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(54) Title: PHARMACEUTICAL COMPOSITIONS FOR ORAL AND TOPICAL ADMINISTRATION

(57) Abstract: A method of increasing viscosity of a pharmaceutical formulation for oral or topical administration comprises the steps of combining: a) an effective amount of one or more hydrophobic active ingredients; b) 5 to 50 % of one or more compounds selected from polyglycerol esters of fatty acids with 6-15 glycerol units; c) 5 to 50 % of one or more compounds selected from polyglycerol esters of fatty acids and/or unsaturated fatty acids with 2-12 glycerol units; d) 5 to 50 % of one or more compounds selected from triglyceride macrogol glycerol esters, partial glycerides or fatty acids or macrogol esters of fatty acids and concurrently the ratio between components b) and d) is from 0.1 : 1 to 10 : 1; and wherein upon dilution with water 1 : 1 by volume the viscosity of the formulation increases by at least 5 times in comparison to the undiluted composition.

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 25 μg/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 = 2.08 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-A-2015339, GB-A-2222770, GB-A-2270842 and GB-A-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 sorbitol, are described in GB-A-2228198.

DE-A-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-A-2248615, are typical microemulsion preconcentrates 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 WO98/05309. 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, WO97/26003 discloses use of polyglycerol acylesters. Besides the above mentioned polyglycerolesters, the vehicle contains glycerol monoacylesters and optional substances selected from anhydrohexosdimethyl derivatives and/or polyethylene glycerols. The formulation can also contain other substances which improve the stability of the vehicle and lipoamino acids 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 the dispersed phase in the 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 gastrointestinal 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 caused 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.

According to a first aspect of the present invention a method of increasing viscosity of a pharmaceutical formulation for oral or topical administration comprises the steps of combining:

a) an effective amount of one or more hydrophobic active ingredients;

b) 5 to 50% of one or more compounds selected from polyglycerol esters of fatty acids of formula (1)

$$CH_2OR\text{-}CHOR\text{-}CH_2O\text{-}[CH_2CHOR\text{-}CH_2O\text{-}]_NCH_2\text{-}CHOR\text{-}CH_2OR \qquad (1)$$

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

c) 5 to 50% of one or more compounds selected from polyglycerol esters of fatty acids and/or unsaturated fatty acids of formula (2)

$$CH_2OR\text{-}CHOR\text{-}CH_2O\text{-}[CH_2CHOR\text{-}CH_2O]_NCH_2\text{-}CHOR\text{-}CH_2OR \qquad (2)$$

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

d) 5 to 50% of one or more compounds 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;

wherein the above percentages are selected to total 100%;

and wherein upon dilution with water 1:1 by volume the viscosity of the formulation increases by at least 5 times in comparison to the undiluted composition.

In preferred formulations a minimum number of excipients are used. This results in economy of manufacture and regulatory requirements. A single compound from each of groups b) to e) is preferred.

According to a second aspect of the present invention there is provided a pharmaceutical formulation for oral or topical administration including

a) an effective amount of one or more hydrophobic active ingredients;

b) 5 to 50% of one or more compounds selected from polyglycerol esters of fatty acids of formula (1)

$$CH_2OR\text{-}CHOR\text{-}CH_2O\text{-}[CH_2CHOR\text{-}CH_2O\text{-}]_NCH_2\text{-}CHOR\text{-}CH_2OR \quad (1)$$

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

c) 5 to 50% of one or more compounds selected from polyglycerol esters of fatty acids and/or unsaturated fatty acids of formula (2).

$$CH_2OR\text{-}CHOR\text{-}CH_2O\text{-}[CH_2CHOR\text{-}CH_2O]_NCH_2\text{-}CHOR\text{-}CH_2OR \quad (2)$$

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

d) 5 to 50% of one or more compounds 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;

wherein the above percentages are selected to total 100%;

and wherein upon dilution with water 1:1 by volume the viscosity of the formulation increases by at least 5 times in comparison to the undiluted composition.

The invention also provides use of a formulation in accordance with the second aspect of this invention for preparation of a dosage form for administration of a class IV substance.

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 on mixing of the phases 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 in water of particles having gel-like properties.

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.

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 caused 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 a particulate gel structure and which facilitate spontaneous dispersion in an aqueous medium. It may also contain components which ensure oxidative or microbial stability, mask the taste, adjust the appearance or 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. Also advantages are obtained when substances from class II and III are used.

According to a third aspect of 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 selected from the group consisting of: fatty acid esters of polyglycerol;

c) 0.1 to 60.0 % of one or more gel-creating substances selected from the group consisting of: 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 the group consisting of: macrogol glycerolesters of fatty acids, macrogol glycerolesters of vegetable oils, macrogol esters of fatty acids, mono- and di- macrogol esters 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 wherein upon dilution with water the formulation forms a dispersion of polymorphous gel particles having a dimension of 0.2 to 500 μm.

Percentages and amounts used in this specification are by weight unless indicated otherwise.

In preferred formulations the ratio of a : c and/or a : e is in the range 0.001 : 1 to 10 : 1.

In contrast particles in liquid-liquid emulsions are generally spherical in shape. Particles of the present invention may have a substantial proportion, for example more than half with a non-spherical shape, for example an ellipsoid, rod-like or string-like shape. Preferably more than half of the particles by weight are elongate having a length more than twice their width or diameter. Formulations of this invention may have a particle size distribution with a median dimension in the range 1 to 100 μm, preferably 5 to 20 μm. Formulations may contain individual particles with a dimension up to 10 μm or more, for example 20 to 50 μm.

The formulations of the present invention may be made by mixing for example my manual stirring or shaking in vitro. Liquid formulations may be mixed with water, milk or other drink before administration. Higher speed stirring is less convenient but may be used, particularly to give smaller particle sizes, for example about 200 nm if desired.

Dosage forms comprising a gel-emulsion preconcentrate, eg in capsules, are mixed with aqueous phase in the GI tract. Sufficient shear forces are applied in the GI tract to form the polymorphous particles of the present invention.

Pharmaceutical compositions in accordance with the present invention may be characterised in that after dilution by mixing with an 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. These substances include immunosuppressives, antitumour chemotherapeutical agents, substances influencing saccharide metabolism, peptides and lipids, agents influencing the calcium channel, non-steroidal antiflogistics and vitamins.

Immunosuppressives are hydrophobic compounds and include N-methylated cyclic undecapeptides. Cyclosporins are preferably used, especially ciclosporin (also known as Ciclosporin or Cyclosporin A), $[Nva]^2$ - ciclosporin (cyclosporin G) and $[Melle]^4$ - ciclosporin. Non-immunosuppressive cyclosporines can also be used, eg $[3'ketoMBmt]^1$-$[Val]^2$-ciclosporin. Various pharmacopoeias have referred to these compounds using different spellings. In this specification these compounds and derivatives thereof are conveniently referred to by the name cyclosporin. 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)

$$CH_2OR\text{-}CHOR\text{-}CH_2O\text{-}[CH_2CHOR\text{-}CH_2O\text{-}]_NCH_2\text{-}CHOR\text{-}CH_2OR \qquad (1)$$

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)		
Polyglycerol-6-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® and from Th. Goldschmidt under the trade mark ISOLAN® or Abitec Corp under the trade name CAPROL®. Commercially available polyglyceryl esters may be mixtures containing predominantly the named ester or a mixture of esters having equivalent properties as determined for example by the hydroxyl value.

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%.

Preferred gelator compounds b) are selected from polyglyceryl esters of C_{12-22} saturated, unsaturated or hydoxylated fatty acids including myristate, laurate, oleates, stearate, linoleate and linolate. C_{16-22} acids are especially preferred. Most preferably C_{16-18}, that is stearate, oleates, laurate, linoleate and linolate. Mixtures may be used. Oleate esters or mixtures thereof are most preferred.

Triglyceryl esters of these acids, in which N = 1, have been found to be particularly suitable, especially for formulation of cyclosporins.

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)

$$CH_2OR\text{-}CHOR\text{-}CH_2O\text{-}[CH_2CHOR\text{-}CH_2O]_NCH_2\text{-}CHOR\text{-}CH_2OR \quad (2)$$

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.

Preferred gel-creating components c) are selected from polyglyceryl esters of C_{8-22} saturated, unsaturated or hydroxylated fatty acids, including myristate, laurate, oleates, stearate, linoleate and linolate. C_{8-18} acids are preferred, C_{8-16} acids being more preferred, including laurate, oleates and myristate. Mixtures may be employed. Oleate is the most preferred.

Polyglyceryl-10-esters of these acids, in which N = 8, have been found to be particularly suitable, especially for formulation of cyclosporins.

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

Especially preferred are macrogol glycerols with vegetable oils eg ricine oil, both hydrogenated and unhydrogenated, almond or maize oil. They are generally prepared by reaction of various quantities of ethylene oxide 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. Alternative alkanols include isomers of propenol and buterol. Mixtures may be employed. 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 amphilicity, 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 WO98/05309;

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

Figure 3 is a graph showing blood levels of cyclosporin in Example 6; and

Figures 4 to 8 are photomicrographs of further dispersions in accordance with this invention.

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 gas-proof stoppers.

Example 2

Hard Gelatin Capsules of Size "Elongated 0"

The following ingredients were employed.

a)	cyclosporin 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

Cyclosporine Containing Solution for Oral Application

The following ingredients were employed.

a)	cyclosporin	5.00 g
b)	polyglyerol(10) oleate	9.50 g
c)	polyglyceryl(3) oleate	15.50 g
d)	POE(40) hydrogenated castor oil (macrogol(1760) hydrogenated ricine-oleic glyceride)	14.00 g
e)	absolute ethanol	6.00 g

Components were mixed and homogenised until the active ingredient was dissolved, followed by filtration and packaging in 50 ml bottles as described in Example 1, to provide an oral solution with 100 mg/ml dosage.

Example 4

Soft Gelatin Capsules

The following ingredients were employed.

Composition of Fill:

a)	cyclosporin	100,00 mg
b)	polyglycerol(10) oleates	210,00 mg
c)	polyglycerol(3) oleates	350,00 mg
d)	POE(40) hydrogenated castor oil	315.00 mg
e)	ethanol	135,00 mg

The fill for soft gelatin capsules was prepared by a procedure similar to that of Example 1. The gelatin capsules were prepared by mixing purified water, glycerol, sorbitol and gelatin. Homogenisation of the solution, addition of the colouring agents and production of 100 mg dosage capsules in conventional manner.

Example 5

Soft Gelatin Capsules of Size Oblong 20:

The following ingredients were employed.

a)	cyclosporin 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 l stainless-steel vessel equipped with a gas-proof 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 6

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 7

Visualisation of Gel Emulsion

Pre-concentrates in accordance with patent application WO98/05309 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 WO98/05309 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 8

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 9

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 10

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 11

Fill for Soft Gelatin Capsules Containing Nifedipine

The following ingredients were employed.

a)	nifedipine	20.00 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

Examples 12 - 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 -cyclosporin A

B -polyglyceryl-10-mono-dioleate (mixture of mono & dioleates)

C_1 -oleyl alcohol

C_2 -polyglyceryl-3-monoleate

D -macrogol(1760) hydrogenated ricine-oleic glyceride

E -ethanol

Example 18

Assessment of Bioavailability and Size Distribution of Particles

A bioavailability study on 12 healthy volunteers was compared bioavailability of two different formulations in soft gelatine capsules each containing 100 mg of cyclosporine (Formulation A-GEM101 and Formulation B-GEM304). These gave a dispersion within the range 1 - 150 μm with Noreal® 100 mg capsules (Formulation C). Visual observation of the novel drug delivery system and precise evaluation of the particle size distributions were carried out.

Based on the visual observation the novel system was referred to as GEM (Gel based Emulsion).

Composition of Cyclosporin Containing Capsule Fills:

Formulation A - GEM 101:

a)	cyclosporin A	1 020 g
b)	polyglyceryl-10-monooleate	2 040 g
c)	polyglyceryl-3-monooleate	3 380 g
d)	macrogol (1760) hydrogenated ricine-oleic glyceride	3 000 g
e)	ethanol	1 330 g

Formulation B -GEM 304:

a)	cyclosporin A	1 020 g
b)	polyglyceryl-10-monooleate	2 630 g
c)	polyglyceryl-3-monooleate	1 580 g
c)	oleyl alcohol	1 105 g
d)	macrogol (1760) hydrogenated ricine-oleic glyceride	2 450 g
e)	ethanol	1 300 g

Particle Size Distributions

The particle size distributions of the novel GEM formulations were valuated using a Mastersizer Micro, version 2.18 (Malvern Instruments Ltd). Histograms of particle size distribution of Formulation A (GEM101) and Formulation B (304) showed that the effective diameter of Formulation A (resp. B) deduced from the histogram was 92.05 μm (36.23 μm).

