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(54) Abstract Title
Preparation of gel emulsions of hydrophobic pharmaceuticals

(57) A pharmaceutical formulation for oral or topical administration including

a) 0.1 to 30.0 % of one or more hydrophobic active ingredients;

b) 0.1 to 60.0 % of one or more hydrophilic fatty acid esters of glycerol;

c) 0.1 to 60.0 % of one or more substances selected from lipophilic esters of polyglycerol with fatty acids (either saturated or unsaturated);

d) 1.0 to 60 % of one or more substances selected from: triglyceride macrogolglycerol esters, partial fatty acid glycerides and partial fatty acid macrogol esters;

e) 5.0 to 30 % of one or more C_2 to C_4 alcohols;

wherein the above percentages are selected to total 100% and the ratio of a : c and/or a : e is in the range 0.001 : 1 to 10 : 1;

to form a solution which upon dilution with water forms a dispersion of polymorphous gel particles having a dimension of 0.2 to 500 μm.

The hydrophobic active ingredient is preferably a cyclosporin or taxane.

The macrogol derivative is preferably a macrogol glycerol with vegetable oils.

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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.

This print takes account of replacement documents submitted after the date of filing to enable the application to comply with the formal requirements of the Patents Rules 1995

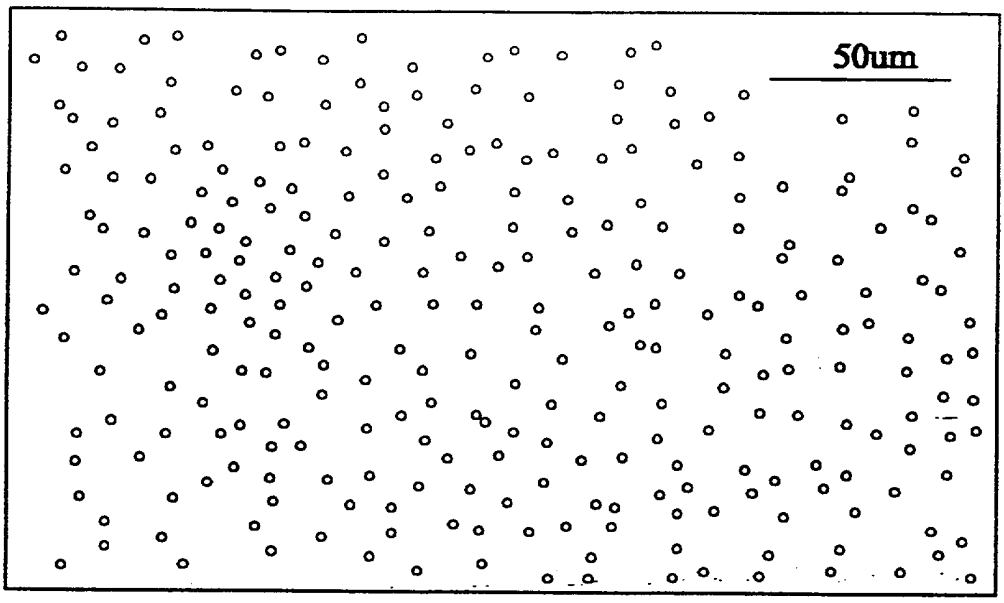


FIG. 1

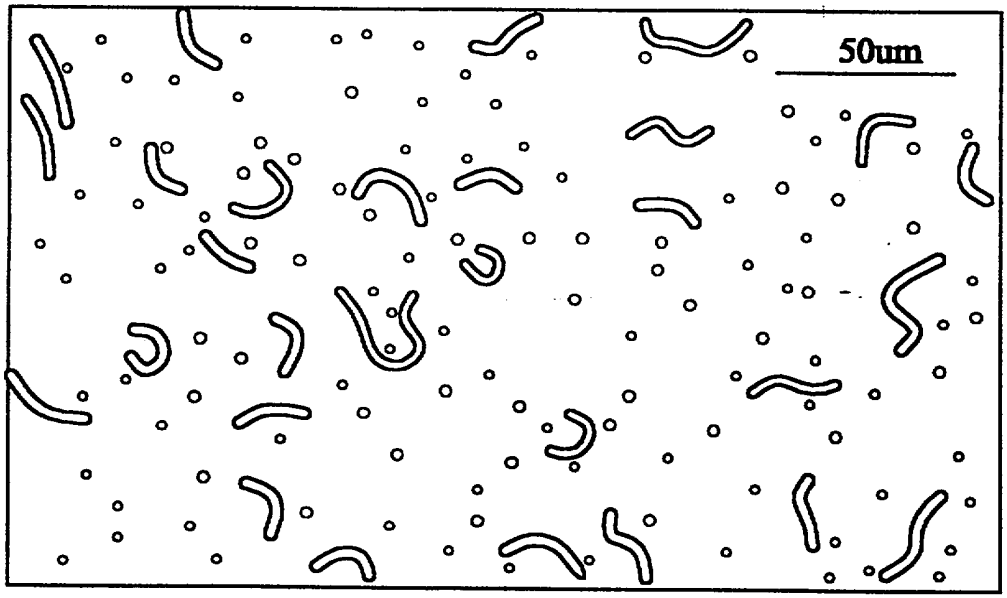


FIG. 2

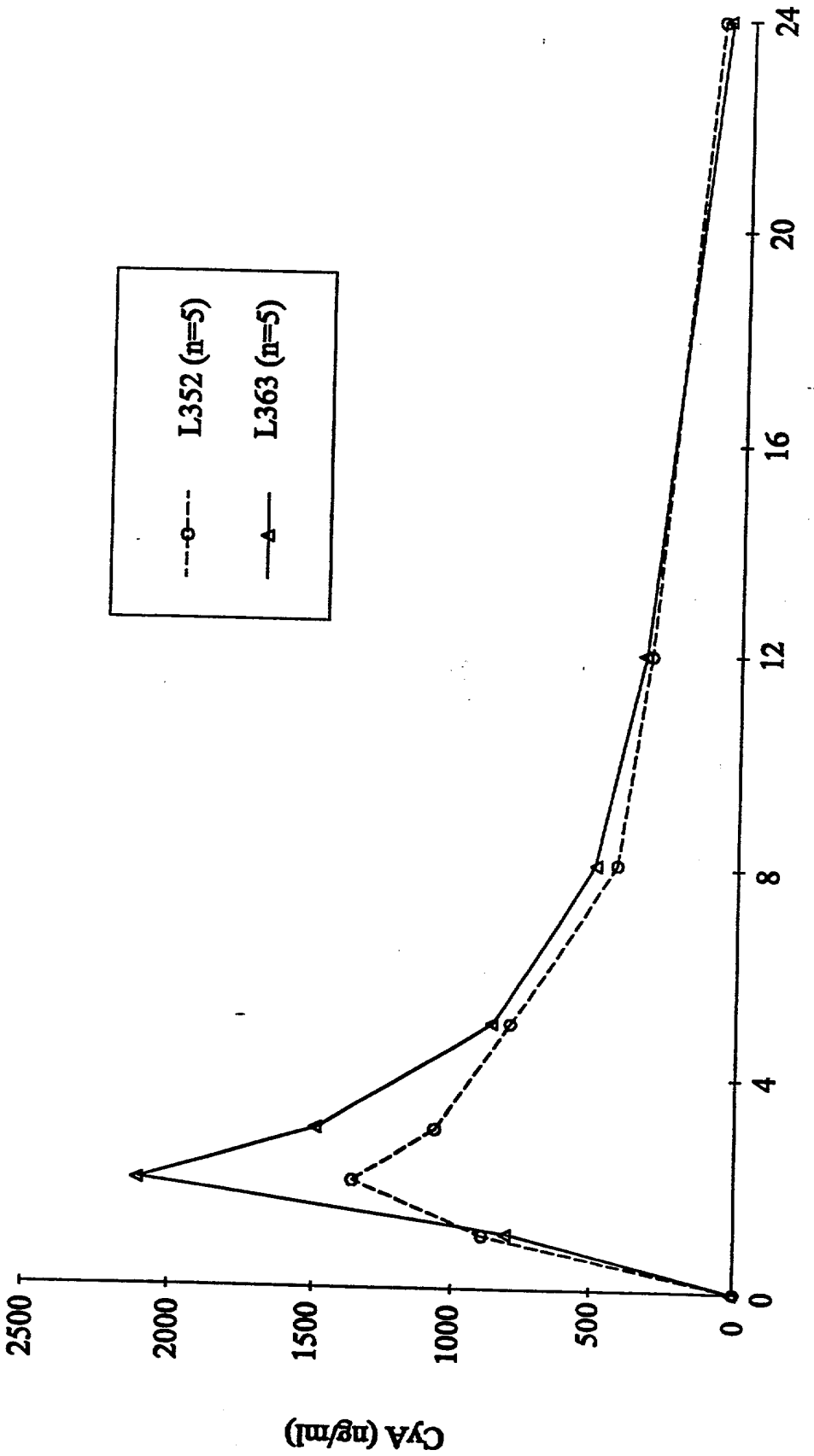

CyA (ng/ml)
2500
2000
1500
1000
500
0
0
4
8
12
16
20
24
time (h)
L352 (n=5)
L363 (n=5)

FIG. 3

PHARMACEUTICAL COMPOSITIONS FOR ORAL AND TOPICAL ADMINISTRATION

This invention relates to pharmaceutical formulations including, as the active ingredient, substances which are poorly soluble in water, for example therapeutically active cyclosporins, taxoides and taxanes.

Cyclosporins are a group of monocyclic, poly-N-methylated undecapeptides, which are naturally produced as secondary metabolites by certain fibrous fungi, especially of general Tolypocladium and Cylindrocarpon. Some therapeutically useful cyclosporin can be prepared by partial synthesis or by special fermentation procedures.

Ciclosoporin (Cyclosporin A) is the first natural substance having selective immunosuppressive effect on lymphoid cells, especially T lymphocytes. It also influences functions of other cells of the immune system to a great extent.

