
| * If the difference in column 1 is less than zero, enter "0" in column 2. | | | TOTAL | | | TOTAL | 2580 |

### APPLICATION AS AMENDED - PART II

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY ADDITIONAL FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT A | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

| | | (Column 1) CLAIMS REMAINING AFTER AMENDMENT | | (Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR | (Column 3) PRESENT EXTRA | SMALL ENTITY RATE($) | SMALL ENTITY ADDITIONAL FEE($) | OR | OTHER THAN SMALL ENTITY RATE($) | OTHER THAN SMALL ENTITY ADDITIONAL FEE($) |
|---|---|---|---|---|---|---|---|---|---|---|
| AMENDMENT B | Total (37 CFR 1.16(i)) | * | Minus | ** | = | x = | | OR | x = | |
| | Independent (37 CFR 1.16(h)) | * | Minus | *** | = | x = | | OR | x = | |
| | Application Size Fee (37 CFR 1.16(s)) | | | | | | | | | |
| | FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j)) | | | | | | | OR | | |
| | | | | | | TOTAL ADD'L FEE | | OR | TOTAL ADD'L FEE | |

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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| APPLICATION NUMBER | FILING or 371(c) DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|
| 14/222,478 | 03/21/2014 | 1621 | 2580 | 17618CON6CON1 (AP) | 27 | 4 |

**CONFIRMATION NO. 9616**

51957
ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

**FILING RECEIPT**

*OC000000067802253*

Date Mailed: 04/16/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

**Inventor(s)**

Andrew Acheampong, Irvine, CA;
Diane D. Tang-Liu, Las Vegas, CA;
James N. Chang, Newport Beach, CA;
David F. Power, San Clemente, CA;

**Applicant(s)**

Allergan, Inc., Irvine, CA

**Assignment For Published Patent Application**

Allergan, Inc., Irvine, CA

**Power of Attorney:** The patent practitioners associated with Customer Number 51957

**Domestic Priority data as claimed by applicant**

This application is a CON of 13/961,828 08/07/2013 PAT 8685930
which is a CON of 11/897,177 08/28/2007 PAT 8618064
and is a CON of 10/927,857 08/27/2004 ABN
which claims benefit of 60/503,137 09/15/2003

**Foreign Applications** for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
*Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

**If Required, Foreign Filing License Granted:** 04/15/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/222,478**

**Projected Publication Date:** 07/24/2014

**Non-Publication Request:** No

**Early Publication Request:** No

**Title**

METHODS OF PROVIDING THERAPEUTIC EFFECTS USING CYCLOSPORIN COMPONENTS

**Preliminary Class**

514

**Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:** No

## PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).