Annales

Examen de qualification en vue de l'inscription sur la liste des personnes qualifiées en matière de propriété industrielle

Mention brevets d'invention

Session 2021

Secteur chimie/pharmacie

Epreuve orale

Edition du 13 septembre 2022

Sommaire

Pages

AVERTISSEMENT

L'Institut national de la propriété industrielle publie pour chaque session d'examen des annales destinées à donner aux candidats une base pour leur préparation à cet examen.

Ces annales regroupent les textes des épreuves écrites de l'examen.

Ces annales sont publiées par secteur technique.

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Cet examen est mis en place conformément à l'arrêté du 23 septembre 2004 modifié portant application des dispositions des articles R. 421-1, R. 421-2 et R. 421-5 à R. 421-8 du code de la propriété intellectuelle.

INSTRUCTIONS AUX CANDIDATS

EPREUVE ORALE

Le choix du secteur technique est effectué par le candidat au moment de l'inscription (mécanique/électricité ou chimie/pharmacie).

Pour cette épreuve, il est remis au candidat le sujet composé soit d'une note décrivant les éléments du contexte à étudier, soit d'une décision de justice à commenter. Il peut être remis également le texte du brevet en cause, les documents de l'art antérieur (en langue française, anglaise ou allemande) et l'objet suspecté d'être contrefaisant ou une description ou une représentation de celui-ci.

L'épreuve orale consiste en un exposé, suivi d'un entretien avec la commission d'examen, sur l'acquisition et l'exploitation d'un brevet en France, notamment sur les aspects techniques, juridiques et/ou contentieux d'un problème de validité, de propriété et/ou de contrefaçon. Lors de l'entretien, des questions concernant la déontologie professionnelle, l'application des conventions européennes ou internationales et des règlements et directives communautaires ainsi que les droits étrangers prévus au règlement de l'examen pourront être posées. Pour la session 2019 les pays sont : Allemagne et Etats-Unis d'Amérique.

Le candidat dispose de 1h30 pour préparer le sujet qu'il traitera devant le jury pendant environ 30 minutes, sans toutefois que cela excède 45 minutes, questions comprises.

Enfin, à la fin de l'épreuve, le candidat ne devra conserver aucun document écrit ou note personnelle, et devra restituer les documents ou objets qui lui ont été éventuellement remis pour analyse.

CHIMIE - EPREUVE ORALE EQF 2021
SUJET

Le benelimus, molécule ayant des effets immunodépresseurs, utilisé comme anti-rejet chez les patients ayant subi une transplantation d'organe, est l'objet d'un brevet EP 1 123 456, délivré en avril 2004 et expiré en 2015, puis d'un certificat complémentaire de protection valable jusqu'en juin 2019, depuis tombé dans le domaine public, qui appartient à la société japonaise TAKI PHARMACEUTICAL. Il est commercialisé sous une forme à libération dite rapide ou immédiate depuis août 2005 par la société SUMO qui détient les autorisations de mise sur le marché.

La société TAKI, leader japonais dans le domaine de l'industrie pharmaceutique, ayant fusionné en 2005 avec la société SINO, devenue SUMO, a déposé une demande de brevet européen le 25 avril 2009, sous priorité de deux demandes de brevets japonais déposées respectivement le 26 avril 2008 et le 29 juillet 2008, pour une formulation à libération prolongée de benelimus. Le brevet européen EP 1 789 101 a été délivré le 16 juillet 2014 et appartient désormais à la société SUMO (après fusion, transfert de propriété régulièrement inscrit au RNB). Ce brevet est mis en oeuvre dans une spécialité à libération prolongée de benelimus (FK007) dénommée Addtrans (très proche des exemples 18 à 21 de EP 1 789 101), qui bénéficie d'une autorisation de mise sur le marché du 23 mai 2013. Le brevet européen EP 1 789 101 tel que délivré porte sur une formulation contenant un macrolide dans une composition de dispersion solide (SDC), qui possède une capacité de libération prolongée excellente, pour une utilisation dans un domaine médical. Il est intitulé " Préparations à libération prolongée d'un macrolide". A la demande du titulaire du brevet, la partie française du brevet EP 1 789 101 a fait l'objet d'une limitation par décision de l'INPI publiée le 04 décembre 2016. Les modifications intervenues portent sur : i) une limitation de la composition de dispersion solide à un mélange d'éthylcellulose («EC») et d'hydroxypropylméthylcellulose (« HPMC»), ii) la présence de lactose en tant qu'excipient, iii) une limitation de la taille des particules à ≤ 250 µm, iv) une limitation du composé de macrolide au benelimus et son hydrate.

La société SUMO vous contacte. Elle détient des informations sur le fait que la société LOLA PHARMACEUTICAL INDUSTRIES Ltd, leader mondial du médicament générique qui dispose d'une filiale en France, la société LOLA SANTE SAS a développé une formulation à libération prolongée générique d'Addtrans conçue à partir de la même molécule, le Benelimus. Ce médicament a la même composition qualitative et quantitative en principe actif ainsi que la même forme pharmaceutique que le médicament Addtrans. Votre client vous précise que LOLA dispose déjà d'une AMM en France pour les produits à libération immédiate de benelimus.

Par ailleurs, la société SUMO vous transmet les documents D1 et D2 qui ont été identifiés par l'Office Européen des brevets lors de l'examen de la demande de brevet européen EP 1 789 101 (voir ci-dessous). D'autre part, il vous précise que le brevet européen EP 1 789 101 n'a pas été opposé après la publication de sa mention de délivrance.

Le document D1 (EP1123456) porte sur une composition stable de dispersion solide de benelimus (KF007) comprenant un polymère cellulosique soluble dans l'eau, ce polymère pouvant être l'Hydroxypropylmethylcellulose (HPMC) tel que l'HMPC 2910. Le document D2 est une revue scientifique sur la solubilité des médicaments et les difficultés de développement de formulation notamment pour les composés peu solubles dans l'eau. Il y est notamment

définie la notion de dispersions solides. L'intérêt de mettre en oeuvre des dérivés cellulosiques solubles dans l'eau tels que

l''Hydroxypropylmethylcellulose (HMPC) (cf. 3.3.4.3) ou encore des polymères insolubles dans l'eau tels que l'Ethylcellulose (EC) (cf. 3.2.4.4) en vue d'améliorer la solubilité d'un composé est également décrit.

Enfin, votre client vous informe que la société LOLA SANTE SAS, basée en France, a travaillé avec une jeune entreprise novatrice (start-up) dans le secteur de l'industrie pharmaceutique pour développer sa formulation à libération prolongée générique d'Addtrans. Cette formulation a fait l'objet d'un dépôt d'une demande de brevet en France, déposée par le gérant de cette start-up et en son nom personnel.