Systemically administered cyclosporin is used therapeutically in organ transplantations or transplantations of bone-marrow. Cyclosporin can be employed for treating a wide variety of autoimmune diseases with inflammatory etiology and also as anti-parasitic agents.

Certain cyclosporins without immunosuppressive activity exhibit an inhibitor effect towards replication of the HIV-1 virus and can be employed in therapy for treatment and prevention of AIDS or AIDS related complex. The group of cyclosporins also include chemomodulators useful for influencing cross resistance of tumour cells to cytostatics.

Bioavailability of cyclosporin is influenced, on one hand, by specific properties of this group of substances, but also by the composition and properties of the particular dosage form. An important role in formulating therapeutic compositions containing cyclosporin is played by their high lipophilicity.

Solubility of these active substances in water typically does not exceed 2.5 mg/100 ml, which value is approximately 100 times lower than needed for regular absorption in the organism. The marked lipophilicity of cyclosporin is evidenced by the

values of their partition coefficients P in the system n-octanol/water. For cyclosporin, values of log P = 21.08 to 2.99 have been reported.

To achieve acceptable bioavailability of cyclosporins formulations which are used in practice form dispersion systems and are characterised by the presence of a hydrophilic phase, a hydrophobic phase and a tensoactive component. The resulting dispersions are either classic emulsions or optically transparent microemulsions. Commercially available compositions for oral administration are known under the trade names Sandimunn®, Sandimunn®-Neoral, Consupren®, Implanta®, Imusporin® as described in GB 2015339, GB 2222770, GB 2270842 and GB 2278780.

Modifications of the preceding systems, where the hydrophilic base is omitted and replaced by partial esters of fatty acids with polyols like propylene glycol, glycerol or soritol, are described in GB 2228198.

German patent application DE 4322826 discloses, as the carrier system for drugs poorly soluble in water, a composition containing polyglyceryl esters of fatty acids as a co-tenside to non-ionic tensides having HLB higher than 10, in the presence of a triacyl glycerol as the lipophilic component.

Formulations containing cyclosporins in a vehicle comprising propylene glycol, mixed mono-, di- and triglyceride and a hydrophilic tenside, disclosed in GB 2248615, are typical microemulsion reconcentrates of the oil-in-water type.

According to biopharmaceutical classification, cyclosporins belong to class IV, ie substances whose solubility in water is bad and bioavailability is poor (G L Amidon, Biopharmaceutics Drug Classification and International Drug Regulation, Capsgel Library, Bornem 1996, p 15 - 30).

Taxoides are a group of natural substances isolated from some strains of Taxus. Taxoides demonstrate antineoplastic effects by influencing cellular mitosis. They are diterpenic substances containing taxanic cyclic grouping with a 4-membered oxitanic ring and an esteric side chain in position C_{13}. Natural paclitaxel and its semisynthetic derivative docetaxel are used for treatment of tumours. Taxanes are even less soluble in water than cyclosporins. Immediately after preparation, paclitaxel solubility in water ranges about 5 μg/ml, however, paclitaxel hydrates which are formed on standing have an equilibrium concentration which is lower by an order of magnitude (0.3 - 0.6 μg/ml).

Compositions based on polyglycerol acylesters are known from the patent literature, eg PCT/GB97/02079. Pharmaceutical compositions for internal application containing cyclosporin as active ingredient and a carrier consisting of one or more partial esters of fatty acids with di- to decaglycerol and partial pentaglycerol to pentadecaglycerol acylesters are disclosed. Compositions prepared this way enable a skilled person to make a dispersion of emulsion type with an average particle size about 1 - 2 μm after dilution. The particles are of spherical character as shown in Figure 1. However, achievement of high bioavailability remains a problem.

Similarly, PCT/GB97/00131 discloses use of polyglycerol acylesters. Besides the above mentioned polyglycerolesters, the vehicle contains glycerol monoacylesters and optional substances selected from anhydrohexosdimethyl derivatives and/or polyethyleneglycerols. The formulation can also contain other substances which improve the stability of the vehicle and lipoaminoacids which are suitable especially for topical products. These compositions provide slightly dispersing systems containing spherical particles.

Other systems utilising polyglycerol esters with fatty acids are microemulsions. In EP-A-670715 or EP-A-334777, esters of fatty acids with polyglycerols are used for pharmaceutical or cosmetic microemulsions or compositions forming microemulsions. As defined in eg Lachman et al; Theory and Practice of Industrial Pharmacy, Lea & Febiger, Philadelphia 1970, p 463, a microemulsion is a clear dispersion of oil-in-water or water-in-oil having a size of dispersed particles in the range 100 - 600 Å. Dispersed particles in a microemulsion are composed of nanodrops or micellar aggregates of dispersed phase in dispersion medium. The shape of dispersed particles is mostly spherical.