Bioequivalence Study Design

An open-label, randomised 3-period crossover study was designed for 12 healthy Caucasian male volunteers, 18 - 45 years of age and with body weights ± 10% of their ideal weights. The test medications and the reference medication were administered in a randomised sequence as single oral doses in the fasted condition. Each dose contained 200 mg cyclosporin (two capsules of 100 mg). The duration of the washout period between treatments was at least 7 days. In each study period, 14 blood samples were to be taken before administration and 20, 40, 60 min, and 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 and 24 hours after administration. Adverse events were monitored during the entire study.

Blood was taken from the antecubital vein into EDTA plastic tubes (Sarstedt Monovettes). The samples were deep-frozen (-20 °C).

Cyclosporine whole blood concentrations were determined by means of a specific RIA. $AUC_{(0-\infty)}$ and Cmax were defined as the primary variables for the evaluation of bioavailability. $AUC_{(0-t)}$, tmax, t1/2, were secondary variables.

From the concentration/time data of the parent compound, the pharmacokinetic parameters were determined for each individual data set by means of non-compartmental analysis using TopFit 2.0.

Cmax and tmax were to be taken directly from the observed concentration-time data. The elimination rate constant (kel) was calculated by log-linear least squares regression analysis of the terminal part of the plasma concentration-time curve. The area under the concentration-time curve (AUC0-t) was calculated up to the last measurable concentration-time point (t) by the linear trapezoidal rule. Extrapolation to infinity (AUC0-t, AUC0-∞) was done by dividing the last observed concentration by elimination rate constant.

Summary of pharmacokinetic data:

Parameter	T1/2 [h]	Tmax [h]	Cmax [ng/ml]	AUC(0-t) [ng*h/ml]	AUC(0-inf) [ng*h/ml]
Formulation: A					
Arit.Mean	6.24	1.33	1372.69	4631.75	4861.85
S.D.	1.3	0.33	351.28	1204.56	1241.87
Geom.Mean	6.12	1.3	1329.84	4483.35	4712.35
Minimum	4.06	1	908.1	2635.32	2873.57
Maximum	8.24	2	1930.3	6432.76	6684.33
Formulation: B					
Arit.Mean	6.41	1.5	1196.49	4430.33	4696.56
S.D.	1.3	0.48	308.26	1032.91	1143.13
Geom.Mean	6.29	1.43	1161.84	4326.15	4576.94
Minimum	4.21	1	851.8	3130.66	3254.08
Maximum	8.93	2.5	1785	6206.13	6643.15
Formulation: C / Reference					
Arit.Mean	6.13	1.33	1358.95	4647.01	4887.55
S.D.	1.32	0.33	380.35	1358.41	1430.5
Geom.Mean	5.99	1.3	1307.19	447208	4705.55
Minimum	3.92	1	820.7	2953.47	3028.58
Maximum	7.87	2	1805.3	7330.08	7686.89

Example 19

Visualisation of Different Formulations

Different shapes of particles can be obtained by dispersal of formulations disclosed in this application. The following compositions when diluted gave dispersions of polymorphous gel particles. The visualisation technique was as described in Example 5.

Formulations A and B from Example 18 were visualized. A discrepancy between the measured (Mastersizer Micro: example 18) and observed particle sizes was caused by use of different dispersal techniques and by averaging of the measured values. Whilst the sample measured by Mastersizer Micro is continuously mixed by high speed mixer, a sample observed by an optical microscope was softly shaken by hand before putting under optical microscope.

The following formulations were also observed and visualised:

Formulation C

a)	cyclosporin A	9.5 %
b)	polyglyceryl-10-monooleate	40.0 %
c)	polyglycerol-3-isostearate	10.0 %
d)	macrogol (1760) hydrogenated ricine-oleic glyceride	28.0 %
e)	ethanol	12.5 %

Formulation D

a)	cyclosporin A	10.0 %
b)	polyglyceryl-10-monolaurate	10.0 %
c)	polyglycerol-3-oleate	40.0 %
d)	macrogol (1760) hydrogenated ricine-oleic glyceride	28.0 %
e)	ethanol	12.0 %

Formulation E

a)	cyclosporin A	10.0 %
b)	polyglyceryl-10-monolaurate	27.0 %
c)	polyglycerol-3-heptaoleate	31.0 %
d)	macrogol (1760) hydrogenated ricine-oleic glyceride	20.0 %
e)	ethanol	12.0 %

Example 20:

Assessment of viscosity of arising gel phases.

Compositions disclosed in this specification may exhibit an increase in viscosity in contact with water or aqueous solutions. This feature is particularly important for ensuring bioavailability of an active substance incorporated in such formulation. The viscosities of compositions from Examples 18 and 19 evaluated experimentally.

The rheological properties of chosen compositions were studied on a rotary viscometer Brookfield DV-III under constant conditions (temperature = 30°C, spindle SC 4 – 27, ultrathermostat Brookfield TC 500, Rheocalc program, 1.3 version).

A standard dilution was used to compare the ability to form a gel phase. Each sample was diluted 1 : 1 (by volume) with water. The viscosity of the diluted sample was evaluated using an up/down symmetric rheological program. All diluted samples were found to be non-Newtonian liquids. Undiluted samples had characteristics of standard (Newtonian) liquids. The samples were compared at the same Shear Rate. Findings are summarised in the table below:

Rheological parameters at the constant Shear Rate = 1.70 sec^{-1}:

Formulation (dilution status)	Shear Stress (N/m^2)	Viscosity (mPa.s)
Formulation A (undiluted)	0.34	200
Formulation A (diluted)	3.91	2300
Formulation C (diluted)	6.97	4100
Formulation D (diluted)	17.2	10100
Formulation E (diluted)	1.53	900

It was conclude that viscosity of the novel systems could be increased by at least 5x when contacted with water or aqueous solution. Such viscosity increases may have positive impact on the adhesion of the nascent phase and consequently provide an improved bioavailability.

CLAIMS

1. A method of increasing viscosity of a pharmaceutical formulation for oral or topical administration comprises the steps of combining:

a) an effective amount of one or more hydrophobic active ingredients;

b) 5 to 50% of one or more compounds selected from polyglycerol esters of fatty acids of formula (1)

$$CH_2OR\text{-}CHOR\text{-}CH_2O\text{-}[CH_2CHOR\text{-}CH_2O\text{-}]_NCH_2\text{-}CHOR\text{-}CH_2OR \quad (1)$$

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

c) 5 to 50% of one or more compounds selected from polyglycerol esters of fatty acids and/or unsaturated fatty acids of formula (2)

$$CH_2OR\text{-}CHOR\text{-}CH_2O\text{-}[CH_2CHOR\text{-}CH_2O]_NCH_2\text{-}CHOR\text{-}CH_2OR \quad (2)$$

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

d) 5 to 50% of one or more compounds 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;

wherein the above percentages are selected to total 100%;

and wherein upon dilution with water 1:1 by volume the viscosity of the formulation increases by at least 5 times in comparison to the undiluted composition.

2. A pharmaceutical formulation for oral or topical administration including

a) an effective amount of one or more hydrophobic active ingredients;

b) 5 to 50% of one or more compounds selected from polyglycerol esters of fatty acids of formula (1)

$CH_2OR\text{-}CHOR\text{-}CH_2O\text{-}[CH_2CHOR\text{-}CH_2O\text{-}]_NCH_2\text{-}CHOR\text{-}CH_2OR$ (1)

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

c) 5 to 50% of one or more compounds selected from polyglycerol esters of fatty acids and/or unsaturated fatty acids of formula (2)

$CH_2OR\text{-}CHOR\text{-}CH_2O\text{-}[CH_2CHOR\text{-}CH_2O]_NCH_2\text{-}CHOR\text{-}CH_2OR$ (2)

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

d) 5 to 50% of one or more compounds 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;

wherein the above percentages are selected to total 100%;

and wherein upon dilution with water 1:1 by volume the viscosity of the formulation increases by at least 5 times in comparison to the undiluted composition.

3. 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: macrogolglycerol esters of fatty acids, macrogolglycerol esters 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 wherein upon dilution with water the formulation forms a dispersion of polymorphous gel particles having a dimension of 0.2 to 500 μm.

4. A method or pharmaceutical formulation as claimed in any preceding claim, wherein the ratio of a : c and/or a : e is in the range 0.001 : 1 to 10 : 1

5. A formulation as claimed in claim 3, wherein component b) is selected from polyglycerol esters of fatty acids of formula (1)

$$CH_2OR\text{-}CHOR\text{-}CH_2O\text{-}[CH_2CHOR\text{-}CH_2O\text{-}]_NCH_2\text{-}CHOR\text{-}CH_2OR \quad (1)$$

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

6. A formulation as claimed in claim 5, wherein R' is $C_{16\text{ - }18}$ saturated or unsaturated alkyl.

7. A formulation as claimed in claim 6, wherein R is selected from the group consisting of oleates, linoleate stearate, linolate, myristate, laurate and mixtures thereof.

8. A formulation as claimed in claim 7, wherein component b) is selected from: polyglyceryl-10-esters of fatty acids.

9. A formulation as claimed in claims 3 to 8, wherein component c) is selected from polyglycerol esters of fatty acids and/or unsaturated fatty acids of formula (2).

$$CH_2OR\text{-}CHOR\text{-}CH_2O\text{-}[CH_2CHOR\text{-}CH_2O]_NCH_2\text{-}CHOR\text{-}CH_2OR \quad (2)$$

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

10. A formulation as claimed in claim 9, wherein R" is C_{16-18} saturated or unsaturated alkyl.

11. A formulation as claimed in claim 10, wherein R is selected from the group consisting of oleate, linoleate, stearate, isostearate, linolate, myristate, laurate and mixtures thereof.

12. A formulation as claimed in any of claims 2 to 11, wherein component c) is selected from: polyglyceryl-3-esters of oleic acid.

13. A formulation as claimed in any of claims 3 to 12, 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.

14. A formulation s claimed in claim 9, wherein component d) is macrogol glycol halogenated castor oil.

15. A formulation as claimed in any of claims 2 to 14, wherein component b) is selected from: polyglyceryl-10-esters of oleic acid; component c) is selected from polyglyceryl-3-esters of oleic acid; and component d) is macrogol (1760) glycerol hydrogenated castor oil.

16. A method or formulation as claimed in claim 2, 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.

17. A method or formulation as claimed in any preceding claims, 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.

18. A method or 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.

19. A method or 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.

20. A pharmaceutical dosage form comprising a gelatin capsule containing a formulation as claimed in any of claims 2 to 19.