Questions :

1. Votre client, la société SUMO, vous consulte afin d'avoir des conseils sur les actions qu'il pourrait engager vis-à-vis de la société LOLA SANTE. Que vous parait-il important de vérifier pour donner suite à cette demande ? Quels conseils pourriez-vous donner à votre client ?

2. Par ailleurs, quelles actions pourraient être engagées par LOLA SANTE vis-à-vis de votre client, la société SUMO?

3. Enfin, en question subsidiaire, vous analyserez la situation juridique relative à un dépôt d'une demande de brevet en son nom personnel par le gérant de la société start-up ayant collaboré avec la société LOLA SANTE SAS.

DOCUMENT 1

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **D1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **11.03.92** (51) Int. Cl.5: **A61K 31/395**, A61K 47/38

(21) Application number:

(22) Date of filing: **14.03.87**

The file contains technical information submitted after the application was filed and not included in this specification

(54) **Solid dispersion composition of FR-900506 substance.**

(30) Priority:

(43) Date of publication of application:
14.10.87

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11.03.92

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:

(74) Representative:

(73) Proprietor: **TAKI PHARMACEUTICAL**

(72)

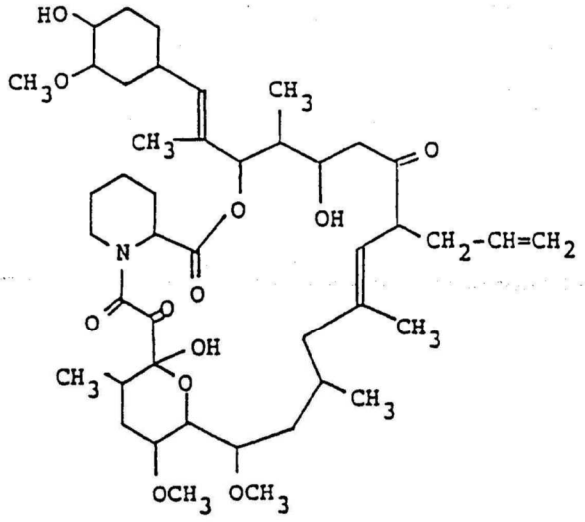
Description

The present invention relates to a pharmaceutical composition in the form of a solid dispersion composition comprising 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (hereinafter referred to as FK007 substance).

More particularly, the present invention relates to a pharmaceutical composition in the form of a solid dispersion composition comprising the FK007 substance and a water-soluble polymer.

Pharmaceutical compositions containing armorphous solids of macrolide antibiotics and cellulose polymer are disclosed in US-A-4 127 647. Methods for preparing solid stable preparations of sensitive active substances , in particular erythromycin as macrolide, by using hydroxypropyl methylcellulose are described in GB-A-1 081 667.

The FK007 substance used in the present invention is novel and can be represented by the following chemical formula:



The FK007 substance was isolated in a pure form from culture broths prepared by fermentation of a FK007 substance-producing strain belonging to genus Streptomyces, among which Streptomyces tsukubaensis No. 9993 has been newly isolated from a soil sample collected at Toyosato-cho, Tsukuba-gun, Ibaraki Prefecture, Japan. And a lyophilized sample of the newly isolated Streptomyces tsukubaensis No. 9993 has been deposited with the Fermentation Research Institute, Agency of Industrial Science and Technology (No. 1-3, Higashi 1-chome, Yatabemachi, Tsukuba-gun, Ibaraki Prefecture, Japan) under the deposit number of FERM P-7886 (deposited date: October 5th, 1984), and then converted to Budapest Treaty route of the same depository on October 19, 1985 under the new deposit number of FERM BP-927.

The FK007 substance possesses pharmacological activities such as immunosuppressive activity and antimicrobial activity as described in the published European patent publication No. 184 (publication date: 1986) and therefore is useful for treatment and prevention of rejection by transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases and infectious diseases.

However, when orally administered, the ratio of the absorption of the FK007 substance into blood is insufficient due to its insolubility into water, and the FK007 substance has the disadvantage of its poor bioavailability in oral administration.

As a result of an extensive study, the inventors of the present invention have discovered the fact that said disadvantage could be overcome by dispersing the FK007 substance with a water-soluble polymer to prepare a solid dispersion composition, and have completed the present invention.

According to the solid dispersion composition of the present invention, solubilization of the substance has been achieved and hence the bioavailability of the FK007 substance in human body can

be drastically improved.

Further, according to the present invention, the FK007 substance become stable and can be released sustainedly, and therefore said substance can be pharmacologically active for a long time in the body and its toxicity can be reduced thereby.

The solid dispersion composition of the present invention is explained in more detail in the following.

The solid dispersion composition of the FK007 substance can be prepared by a conventional method, for example;

(1) dissolving the FK007 substance in an organic solvent, and

(2) adding a water-soluble polymer to the resultant solution, and

(3) if necessary, suspending the additives such as excipient and disintegrator, in the resultant suspension or solution, and then

(4) removing the organic solvent from the resultant homogeneous suspension in a conventional manner.

And, in case that more homogeneous solid dispersion composition is desired, the homogeneous suspension is prepared in the above procedure (2) and then subjected to the following subsequent procedures.

(5) dissolving the suspension prepared in the above procedure (2) in an organic solvent, and

(6) if necessary, suspending the additives such as excipient and disintegrator, in the resultant homogeneous solution, and then

(7) removing the organic solvent in a conventional manner.

The organic solvents to be used in the procedure (1) are not restrictive and are any solvents which are capable of dissolving the FK007 substance such as alcohol (e.g. methanol, ethanol, propanol or isopropyl alcohol,), ethyl acetate and diethyl ether, in which the preferable ones may be lower alkanols.

The water-soluble polymers to be used in the procedure (2) may be a water-soluble cellulose polymer which is capable of dispersing the FK007 substance, such as hydroxypropyl methylcellulose. The hydroxypropyl methylcellulose can be used with various viscosities.

The quantity of the water-soluble polymer is not restrictive and is any one, by which the FK007 substance can be dispersed, and suitable quantitative ratio of the water-soluble polymer and the FK007 substance by weight may be from 0.1:1 to 20:1, preferably 0.3:1 to 10:1, more preferably 0.5:1 to 5:1, and the most preferably 1:1.

The additives to be optionally used in the procedures (3) and (6) may be a conventional ones used in the field of pharmaceutical preparation such as excipients (e.g. lactose, sucrose, starch or mannitol,), and disintegrators (e.g. croscarmellose sodium, carboxymethyl cellulose calcium, low substituted hydroxypropyl cellulose, sodium starch glycolate or microcrystalline cellulose,), and these excipients and disintegrators can be used at the same time or independently.