Similarly, CZ-A-283516 describes use of polyglycerol acylesters as one of the components of vehicle which forms lyotropic liquid crystals in contact with an aqueous phase. In accordance with this specification and other patents (eg EP-A-314689 or EP-A-126751), only pharmaceutical compositions based on systems providing lyotropic liquid crystals are suitable and advantageous for formulations of biologically active substances which dissolve in the given system and/or have hydrophobic character. At the same time the capability of formation of a liquid crystal phase in vivo after application into the GI tract is associated with high bioavailability of hydrophobic pharmaceutical compositions.

According to a draft of the article Cyclosporine Modified Capsules for USP 23, published in Pharmaceopeial Forum Volume 24, Number 3, 1998, p 6155, high bioavailability of cyclosporin is conditioned by dispersion of a pharmaceutical composition in the form of a pre-concentrate after administration of a microemulsion into GI tract. The draft recommends to test whether the dispersion arising after dilution of such composition provides particles of mean size 50 nm in the dispersed phase. This topic is discussed in several patents which however do not disclose use of polyglycerol esters of higher fatty acids.

However, it has been surprisingly found out that high bioavailability of cyclosporins and taxanes after oral application can be achieved using a system neither based on liquid crystals nor a microemulsion. It was also found that a system prepared in accordance with the present invention does not result in a dispersion of the emulsion type.

Unexpectedly it has been found that particles which are formed spontaneously or almost spontaneously have a non-spherical character. At the same time, no sign of anisotropic grouping of molecules was found even if the particles formed exhibited a dramatic increase in viscosity. From these findings it appears that it is a dispersion of particles having gel-like properties in water.

In this specification particles of gel-like character are to be understood as those whose stable shape or conformation in the dispersion is non-spherical. Non-spherical particles are those having at least two different perpendicular dimensions.

In this specification a gel emulsion (GEM) is to be understood as a dispersion of particles of gel character in an aqueous phase.

In a pre-concentrate of gel emulsion (PRO-GEM) is to be understood as a composition which results in a gel emulsion after dilution or in contact with an aqueous phase.

The formation of gel particles is conditioned by interaction between a hydrophilic gelator (an agent which causes formation of gel) and a lipophilic gel-creating phase. Such a composition may contain components which participate in the formation of particulate gel structure and which facilitate spontaneous dispersion in an aqueous medium. It may also contain components which ensure oxidative or microbial stability, masking the taste,

adjusting the appearance or to facilitate dissolution of active ingredients in the mixture. The composition may also contain components which adjust viscosity.

Pharmaceutical compositions in accordance with the present invention may be used to formulate active substances from class IV according to the biopharmaceutical classification.

According to the present invention a pharmaceutical formulation for oral or topical administration comprises

a) 0.1 to 30.0 % of one or more hydrophobic active ingredients;

b) 0.1 to 60.0 % of one or more gelators comprising fatty acid esters of polyglycerol;

c) 0.1 to 60.0 % of one or more gel-creating substances selected from esters of polyglycerol with fatty acids and/or unsaturated fatty alcohols;

d) 1.0 to 60 % of one or more co-gelator substances selected from: macrogolglycerolester of fatty acids, macrogolglycerolester of vegetable oils, macrogolesters of fatty acids, mono- and di- macrogolesters of mono-, di- and tri-acylglycerols.

e) 5.0 to 30 % of one or more C_2 to C_4 alcohols;

wherein the above percentages are selected to total 100% and the ratio of a : c and/or a : e is in the range 0.001 : 1 to 10 : 1;

and wherein upon dilution with water the formulation forms a dispersion of polymorphous gel particles having a dimension of 0.2 to 500 μm.

Weights, percentages and amounts used in this specification are by weight unless indicated otherwise.

Pharmaceutical compositions in accordance with the present invention may be characterised in that after dilution by aqueous phase in ratio from approx 1 : 5 (composition : aqueous phase) to approx 1 : 100, a dispersion of gel particles in water with mean size of particles between 0.2 - 500 μm is obtained. Such dispersion may be referred to as a gel emulsion (GEM).

Gel emulsion pre-concentrates (PRO-GEM) may be administered in the form of a pre-concentrate or in single-dose dosage forms such as capsules.

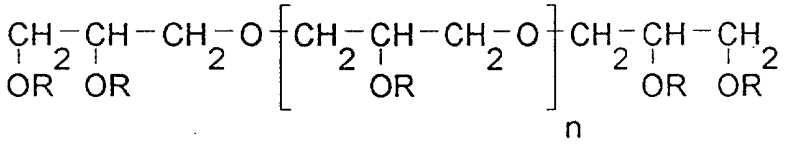
Component a) includes biologically active ingredients, which are insufficiently soluble in water for conventional formulation and so their bioavailability is low. According to this biopharmaceutical classification, these are substances of group 2 and 4, with low water solubility. The substances belong into a group of immunosuppressives, antitumour chemotherapeutical agents, substances influencing saccharide metabolism, peptides and lipids, agents influencing the calcium channel, non-steroidal antiflogistics and vitamins.