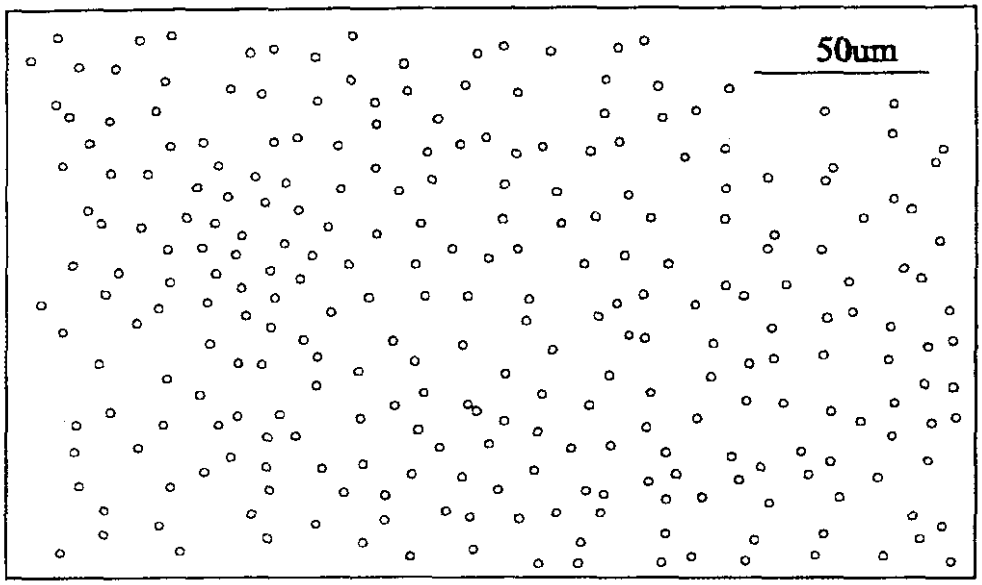

FIG. 1

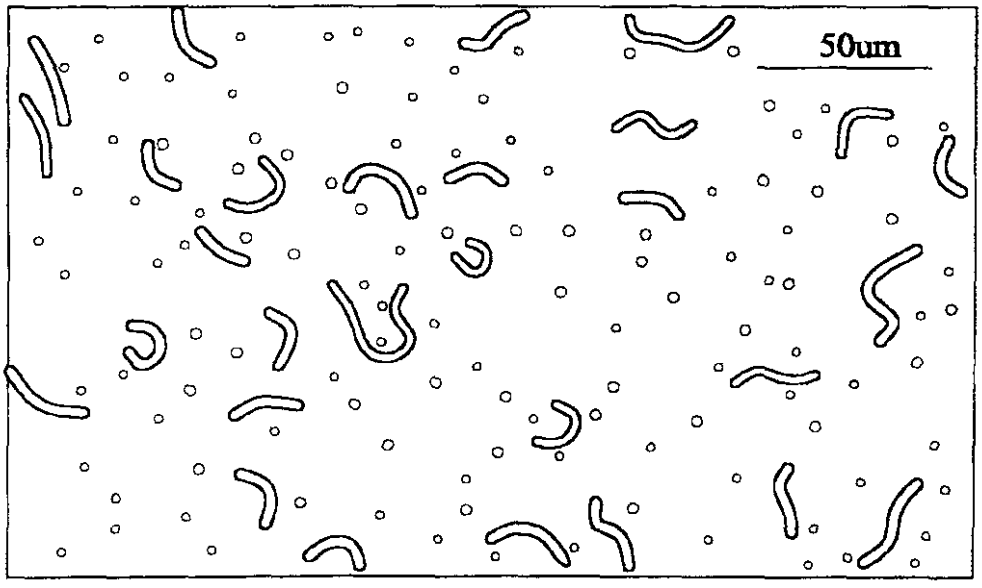

FIG. 2

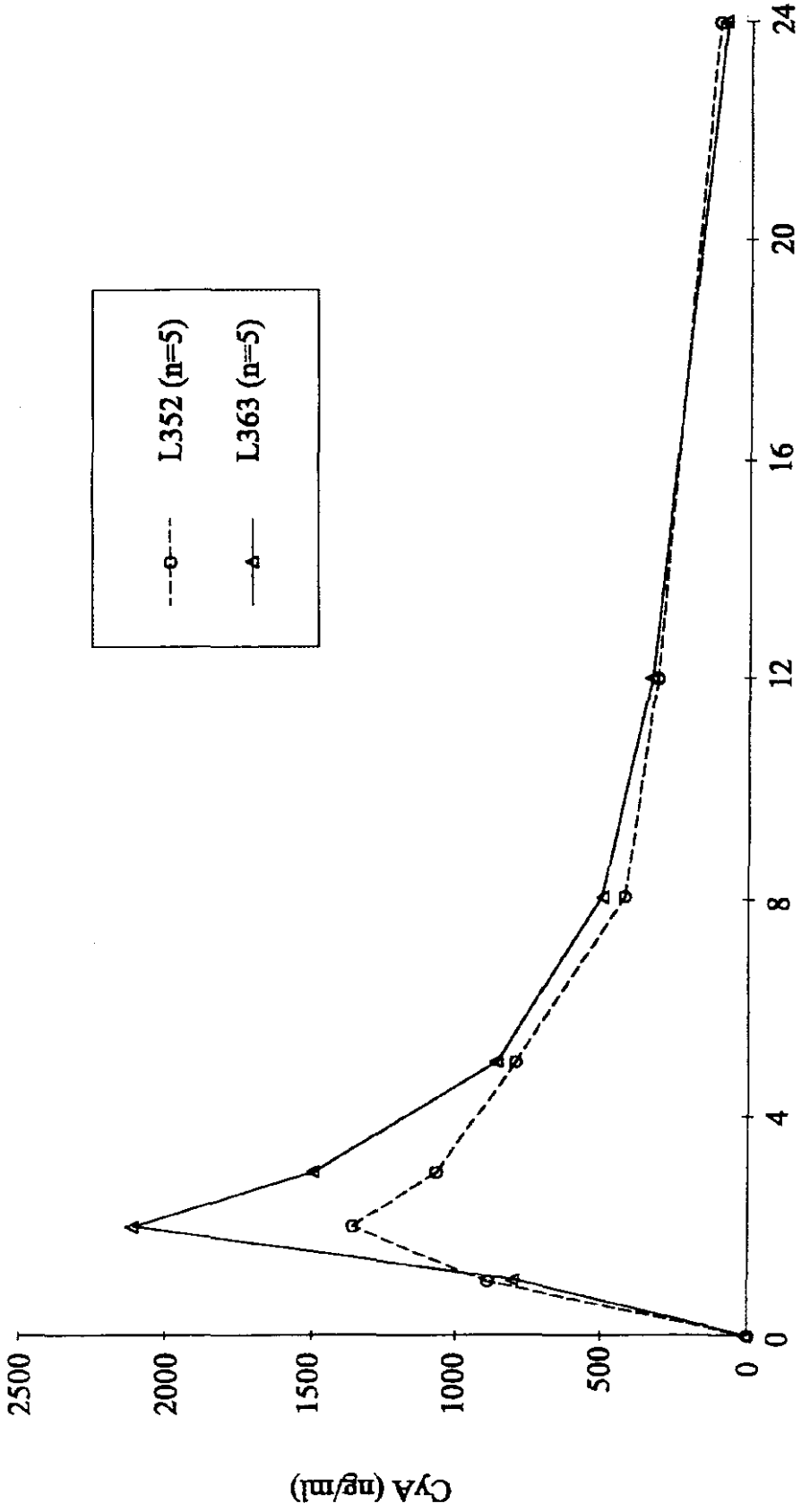
CyA (ng/ml)
2500
2000
1500
1000
500
0
0
4
8
12
16
20
24
time (h)
L352 (n=5)
L363 (n=5)

