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[54] **GALENICAL FORMULATIONS**

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 abandoned.

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[52] **U.S. Cl.** ..... **424/450**; 424/400; 514/11;  
 514/937; 514/938

[58] **Field of Search** ..... 624/450, 400;  
 514/11, 937, 938-943

[56] **References Cited****U.S. PATENT DOCUMENTS**

3,929,992 12/1975 Sehgal et al. .  
 4,388,307 6/1983 Cavanak .  
 4,719,239 1/1988 Muller et al. .  
 4,831,018 5/1989 Kirsh et al. .  
 4,987,139 1/1991 Chen et al. .  
 5,104,871 4/1992 Bell et al. .  
 5,169,851 12/1992 Hughes et al. .  
 5,190,950 3/1993 Beattie et al. .  
 5,206,018 4/1993 Sehgal et al. .  
 5,215,995 6/1993 Honbo et al. .  
 5,318,895 6/1994 Kahn et al. .  
 5,342,625 8/1994 Hauer et al. .  
 5,741,512 4/1998 Hauer ..... 424/450

**FOREIGN PATENT DOCUMENTS**

41795 12/1981 European Pat. Off. .  
 184162 6/1986 European Pat. Off. .  
 302370 2/1989 European Pat. Off. .  
 361928 4/1990 European Pat. Off. .  
 401747 12/1990 European Pat. Off. .  
 423 714 4/1991 European Pat. Off. .  
 427680 5/1991 European Pat. Off. .  
 428169 5/1991 European Pat. Off. .  
 444659 9/1991 European Pat. Off. .  
 483842 5/1992 European Pat. Off. .  
 532862 3/1993 European Pat. Off. .  
 533433 3/1993 European Pat. Off. .  
 679118 12/1991 Switzerland .  
 907430 10/1962 United Kingdom .  
 1322306 7/1973 United Kingdom .  
 2222770 3/1990 United Kingdom .  
 2247620 3/1992 United Kingdom .  
 2248184 4/1992 United Kingdom .  
 2249027 4/1992 United Kingdom .  
 2257359 1/1993 United Kingdom .  
 2271121 4/1994 United Kingdom .  
 90/14094 11/1990 WIPO .  
 91/19495 12/1991 WIPO .  
 92/21341 12/1992 WIPO .  
 93/20833 10/1993 WIPO .

**OTHER PUBLICATIONS**

Charman et al., Pharm. Res., vol. 9, No. 1, 87-92 (1992).  
 Chemical Abstract JP 85-133882 Jun. 1985.

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[57] **ABSTRACT**

A pharmaceutical composition containing macrolide, e.g. a rapamycin compound in an emulsion concentrate or microemulsion concentrate for oral administration. The carrier medium for the rapamycin compound includes a hydrophilic phase, a lipophilic phase and a surfactant. The composition is stable and provides high absorption efficiency.

**7 Claims, No Drawings**

**Par Pharm., Inc.**  
**Exhibit 1123**  
**Par Pharm., Inc. v. Novartis AG**  
**Case IPR2016-01479**

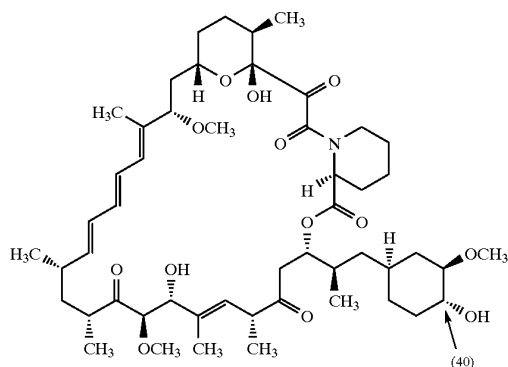
## GALENICAL FORMULATIONS

This is a continuation of application Ser. No. 08/248,993, filed May 25, 1994 now abandoned.

This invention relates to galenic formulations containing macrolides, e.g. compounds of the rapamycin class. In particular this invention relates to galenic formulations which are in the form of micro-emulsions, micro-emulsion pre-concentrates, emulsion or emulsion-preconcentrate.