Immunosuppressives are hydrophobic compositions and include N-methylated cyclic undecapeptides. Cyclosporins are preferably used, especially ciklosporin (also known as Ciklosporin or Cyklosporin A), $[Nva]^2$ - ciklosporin (cyklosporin G) and $[Melle]^4$ - ciklosporin. Non-immunosuppressive cyclosporines can also be used, eg $[3'ketoMBmt]^1$-$[Val]^2$-ciclosporin. Other immunosuppressives can be used too, eg macrolides produced by grampositive Streptomyces bacteria (rapamycine, tacrolimus) or their derivatives.

Antitumour chemotherapeutic agents include taxanes, preferably docetaxel or paclitaxel.

Other biologically active ingredients which may be formulated in accordance with this invention may be selected from: diclofenac, ibuprofen, nifedipine, triamcinolone, tocopherol etc. In accordance with the present invention, the compositions can contain as much as 30% of the active ingredient.

Component b) which may be considered as a gelator is selected from polyglycerol esters of fatty acids, of general formula (I)



(I)

where n is an integer from 4 - 13 and R = H or CO.R^1 wherein R^1 is C_{8-22} saturated, unsaturated or hydroxylated alkyl and wherein at least one group R is not hydrogen.

Preferred components b) are polyglycerol esters and partial esters of medium or long chain fatty acids. These preferably have a HLB value not less than 10.

Polyglycerol esters with fatty acids are generally prepared by either partial or full esterification of polyglycerols by corresponding fatty acids or trans-esterification of vegetable oils with polyglycerol. Each polyglycerol monoester may be characterised by a saponification number. The level of polymerization is best indicated by the hydroxyl number. Polyglycerol esters with HLB value greater than about 10 may be considered to be hydrophilic. Polyglycerol esters with a HLB value less than about 9 may be considered lipophilic. Substances suitable for the components b) include the following:

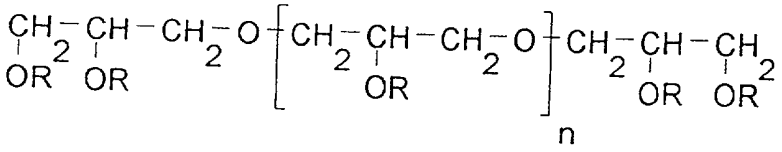
Name (INCI)	**Number of glycerol units**	**HLB**
Polyglycerol-60-monolaurate	6	14.5
Polyglyceryl-10-monolaurate	10	15.5
Polyglyceryl-10-monomyristate	10	14.0
Polyglyceryl-10-monostearate	10	12.0
Polyglyceryl-10-mono-dioleate	10	11.0
Polyglyceryl-10-diisostearate	10	10.0
Polyglyceryl-6-monomyristate	6	11.0
Polyglyceryl-8-monooleate	8	11.0
Polyglyceryl-10-monooleate	10	12.0

The above mentioned polyglycerols esters are available from Nikko Chemicals Co under the trade name NIKKOL®, Durkee Foods under the trade name SANTONE® or Abitec Corp under the trade name CAPROL®.

Polyglycerols esters of components b) and c) for use in the compositions of this invention preferably meet the following purity requirements:

acid no = max 6; heavy metals content = max 10 ppm; water content = max 2%; content of Na salts of fatty acids = max 2% (as Na stearate); total ash = max 1%.

Component c), which may be considered as a gel-creating substance, is selected from polyglycerol esters of fatty acids and/or unsaturated fatty alcohols, and is preferably of general formula (2)



(2)

wherein n is an integer from 0 - 10 and R = H or CO.R" wherein R" is C_{8-22} saturated, unsaturated or hydroxylated alkyl, and wherein while at least one group R is not hydrogen.

Preferred components c) are polyglycerol esters and partial esters of fatty acids and/or fatty alcohols. Preferred components c) have a HLB value not greater than 9. Substances suitable for components c) include the following:

Name (INCI)	**Number of glycerol units**	**HLB**
Polyglyceryl-3-monooleate	3	6.5
Polyglyceryl-6-dioleate	6	8.5
Polyglyceryl-10-tetraoleate	10	6.2
Polyglyceryl-10-decaoleate	10	3.5
Polyglyceryl-2-monostearate	2	5.0
Polyglyceryl-10-pentastearate	10	3.5

The above mentioned polyglycerols esters are available from Nikko Chemicals Co under the name NIKKOL®; or Abitec Corp under the trade name CAPROL®.

Preferred components c) include gel-creating substances selected from polyglycerol esters of fatty acids and/or unsaturated fatty alcohols is in accordance with

the present invention a substance especially selected from C_{8-22} unsaturated fatty alcohols. Preferably oleyl alcohol (9-octadecen-1 ol) can be used for example meeting the following purity requirements:

Mr = 268,49; refractive index = 1,458 - 1,460; acid no < 1; hydroxyl no = 205 - 215; iodine no = 85 - 95.

Component d), which may be considered to be a co-gelator, may be selected from: macrogolglycerolesters of fatty acids. These may be esters of C_{8-22} fatty acids, unhydrogenated or hydrogenated with macrogol glycerols.