The quantity of the additives is not restrictive and suitable quantitative ratio of the excipient or disintegrator and the FK007 substance by weight, if used, may be from 0.1:1 to 20:1, preferably 0.5:1 to 5:1, and more preferably 1:1 to 3:1, respectively.

The organic solvents to be used in the procedure (5) are not restrictive and are any solvents capable of dissolving the suspension of the preceding procedure (2), such as chloroform and dichloromethane.

The solid dispersion composition of the present invention prepared by the above-mentioned procedures can be used by itself as a pharmaceutical preparation for oral administration and also can be converted into various dosage forms such as powders, fine granules, granules, tablets, capsules and injections, according to a conventional manner. If desired, conventional coloring agents, sweeting agents, flavouring agents, diluents and lubricants, (e.g. sucrose, lactose, starch, crystalline cellulose, synthetic aluminum silicate, magnesium stearate and talc) may be compounded with the solid dispersion composition.

The solid dispersion composition of the FK007 substance and the various preparations thereof prepared by optionally converting said solid dispersion composition into various dosage forms as mentioned above, have remarkably improved solubility and absorptiveness into blood in comparison to the crystals of the FK007 substance per se.

In order to show the usefulness of the solid dispersion composition of the present invention, the test results are given in the following.

[I] Dissolution Test:

Test Samples

(A) Solid dispersion composition of the FK007 substance prepared in Example 2;

(B) Solid dispersion composition of the FK007 substance prepared in Example 4;

(C) Crystals of the FK007 substance per se prepared in Reference;

Test Method

The tests were carried out according to the paddle method prescribed in Method 2 of the dissolution test in The Pharmacopoeia of Japan (tenth edition) using water as test solution and the dissolution rate at 100 rpm after the specified minutes from the beginning of each dissolution test was measured.

Test Results

The dissolution rate of the solid dispersion composition of the FK007 substance is shown in the following table.

Test Samples	Dissolution Rate (%)			
	15 min.	30 min.	60 min.	90 min.
A	54.5	74.6	88.2	93.0
B	74.0	91.8	100	100
C	0	0	5.0	10.8

[II] Bioavailability Test

Test Sample

Solid dispersion composition of the FK007 substance prepared in Example 2;

Test Method

The above sample, which contains 10 mg/kg of the FK007 substance, was orally administered to several dogs, which had been withheld from any food overnight in a crossover design. The plasma concentration of the FK007 substance was determined by high performance liquid chromatography at 1, 2, 4 and 6 hours after administration.

Test Results

The plasma concentrations of the FK007 substance at each time are shown in the following table.

Time (hours)	Plasma Concentrations (μg/ml)
1	0.44
2	0.69
4	0.53
6	0.45

As clearly seen from the above two test results, the solid dispersion composition of the present invention possesses good dissolution rate and pattern, and further good bioavailability.

The present invention is explained according to the following Examples.

Reference

Isolation of Streptomyces tsukubaensis No. 9993

Streptomyces tsukubaensis No. 9993 was isolated by using dilution plate techniques as shown in the following.

About one gram soil which was collected at Toyosato-cho, Tsukuba-gun, Ibaraki Prefecture, Japan, was added to a sterile test tube and the volume made up to 5 ml with sterile water. The mixture was then blended for 10 second by a tube buzzer and kept on 10 minutes. The supernatant was sequentially diluted by 100 fold with sterile water. The diluted solution (0.1 ml) was spread on Czapek agar supplemented with thiamine hydrochloride (saccharose 30 g, sodium nitrate 3 g, dipotassium phosphate 1 g, magnesium sulfate 0.5 g, potassium chloride 0.5 g, ferrous sulfate 0.01 g, thiamine hydrochloride 0.1 g, agar 20 g, tap water 1000 ml; pH 7.2) in a Petri dish. The growing colonies developed on the plates after 21 days incubation at 30 ° C were transferred to slants [yeast-malt extract agar (ISP-medium 2)], and cultured for 10 days at 30 ° C. Among of the colonies isolated, the Streptomyces tsukubaensis No. 9993 could be found.

Fermentation

A preculture medium (100 ml) containing glycerin (1%), corn starch (1%), glucose (0.5%), cottonseed meal (1%), corn steep liquor (0.5%), dried yeast (0.5%) and calcium carbonate (0.2%) at pH 6.5 was poured into a 500 ml-Erlenmeyer flask and sterilized at 120 ° C for 30 minutes. A loopful of slant culture of Streptomyces tsukubaensis No. 9993 was inoculated to the medium and cultured at 30 ° C for four days. The resultant culture was transferred to the same preculture medium (20 liters) in 30 liters jar-fermentor which had been sterilized at 120 ° C for 30 minutes in advance. After the culture was incubated at 30 ° C for 2 days, 16 liters of the preculture was inoculated to a fermentation medium (1600 liters) containing soluble starch (4.5%), corn steep liquor (1%), dried yeast (1%), calcium carbonate (0.1%) and Adekanol (defoaming agent, Trade Mark, maker Asahi Denka Co.) (0.1%) at pH 6.8 in 2 ton tank which had been sterilized at 120 ° C for 30 minutes in advance and cultured at 30 ° C for 4 days.

Isolation and Purification

The cultured broth thus obtained was filtered with an aid of diatomaseous earth (25 kg). The mycelial cake was extracted with acetone (500 liters), yielding 500 liters of the extract. The acetone extract from mycelium and the filtrate (1350 liters) were combined and passed through a column of a non-ionic adsorption resin "Diaion HP-20" (Trade Mark, maker Mitsubishi Chemical Industries Ltd.) (100 liters). After washing with water (300 liters) and 50% aqueous acetone (300 liters), elution was carried out with 75% aqueous acetone. The eluate was evaporated under reduced pressure to give residual water (300 liters). This residue was extracted with ethyl acetate (20 liters) three times. The ethyl acetate extract was concentrated under reduced pressure to give an oily residue. The oily residue was mixed with twice weight of acidic silica gel (special silica gel grade 12, maker Fuji Devison Co.), and this mixture was slurried in ethyl acetate. After evaporating the solvent, the resultant dry powder was subjected to column chromatography of the same acidic silica gel (8 liters) which was packed with n-hexane The column was developed with n-hexane (30 liters), a mixture of n-hexane and ethyl acetate (4:1 v/v, 30 liters) and ethyl acetate (30 liters). The fractions containing the object compound were collected and concentrated under reduced pressure to give an oily residue. The oily residue was mixed with twice weight of acidic silica gel and this mixture was slurried in ethyl acetate. After evaporating the solvent, the resultant dry powder was rechromatographed on acidic silica gel (3.5 liters) packed with n-hexane. The column was developed with n-hexane (10 liters), a mixture of n-hexane and ethyl acetate (4:1 v/v, 10 liters) and ethyl acetate (10 liters). Fractions containing the object compound were collected and concentrated under reduced pressure to give a yellowish oil. The oily residue was dissolved in a mixture of n-hexane and ethyl acetate (1:1 v/v, 300 ml) and subjected to column chromatography of silica gel (maker Merck Co., Ltd. 230-400 mesh) (2 liters) packed with the same solvents system. Elution was curried out with a mixture of n-hexane and ethyl acetate (1:1 v/v, 10 liters and 1:2 v/v 6 liters) and ethyl acetate (6 liters).