The macrolide may contain e.g. 1, 2 or 3 ring oxygen or nitrogen or other atoms besides carbon atoms. It may have side chains, e.g. in the form of fused rings, or substituents, e.g. oxy groups. It may contain double bonds. It may contain e.g. from 15 to 35 ring atoms e.g. of carbon.

Rapamycin is a macrolide antibiotic produced by *Streptomyces hygroscopicus*. It has been found to be pharmaceutically useful in a variety of applications, particularly as an immunosuppressant for use in the treatment and prevention of organ transplant rejection and autoimmune diseases. Rapamycin has the following structure:



(Kessler, H., et al., Helv. Chim. Acta (1993) 76: 117; U.S. Pat. No. 3,929,992). Large numbers of derivatives of rapamycin have been synthesized, including for example those disclosed in U.S. Pat. Nos. 5,221,670 and 5,221,740, certain acyl and aminoacyl-rapamycins (see for example U.S. Pat. No. 4,316,885, U.S. Pat. No. 4,650,803, and U.S. Pat. No. 5,151,413), and carbonates and amide esters (see for example EP 509795 and 515140) 27-desmethyl-rapamycin (see for example WO 92/14737), 26-dihydro-rapamycin (see for example U.S. Pat. No. 5,138,051), alkoxyster derivatives (see for example U.S. Pat. No. 5,233,036), and certain pyrazole derivatives (U.S. Pat. No. 5,164,399). Rapamycin and its structurally similar analogs and derivatives are termed collectively as "compounds of the rapamycin class" in this specification.

Compounds of the rapamycin class are extremely potent immunosuppressants and have also been shown to have antitumor and antifungal activity. However their utility as pharmaceuticals especially on oral administration has been restricted by their very low solubility, low and variable bioavailability and their high toxicity. Little is known concerning the causes of these properties and the site of absorption. Thus low bioavailability may be thought to be due to extensive metabolism of the macrolide ring and not solvable by a galenic formulation.

Therefore there is a need for an acceptable pharmaceutical composition that contains compounds of the rapamycin class.

FK506 is a macrolide immunosuppressant that is produced by *Streptomyces tsukubaensis* No 9993. The structure

of FK506 is given in the appendix to the Merck Index, as item A5. Also a large number of related compounds which retrain the basic structure and immunological properties of FK506 are also known. These compounds are described in a large number of publications, for example EP 184162, EP 315973, EP 323042, EP 423714, EP 427680, EP 465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936, EP 532088, EP 532089, WO 93/5059 and the like. Little is known concerning the biopharmaceutical properties of such compounds. These compounds are termed collectively "FK506 compounds" in this specification.

It has now been surprisingly found that stable compositions containing macrolides that offer high absorption efficiency, can be obtained by formulating the macrolide with certain carrier media.

Accordingly, this invention provides a pharmaceutical composition comprising a macrolide and a carrier medium comprising a hydrophilic phase, a lipophilic phase and a surfactant.

In another aspect the invention provides a pharmaceutical composition which comprises an orally administrable active agent which is other than a cyclosporin and a micro-emulsion preconcentrate carrier medium therefor which comprises

- i) a reaction product of castor oil and ethylene oxide,
- ii) a transesterification product of a vegetable oil and glycerol comprising predominantly linoleic acid or oleic acid mono-, di- and tri-glycerides, or a polyoxy-alkylated vegetable oil,
- iii) 1,2 propylene glycol and
- iv) ethanol.

The pharmaceutical composition is stable and results in surprisingly high and consistent absorption efficiency when administered orally. Therefore the macrolide may be administered in lower doses, which alleviates toxicity problems. For example, in animal trials in which the pharmaceutical compositions are administered orally, the pharmaceutical compositions resulted in high bioavailabilities. Hence the pharmaceutical compositions have very surprising properties which offer great advantages.

Preferably the composition is in the form of a "micro-emulsion preconcentrate" or "emulsion preconcentrate", in particular of the type providing o/w (oil-in-water) micro-emulsions or emulsions. However the composition may be in the form of a microemulsion or an emulsion which additionally contains an aqueous phase; preferably water.

A "microemulsion preconcentrate" is defined in this specification as being a formulation which spontaneously forms a microemulsion in an aqueous medium, for example, in water or in the gastric juices after oral application.