Especially preferred are macrogol glycerols with vegetable oils eg ricine oil, both hydrogenated and unhydrogenated, almond or maize oil. They are generarly prepared by reaction of various quantities of ethyleneoxide and the appropriate type of oil under known conditions. Especially preferred are the following substances characterised by the number of reacted ethylene oxide mols (1 + m + n + x + y + z) and HLB value.

	(1+m+n+x+y+z)	**HLB**
macrogol(1540) ricine-oleic glyceride	35	12-14
macrogol(1760) hydrogenated ricine-oleic glyceride	40	12.5-16
macrogol(2200) hydrogenated ricine-oleic glyceride	50	13.5
macrogol(2640) hydrogenated ricine-oleic glyceride	60	14.5
macrogol(3520) hydrogenated ricine-oleic glyceride	80	15
macrogol(4400) hydrogenated ricine-oleic glyceride	100	16.5
macrogol(2640 almond-oleic glyceride	60	15
macrogol(2640) maize-oleic glyceride	60	15

Characteristic physical and chemical parameters of the above mentioned substances are:

acid no ≤ 2; hydroxyl no = 40 - 60; iodine no < 1*; saponification no = 40 - 70; water content < 3%;

(*- for macrogol(1540) ricine-oleic glyceride = 28 - 32).

These substances are commercially available under the trade names eg Cremophor®, Nikkol®, Simulsol®, Mapeg®, Crovol®.

Special mixed mono- and d- macrogolesters of mono-, di- and triacylglycerol commercially available under the trade name Gelucire® are also preferred. Especially preferred products are available under the name Gelucire® 50/13 and 44/14. Preferred physicochemical properties are:

acid no < 2,00; saponification no = 65 - 95; iodine no < 2; hydroxyl no = 36 - 56; peroxide no < 6; alkaline impurities < 80 ppm; free glycerol < 3,00 %.

Alternative compositions preferred for use as compound d) are macrogolesters of fatty acids eg macrogol(660)-12-hydroxystearate commercially available under the trade name Solutol® HS 15 having an acid no < 1; water content < 0.5%; saponification no = 53 - 63 and hydroxyl no = 90 - 110.

Component d) is usually present in the compositions in an amount of 1 - 60 %, preferably in the range 5 - 50 % and most preferably 15 - 50% and most preferably 15 - 40 %.

Component e) is selected from C_2 - C_4 alkanols, preferably ethyl alcohol of pharmaceopoeial quality. In topical applications, propan-2-ol, or 2-methyl-1-propanol, are preferred.

Other excipients which can be employed in compositions of the present invention are those which influence physicochemical and microbial stability (eg antioxidants, anti-microbial additives such as tocopherol, methyl paraben), organoleptic properties (eg taste correctors based on natural or nature identical aromas) or physical properties which may limit processing (eg viscosity or melting point). The following can be included among

such substances: water or other pharmaceutically acceptable solvents, hydrophilic colloids eg selected from derivatives of cellulose, chitosans, alginate, polycarbophile etc.

Compositions based on a gel pre-concentrate may be characterised in that they disperse into particles of gel character primarily of irregular shape after application into an aqueous medium. High bioavailability of such compositions is associated with bioadhesion. As a result of their amphiphility, these particles are less liable to coalescence and may be homogenously dispersed in an aqueous medium. In contact with a lipophilic surface they remain on the surface and so provide a sufficient concentration gradient to enable drug penetration through the membrane due to their viscosity and adhesivity.

The invention is further described by means of example but not in any limitative sense with reference to the accompanying drawings of which:

Figure 1 is a photomicrograph of a dispersion in accordance with PCT/GB97/02079;

Figure 2 is a photomicrograph of a dispersion in accordance with the present invention; and

Figure 3 is a graph showing blood levels of cyclosporin in example 6.

Example 1

Cyclosporine-containing solution for oral or topical application:

The following ingredients were employed.

a)	cyclosporin A	3600 g
b)	polyglycerol-10-mono-dioleate	7200 g
c)	oleyl alcohol	7200 g
d)	macrogol(1760) hydrogenated ricine-oleic glyceride	14400 g
e)	ethanol	4000 g
f)	D-α-tocopherol	180 g

Composition a) was mixed with compositions e) and c). The whole mixture was then homogenized until the active ingredient was dissolved. Then, compositions b) and d) and any other auxiliary ingredients were added. After complete homogenization the

resulting solution was filtered through a hydrophobic membrane GVHP (Millipore) of porosity 0.2 - 5.0 μm into a gasproof vessel under an inert atmosphere. When required for use the filtered solution was packed under an inert atmosphere into 50 ml bottles equipped with gasproof stoppers.

Example 2

Hard gelatin capsules of size "Elongated 0"

The following ingredients were employed.

a)	cyclosporine A	50.0 mg
b)	polyglyceryl-10-monooleate	100.0 mg
c)	polyglyceryl-3-monooleate	15.0 mg
d)	macrogol(2640) hydrogenated ricine-oleic glyceride	140.0 mg
e)	ethanol	80.0 mg

The fill for hard gelatin capsules was prepared using working procedure identical to that of Example 1 and filled into hard gelatin capsules of size "EO".