Fractions containing the first object compound were collected and concentrated under reduced pressure to give FK007 substance in the form of white powder (34 g). This white powder was dissolved in acetonitrile and concentrated under reduced pressure. This concentrate was kept at 5 ° C overnight and prisms (22.7 g) were obtained. Recrystallization from the same solvent gave purified FK007 substance (13.6 g) as colorless prisms.

Infrared Absorption Spectrum:

5

$\nu_{max}^{CHCl_3}$: 3680, 3580, 3520, 2930, 2870, 2830, 1745, 1720, 1700, 1645, 1450, 1380, 1350, 1330, 1310, 1285, 1170, 1135, 1090, 1050, 1030, 1000, 990, 960(sh), 918 cm^{-1}

Example 1

FK007 substance	1g
Hydroxypropyl methylcellulose 2910 (TC-5R)	1g
Lactose	3g
Total	5g

The FK007 substance (1 g) was dissolved in ethanol (10 ml), and thereto was added hydroxypropyl methylcellulose 2910 (Trade Mark: TC-5R, Maker: Shin-Etsu Chemical Co., Ltd.) (1 g) to prepare a suspension. To this suspension was added dichloromethane (5 ml) to prepare a homogeneous solution. Lactose (3 g) was homogeneously suspended to this solution and then the organic solvent was removed by evaporation. The residual product was dried under reduced pressure for 10 hours by vacuum dryer, milled for 2 minutes by coffee mill and then passed through a sieve (32 mesh) to give the above-identified solid dispersion composition of the FK007 substance (5 g).

Example 2

FK007 substance	1g
Hydroxypropyl methylcellulose 2910 (TC-5R)	1g
Lactose	2g
Croscarmellose sodium (Ac-Di-Sol)	1g
Total	5g

The FK007 substance (1 g) was dissolved in ethanol (10 ml), and thereto was added hydroxypropyl methylcellulose 2910 (TC-5R) (1 g) to prepare a suspension. To this suspension was added dichloromethane (5 ml) to prepare a homogeneous solution. Lactose (2 g) and croscarmellose sodium (Trade Mark: Ac-Di-Sol, Maker: Asahi Chemical Industry Co., Ltd.) were homogeneously suspended to this solution and then the organic solvent was removed by evaporation. The residual product was dried under reduced pressure for 10 hours by vacuum dryer, milled for 2 minutes by coffee mill and then passed through a sieve (32 mesh) to give the above-identified solid dispersion composition of the FK007 substance (5 g).

Example 3

FK007 substance	1g
Hydroxypropyl methylcellulose 2910 (TC-5R)	1g
Lactose	1g
Croscarmellose sodium (Ac-Di-Sol)	2g
Total	5g

The above-identified solid dispersion composition of the FK007 substance (5 g) was obtained in substantially the same manner to that of Example 2.

Example 4

FK007 substance	1g
Hydroxypropyl methylcellulose 2910 (TC-5R)	1g
Croscarmellose sodium (Ac-Di-Sol)	3g
Total	5g

The FK007 substance (1 g) was dissolved in ethanol (10 ml), and thereto was added hydroxypropyl methylcellulose 2910 (TC-5R) (1 g) to prepare a suspension. To this suspension was added dichloromethane (5 ml) to prepare a homogeneous solution. Croscarmellose sodium (Ac-Di-Sol) (3 g) was homogeneously suspended to this solution and then the organic solvent was removed by evaporation. The residual product was dried under reduced pressure for 10 hours by vacuum dryer, milled for 2 minutes by coffee mill and then passed through a sieve (32 mesh) to give a solid dispersion composition of the FK007 substance (5 g).

Example 5

FK007 substance

Hydroxypropyl methylcellulose 2910 (TC-5R)

The solid dispersion compositions comprising various ratio of the above two ingredients were obtained by the following method.

[Method]

The FK007 substance (1 g) was dissolved in ethanol (10 ml), and thereto was added hydroxypropyl methylcellulose 2910 (TC-5R) (each 0.5 g, 1 g, 3 g or 5 g) to prepare a suspension. To this suspension was added dichloromethane (5 ml) to prepare a homogeneous solution. The organic solvent was removed from the solution by evaporation, and the residue was dried under reduced pressure for 10 hours by vacuum dryer, milled for 2 minutes by coffee mill and passed through a sieve (32 mesh) to give the above-identified solid dispersion composition in the following ratio.

The ratio of the FK007 substance : hydroxypropyl methylcellulose 2910 by weight are 1:0.5, 1:1, 1:3 and 1:5.

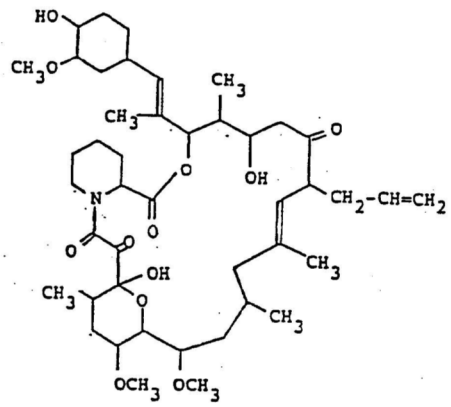
Example 6

FK007 substance	1 g
Hydroxypropyl methylcellulose 2910 (TC-5R)	1 g
Total	2 g

The FK007 substance (1 g) was dissolved in ethanol (10 ml), and thereto was added hydroxypropyl methylcellulose 2910 (TC-5R) (1 g) to prepare a suspension. The organic solvent was removed by evaporation from the suspension, and the residue was dried under reduced pressure for 10 hours by vacuum dryer, milled for 2 minutes by coffee mill and then passed through a sieve (32 mesh) to give the above-identified solid dispersion composition of the FK007 substance (2 g).

Claims

1. A pharmaceutical composition in the form of a solid dispersion containing FK007 substance of the following chemical formula:



and a water-soluble cellulose polymer.

2. The pharmaceutical composition of Claim 1, in which a water-soluble cellulose polymer is hydroxypropyl methyl cellulose.

3. The pharmaceutical composition of Claim 2, in which the FK007 substance and hydroxypropyl methylcellulose are in the ratio of 1:0.5 to 1:5 by weight.