FIG. 3

Formation A

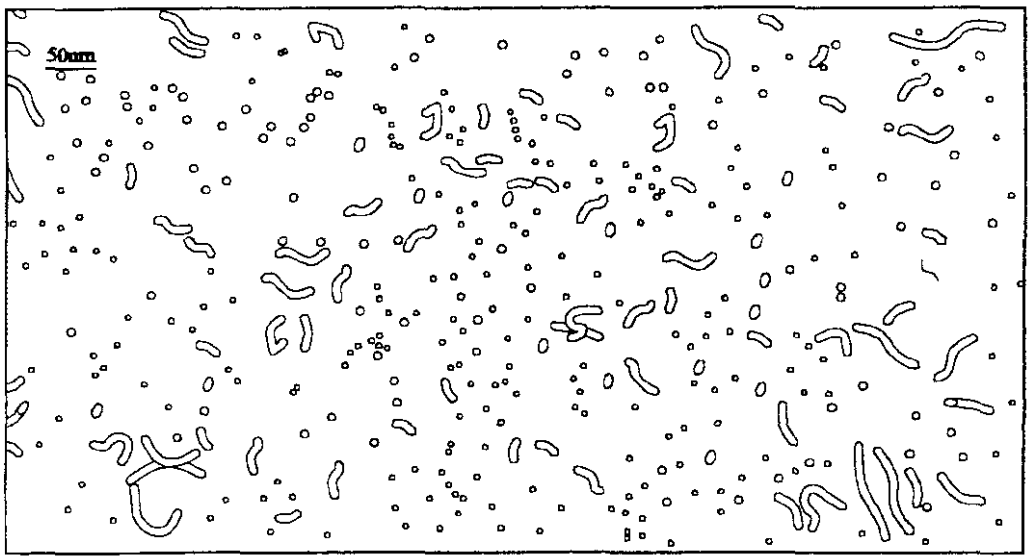

FIG. 4

Formation B

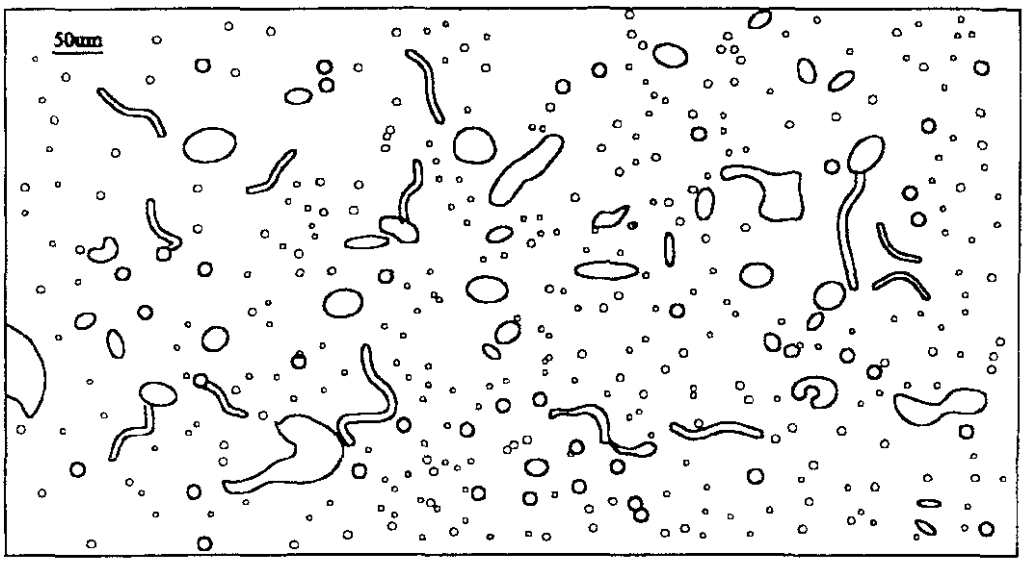

FIG. 5

Formation C

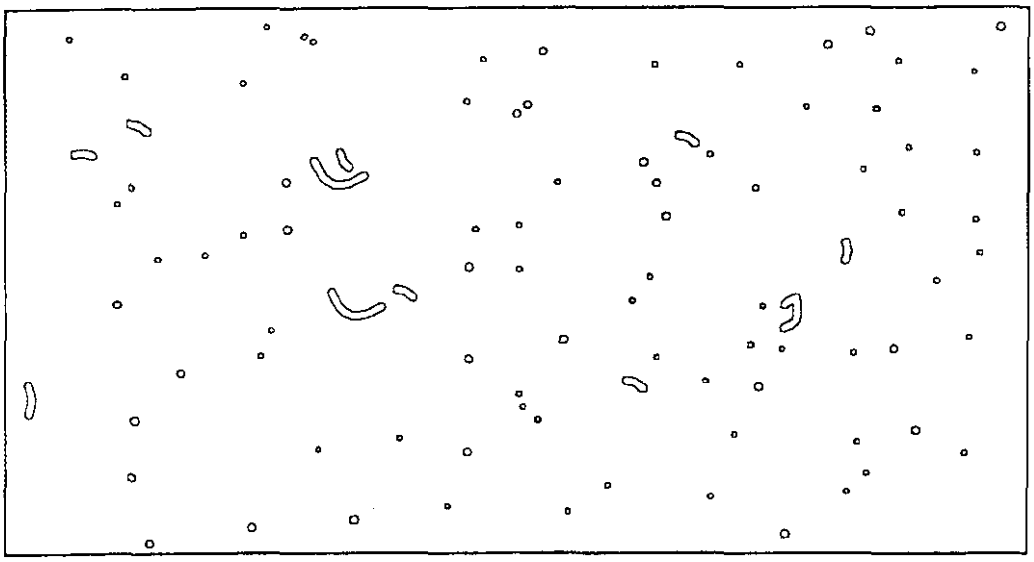

FIG. 6

Formation D

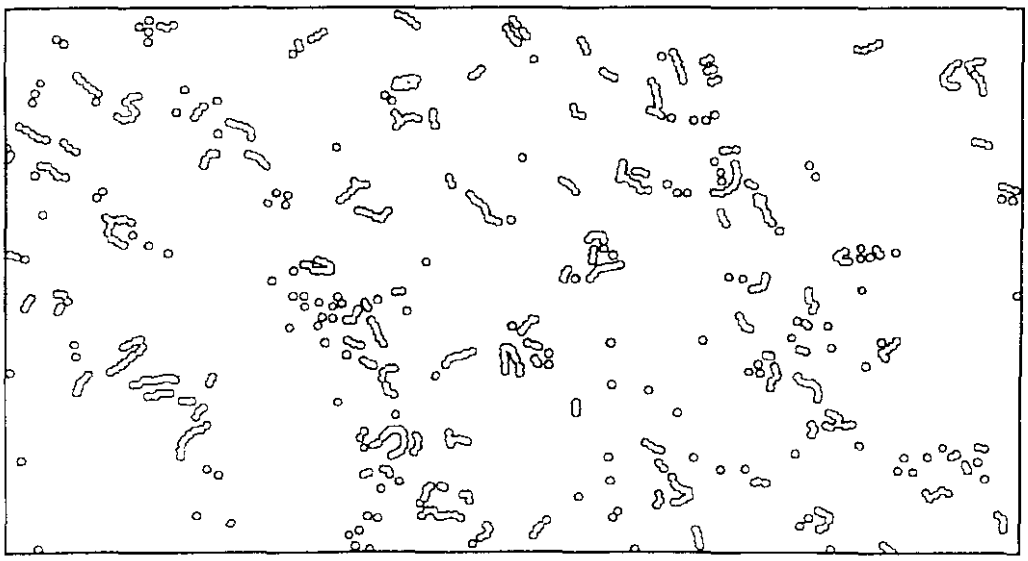

FIG. 7

Formation E

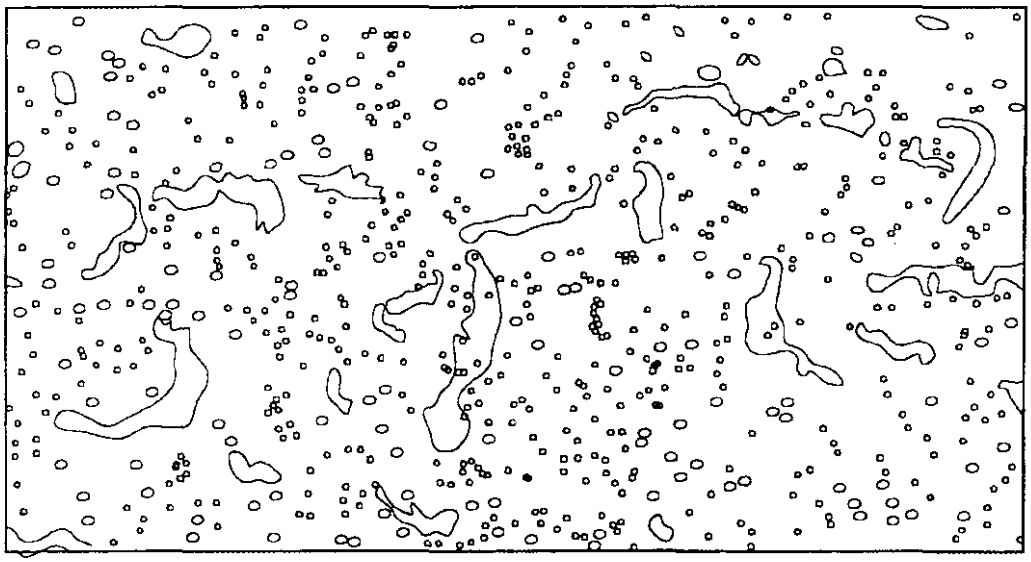

FIG. 8

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/GB 00/03161

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/14 A61K9/48 A61K9/127

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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 practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 10747 A (JEGOROV ALEXANDER ;GALENA AS (CZ); ANDRYSEK TOMAS (CZ); HUSEK ALES) 19 March 1998 (1998-03-19) cited in the application	1,2,4, 9-11, 18-20
A	page 1, paragraph 3 page 4, line 16 page 4, line 27 - last line page 5, line 18 - line 24 page 6, line 2 - line 10 page 6, line 22 - line 24 page 7, line 1 - line 6 page 8, last paragraph -page 9, line 24 page 11, paragraph 1 -page 12, last paragraph page 19, paragraph 1; examples 5,14 claims 1,3,5,8,9,11	3,5-8, 13-17

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"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.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Internat' Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 00002 A (CHONG KUN DANG CORP) 7 January 1999 (1999-01-07) page 2, line 3 - line 5 page 8, line 25 -page 9, line 15 page 15, line 22 -page 16, line 7 page 18, line 2 - line 12 page 19, line 6 - line 10 page 20, line 26 -page 21, line 16; claims 1,2,5,8,15-20,23,24; examples 7,10	1,2,4, 9-11,14, 18-20
X	WO 98 40051 A (ABBOTT LAB) 17 September 1998 (1998-09-17) page 2, line 26 - line 33 page 5, line 9 - line 17 page 6, line 1 - line 4 page 13, line 12 - line 14; claim 1; example 27; table 1	1,2,4, 9-11,14, 18-20

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[54]发明名称 用于口服或局部给药的药物组合物

[57]摘要

提高经口服或局部给药的药物制剂粘度的方法，其中包括合并以下物质的步骤：a)有效量的一种或多种疏水性活性组分；b)5－50%的一种或多种化合物，选自具有6－15个甘油单元的脂肪酸聚甘油酯；c)5－50%的一种或多种化合物，选自具有2－12个甘油单元的脂肪酸和/或不饱和脂肪酸聚甘油酯；d)5－50%的一种或多种化合物，选自甘油三酯聚乙二醇甘油酯、偏甘油酯或脂肪酸或脂肪酸聚乙二醇酯，其中组分b)与d)的比例为0.1：1－10：1；与未稀释的组合物相比，所述制剂用1：1体积的水稀释后其粘度至少增加5倍。

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1. 提高经口服或局部给药的药物制剂粘度的方法，其中包括合并以下物质的步骤:

a)有效量的一种或多种疏水性活性组分;

b)5-50%的一种或多种化合物，选自式(1)脂肪酸的聚甘油酯，

$$CH_2OR-CHOR-CH_2O-[CH_2CHOR-CH_2O-]_NCH_2-CHOR-CH_2OR \quad (1)$$

其中 n 为 4-13 的整数和 R 为 H 或 CO. R'，其中 R'为 C_{8-22} 饱和、不饱和或羟基化烷基，且至少有一个 R 不是氢;

c)5-50%的一种或多种化合物，选自式(2)脂肪酸和/或不饱和脂肪酸的聚甘油酯，

$$CH_2OR-CHOR-CH_2O-[CH_2CHOR-CH_2O]_NCH_2-CH_2OR \quad (2)$$

其中 n 为 0-10 的整数和 R = H 或 CO. R″，其中 R″为 C_{8-22} 饱和、不饱和或羟基化烷基，且至少有一个 R 不是氢;

d)5-50%的一种或多种化合物，选自甘油三酯聚乙二醇甘油酯，偏甘油酯或脂肪酸或脂肪酸的聚乙二醇酯，其中合成这些物质时反应的环氧乙烷的平均量为 50-150 摩尔，并且组分 b)与 d)的比例为 0.1: 1-10: 1;

其中上述百分比总和为 100%;

与未稀释的组合物相比，所述制剂用 1: 1 体积的水稀释后其粘度至少增加 5 倍。

2. 一种经口服或局部给药的药物制剂，其中包括:

a)有效量的一种或多种疏水性活性组分;

b)5-50%的一种或多种化合物，选自式(1)脂肪酸的聚甘油酯，

$$CH_2OR-CHOR-CH_2O-[CH_2CHOR-CH_2O-]_NCH_2-CHOR-CH_2OR \quad (1)$$

其中 n 为 4-13 的整数和 R 为 H 或 CO. R'，其中 R'为 C_{8-22} 饱和、不饱和或羟基化烷基，且至少有一个 R 不是氢;

c)5-50%的一种或多种化合物，选自式(2)脂肪酸和/或不饱和脂肪酸的聚甘油酯，

$$CH_2OR-CHOR-CH_2O-[CH_2CHOR-CH_2O]_NCH_2-CH_2OR \quad (2)$$

其中 n 为 0-10 的整数和 R = H 或 CO. R″，其中 R″为 $C_{8\ 22}$饱和、不饱和或羟基化烷基，且至少有一个 R 不是氢;

d)5-50%的一种或多种化合物，选自甘油三酯甘油三酯聚乙二醇甘油酯，偏甘油酯或脂肪酸或脂肪酸的聚乙二醇酯，其中合成这些物质时反应的环氧乙烷的平均量为 50-150 摩尔，并且组分 b)与 d)的比例为 0.1:1-10: 1;

其中上述百分比总和为 100%;

与未稀释的组合物相比，所述制剂用 1: 1 体积的水稀释后其粘度至少增加 5 倍。

3. 一种经口服或局部给药的药物制剂，其中包括:

a)0.1-30.0 % 的一种或多种疏水性活性组分;

b)0.1-60.0 %的一种或多种凝胶化剂 ，包括聚甘油的脂肪酸酯;

c)0.1-60.0 %的一种或多种胶凝化物质，选自脂肪酸和/或不饱和脂肪醇的聚甘油酯;

d)1.0-60 %的一种或多种共胶凝剂，选自: 脂肪酸的聚乙二醇甘油酯，植物油的聚乙二醇甘油酯，脂肪酸的聚乙二醇酯，一-、二-和三酰甘油的一-和二-聚乙二醇酯;

e) 5.0-30 % 的一种或多种 C_2-C_4 醇;

其中上述百分比的总和为 100%;

所述制剂用水稀释后可形成大小为 0.2-500μm 多形性凝胶微粒的分散体。

4. 如前述任一权利要求的方法或药物制剂，其中 a: c 和/或 a: e 的比例为 0.001:1-10: 1。

5. 如权利要求 3 的制剂，其中组分 b)选自式(1)脂肪酸的聚甘油酯:

$$CH_2OR-CHOR-CH_2O-[CH_2CHOR-CH_2O-]_NCH_2-CHOR-CH_2OR \quad (1)$$

其中 n 为 4-13 的整数和 R 为 H 或 CO. R'，其中 R'为 C_{8-22}饱和、不饱和或羟基化烷基，且至少有一个 R 不是氢。

6. 如权利要求 5 的制剂，其中 R'为 C_{16-18}的饱和或不饱和烷基。

7. 如权利要求 6 的制剂，其中 R 选自油酸酯、亚油酸硬脂酸酯、亚油酸酯、豆蔻酸酯、月桂酸酯及其混合物。

8. 如权利要求 7 的制剂，其中组分 b)选自脂肪酸的聚甘油-10-酯。

9. 如权利要求 3-8 的制剂，其中组分 c)选自式(2)脂肪酸和/或不饱和脂肪酸的聚甘油酯:

$$CH_2OR-CHOR-CH_2O-[CH_2CHOR-CH_2O]_NCH_2-CH_2OR \quad (2)$$

其中 n 为 0-10 的整数和 R = H 或 CO. R″，其中 R″为 C_{8-22} 饱和、不饱和或羟基化烷基，且至少有一个 R 不是氢。

10. 如权利要求 9 的制剂，其中 R″为 C_{16-18} 饱和或不饱和烷基。

11. 如权利要求 10 的制剂，其中 R 选自油酸酯、亚油酸硬脂酸酯、亚油酸酯、豆蔻酸酯、月桂酸酯及其混合物。

12. 如权利要求 2-11 之一的制剂，其中组分 c)选自油酸的聚甘油-3-酯。

13. 如权利要求 3-12 之一的制剂，其中组分 d)选自甘油三酯甘油三酯聚乙二醇甘油酯，偏甘油酯或脂肪酸或脂肪酸的聚乙二醇酯，其中合成这些物质时反应的环氧乙烷的平均量为 50-150 摩尔，并且组分 b)与 d)的比例为 0.1: 1-10: 1。

14. 如权利要求 9 的制剂，其中组分 d)为聚乙二醇卤化蓖麻油。

15. 如权利要求 2-14 之一的制剂，其中组分 b)选自油酸的聚甘油-10-酯;组分 c)选自油酸的聚甘油-3-酯;和组分 d)选自聚乙二醇 (1760) 甘油氢化蓖麻油。

16. 如权利要求 2 的方法或制剂，其中组分 a)选自环孢菌素，尤其是环孢菌素 A，环孢菌素 D 或环孢菌素 G，其中 a: c+e 的比例为 1.001:1-1.5: 1.