Example 3

Soft gelatin capsules of size oblong 20:

The following ingredients were employed.

a)	cyclosporine A	100.0 mg
b)	polyglyceryl-6-monolaurate	120.0 mg
c)	polyglyceryl-10-tetraoleate	410.0 mg
d)	Gelucire 50/13	300.0 mg
e)	ethanol	170.0 mg

The fill for soft gelatin capsules was prepared by a procedure identical to that of Example 1. The fill was filtered into a 20 1 stainless-steel vessel equipped with a gasproof stopper. The fill was kept in inert atmosphere between filtration and encapsulation.

Encapsulation was carried out using a conventional procedure into standard type of gelatin mixture.

Example 4

Hard HPMC capsules (Shionogi Qualicaps) of size 3:

The following ingredients were employed.

a)	cyclosporin A	25.0 mg
b)	polyglyceryl-10-myristate	50.0 mg
c)	polyglyceryl-10-pentastearate	70.0 mg
d)	macrogol(2640) almond-oleic glyceride	75.0 mg
e)	ethanol	30.0 mg

Composition a) was mixed with compositions e) and b). The mixture was heated to 40 - 50°C and homogenised until composition a) was dissolved. Then, composition d) was added. Finally, composition c) was added. The mixture was continuously mixed. The temperature of the mixture did not exceed 60°C during preparation. After complete dissolution and homogenization of all ingredients the product is filtered through a pre-filter and filled into hard cellulose capsules (eg supplied by Syntapharm) of size 3.

Example 5

Visualisation of gel emulsion

Pre-concentrates in accordance with patent application PCT/GB97/02079, Example 1 and as disclosed in Example 1 of this invention were each diluted with water in ratio 1 : 20 (product : water) and dispersed on a laboratory shaker (IKA HS - B20) for 10 minutes at temperature 25 ± 1°C. Pictures of the dispersed samples were taken by means of a COHU camera connected to an optical microscope. The pictures were evaluated by means of software LUCIA™ (Laboratory Imaging Inc). Photomicrography of a dispersion of the emulsion type in accordance with PCT/GB97/02079 is shown in Figure 1. Photomicrography of a dispersion of the type of gel emulsion arising from a pre-concentrate according to Example 1 of the present invention is represented by Figure 2.

Example 6

Verification of bioavailability of medicinal products on base of pre-concentrate of gel emulsion

The composition according to Example 1 was compared with the commercially available microemulsion product Neoral® oral solution. The composition according to Example 1 was given clinical code L363, Neoral® oral solution was tested under code L352.

Pharmacokinetics were compared after single-dose administration of 100 mg cyclosporine to five beagle dogs in a two-phase experiment. Males of 12 - 36 months of age and weight 9 - 15 kg were fed using a standard pellet diet in quantity 300 g per day with water ad libitum. The product was administered after 18 hour fasting. Blood samples were collected from the antebrachial vein in intervals of 0, 1, 2, 3, 5, 8, 12 and 24 hour. The blood samples were stabilized using complexone and kept in a refrigerator until analysis was performed by non-specific radioimmunoassay. Comparison of mean bioavailabilities represented by mean values of cyclosporin A blood concentration is shown in Figure 3. It is clear from the comparison that bioavailability of products based on a gel emulsion pre-concentrate which created a dispersion of non-spherical particles of mean size 0.2 - 500 μm after dilution with water, was comparable or higher than that of products forming microemulsion of average size of particles about 100 nm.

Example 7

Fills for soft gelatin capsules containing paclitaxel:

The following ingredients were employed.

a)	paclitaxel	78.75 mg
b)	polyglyceryl-10-mono-dioleate	205.00 mg
c)	polyglyceryl-3-monooleate	129.50 mg
c)	oleyl alcohol	205.00 mg
d)	macrogol(1760) hydrogenated ricine-oleic glyceride	302.00 mg
e)	ethanol	129.50 mg

Example 8

Composition of soft gelatin capsules

The following ingredients were employed.

a)	paclitaxel	78.75 mg
a)	[3'ketoMBmt][1]-[Val][2]-cyclosporin	52.50 mg
b)	polyglyceryl-10-mono-dioleate	187.50 mg
c)	oleyl alcohol	187.50 mg
c)	polyglyceryl-3-monooleate	112.50 mg
d)	macrogol(1760) hydrogenated ricine-oleic glyceride	302.00 mg
e)	ethanol	129.50 mg

Example 9

Fill for soft gelatin capsules containing nifedipine

The following ingredients were employed.

a)	nifedipine	20.00 mg
b)	polyglyceryl-10-nono-dioleate	205.00 mg
c)	polyglyceryl-3-monooleate	129.50 mg
c)	oleyl alcohol	205.00 mg
d)	macrogol(1760) hydrogenated ricine-oleic glyceride	302.00 mg
e)	ethanol	129.50 mg

Examples 10 - 17

Table 1 gives further examples of preparations illustrating the invention. The method of preparation was identical to that of Example 1.