A "microemulsion" is a non-opaque or substantially non-opaque colloidal dispersion that is formed spontaneously or substantially spontaneously when its components are brought into contact. A microemulsion is thermodynamically stable and contains dispersed particles of a size less than about 2000 Å. Generally microemulsions comprise droplets or particles having a diameter of less than about 1500 Å; typically from 30 to 1000 Å. Further characteristic can be found in British patent application 2 222 770 A; the disclosure of which is incorporated herein by reference.

An "emulsion preconcentrate" is defined in this specification as being as being a formulation which spontaneously forms an emulsion in an aqueous medium, for example, in water or in the gastric juices after oral application. The emulsion formed is opaque, thermodynamically stable and contains dispersed droplets of a size greater than about 100 nm, more usually greater than about 200 nm. Often bimodal

size range distributions are obtained. The emulsion concentrates are preferably of the type providing o/w (oil-in-water) emulsions.

A "pharmaceutical composition" means a composition in which the individual components or ingredients are themselves pharmaceutically acceptable and, when a particular form of administration is foreseen, are suitable or acceptable for that form of administration.

The lipophilic phase may comprise 10 to 85% by weight of the carrier medium; preferably 15 to 70% by weight, more preferably 20 to 60% by weight and even more preferably about 25% by weight.

The surfactant may comprise 5 to 80% by weight of the carrier medium; preferably 10 to 70% by weight, more preferably 20 to 60% by weight and even more preferably about 40% by weight.

The hydrophilic phase may comprise 10 to 50% by weight of the carrier medium; preferably 15 to 40% by weight, more preferably 20 to 35% by weight and even more preferably about 30% by weight.

The macrolide is preferably present in an amount of 1 to 15% by weight of the composition; more preferably about 2 to 10%.

The macrolide may be rapamycin or an O-substituted derivative in which the hydroxy in position 40 of the formula illustrated above is replaced by  $-\text{OR}_1$  in which  $\text{R}_1$  is hydroxyalkyl, hydroalkoxyalkyl, acylaminoalkyl and aminoalkyl; for example 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin and 40-O-(2-acetaminoethyl)-rapamycin. These O-substituted derivatives may be produced by reacting Rapamycin (or dihydro or deoxorapamycin) with an organic radical attached to a leaving group (for example RX where R is the organic radical which is desired as the O-substituent, such as an alkyl, allyl, or benzyl moiety, and X is a leaving group such as  $\text{CCl}_3\text{C}(\text{NH})\text{O}$  or  $\text{CF}_3\text{SO}_3$ ) under suitable reaction conditions. The conditions may be acidic or neutral conditions, for example in the presence of an acid like trifluoromethanesulfonic acid, camphorsulfonic acid, p-toluenesulfonic acid or their respective pyridinium or substituted pyridinium salts when X is  $\text{CCl}_3\text{C}(\text{NH})\text{O}$  or in the presence of a base like pyridine, a substituted pyridine, diisopropylethylamine or pentamethylpiperidine when X is  $\text{CF}_3\text{SO}_3$ .

A preferred compound is 40-O-(2-hydroxy)ethyl rapamycin (hereinafter compound A) as disclosed in PCT/EP/93/02604.

Examples of compounds of the FK506 class are those mentioned above. They include for example FK506, ascmycin and other naturally occurring compounds. They include also synthetic analogues.

A preferred compound of the FK506 class is disclosed in EP 427 680, e.g. Example 66a. Other preferred compounds are disclosed in EP 465 426.

The hydrophilic phase may be selected from Transcutol (which has the formula  $\text{C}_2\text{H}_5-[\text{O}-(\text{CH}_2)_2]_2-\text{OH}$ ), Glycofurool (also known as tetrahydrofurfuryl alcohol polyethylene glycol ether) and 1,2-propylene glycol, or mixtures thereof, and is preferably 1,2-propylene glycol. The hydrophilic phase may include further hydrophilic co-components, for example lower alkanols such as ethanol. These co-components will generally be present in partial replacement of other components of the hydrophilic phase. While the use of ethanol in the compositions is not essential, it has been found to be of particular advantage when the compositions are to be manufactured in soft gelatine, encapsulated form. This is because storage characteristics are

improved, in particular the risk of rapamycin precipitation following encapsulation procedures is reduced. Thus the shelf life stability may be extended by employing ethanol or some other such co-component as an additional ingredient of the hydrophilic phase. The ethanol may comprise 0 to 60% by weight of the hydrophilic phase; preferably 20 to 55% by weight and more preferably about 40 to 50% by weight. Small quantities of liquid polyethylene glycols may also be included in the hydrophilic phase.