4. The pharmaceutical composition of Claim 3, in which the FK007 substance and hydroxypropyl methylcellulose are in the ratio of 1:1 by weight.

5. A process for preparing a pharmaceutical composition in the form of a solid dispersion containing FK007 substance and a water-soluble cellulose polymer, which is characterized by (i) dissolving the FK007 substance in an organic solvent, and (ii) adding a water-soluble cellulose polymer to the resultant solution, and (iii) if necessary, suspending the additives in the resultant suspension or solution, and then (iv) removing the organic solvent therefrom.

6. A process for preparing a pharmaceutical composition in the form of a solid dispersion containing FK007 substance and a water-soluble cellulose polymer, which is characterized by (i) dissolving the FK007 substance in an organic solvent, and (ii) suspending a water-soluble cellulose polymer in the resultant solution, and (iii) dissolving the resultant suspension in an organic solvent, and (iv) if necessary, suspending the additives in the resultant homogeneous solution, and then (v) removing the organic solvent therefrom.

DOCUMENT 2

D2

ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 50 (1996) 47–60

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.com/locate/ejphabio

Review article

Improving drug solubility for oral delivery using solid dispersions

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Abstract

The solubility behaviour of drugs remains one of the most challenging aspects in formulation development. With the advent of combinatorial chemistry and high throughput screening, the number of poorly water soluble compounds has dramatically increased. Although solid solutions have tremendous potential for improving drug solubility, 40 years of research have resulted in only a few marketed products using this approach. With the introduction of new manufacturing technologies such as hot melt extrusion, it should be possible to overcome problems in scale-up and for this reason solid solutions are enjoying a renaissance. This article begins with an overview of the historical background and definitions of the various systems including eutectic mixtures, solid dispersions and solid solutions. The remainder of the article is devoted to the production, the different carriers and the methods used for the characterization of solid dispersions.

Keywords: Solid solution; Solid dispersion; Eutectic mixture; Amorphous state; Bioavailability; Solubility; Dissolution

1. Introduction

Together with the permeability, the solubility behaviour of a drug is a key determinant of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole and chloramphenicol come immediately to mind. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

Consideration of the modified Noyes–Whitney equation [1,2] provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability:

$$\frac{dC}{dt} = \frac{AD(C_s - C)}{h}$$

where dC/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, C_s is the solubility of the compound in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions. Of these possibilities, changes in the hydrodynamics are difficult to invoke in vivo and the maintenance of sink conditions will depend on how permeable the gastrointestinal mucosa is to the compound as well as on the composition and volume of the lumenal fluids. Although some research effort has been directed towards permeability enhancement using appropriate excipients, results to date have not been particularly encouraging. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution; the likely magnitude of the food effect can be forecasted from dissolution tests in biorelevant media [3]. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches.

Table 1 summarizes the various formulation and chemi-

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Table 1
Approaches to improve the solubility or to increase the available surface area for dissolution

I. Physical modifications
Particle size
Micronization
Nanosuspensions
Modifications of the crystal habit
Polymorphs
Pseudopolymorphs (including solvates)
Complexation/solubilization
Use of surfactants
Use of cyclodextrines
Drug dispersion in carriers
Eutectic mixtures
Solid dispersions (non-molecular)
Solid solutions
II. Chemical modification
Soluble prodrugs
Salts

cal approaches that can be taken to improve the solubility or to increase the available surface area for dissolution.

Of the physical approaches, review articles have already been published on the use of polymorphs [4], the amorphous form of the drug [5] and complexation [6,7]. Decreasing the particle size of the compound by milling the drug powder theoretically results in an increase in the available area for dissolution, but in some cases the micronized powder tends to agglomerate, thereby at least partly negating the milling procedure. Presenting the compound as a molecular dispersion combines the benefits of a local increase in the solubility (within the solid solution) and maximizing the surface area of the compound that comes in contact with the dissolution medium as the carrier dissolves. This review is therefore devoted to a discussion of the use of molecular and near-molecular dispersions for the optimization of oral delivery of poorly soluble drugs.

2. Definitions

2.1. Simple eutectic mixtures

No review of solid dispersions would be complete without a brief description of eutectic mixtures, which are the cornerstone of this approach to improving bioavailability of poorly soluble compounds. A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state (Fig. 1). When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a comelt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components.

When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug [9,10]. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

2.2. Solid solutions

Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. Solid solutions of a poorly water soluble drug dissolved in a carrier with relatively good aqueous solubility are of particular interest as a means of improving oral bioavailability. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions [11] and the dissolution rate is determined by the dissolution rate of the carrier. By judicious selection of a carrier, the dissolution rate of the drug can be increased by up to several orders of magnitude.

Solid solutions can be classified according to two methods. First, they can be classified according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous).

2.2.1. Continuous and discontinuous solid solutions

2.2.1.1. Continuous solid solutions In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

2.2.1.2. Discontinuous solid solutions In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical

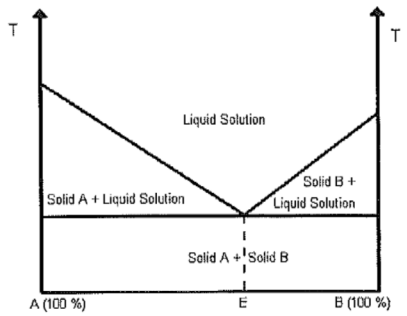

Fig. 1. Phase diagram for a eutectic system (reproduced with modifications from Ref. [8]).

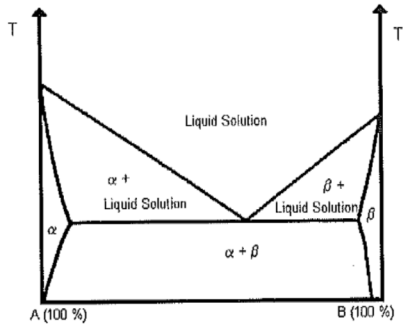

Fig. 2. Phase diagram for a discontinuous solid solution (reproduced with modifications from Ref. [8]).

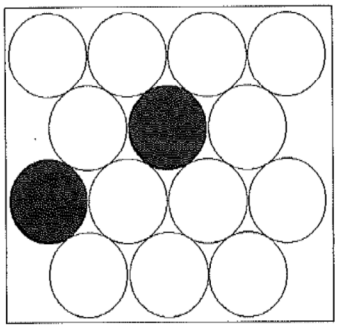

Fig. 3. Substitutional crystalline solid solution (reproduced with modifications from Ref. [13]).

phase diagram is shown in Fig. 2. α and β show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Note that below a certain temperature, the mutual solubilities of the two components start to decrease. Due to practical considerations it has been suggested by Goldberg et al. [11] that the term 'solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two components but also on the dose of the drug component. The upper limit for the mass of a tablet or capsule is about 1 g. Assuming that the solubility of the drug in the carrier is 5%, doses of above 50 mg would not be feasible with this strategy. Obviously, if the drug solubility in the carrier is significantly higher than 5%, larger doses can be entertained.