Table 1

Example No/Component	A	B	C_1	C_2	D	E
10	10.0	19.0	19.0	12.0	28.0	12.0
11	10.0	23.0	19.0	15.0	28.0	5.0
12	10.0	13.0	19.0	8.0	28.0	20.0
13	0.1	5.0	19.9	15.0	50.0	10.0
14	10.0	37.0	19.0	12.0	10.0	12.0
15	10.0	1.0	19.0	30.0	28.0	12.0
16	0.1	21.1	---	34.7	31.1	13.0
17	30.0	10.0	15.0	6.0	22.0	17/0

The following raw materials were used in Examples 10 - 17:

A -cyclosporine A

B -polyglyceryl-10-mono-dioleate

C_1 -oleyl alcohol

C_2 -polyglyceryl-3-monoleate

D -macrogol(1760) hydrogenated ricine-oleic glyceride

E -ethanol

CLAIMS

1. A pharmaceutical formulation for oral or topical administration including

a) 0.1 to 30.0 % of one or more hydrophobic active ingredients;

b) 0.1 to 60.0 % of one or more gelators comprising fatty acid esters of polyglycerol;

c) 0.1 to 60.0 % of one or more gel-creating substances selected from esters of polyglycerol with fatty acids and/or unsaturated fatty alcohols;

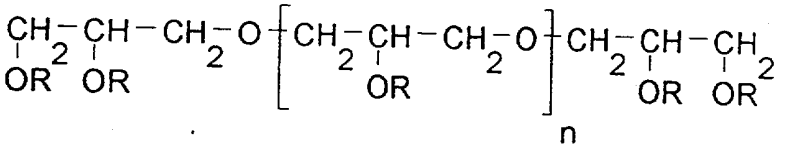
d) 1.0 to 60 % of one or more co-gelator substances selected from: macrogolglycerolester of fatty acids, macrogolglycerolester of vegetable oils, macrogolesters of fatty acids, mono- and di- macrogolesters of mono-, di- and tri-acylglycerols.

e) 5.0 to 30 % of one or more C_2 to C_4 alcohols;

wherein the above percentages are selected to total 100% and the ratio of a : c and/or a : e is in the range 0.001 : 1 to 10 : 1;

and wherein upon dilution with water the formulation forms a dispersion of polymorphous gel particles having a dimension of 0.2 to 500 μm.

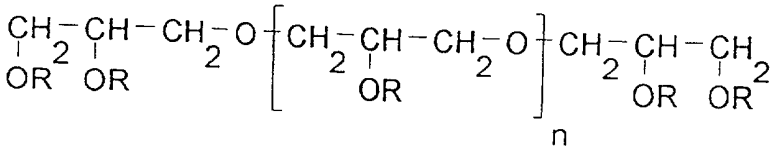
2. A formulation as claimed in claim 1, wherein component b) is selected from polyglycerol esters of fatty acids of formula (1)



(1)

wherein n is an integer from 4 to 13 and R is H or CO.R' wherein R' is C_{8-22} saturated, unsaturated or hydroxylated alkyl and wherein at least one group R is not hydrogen.

3. A formulation as claimed in claim 1 or 2, wherein component c) is selected from polyglycerol esters of fatty acids and/or unsaturated fatty acids of formula (2).



(2)

wherein n is an integer from 0 - 10 and R = H or CO.R" wherein R" is C_{8-22} saturated, unsaturated or hydroxylated alkyl, and wherein while at least one group R is not hydrogen.

4. A formulation as claimed in any preceding claim, wherein component d) is selected from triglyceride macrogol glycerol esters, partial glycerides or fatty acids or macrogol esters of fatty acids in which the average quantity of reacted ethylene oxide in the synthesis of these substances ranges between 50 to 150 mols and concurrently the ratio between components b) and d) is from 0.1 : 1 to 10 : 1.

5. A formulation as claimed in any preceding claim, wherein the component a) is selected from cyclosporins especially cyclosporin A, cyclosporin D or cyclosporin G, wherein the ratio of components a : c + e is 1.001 : 1 to 1.5 : 1.

6. A formulation as claimed in any of claims 1 to 5, wherein component a) is selected from taxanes, especially docataxel or paclitaxel, wherein the ratio between components a : c + e is 0.001 : 1 to 1.5 : 1.

7. A formulation as claimed in any preceding claim, wherein component a) includes at least one substance selected from the group comprising cyclosporins and at least one substance selected from the group comprising taxanes.

8. A formulation as claimed in any preceding claim, further including excipients to modify the physical, chemical, microbial stability, organoleptic or physical processing properties of the formulation.

Application No: GB 9919288.2
Claims searched: 1-8

Examiner: Diane Davies
Date of search: 26 February 2001

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.S): A5B: BLB, BNB

Int Cl (Ed.7): A61K 9/08, 38/13, 47/14

Other: Online databases: CAS-ONLINE, EPODOC, JAPIO, WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
A	WO 9805309 A	(Galena AS) Whole document: cyclosporin compositions containing polyglycerol fatty esters.	
A	WO 9726003 A	(Galena AS) Whole document: cyclosporin compositions containing polyglycerol fatty esters.	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.