Preferred lipophilic phase components are medium chain fatty acid triglycerides, mixed mono-, di-, tri-glycerides, and transesterified ethoxylated vegetable oils. Suitable medium chain fatty acid triglycerides are those known and commercially available under the trade names Miglyol, Captex, Myritol, Capmul, Captex, Neobee and Mazol; Miglyol 812 being the most preferred. These triglycerides are described in Fiedler, H. P. "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor, D-7960 Aulendorf, 3rd revised and expanded edition (1989), the contents of which are hereby incorporated by reference.

The mixed mono-, di-, tri-glycerides preferably comprise mixtures of  $\text{C}_{12-20}$  fatty acid mono-, di- and tri-glycerides, especially mixed  $\text{C}_{16-18}$  fatty acid mono-, di- and triglycerides. The fatty acid component of the mixed mono-, di- and tri-glycerides may comprise both saturated and unsaturated fatty acid residues. Preferably however they are predominantly comprised of unsaturated fatty acid residues; in particular  $\text{C}_{18}$  unsaturated fatty acid residues. Suitably the mixed mono-, di-, tri-glycerides comprise at least 60%, preferably at least 75%, more preferably at least 85% by weight of a  $\text{C}_{18}$  unsaturated fatty acid (for example linolenic, linoleic and oleic acid) mono-, di- and tri-glycerides. Suitably the mixed mono-, di-, tri-glycerides comprise less than 20%, for example about 15% or 10% by weight or less, saturated fatty acid (for example palmitic and stearic acid) mono-, di- and tri-glycerides.

The mixed mono-, di-, tri-glycerides are preferably predominantly comprised of mono- and di-glycerides; for example mono- and di-glycerides comprise at least 50%, more preferably at least 70% based on the total weight of the lipophilic phase. More preferably, the mono- and di-glycerides comprise at least 75% (for example about 80% or 85% by weight of the lipophilic phase).

Preferably the monoglycerides comprise from about 25 to about 50%, based on the total weight of the lipophilic phase, of the mixed mono-, di-, tri-glycerides. More preferably from about 30 to about 40% (for example 35 to 40%) monoglycerides are present.

Preferably the diglycerides comprise from about 30 to about 60%, based on the total weight of the lipophilic phase, of the mixed mono-, di-, tri-glycerides. More preferably from about 40 to about 55% (for example 48 to 50%) diglycerides are present.

The triglycerides suitably comprise at least 5% but less than about 25%, based on the total weight of the lipophilic phase, of the mixed mono-, di-, tri-glycerides. More preferably from about 7.5 to about 15% (for example from about 9 to 12%) triglycerides are present.

The mixed mono-, di-, tri-glycerides may be prepared by admixture of individual mono-, di- or tri-glycerides in appropriate relative proportion. Conveniently however they comprise transesterification products of vegetable oils, for example almond oil, ground nut oil, olive oil, peach oil, palm oil or, preferably, corn oil, sunflower oil or safflower oil and most preferably corn oil, with glycerol.

Such transesterification products are generally obtained by heating the selected vegetable oil with glycerol, at high

temperature in the presence of an appropriate catalyst under an inert atmosphere with continuous agitation (for example in a stainless steel reactor) to effect trans-esterification or glycerolysis. In addition to their mono-, di- and tri-glyceride components, the transesterification products also generally comprise minor amounts of free glycerol. The amount of free glycerol present is preferably less than 10%, more preferably less than 5%, most preferably about 1 or 2% by weight based on the total weight of free glycerol plus mono-, di- and tri-glycerides.

Preferably some of the glycerol is first removed to give a "substantially glycerol free batch" when soft gelatine capsules are to be made.