2.2.2. Substitutional crystalline, interstitial crystalline and amorphous solid solutions

2.2.2.1. Substitutional crystalline solid solutions Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules. A substitutional crystalline solid dispersion is depicted in Fig. 3. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules [12].

2.2.2.2. Interstitial crystalline solid solutions In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice (Figs. 4 and 5). As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter [14]. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

2.2.2.3. Amorphous solid solutions In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent (Fig. 6). Using griseofulvin in citric acid, Chiou and Riegelman [16] were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose.

Polymer carriers are particularly likely to form amorphous solid solutions as the polymer itself is often present in the form of an amorphous polymer chain network. In addition, the solute molecules may serve to plasticize the polymer, leading to a reduction in its glass transition temperature.

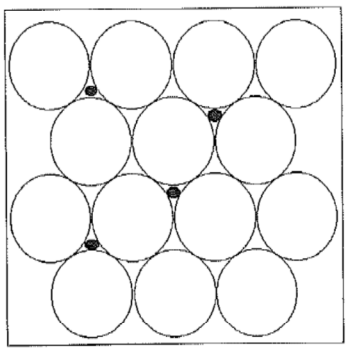

Fig. 4. Interstitial crystalline solid solution (reproduced with modifications from Ref. [13]).

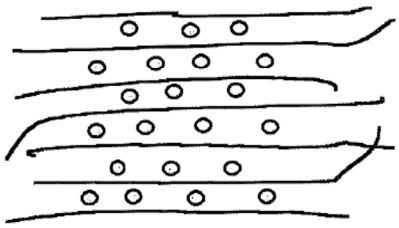

Fig. 5. Interstitial solid solutions of small molecules in the crystalline parts of a polymer (reproduced with modifications from Ref. [15]).

3. Formulation of solid solutions

In the early 1960s, Sekiguchi et al. reported that formulation of eutectic mixtures could lead to an improvement in the release rate and thereby the bioavailability of poorly soluble drugs. Eutectic combinations such as sulphathiazole/urea [9] and chloramphenicol/urea [17] served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier. Both preparations exhibited faster release and better bioavailability than conventional formulations. The explanation offered for this behaviour was that, after dissolution of the urea, a fine suspension of drug particles was exposed to the dissolution medium (or GI fluids) and that both the smaller particle size and better wettability of the drug particles in this suspension contributed to a faster dissolution rate.

The next development was the preparation of solid solutions by Levy [18] and Kanig [19]. In contrast to a eutectic mixture, the dispersed component in a solid solution is molecularly dispersed. In a very informative series of publications, Goldberg [10,11,20,21] discussed the theoretical and practical advantages of solid solutions over eutectic mixtures. The improvement in dissolution characteristics was at first attributed 100% to the reduction in particle size. Molecular dispersion represents the ultimate in particle size reduction [21], and after the carrier has dissolved, the drug is molecularly dispersed in the dissolution medium, i.e. is present in solution form. A further reason for the improvement in the dissolution rate is that the drug has no crystal structure in the solid solution [22]. Therefore, the energy normally required to break up the crystalline structure of the drug before it can dissolve is not a limitation to the release of the drug from a solid solution. After the solid solution has dissolved, the drug is present as a supersaturated solution. In some cases, the carrier may serve to inhibit precipitation of the drug from the supersaturated solution [23–25]. It has also been speculated that, if the drug does precipitate, it will precipitate out as a metastable polymorph with a high solubility compared to that of the most stable form [24,26]. A further way in which a solid solution could enhance dissolution is through improvement of the wettability of the drug [13]. Even carriers that are not surface active, e.g. urea and citric acid, can improve wetting characteristics. Of course, if carriers with surface activity such as cholic acid, bile salts [27], cholesterol esters [28] and lecithin [29] are used, the improvements in wetting can be much greater. Another way in which the carrier can influence the drug's dissolution properties is via direct solubilization or a cosolvent effect.

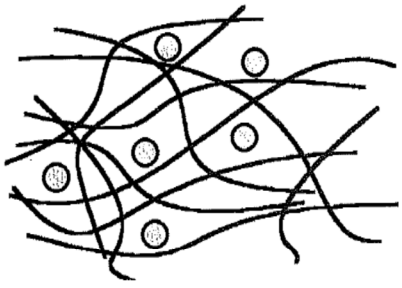

Fig. 6. Amorphous solid solution (reproduced with modifications from Ref. [15]).

The relationship between the release characteristics of the solid solution and a physical mixture of the two components varies with the drug/carrier combination. For example, the release rate from a solid solution of prednisolone in Cremophore® is almost identical with the release rate from a simple mixture of the two components [30]. A physical mixture of glyburide and PEG 6000 exhibited better solubility and faster dissolution than that of the pure drug [31]. The solubility of paracetamol is greater in urea than alone [10]. However, the solubility of sulfathiazole is adversely affected by mixing with urea [9]. In general, dissolution rates are compared among the pure drug, a physical mixture and the solid solution to assess the benefits of preparing a solid solution.

3.1. Methods for preparing solid solutions

3.1.1. Hot melt method

Sekiguchi and Obi [9] used a hot melt method to prepare simple eutectic mixtures. Sulphathiazole and urea were melted together at a temperature above the eutectic point and then cooled in an ice bath. The resultant solid eutectic was then milled to reduce the particle size. Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix. Whether or not a molecular dispersion can be achieved depends on the degree of supersaturation and rate of cooling attained in the process. In other words, the process has an effect on the resultant dispersion and can be varied to optimize the product. Sekiguchi et al. [17] and Chiou and Riegelman [16] accelerated the cooling rate by snap-cooling on stainless steel plates. Kanig [19] introduced the variation of spraying the hot melt onto a cold surface. A further

approach is to prepare the solid dispersion by injection molding, as demonstrated by Wacker et al. [32].

An important prerequisite to the manufacture of solid solutions by the hot melt method is the miscibility of the drug and the carrier in the molten form. When there are miscibility gaps in the phase diagram, this usually leads to a product that is not molecularly dispersed. Another important limitation to the hot melt method is the thermostability of the drug and the carrier. If too high a temperature is required, the drug may decompose or evaporate. Of course, oxidative reactions can be avoided by processing in an inert atmosphere or under vacuum, while evaporation can be avoided by processing in a closed system.