17. 如前述任一权利要求的方法或制剂，其中组分 a)选自紫杉烷，尤其是紫杉特尔或紫杉醇，其中 a: c+e 的比例为 0.001:1-1.5: 1。

18. 如前述任一权利要求的方法或制剂，其中组分 a)包括至少一种选自环孢菌素的物质和至少一种选自紫杉烷的物质。

19. 如前述任一权利要求的方法或制剂，还包括用于改善制剂的物

理、化学、微生物稳定性、感官和加工性质的赋形剂。

20. 一种含有如权利要求 2-19 之一制剂的明胶胶囊剂。

用于口服或局部给药的药物组合物

本发明涉及药物制剂，其中包括低水溶性活性组分，例如治疗活性的环孢菌素、紫杉烷二萜类(taxoides)和紫杉烷。

环孢菌素为聚-N-甲基化单环十一肽，它是某些放线(fibrous)真菌、尤其是普通 Tolypocladium 和柱孢的次生代谢物产物。采用部分合成或特殊发酵方法可制得某些具有治疗应用价值的环孢菌素。

环孢菌素(环孢菌素 A)是第一个对淋巴细胞、尤其是 T 淋巴细胞具有选择性免疫抑制作用的天然物质。在很大程度上，它对免疫系统其他细胞的功能也有影响。

在器官移植或骨髓移植时，可全身给予环孢菌素进行治疗。环孢菌素可用于治疗多种具有炎性病因的自身免疫疾病并可用作抗寄生虫剂。

某些没有免疫抑制活性的环孢菌素对HIV-1病毒的复制有抑制作用，这可用于治疗和预防 AIDS 或与 AIDS 相关的综合征。环孢菌素类还包括可影响癌细胞对细胞抑制剂交叉抗药性的化学调节剂。

环孢菌素的生物利用度受其自身的特定性质影响，一方面还受组合物和特定剂型的性能影响。环孢菌素的高度亲脂性对含环孢菌素治疗性组合物的制备有重要影响。

典型地，这些活性物质的水溶解度不超过 25μg/ml，该值比机体所需的正常吸收水平约低 100 倍。环孢菌素在正-辛醇/水系统中的分配系数 P 证实其具有显著的亲脂性。有报道环孢菌素的 log P =2.08- 2.99。

为了使环孢菌素制剂达到可接受的生物利用度，可采用粒子形态的分散体系统，其特征在于包括亲水相、疏水相和表面活性组分。所得分散体为典型的乳剂或光学透明的微乳。市售的口服用组合物如 GB-A2015339、GB-A-2222770、GB-A-2270842 和 GB-A-2278780 中描述的商品 Sandimunn®、Sandimunn®-Neoral、Consupren®、Implanta® 和 Imusporin®。

也可对在先的系统加以改进，例如除掉亲水基并用脂肪酸的多元醇偏酯取代，其中多元醇如丙二醇、甘油或山梨醇，可参见 GB-A-2228198 中的描述。

DE-A-4322826 公开了一种用于低水溶性药物的载体系统，所述组合物含有脂肪酸聚甘油酯作为 HLB 值高于 10 的非离子表面活性剂的辅助表面活性剂，其中以三酰甘油为亲脂性组分。

GB-A-2248615 公开了含有环孢菌素的典型的 O/W 型微乳预浓缩物，所述制剂中的载体包括丙二醇、一-,二-和三-甘油酸酯混合物和亲水性表面活性剂。

按照生物药剂学分类，环孢菌素菌素属于第 IV 类，即其水溶性和生物利用度均较低 (G L Amidon，药物的生物药剂学分类和国际药物条例，Capsgel Library，Bornem 1996 年，15-30 页)。

紫杉烷二萜类化合物是从紫杉的某些株中分离出来的一类天然物质。紫杉烷二萜类化合物可影响细胞有丝分裂而具有抗肿瘤效力。它们是二萜类物质，为具有 4 元环氧丙烷(oxitanic)环的紫杉烷环，其 C_{13} 上具有酯侧链。天然的紫杉醇及其半合成衍生物紫杉特尔(docetaxel)可用于肿瘤的治疗。紫杉烷的水溶性比环孢菌素低。制备后紫杉醇的水溶解度约为 5μg/ml，然而标准制备的紫杉醇水合物，其平衡浓度的数量级较低(0.3-0.6μg/ml)。

含聚甘油酰基酯的组合物在专利文献已属已知，例如 WO98/05309。该国际申请公开的药物组合物包括活性组分环孢菌素和载体，所述载体由一种或多种脂肪酸的二-至十-甘油偏酯、偏五甘油-至十五-甘油酰基酯构成。使用上述组合物，本领域技术人员可制备乳剂型分散体组合物，稀释后的平均粒径约为 1-2μm。其粒子呈图 1 所示的球形。然而，如何达到较高的生物利用度依然是一个问题。

同样地，WO97/26003 也公开了聚甘油酰基酯的应用。除了上述聚甘油酯，所述载体还包括甘油一酰基酯和任选的 anhydrohexosdimethyl 衍生物和/或聚乙烯甘油。该制剂中还含有其他物质以提高载体的稳定性和尤其是适于局部应用的 lipoamino acids。这些组合物提供了含有球形粒

子的微分散系统。

其他系统如微乳也应用脂肪酸聚甘油酯。在 EP-A-670715 或 EP-A-334777 中，药物或化妆品微乳或可形成微乳的组合物采用了脂肪酸聚甘油酯。如 Lachman 等在“工业药剂学理论与实践”，Lea & Febiger，费城，1970 年，463 页所定义的，微乳是 O/W 或 W/O 型的透明分散体，其分散粒子的粒径约为 100-600 埃。微乳中的分散粒子由分散介质中分散相的纳米粒或胶束聚集体所构成，其中分散粒子多为球形。

同样地，CZ-A-283516 公开了与水相接触可形成亲液液晶的载体，该载体的一个组分为聚甘油酰基酯。按照该说明书和其他专利(例如 EP-A-314689 或 EP-A126751)，以亲液液晶系统为基础的药物组合物，对于那些含有可溶于所述系统的和/或疏水性生物活性物质的制剂是适宜和有利的。另外，进入胃肠道后在体内形成亲液液晶相的能力，与疏水性药物组合物的高生物利用度也有关系。

按照 USP23 关于环孢菌素改良胶囊剂的描述(Pharmaceopeial Forum，24 卷，3 期，1998 年，6155 页)，服用的微乳进入胃肠道后，形成预浓缩物形式的药物组合物分散体，可提高环孢菌素的生物利用度。该方案指出，应检验这种组合物稀释后是否形成了可在分散相中提供平均粒径为 50 nm 粒子的所述分散体。几个专利均对这一问题进行了讨论，但是均未教导使用高级脂肪酸的聚甘油酯。

首先，本发明涉及提高经口服或局部给药的药物制剂粘度的方法，其中包括合并以下物质的步骤:

a)有效量的一种或多种疏水性活性组分;

b)5-50%的一种或多种化合物，选自式(1)脂肪酸的聚甘油酯，

$$CH_2OR-CHOR-CH_2O-[CH_2CHOR-CH_2O-]_NCH_2-CHOR-CH_2OR \quad (1)$$

其中 n 为 4-13 的整数和 R 为 H 或 CO. R'，其中 R'为 C_{8-22} 饱和、不饱和或羟基化烷基，且至少有一个 R 不是氢;

c)5-50%的一种或多种化合物，选自式(2)脂肪酸和/或不饱和脂肪酸的聚甘油酯，

$$CH_2OR-CHOR-CH_2O-[CH_2CHOR-CH_2O]_NCH_2-CH_2OR \quad (2)$$

其中 n 为 0-10 的整数和 R = H 或 CO. R″，其中 R″为 C_{8-22} 饱和、不饱和或羟基化烷基，且至少有一个 R 不是氢;

d)5-50%的一种或多种化合物，选自甘油三酯聚乙二醇酯，偏甘油酯或脂肪酸或脂肪酸的聚乙二醇酯，其中合成这些物质时反应的环氧乙烷的平均量为 50-150 摩尔，并且组分 b)与 d)的比例为 0.1：1-10：1;

其中上述百分比总和为 100%;

与未稀释的组合物相比，所述制剂用 1：1 体积的水稀释后其粘度至少增加 5 倍。

在一个优选制剂中，采用了最小量的赋形剂。这对生产成本和管理是有利的。优选采用 b)-e)的单一化合物。

另一方面，本发明提供经口服或局部给药的药物制剂，其中包括:

a)有效量的一种或多种疏水性活性组分;

b)5-50%的一种或多种化合物，选自式(1)脂肪酸的聚甘油酯，

$$CH_2OR-CHOR-CH_2O-[CH_2CHOR-CH_2O-]_NCH_2-CHOR-CH_2OR \quad (1)$$

其中 n 为 4-13 的整数和 R 为 H 或 CO.R'，其中 R'为 C_{8-22} 饱和、不饱和或羟基化烷基，且至少有一个 R 不是氢;

c)5-50%的一种或多种化合物，选自式(2)脂肪酸和/或不饱和脂肪酸的聚甘油酯，

$$CH_2OR-CHOR-CH_2O-[CH_2CHOR-CH_2O]_NCH_2-CH_2OR \quad (2)$$

其中 n 为 0-10 的整数和 R = H 或 CO. R″，其中 R″为 C_{8-22} 饱和、不饱和或羟基化烷基，且至少有一个 R 不是氢;

d)5-50%的一种或多种化合物，选自甘油三酯聚乙二醇酯，偏甘油酯或脂肪酸或脂肪酸的聚乙二醇酯，其中合成这些物质时反应的环氧乙烷的平均量为 50-150 摩尔，并且组分 b)与 d)的比例为 0.1：1-10：1;

其中上述百分比总和为 100%;

与未稀释的组合物相比，所述制剂用 1：1（体积）的水稀释后其粘度至少增加 5 倍。

本发明也提供采用上述制剂在制备适于 IV 类药物的给药剂型中的用途。

令人惊奇地发现，口服既非液晶又非微乳的系统后，也能使环孢菌素和紫杉烷具有较高的生物利用度。同时还发现，本发明并不形成乳剂类型的分散体。出人意料地发现，混合不同相时所自发或几乎自发形成的粒子是非球形的。另外，即使所形成粒子的粘度急剧增加，也未发现分子的各向异性现象。上述现象表明，本发明是凝胶样特性粒子在水中的分散体 。

在本说明书中，凝胶样特性粒子可理解为在分散体中的其稳定形状或构象是非球形的。非球形粒子至少具有两个不同的垂直径(perpendicular dimension)。

在本说明书中，凝胶乳(GEM)可理解为在水相中表现出凝胶样特性的粒子的分散体。

凝胶乳的预浓缩物(PRO-GEM)，可理解为经稀释或与水相接触后可形成凝胶乳的组合物。

亲水性凝胶化剂(gelator，可引起凝胶化的试剂)与亲脂性胶凝剂相反应可形成凝胶粒子。该组合物中含有某些组分，它参与微粒状凝胶结构的形成，并促进在水性介质中自动形成分散体。其中还可含有抗氧剂和微生物稳定剂、掩味剂、调节外观或促进组合物中活性组分溶解的组分。组合物中还可含有调节粘度的组分。

本发明药物组合物可用于制备生物药剂学分类为 IV 型的活性物质的制剂。这对于 II 和 III 型活性物质也有利。

另一方面，本发明还提供经口服或局部给药的药物制剂，其中包括；

a) 0.1-30%的一种或多种疏水性活性组分；

b) 0.1-60%的一种或多种化合物，选自聚甘油脂肪酸酯；

c) 0.1-60%的一种或多种凝胶化物质，选自脂肪酸和/或不饱和脂肪醇的聚甘油酯；

d)1.0-60 %的一种或多种辅助凝胶化物质，选自脂肪酸的聚乙二醇甘油酯、植物油的聚乙二醇甘油酯、脂肪酸的聚乙二醇酯、一-、二-和三-酰基甘油的一-和二-聚乙二醇酯；

e)5-30%的一种或多种 C_2-C_4 醇；

其中上述百分比总和为100%;

和所述制剂用水稀释后可形成大小为 0.2-500μm 的多形性(polymorphous)分散体。

除非另有所指，本发明说明书中的百分率和含量均以重量表示。

在一个优选制剂中，a：c和/或a：e的比例为0.001:1-10：1。

与粒子通常为球形的液-液乳剂不同的是，本发明大部分、例如半数以上的粒子为非球形，例如椭圆形、柱形或线形。优选50%以上的粒子为长度两倍于宽度的细长型。本发明制剂粒子的中间大小为1-100μm、优选5-20μm。其中可含有大小高达10μm或更大例如20-50μm的个别粒子。

采用混合可制得本发明制剂，例如体外手工搅拌或振荡。服用前与水、奶或其他饮料混合可形成液体制剂。高速搅拌虽然少用，但特别适于制备较小粒径例如约200 nm的制剂。

置于例如胶囊剂剂型中的凝胶乳预浓缩物，在胃肠道中可与水相混合。胃肠道中足够的剪切力可形成本发明多形性粒子。

本发明药物组合物的特征在于：与未稀释的组合物相比，所述制剂用约1：5-1：1：100(组合物：水相)的水相稀释后，可形成粒子平均粒径0.2-500μm的分散体。该分散体即为凝胶乳(GEM)。