Trans-esterification products of corn oil and glycerol provide particularly suitable mixed mono-, di-, and tri-glycerides. An example of a suitable mixed glyceride product is the trans-esterification product commercially available under the trade name MAISINE. This product is comprised predominantly of linoleic and oleic acid mono-, di- and tri-glycerides together with minor amounts of palmitic and stearic acid mono-, di- and tri-glycerides (corn oil itself being comprised of about 56% by weight linoleic acid, 30% oleic acid, about 10% palmitic and about 3% stearic acid constituents). The physical characteristics of MAISINE [available from the company Etablissements Gattefossé, of 36, Chemin de Genas, P.O. Box 603, 69804 Saint-Priest, Cedex (France)] are: up to 10% (typically 3.9 to 4.9% or, in "substantially glycerol free" batches, about 0.2%) free glycerol; about 35% (typically 30 to 40% or, in "substantially glycerol free" batches, about 32 to 36%, for example about 36%) mono-glycerides; about 50% (or, in "substantially glycerol free" batches about 46 to 48%) di-glycerides; about 10% (or, in "substantially glycerol free" batches, about 12 to 15%) tri-glycerides; and about 1% free oleic acid.

Further physical characteristics for MAISINE are: an acid value of maximum about 2, an iodine no. of about 85 to 105, a saponification no. of about 150 to 175 (Fiedler "Lexikon der Hilfsstoffe", 3rd revised and expanded edition (1989) Vol. 2, p.768). The fatty acid content for MAISINE is typically: about 11% palmitic acid; about 2.5% stearic acid; about 29% oleic acid; about 56% linoleic acid; and 1.5% other acids.

It is especially preferred that the mixed mono-, di-, and tri-glycerides are clear and remain clear for more than 20 days upon storage at temperatures of 20° C. to 25° C. Also, a sample of the mixed mono-, di-, and tri-glycerides, which has been kept in a refrigerator at about between 2 and 80° C. for 24 hours and then held at room temperature for 1 hour, should be clear.

Preferably the mono-, di-, tri-glycerides have a low saturated fatty acid content. Mixed mono-, di-, tri-glycerides meeting these requirements may be obtained from commercially available products by separation techniques as known in the art (for example freezing procedures coupled with separation techniques such as centrifugation) to remove the saturated fatty acid components and enhance the unsaturated fatty acid component content. Typically the total saturated fatty acid component content will be less than 15%, (for example <10%, or <5%) by weight based on the total weight of the lipophilic phase. A reduction of the content of saturated fatty acid component in the mono-glyceride fraction may be observed after being subjected to the separation technique. A suitable process is described in WO 93/09211. The mixed mono-, di-, tri-glycerides thus preferably contain lesser quantities of saturated fatty acids (e.g. palmitic and stearic acids) and relatively greater quantities of unsaturated fatty acids (e.g. oleic and linoleic acids) than the starting material.

A suitable example of a mixed mono-, di-, tri-glyceride product containing lesser quantities of saturated fatty acids contains : 32 to 36% mono-glycerides, 45 to 55% di-glycerides and 12 to 20% tri-glycerides, by weight based on the total weight of the lipophilic phase. Further characteristics include the following:

Fatty acid content (as determined as the methyl ester by chromatography)	Methyl linoleate 53 to 63%, Methyl oleate 24 to 34%, Methyl linoleate 0 to 3% Methyl arachate 0 to 3%, Methyl palmitate 6 to 12%, Methyl stearate 1 to 3%
Relative Density	0.94 to 0.96
Hydroxyl Value	140 to 210
Iodine Value	110 to 20
Peroxide Value	<4.0
Free Glycerol	<1.0
Saponification no	about 150 to 185
Acid value	max. about 2

Mixed mono-, di-, tri-glycerides complying with these characteristics are referred to in this specification as "refined glycerol-transesterified corn oils". The "refined glycerol-transesterified corn oils" have the advantage of remaining stable for a long time.

The lipophilic phase may alternatively comprise suitable transesterified ethoxylated vegetable oils such as those obtained by reacting various natural vegetable oils (for example, maize oil, kernel oil, almond oil, ground nut oil, olive oil, soybean oil, sunflower oil, safflower oil and palm oil, or mixtures thereof) with polyethylene glycols that have an average molecular weight of from 200 to 800, in the presence of an appropriate catalyst. These procedures are known and an example is described in U.S. Pat. No. 3,288, 824. Transesterified ethoxylated corn oil is particularly preferred.