Because of these limitations, the solvent method became more popular in the 1970s and 1980s. In recent years, however, the hot melt method has enjoyed a renaissance in the form of hot melt extrusion. Extrusion of moistened powders has been well known in the pharmaceutical sciences for many years [33]. Hot melt extrusion is a very common way of processing plastics in the polymer industry, but Speiser [34,35] and Hüttenrach [36] were the first to adapt the process for pharmaceutical purposes. In recent years, this method has been applied to the manufacture of solid solutions. A scheme of a hot melt extruder is shown in Fig. 7. The drug/carrier mix is typically processed with a twin-screw extruder of the same type used in the polymer industry. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermolabile to be processed.

A further alternative for processing thermolabile substances is by hot-spin-melting. Here, the drug and carrier are melted together over an extremely short time in a high speed mixer and, in the same apparatus, dispersed in air or an inert gas in a cooling tower. Some drugs that have been processed into solid dispersions using hot-spin-melting to

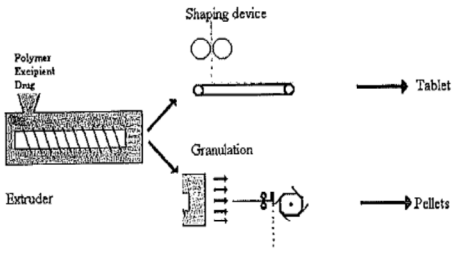

Fig. 7. Scheme of a hot melt extruder (reproduced with modifications from Ref. [37]).

date include testosterone [38], progesterone [39] and dienogest [40].

3.1.2. Solvent method

Until the advent of the solvent method, solid solutions were prepared exclusively by the melting method. Tachibani and Nakumara [41] were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier polyvinylpyrrolidone (PVP). The evaporation method was then taken up by Mayersohn and Gibaldi [42]. By dissolving both griseofulvin and PVP in chloroform, and then evaporating the solvent, they were able to achieve a solid dispersion. The release rate of griseofulvin from the solid dispersion was five to 11 times higher than that of micronized drug, depending on the drug/carrier ratio. Bates [43] introduced the term coprecipitates to describe solid dispersions that are manufactured by the solvent evaporation method. Although the term coprecipitate is strictly speaking inaccurate in this case, it is still widely used in this sense today. Simonelli et al. [44] used the term coprecipitate more correctly to describe a solid dispersion of sulphathiazole and PVP that had been precipitated from a solution in sodium chloride by the addition of hydrochloric acid. Solid dispersions and solutions that are manufactured by the solvent evaporation method should really be called coevaporates and not coprecipitates.

An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by any one of a number of methods. Temperatures used for solvent evaporation usually lie in the range 23–65°C [45,46]. The solvent can also be removed by freeze-drying [31] or by spray-drying [47]. It must be remembered that when an organic solvent is to be removed, small variations in the conditions used can lead to quite large changes in product performance. Another point to consider is the importance of thoroughly removing all of the solvent, since most of the organic solvents used have toxicity issues.

With the discovery of the solvent method, many of the problems associated with the melting method were solved. For example, it was then possible to form solid dispersions of thermolabile substances. Likewise, many polymers that could not be utilized for the melting method due to their high melting points (e.g. PVP) could be now considered as carrier possibilities. As a result, for many years the solvent method was the method of choice for polymer-based systems. With time, however, the ecological and subsequent economic problems associated with the use of organic polymers began to make solvent-based methods more and more problematic. For these reasons, hot melt extrusion is the current method of choice for the manufacture of solid dispersions.

3.2. Carriers

3.2.1. Polyethylene glycol (PEG)

3.2.1.1. General characteristics of PEGs Polyethylene glycols (PEG) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200–300 000. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1500–20 000 are usually employed. As the MW increases, so does the viscosity of the PEG. At MW of up to 600, PEGs are fluid, in the range 800–1500 they have a consistency that is best described as vaseline-like, from 2000 to 6000 they are waxy and those with MW of 20 000 and above form hard, brittle crystals at room temperature. Their solubility in water is generally good, but decreases with MW. A particular advantage of PEGs for the formation of solid dispersions is that they also have good solubility in many organic solvents. The melting point of the PEGs of interest lies under 65°C in every case (e.g. the m.p. of PEG 1000 is 30–40°C, the m.p. of PEG 4000 is 50–58°C and the m.p. of PEG 20 000 is 60–63°C) [48]. These relatively low melting points are advantageous for the manufacture of solid dispersions by the melting method. Additional attractive features of the PEGs include their ability to solubilize some compounds [31] and also to improve compound wettability. Even the dissolution rate of a relatively soluble drug like aspirin can be improved by formulating it as a solid dispersion in PEG 6000 [49].

3.2.1.2. Influence of the PEG chain length PEGs of MW 4000–6000 are the most frequently used for the manufacture of solid dispersions, because in this MW range the water solubility is still very high, but hygroscopy is not a problem and the melting points are already over 50°C. If a PEG with too low a MW is used, this can lead to a product with a sticky consistency that is difficult to formulate into a pharmaceutically acceptable product [50]. PEGs with higher MW have also been used with success: products containing PEG 8000 [51] and 10 000 [52] showed enhanced dissolution rates compared to the pure drug.

The importance of the carrier to performance of the solid dispersion was illustrated in a study of 14 different drugs formulated as solid dispersions in PEG 6000 [53]. In this study, Dubois and Ford showed that, when the drug is present in a low drug/carrier ratio (<2% in the case of phenylbutazone, up to 15% in the case of paracetamol), the release rate is dependent only on the carrier and not on the drug properties. Results with indomethacin showed similar behaviour. Further studies indicated that the release rate is inversely proportional to the chain length of the PEG [54]. Similar results were obtained with etoposide [50] and griseofulvin [16]. However, other studies revealed contradictory behaviour. For example, glyburide release from a solid dispersion in PEG 6000 was faster than from a similar dispersion in PEG 4000 [31]. Possible reasons for the better release from PEG 6000 are that the PEG 6000 was able to dissolve more of the drug than the PEG 4000, leading to a greater percentage drug in the molecularly dispersed form, and that the higher viscosity of the PEG 6000 hindered precipitation of the drug following dissolution of the carrier.

A comprehensive study of phenylbutazone/PEG solid dispersions indicated that the release is dependent on the PEG MW [54]. When the percentage of drug used was low (0.5–2%), the release followed the rank order PEG 1500 > 4000 > 6000 > 20 000, at percentages of 3 and 4% the rank order was PEG 1500 > 4000 > 20 000 > 6000 and at a 5% loading the order was 20 000 > 4000 > 1500 > 6000. Since the rank order could be clearly correlated with the crystallinity of the solid dispersion, the authors concluded that the release is dependent on the extent to which a molecular dispersion can be formed. On the other hand, contradictory results were obtained with chloramphenicol/PEG solid dispersions, for which the rank order of release was PEG 6000 > 4000 > 12 000 > 20 000 [55]. In yet other cases, the MW of the PEG had no influence at all on the release rate. For example, Mura et al. [56] showed that 10% dispersions of naproxen in PEG 4000, 6000 and 20 000 all exhibited similar release.