凝胶乳预浓缩物(PRO-GEM)可以预浓缩物形式或以单剂量剂型如胶囊剂形式给药。

组分 a)包括在常规制剂中水溶性和生物利用度较低的生物活性组分。按照这种生物药剂学分类，这些物质为2和4类低水溶性物质。这些物质包括：免疫抑制剂、抗肿瘤化学治疗剂、影响糖类代谢的物质、肽和类脂、影响钙通道的试剂、非甾类antiflogistics和维生素。

免疫抑制剂为疏水性化合物，包括N-甲基化的11环肽。优选采用环孢菌素，尤其是环孢菌素(即环孢菌素或环孢菌素A)、$[Nva]^2$-环孢菌素(环孢菌素G)和$[Melle]^4$-环孢菌素。也可采用非免疫抑制性环孢菌素，例如$[3'ketoMBmt]^1$-$[Val]^2$-环孢菌素。不同药典对这些混合物名称的拼法不同。在本发明说明书中，所述化合物及其衍生物指环孢菌素。也可

采用其他非免疫抑制剂，例如革兰氏阳性链霉菌产生的大环内酯(雷帕霉素、tacrolimus)及其衍生物。

抗肿瘤的化学治疗剂包括紫杉烷，优选为紫杉特尔或紫杉醇。

适于本发明的其他生物活性组分选自：双氯芬酸、布洛芬、硝苯地平、曲安奈德、生育酚等。本发明组合物可含有 30% 的活性组分。

凝胶化剂组分 b)选自选自式(1)脂肪酸的聚甘油酯:

$$CH_2OR-CHOR-CH_2O-[CH_2CHOR-CH_2O-]_NCH_2-CHOR-CH_2OR \quad (1)$$

其中 n 为 4-13 的整数和 R 为 H 或 CO. R^1，其中 R^1 为 C_{8-22} 饱和、不饱和或羟基化烷基，且至少有一个 R 不是氢。

组分 b)优选为中等或长链脂肪酸的聚甘油酯和偏酯，优选其 HLB 值低于 10。

一般，采用相应的脂肪酸对聚甘油进行偏-或完全酯化作用，或对具有聚甘油的植物油进行反式酯化，可制得聚甘油脂肪酸酯。每种聚甘油单酯间用其皂化数目区别。羟基数目是聚合的程度的最佳指示。HLB 值高于 10 的聚甘油酯为亲水性的。HLB 值低于 10 聚甘油酯为亲脂性的。适宜的组分 b)包括:

名称(INCI)		
聚甘油-6--一月桂酸酯	6	14.5
聚甘油-10--一月桂酸酯	10	15.5
聚甘油-10--一豆蔻酸酯	10	14.0
聚甘油-10--一硬脂酸酯	10	12.0
聚甘油-10---二油酸酯	10	11.0
聚甘油-10-二异硬脂酸酯	10	10.0
聚甘油-6--一豆蔻酸酯	6	11.0
聚甘油-8--一油酸酯	8	11.0
聚甘油-10-油酸酯	10	12.0

上述聚甘油可购自 Nikko 化学公司的 NIKKOL®、Durkee 食品公司的

SANTONE®和 Th. Goldschmidt 公司的 ISOLAN®或 Abitec 公司的 CAPROL®。市售聚甘油酯主要含有上述列举酯的混合物或具有相同特性如羟基值的酯的混合物。

本发明所用的聚甘油酯组分 b)和 c)优选符合下述纯度标准:

最高酸值= 6; 最高重金属含量=10 ppm; 最高水含量=2%; 脂肪酸钠盐的最高含量= 2% (如硬脂酸钠计盐); 最高总灰分= 1 %。

凝胶化剂 b)优选选自 C_{12-22}饱和、不饱和或羟基化脂肪酸的聚甘油酯,其中脂肪酸选自豆蔻酸酯、月桂酸酯、油酸酯、硬脂酸酯、亚油酸酯和亚麻酸酯(linolate)。尤其优选为 C_{16-22}的酸。最优选的 C_{16-18}为硬脂酸酯、油酸酯、月桂酸酯、亚油酸酯和亚麻酸酯。也可采用其混合物。最优选为油酸酯或其混合物。

其中 N = 1 的上述酸的三甘油基酯特别适宜、尤其适于环孢菌素制剂。

胶凝化物质组分 c)选自式(2)脂肪酸和/或不饱和脂肪醇的聚甘油酯:

$$CH_2OR-CHOR-CH_2O-[CH_2CHOR-CH_2O]_NCH_2-CH_2OR \quad (2)$$

其中 n 为 0-10 的整数和 R = H 或 CO. R″, 其中 R″为 C_{8-22}饱和、不饱和或羟基化烷基, 且至少有一个 R 不是氢。

组分 c)优选为脂肪酸和/或脂肪醇的聚甘油酯和偏酯。优选组分 c)的 HLB 值低于 9。适宜的组分 c) 包括:

名称(INCI)	甘油单位数目	HLB 值
聚甘油-3-一油酸酯	3	6.5
聚甘油-6-二油酸酯	6	8.5
聚甘油-10-四油酸酯	10	6.2
聚甘油-10-十油酸酯	10	3.5
聚甘油-2-一硬脂酸酯	2	5.0
聚甘油-10-戊硬脂酸酯	10	3.5

上述聚甘油酯可购自 Nikko 化学公司的 NIKKOL®; 或 Abitec 公司 CAPROL®。

本发明组分 c)优选包括胶凝化物质，它选自脂肪酸和/或不饱和脂肪醇、尤其是 C_{8-22} 不饱脂肪醇的聚甘油酯。优选采用符合以下纯度标准的示例油醇(9-十八烯-1-醇):

分子量=268,49; 折光率=1,458-1,460; 酸值<1; 羟基数= 205-215; 碘值= 85-95。

优选胶凝化组分 c)选自 C_{8-22} 饱和、不饱和或羟基化脂肪酸的聚甘油酯，其中脂肪酸选自豆蔻酸酯、月桂酸酯、油酸酯、硬脂酸酯、亚油酸酯和亚麻酸酯。尤其优选为 C_{8-18}、更优选为 C_{8-16} 酸，包括月桂酸酯、油酸酯和豆蔻酸酯。也可采用其混合物。最优选为油酸酯。

其中 N =8 的上述酸的聚甘油-10-酯特别适宜，尤其适于环孢菌素制剂。

辅助凝胶化组分 d)选自脂肪酸的聚乙二醇甘油酯，包括 C_{8-22} 饱和、或不饱脂肪酸的聚乙二醇甘油酯。

尤其优选为聚乙二醇甘油的植物油例如氢化或非氢化蓖麻油、杏仁油或玉米油酯。采用不同量的环氧乙烷和适宜类型的油类，于已知条件下可制得上述物质。尤其优选采用参与反应的环氧乙烷摩尔数(1 + m + n + x + y + Z)和 HLB 值，对下述物质进行特性描述。

	(1+m+n+x+y+z)	HLB 值
聚乙二醇(1540)蓖麻油甘油酯	35	12-14
聚乙二醇(1760)氢化蓖麻油甘油酯	40	12.5-16
聚乙二醇(2200)氢化蓖麻油甘油酯	50	13.5
聚乙二醇(2640)氢化蓖麻油甘油酯	60	14.5
聚乙二醇(3520)氢化蓖麻油甘油	80	15

酯		
聚乙二醇(4400)氢化蓖麻油甘油酯	100	16.5
聚乙二醇(2640)杏仁油甘油酯	60	15
聚乙二醇(2640)玉米油甘油酯	60	15

上述物质的物理和化学参数为:

酸值≤2; 羟基数= 40-60; 碘值< 1*; 皂化值= 40-70; 含水量< 3%; (*- 聚乙二醇(1540)蓖麻油甘油酯= 28-32)。

上述物质为市售产品如 Cremophor®、Nikkol®、Simulsol®、Mapeg®、Crovol®。

也优选采用一-、二-和三酰甘油的一-和二-聚乙二醇酯混合物, 如 Gelucire®, 尤其是 Gelucire® 50/13 和 44/14。优选其物化参数为:

酸值< 2,00; 皂化值= 65-95; 碘值<2; 羟基数=36-56; 过氧化值< 6; 碱性杂质<80 ppm; 游离甘油< 3,00 %。

优选用作化合物 d)的其他组合物为脂肪酸的聚乙二醇酯, 例如聚乙二醇 (660)-12-羟硬脂酸酯, 其商品名为 Solutol®HS 15, 其酸值< 1; 含水量<0.5%; 皂化值= 53 -63 和羟基数= 90-110。

组合物中组分 d)的含量通常为 1-60 %, 优选为 5-50 %和最优选为 15-50%和最优选为 15-40 %。

组分 e)选自 C_2-C_4 链烷醇, 优选为药典标准的乙醇。其他链烷醇包括丙烯醇和丁烯醇(buterol)的异构体。也可采用混合物。局部施用时优选采用丙基-2-醇或 2-甲基-1-丙醇。

适用于本发明组合物的其他赋形剂包括: 对制剂的物化和微生物稳定性(例如抗氧剂, 抗菌添加剂如生育酚、尼泊金甲酯)、感官性能(例如含天然或类似天然芳香的矫味剂)或物理加工性质(例如粘度或熔点)有影响的物质。可选自水或其他药用溶剂、选自如纤维素、壳聚糖、藻酸盐或 polycarbophile 等衍生物的亲水胶体。

含凝胶预浓缩物的组合物, 其特征在于: 当施用到水性介质后可分

散成具有凝胶特性的颗粒，所述颗粒主要为不规则形状的粒子。 该组合物的较高生物利用度与其生物粘附性有关。其中的颗粒由于具有双亲性而不易聚集合并，可均匀地分散于水性介质中。与亲脂性表面接触时，所述颗粒借助于其粘度和粘合力而富集在表面上，可提供足够的浓度梯度使药物透过膜。

结合下述附图，通过实施例对本发明作进一步的非限定描述：

图 1 为 WO98/05309 分散体的显微照片；

图 2 为本发明分散体的显微照片；

图 3 为实施例 6 中环孢菌素的血药浓度曲线；和

图 4-8 为本发明其他分散体的显微照片

实施例 1

经口服或局部施用的含环孢霉素溶液

采用了下述组分。

a)	环孢菌素 A	3600 g
b)	聚甘油-10----二油酸酯	7200 g
c)	油醇	7200 g
d)	聚乙二醇(1760)氢化蓖麻油甘油酯	14400 g
e)	乙醇	4000 g
f)	D-α-生育酚	180 g

将组分 a)、e)和 c)混合。混合物匀化至活性组分溶解。然后，加入组分 b)、d)和其他辅剂。完全匀化后，于惰性气氛下，用孔隙率为 0.2-5.0 μm 的疏水膜 GVHP(Millipore)，将所得溶液过滤到不透气容器中。使用时，可在惰性气氛下将滤液装入配有不透气塞子的 50 ml 瓶中。

实施例 2

细长形0号硬明胶胶囊

采用了下述组分。

a)	环孢菌素A	50.0 mg
b)	聚甘油-10--一油酸酯	100.0 mg
c)	聚甘油-3--一油酸酯	15.0 mg
d)	聚乙二醇(2640)氢化蓖麻油甘油酯	140.0 mg
e)	乙醇	80.0 mg

按实施例1方法，制备硬明胶胶囊填充物，然后填入“EO(细长行0号)”硬明胶胶囊中。

实施例3

经口服施用的含环孢霉素溶液

采用了下述组分。

a)	环孢菌素	5.00 g
b)	聚甘油(10)油酸酯	9.50 g
c)	聚甘油(3)油酸酯	15.50 g
d)	POE(40)氢化蓖麻油（聚乙二醇(1760)氢化蓖麻油甘油酯）	14.00 g
e)	无水乙醇	6.00 g

按实施例1方法，将组分混合、匀化至活性组分溶解，过滤后装入配有不透气塞子的50 ml瓶中，提供剂量100 mg/ml的口服溶液。

实施例4

软明胶胶囊

采用了下述组分.

a)	环孢菌素	100,00mg
b)	聚甘油(10)油酸酯	210,00mg
c)	聚甘油(3)油酸酯	350,00mg
d)	POE(40)氢化蓖麻油	315,00mg
e)	乙醇	135,00mg

按实施例 1 方法，制备软明胶胶囊填充物。混合净化水、甘油、山梨醇和明胶，制备明胶胶囊。均化溶液，加入着色剂，按常规方法制得 100 mg 剂量的胶囊剂。

实施例 5

长圆形 20 号软明胶胶囊

采用了下述组分。

a)	环孢菌素 A	100.0mg
b)	聚甘油-6--月桂酸酯	120.0mg
c)	聚甘油-10-四油酸酯	410.0 mg
d)	Gelucire 50/13	300.0mg
e)	乙醇	170.0mg