Transesterified ethoxylated vegetable oils are known and are commercially available under the trade name LABRAFIL (H. Fiedler, *loc cit*, vol 2, page 707). Examples are LABRAFIL M 2125 CS (obtained from corn oil and having an acid number of less than about 2, a saponification number of 155 to 175, an HLB value of 3 to 4, and an iodine number of 90 to 110), and LABRAFIL M 1944 CS (obtained from kernel oil and having an acid number of about 2, a saponification number of 145 to 175 and an iodine number of 60 to 90). LABRAFIL M 2130 CS (which is a transesterification product of a C<sub>12-18</sub> glyceride and polyethylene glycol and which has a melting point of about 35 to 40° C., an acid number of less than about 2, a saponification number of 185 to 200 and an iodine number of less than about 3) may also be used. The preferred transesterified ethoxylated vegetable oil is LABRAFIL M 2125 CS which can be obtained, for example, from Gattefossé, Saint-Priest Cedex, France.

Examples of suitable surfactants are:

i) reaction products of a natural or hydrogenated castor oil and ethylene oxide. The natural or hydrogenated castor oil may be reacted with ethylene oxide in a molar ratio of from about 1:35 to about 1:60, with optional removal of the polyethyleneglycol component from the products. Various such surfactants are commercially available. The polyethyleneglycol-hydrogenated castor oils available under the trade name CREMOPHOR are especially suitable. Particularly suitable are CREMOPHOR RH 40, which has a saponification number of about 50 to 60, an acid number less than about 1, a water content (Fischer) less than about 2%, an  $n_D^{60}$  of about 1.453 to 1.457 and an HLB of about 14 to 16; and CREMOPHOR RH 60, which has a saponification

number of about 40 to 50, an acid number less than about 1, an iodine number of less than about 1, a water content (Fischer) of about 4.5 to 5.5%, an  $n_D^{25}$  of about 1.453 to 1.457 and an HLB of about 15 to 17. An especially preferred product of this class is CREMOPHOR RH40. Also suitable are polyethyleneglycol castor oils such as that available under the trade name CREMOPHOR EL, which has a molecular weight (by steam osmometry) of about 1630, a saponification number of about 65 to 70, an acid number of about 2, an iodine number of about 28 to 32 and an  $n_D^{25}$  of about 1.471. Similar or identical products which may also be used are available under the trade names NIKKOL (e.g. NIKKOL HCO-40 and HCO-60), MAPEG (e.g. MAPEG CO-40h), INCROCAS (e.g. INCROCAS 40), and TAGAT (e.g. TAGAT RH 40). These surfactants are further described in Fiedler *loc. cit.*

- ii) Polyoxyethylene-sorbitan-fatty acid esters, for example mono- and tri-lauryl, palmityl, stearyl and oleyl esters of the type known and commercially available under the trade name TWEEN (Fiedler, *loc. cit.* p.1300-1304) including the products TWEEN

20 [polyoxyethylene(20)sorbitanmonolaurate],  
 21 [polyoxyethylene(4)sorbitanmonolaurate],  
 25 [polyoxyethylene(20)sorbitanmonopalmitate],  
 60 [polyoxyethylene(20)sorbitanmonostearate],  
 65 [polyoxyethylene(20)sorbitantristearate],  
 80 [polyoxyethylene(20)sorbitanmonooleate],  
 81 [polyoxyethylene(5)sorbitanmonooleate],  
 85 [polyoxyethylene(20)sorbitantriolate].  
 Especially preferred products of this class are TWEEN 40 and TWEEN 80.

- iii) Polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters of the type known and commercially available under the trade name MYRJ (Fiedler, *loc. cit.*, 2, p.834-835). An especially preferred product of this class is MYRJ 52 having a  $D^{25}$  of about 1.1., a melting point of about 40 to 44° C., an HLB value of about 16.9., an acid value of about 0 to 1 and a saponification no. of about 25 to 35.