按实施例 1 方法，制备软明胶胶囊填充物。将填充物过滤到过配有不透气塞子的 20 升不锈钢容器中。填充物的过滤及包囊操作应在惰性气氛下进行。采用标准型明胶混合物，用常规方法包囊。

实施例 6

3 号硬 HPMC 胶囊(Shionogi Qualicaps)

采用了下述组分。

a)	环孢菌素 A	25.0mg
b)	聚甘油-10-豆蔻酸酯	50.0mg
c)	聚甘油-10-戊硬脂酸酯	70.0 mg
d)	聚乙二醇(2640)杏仁油甘油酯	75.0mg
e)	乙醇	30.0mg

将组分 a)、e)和 b)混合。混合物加热到 40-50℃并均化至组分 a)溶解。然后加入组分 d)。最后加入组分 c)。混合物连续混合。制备过程的温度不要超过 60℃。至所有组分完全溶解、均化后，用预滤器过滤，装入 3 号硬明胶胶囊(例如 Syntapharm 公司提供)中。

实施例 7

凝胶乳造影

用 1:20(产品:水)的水，稀释 WO98/05309 实施例 1 及本发明实施例 1 公开的预浓缩物，并于 25 ±1℃下，用实验室用震荡器 (IKA HS-B20)分散 10 分钟。用连有光学显微镜的 COHU 照相机拍摄分散样品照片。用 LUCIA™ (Laboratory 成像公司)软件分析照片。图 1 为 WO98/05309 乳剂型分散体的显微照片。图 2 为本发明由预浓缩物形成的凝胶乳分散体的显微照片。

实施例 8

对含有凝胶乳预浓缩物的药用产品的生物利用度评估

将实施例 1 组合物与市售的微乳产品 Neora®口服液比较。临床施用的实施例组合物和 Neora®口服液分别记为 L363 和 L352。

采用双阶段试验，5 只 beagle 犬分别给予 100 mg 的单剂量环孢菌素，然后进行药动学比较。体重为 9-15 kg 的 12-36 月龄雄性犬饲以 300 g/天的标准粒状食物，期间自由进水。禁食 18 小时后给予待试产品。于第

0、1、2、3、5、8、12 和 24 小时，从前臂静脉采集血样。血样用络合酮稳定化处理，并保存在冰箱中，供非专属性放射免疫分析。图 3 为以环孢菌素 A 平均血药浓度表示的平均生物利用度比较结果。该结果清楚地表明，与可形成粒径约 100 nm 的微乳产品相比，用水稀释后可形成平均粒径为 0.2-500μm 非-球形粒子分散体的凝胶乳预浓缩物的生物利用度相同或更高。

实施例 9

含有紫杉醇软明胶胶囊的填充物:

采用了下述组分。

a)	紫杉醇	78.75mg
b)	聚甘油-10----二油酸酯	205.00mg
c)	聚甘油-3---油酸酯	129.50 mg
c)	油醇	205.00mg
d)	聚乙二醇(1760)氢化蓖麻油甘油酯	302.00 mg
e)	乙醇	129.50 mg

实施例 10

软明胶胶囊组合物:

采用了下述组分。

a)	紫杉醇	78.75mg
a)	[3' ketoMBmt]^{1}-[Val]^{2} -环孢菌素	52.50 mg
b)	聚甘油-10----二油酸酯	187.50mg
c)	油醇	187.50mg
c)	聚甘油-3---油酸酯	112.50mg
d)	聚乙二醇(1760)氢化蓖麻油甘油酯	302.00 mg
e)	乙醇	129.50 mg

实施例 11

含有硝苯地平软明胶胶囊的填充物:

采用了下述组分。

a)	硝苯地平	20.00mg
b)	聚甘油-10----二油酸酯	205.00mg
c)	聚甘油-3--一油酸酯	129.50 mg
c)	油醇	205.00mg
d)	聚乙二醇(1760)氢化蓖麻油甘油酯	302.00 mg
e)	乙醇	129.50 mg

实施例 12-17

表 1 列出了用以示例说明本发明的其他实施例，其制备方法同实施例 1。

表 1

实施例编号/成分	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

实施例 10-17 采用了以下原材料:

A -环孢菌素 A

B -聚甘油-10----二油酸酯(一-与二油酸酯的混合物)

C_1 -油醇

C_2 -聚甘油-3--一油酸酯

D -聚乙二醇(1760)氢化蓖麻油甘油酯

E -乙醇

实施例 18

对生物利用度和颗粒粒度分布的评估

采用 12 个健康志愿者，比较均含有 100 mg 环孢菌素的两种制剂(制剂 A-GEM101 和制剂 B-GEM304)的生物利用度。给予受试者 100 mg 含有 1-150μm Neora®分散体的胶囊(制剂 C)。观察这种新颖的给药系统，并对粒度分布进行精确评估。

经观察确定这种新颖的给药系统为 GEM (凝胶乳)。

含有环孢菌素的胶囊的填充物组合物:

制剂 A-GEM 101:

a)	环孢菌素 A	1020 g
b)	聚甘油-10--一油酸酯	2040 g
c)	聚甘油-3--一油酸酯	3380 g
d)	聚乙二醇(1760)氢化蓖麻油甘油酯	3000 g
e)	乙醇	1300 g

制剂 B-GEM 304:

a)	环孢菌素 A	1020 g
b)	聚甘油-10--一油酸酯	2630 g
c)	聚甘油-3--一油酸酯	1580 g
c)	油醇	1105 g
d)	聚乙二醇(1760)氢化蓖麻油甘油酯	2450 g
e)	乙醇	1300 g

粒度分布

采用 Mastersizer Micro, 2.18 型(Malvern 仪器公司)评估种新颖的 GEM 制剂的粒度分布。从制剂 A (GEM101)和制剂 B (304)的粒度分布直方图可推断出，制剂 A(尤其是 B)的有效径为 92.05μm (36.23μm)。

生物等效性研究方案

试验采用公开标签的随机 3 周期交叉试验方案，选用 12 个健康的白种志愿者，年龄为 18-45 岁和体重 ±10% 他们的理想体重。于禁食状态下，随机顺序给予口服单剂量的待试药物和参照药物。每一剂量均含 200mg 环孢菌素(两个 100 mg 的胶囊)。治疗中的洗净期至少为 7 天。在每一试验期内，分别于给药前，及给药后的第 20、40、60 分钟和第 1.5、2、2.5、3、4、5、6、,8、12、24 小时采集 14 个血样。监测整个研究过程中的副作用。

从肘前静脉采血并收到涂有 EDTA 的塑料管(Sarstedt Monovettes)中。上述样品需深度冷冻(-20℃)。

采用专属放射免疫分析测定环孢菌素全血浓度。$AUC_{(0-\infty)}$和 C_{max} 定义为生物利用度评估的初级变量。$AUC_{(0-t)}$、T_{max}、$T_{1/2}$ 为二级变量。

从本发明化合物的浓度/时间数据，应用非隔室分析 TopFit 2.0，计算出每一个体数据的药动学参数。

从测得的浓度-时间数据，可直接推出 C_{max} 和 T_{max}。对血药浓度-时间曲线的末端部进行对数-线性最小二乘回归，可求得消除速率常数(kel)。对零时至最后可测出血药浓度的时间点(t)进行线性梯形法计算，可求得血药浓度-时间曲线下面积($AUC_{(0-t)}$)。终浓度除以消除速率常数得到外推到无限时的面积($AUC_{(0-t)}$，$AUC_{(0-\infty)}$)。

药动学数据一览表:

参数	$T_{1/2}$ [h]	T_{max} [h]	C_{max} [ng/ml]	$AUC_{(0-t)}$ [ng*h/ml]	$AUC_{(0-inf)}$ [ng*h/ml]
制剂 A					
数学均值	6.24	1.33	1372.69	4631.75	4861.85
标准偏差	1.3	0.33	351.28	1204.56	1241.87
几何均值	6.12	1.3	1329.84	4483.35	4712.35
最小值	4.06	1	908.1	2635.32	2873.57
最大值	8.24	2	1930.3	6432.76	6684.33
制剂 B					
数学均值	6.41	1.5	1196.49	4430.33	4696.56
标准偏差	1.3	0.48	308.26	1032.91	1143.13
几何均值	6.29	1.43	1161.84	4326.15	4576.94
最小值	4.21	1	851.8	3130.66	3254.08
最大值	8.93	2.5	1785	6206.13	6643.15
制剂 C/参考					
数学均值	6.13	1.33	1358.95	4647.01	4887.55
标准偏差	1.32	0.33	380.35	1358.41	1430.5
几何均值	5.99	1.3	1307.19	4472.08	4705.55
最小值	3.92	1	820.7	2953.47	3028.58
最大值	7.87	2	1805.3	7330.08	7686.89

实施例 19

不同制剂的造影

本发明制剂分散后可获得不同形态的粒子。以下组合物经稀释可形成凝胶粒子分散体。造影方法如实施例 5。

对实施例 18 的制剂 A 和 B 进行造影。采用不同分散技术和对测量数据求平均值，可使颗粒大小的实测值与观测值间产生偏差(Mastersizer Micro: 实施例 18)。用 Mastersizer Micro 测量时采用高速混合器连续混合，用光学显微镜观察的样品在置于光学显微镜前需经手工温和地摇荡。

对以下制剂也进行了观察和造影:

制剂 C

a)	环孢菌素 A	9.5 %
b)	聚甘油-10--一油酸酯	40.0 %
c)	聚甘油-3-异硬脂酸酯	10.0 %
d)	聚乙二醇(1760)氢化蓖麻油甘油酯	28.0 %
e)	乙醇	12.5 %

制剂 D

a)	环孢菌素 A	10.0%
b)	聚甘油-10--一月桂酸酯	10.0 %
c)	聚甘油-3-油酸酯	40.0 %
d)	聚乙二醇(1760)氢化蓖麻油甘油酯	28.0 %
e)	乙醇	12.0 %

制剂 E

a)	环孢菌素 A	10.0%
b)	聚甘油-10--一月桂酸酯	27.0 %
c)	聚甘油-3-七油酸酯	31.0 %
d)	聚乙二醇(1760)氢化蓖麻油甘油酯	20.0 %
e)	乙醇	12.0 %

实施例 20

对形成凝胶相的粘度的评估

本发明组合物在与水或水性溶液接触时其粘度增加。该特征对于确保制剂中活性物质具有较高生物利用度是非常重要的。我们对实施例 18 和 19 的组合物进行了粘度试验评估。

于恒定条件下(温度=30℃, spindle SC4-27, 超级恒温器 Brookfield TC 500, Rheocalc 程序, 1.3 版), 采用旋转粘度计 Brookfield DV-III, 研究待试组合物的流变学特性。

采用标准稀释, 比较形成凝胶相的能力。每一样品均用 1: 1 体积的水稀释。采用上/下对称性流变程序分析稀释样品的粘度。所有稀释样品均为非牛顿流体。未稀释样品具有标准(牛顿)流体特征。于相同剪切速率进行样品比较。结果见下表:

恒定剪切速率= 1.70 秒$^{-1}$ 时的流变参量:

制剂 (稀释状态)	剪切应力 (N/m^2)	粘度 (mPa·s)
制剂 A (未稀释)	0.34	200
制剂 B (稀释)	3.91	2300
制剂 C (稀释)	6.97	4100
制剂 D (稀释)	17.2	10100
制剂 E (稀释)	1.53	900