- iv) Polyoxyethylene-polyoxypropylene co-polymers and block co-polymers, for example of the type known and commercially available under the trade names PLURONIC, EMKALYX and POLOXAMER (Fiedler, *loc. cit.*, 2, p. 959). An especially preferred product of this class is PLURONIC F68, having a melting point of about 52° C. and a molecular weight of about 6800 to 8975. A further preferred product of this class is POLOXAMER 188.

- v) Dioctylsulfosuccinate or di-[2-ethylhexyl]-succinate (Fiedler, *loc. cit.*, 1, p. 107-108).

- vi) Phospholipids, in particular lecithins (Fiedler, *loc. cit.*, 2, p. 943-944). Suitable lecithins include, in particular, soya bean lecithins.

- vii) Propylene glycol mono- and di-fatty acid esters such as propylene glycol dicaprylate (also known and commercially available under the trade name MIGLYOL 840), propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, propylene glycol stearate and so forth (Fiedler, *loc. cit.*, 2, p. 808-809).

It will also be appreciated that the components of the carrier medium may contain unreacted starting materials, e.g. polyethylene glycol.

The surfactant selected preferably has an HLB of at least 10.

Preferably the relative proportion of hydrophilic phase component(s), the lipophilic phase and the surfactant lie within the "microemulsion" region on a standard three way plot. The compositions thus obtained are microemulsion preconcentrates of high stability that are capable, on addition to water, of providing microemulsions having an average particle size of <1.500 Å and stable over periods in excess of 24 hours.

The microemulsion preconcentrate compositions show good stability characteristics as indicated by standard stability trials, for example having a shelf life stability of up to three years, and even longer.

Alternatively the components may be selected to provide an emulsion preconcentrate. The emulsion preconcentrate compositions also show good stability characteristics as indicated by standard stability trials, for example having a shelf life stability of up to three years, and even longer.

The pharmaceutical composition may also include further additives or ingredients, for example antioxidants (such as ascorbyl palmitate, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT) and tocopherols) and/or preserving agents. These additives or ingredients may comprise about 0.05 to 1% by weight of the total weight of the composition. The pharmaceutical composition may also include sweetening or flavoring agents in an amount of up to about 2.5 or 5% by weight based on the total weight of the composition. Preferably the antioxidant is a-tocopherol (vitamin E).

The pharmaceutical composition may also include one or more other immunosuppressants such as, for example, a cyclosporin or if a rapamycin is present a FK506 compound as described above. Cyclosporins comprise a class of cyclic, poly-N-methylated undecapeptides, generally possessing immunosuppressive, anti-inflammatory, anti-viral and/or anti-parasitic activity, each to a greater or lesser degree. The first of the cyclosporins to be identified was the fungal metabolite Cyclosporin A, or Cyclosporine, and its structure is given in The Merck Index, 11th Edition; Merck & Co., Inc.; Rahway, N.J., USA (1989) under listing 2759. Later cyclosporins to be identified are cyclosporins B, C, D and G which are also listed in the Merck Index under listing 2759. A large number of synthetic analogs are also known and representative examples are disclosed in EP 296 122, EP 484 281 and GB 2222770. These compounds are termed collectively "cyclosporins" in this specification.

The pharmaceutical composition exhibits especially advantageous properties when administered orally; for example in terms of consistency and high level of bioavailability obtained in standard bioavailability trials, e.g. 2 to 4 times higher than emulsions. These trials are performed in animals or healthy volunteers using HPLC or a specific or nonspecific monoclonal kit to determine the level of the macrolide in the blood. For example, in the test described in Example 3, 10 mg of rapamycin is administered p.o. to rats and the surprisingly high  $C_{max}$  values of between 2670 and 3400 ng/ml are detected by ELISA using a specific monoclonal antibody. Also, in the test described in Example 4, an emulsion preconcentrate and a microemulsion preconcentrate composition are found to have much better pharmacokinetic properties than a standard solvent system.

Pharmacokinetic parameters, for example absorption and blood levels, also become surprisingly more predictable and problems in administration with erratic absorption may be eliminated or reduced. Additionally the pharmaceutical composition is effective with tenside materials, for example bile salts, present in the gastrointestinal tract. That is, the

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Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.