由以上可以推断出: 该新型系统与水或水性溶液接触后, 其粘度至少增加 5 倍。这种粘度的增加, 对新生相的粘合力有积极的影响, 并因此而提高生物利用度。

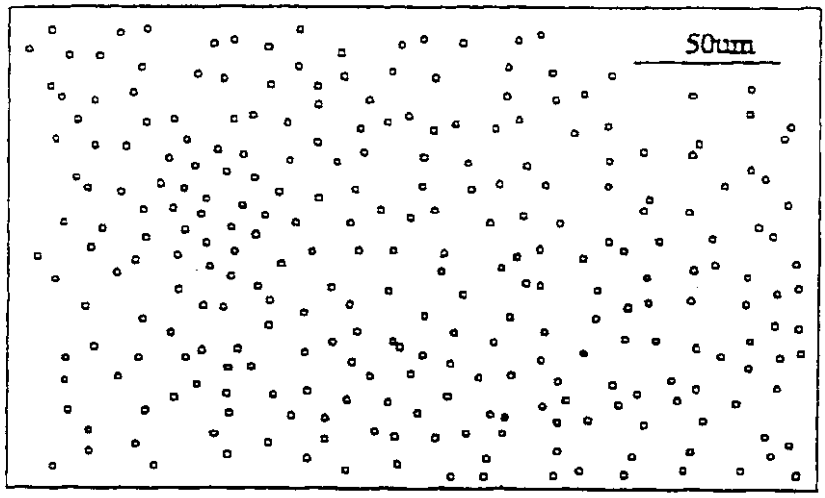

图 1

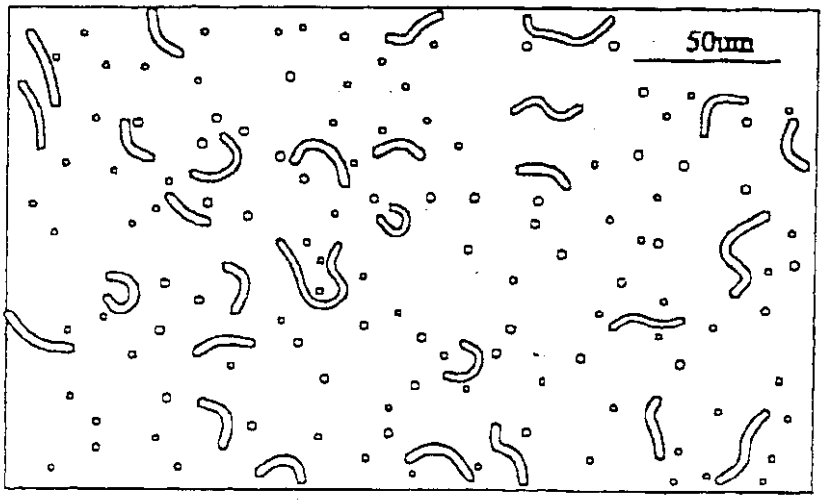

图 2

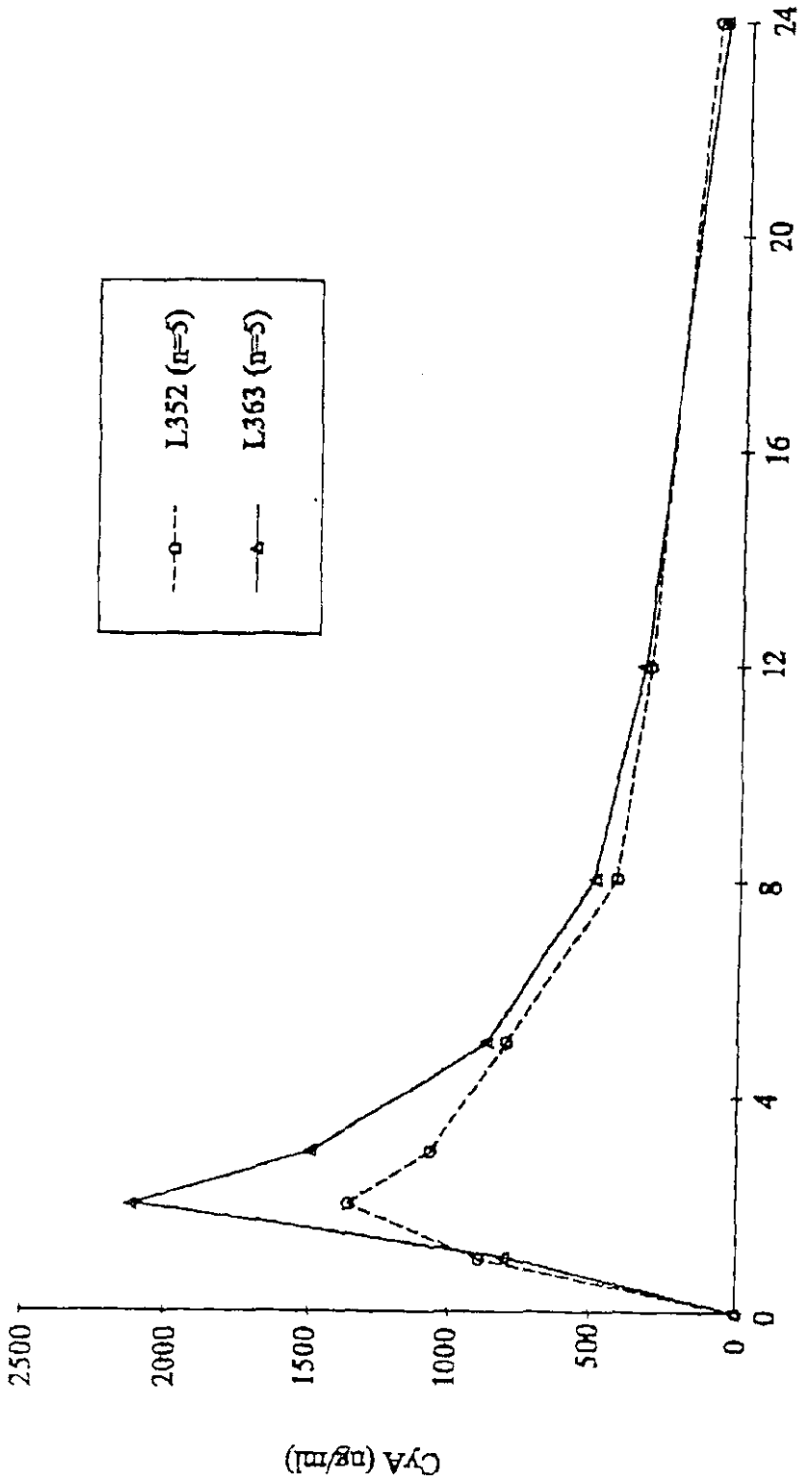
L352 (n=5)
L363 (n=5)
CyA (ng/ml)
2500
2000
1500
1000
500
0
0
4
8
12
16
20
24
时间（小时）

图 3

制剂 A

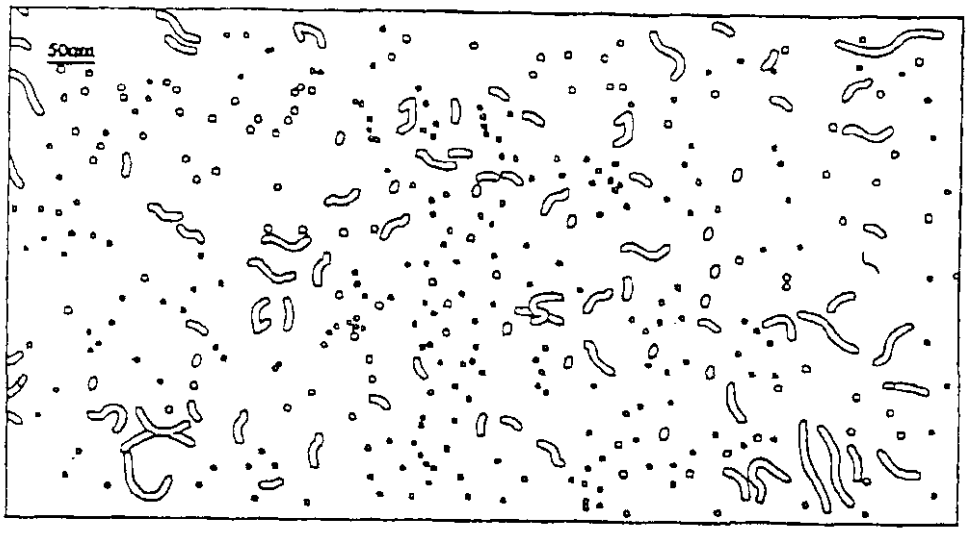

图 4

制剂 B

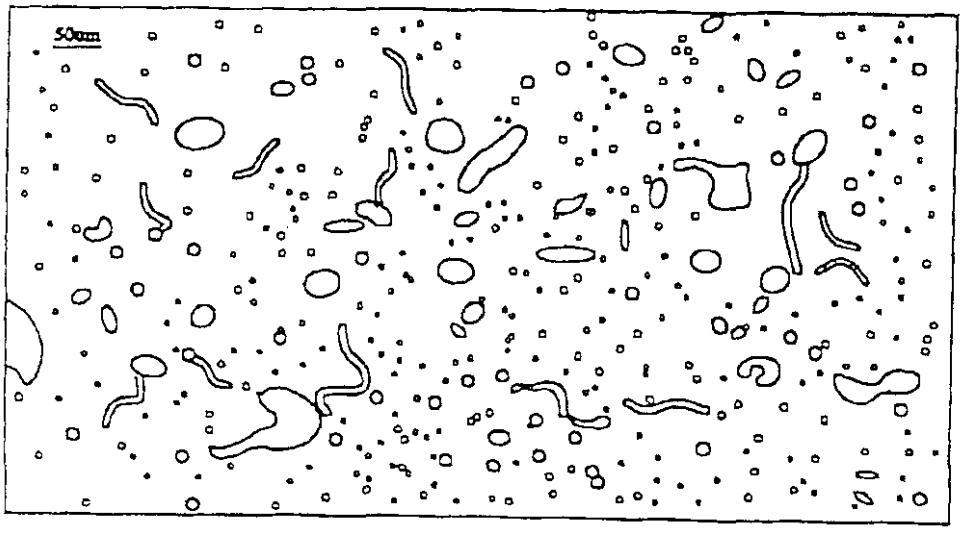

图 5

制剂 C

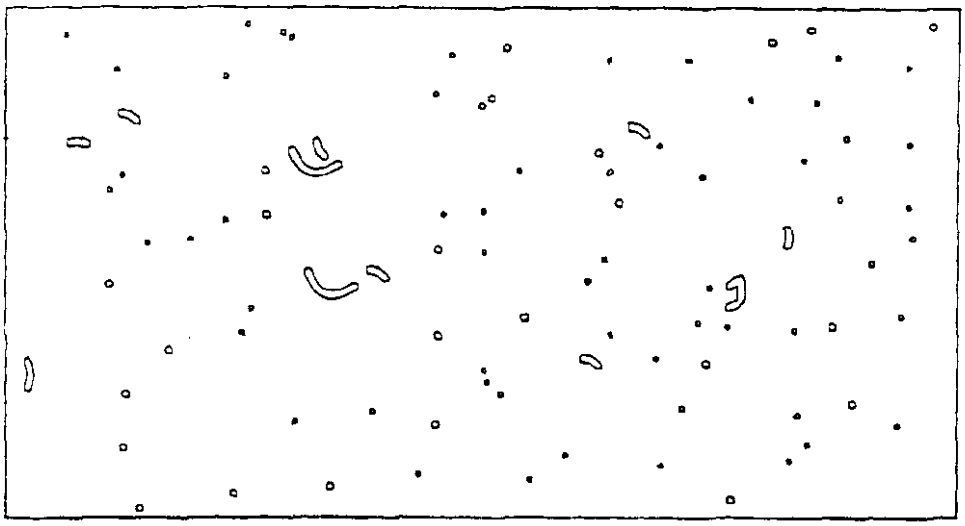

图 6

制剂 D

图 7

制剂 E

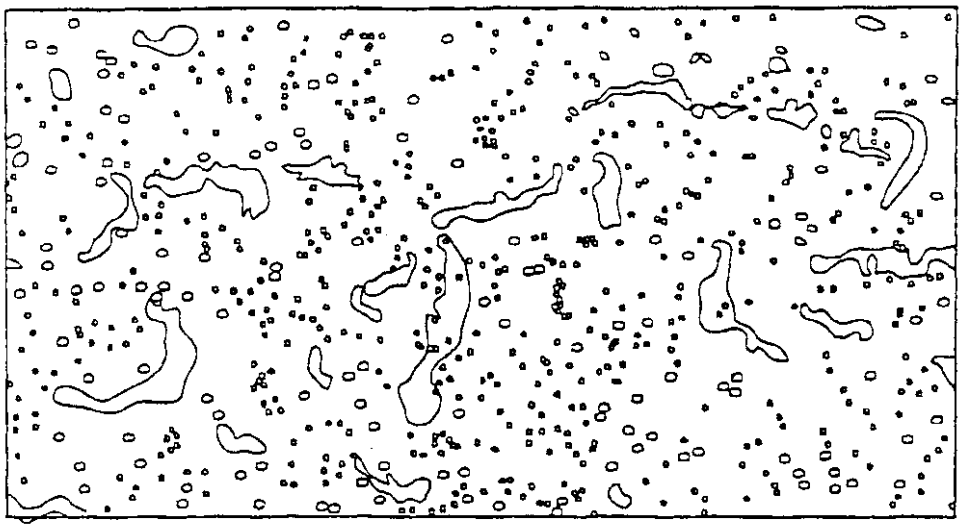

图 8