3.2.1.3. Influence of the drug/PEG ratio The drug/carrier ratio in a solid dispersion is one of the main influences on the performance of a solid dispersion. If the percentage of the drug is too high, it will form small crystals within the dispersion rather than remaining molecularly dispersed. On the other hand, if the percentage of the carrier is very high, this can lead to the complete absence of crystallinity of the drug and thereby enormous increases in the solubility and release rate of the drug. Lin and Cham [57] showed that solid dispersions of naproxen in PEG 6000 released drug faster when a 5 or 10% naproxen loading was used than when a 20, 30 or 50% loading was used. These results could be explained on the basis of X-ray diffraction results, which indicated that dispersions with low loading levels of naproxen were amorphous whereas those with high loadings were partly crystalline. However, the upper limit to the percentage carrier that can be employed is governed by the ability to subsequently formulate the solid dispersion into a dosage form of administrable size.

3.2.1.4. Drug/PEG systems Griseofulvin is probably the most studied drug with respect to dispersion in PEGs. Chiou and Riegelman [16] were able to achieve a noticeable increase in the release rate of griseofulvin from solid dispersions in PEG 4000, 6000 and 20 000. The fruit of research with PEG/griseofulvin combinations is the marketed product, Gris-PEG®. More recent studies with griseofulvin and PEGs have focussed on mixtures with various emulsifying agents. Sjökvist et al. [58] introduced small quantities of polysorbate 80, polyethylenedodecylether (Brij® 35), sodium dodecylsulphate (SLS) and dodecylamonium bromide into 10% w/w dispersions

of griseofulvin in PEG 3000 and by doing so were able to achieve substantial increases in both the rate and extent of dissolution. Best results were obtained with SLS. Other combination systems, such as a griseofulvin/PEG 6000/talc system [47] could only achieve similar results to that of the two-component dispersion. However, the talc system had the advantages of being easier to process and being less tacky.

An increase in the release rate by formulation as a solid dispersion in PEG 4000 has been observed for many drugs, including oxazepam [59], piroxicam [60] zolpidem [61] and glyburide [31]. In some cases, in vivo data have verified the importance of the increase in release rate to the bioavailability of the drug in question. Arias et al. [62] were able to show that a doubling of the release rate in vitro could be translated into an increase in the diuretic effect of triamterene in rats. A good correlation between release data from solid dispersions of nifedipine in PEG 6000 and the elimination of the drug in urine was documented in human studies [63]. Similarly, a two-fold increase in the release rate of carbamazepine achieved by formulation as a solid dispersion in PEG 4000 and 6000 was translated into an increase in the bioavailability relative to a suspension of the drug and the marketed product, Tegretol® [46]. However, even better results could be achieved with a hydroxypropyl-β-cyclodextrin complex. Norfloxacin/PEG 6000 solid dispersions also produce a moderate increase in bioavailability [64]. Further drugs which exhibit elevated release rates when formulated as PEG solid dispersions include Sr33557, a new calcium antagonist [65], ketoprofen [66], oxazepam [67], nifedipine [68], phenytoin [69], ursodeoxycholic acid [70], fenofibrate [71] and prednisolone [30].

There have also been several studies with PEGs of higher MW. Perng et al. [51] achieved a ten-fold increase in the release rate of an experimental 5-lipoxygenase inhibitor with PEG 8000 using a hot melt method. Studies of coevaporates of ibuprofen with PEG 10 000, with the talc system and with mixtures of the two indicated that the mixture of the PEG with talc produced the best results [52].

3.2.1.5. Problems with PEGs In general, there are few toxicity concerns associated with the PEGs and they are approved for many purposes as excipients. The low molecular weight PEGs do, however, tend to show slightly greater toxicity than those of higher molecular weight [48]. In addition, a great number of drugs are compatible with the PEGs. A few cases have been observed in which the PEG proved to have stability problems during manufacture by the hot melt method. A reduction in the PEG chain length was observed for combinations with disulfiram, furosemide, chlorothiazide and chlorpropamide [53]. Another difficulty can lie in the subsequent formulation of the solid dispersion into an acceptable dosage form. If the dispersion is too soft it can be difficult if not impossible to manufacture a tablet dosage form. This is most likely to occur if a PEG with too low a MW is used or if the drug has a plasticizing effect on the PEG [50].

3.2.2. Polyvinylpyrrolidone (PVP)

3.2.2.1. General characteristics of PVP Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3 000 000. These can be classified according to the K value, which is calculated using Fikentscher's equation [72]. Table 2 provides an overview of the relationship between the K value and the approximate molecular weight of PVP.

The glass transition temperature of a given PVP is dependent not only on its MW but also on the moisture content. In general, the glass transition temperature (T_g) is high; for example, PVP K25 has a T_g of 155°C [73]. For this reason PVPs have only limited application for the preparation of solid dispersions by the hot melt method. Due to their good solubility in a wide variety of organic solvents, they are particularly suitable for the preparation of solid dispersions by the solvent method. Similarly to the PEGs, PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for flufenamic acid [74].

3.2.2.2. Influence of the PVP chain length The chain length of the PVP has a very significant influence on the dissolution rate of the dispersed drug from the solid dispersion. The aqueous solubility of the PVPs becomes poorer with increasing chain length and a further disadvantage of the high MW PVPs is their much higher viscosity at a given concentration [72]. Studies with coevaporates of chloramphenicol and PVP revealed that the dissolution of chloramphenicol was slower when PVPs of higher MW were used as the carrier [55]. Similarly, the slower dissolution of indomethacin from PVP K90 compared to PVP K12 was attributed to the higher viscosity generated by PVP K90 in the diffusion boundary layer adjacent to the dissolving surface of the dispersion [24]. Other drugs for which release is known to be slower when incorporated in PVPs of higher MW include sulphathiazole [44] and phenytoin [69]. In the case of probucol, however, a somewhat different relationship was seen: here the rank order of release rate was PVP K30 > K25 > K90 [75]. In

Table 2
K values of PVP and the corresponding molecular weights [72]

K value	Approximate molecular weight
12	2500
15	8000
17	10000
25	30000
30	50000
60	400000
90	1000000
120	3000000

general, though, the dependency of the release rate on MW is clearer for the PVPs than in the case of solid dispersions prepared with PEGs.

3.2.2.3. Drug/PVP ratio Similarly to PEG, solid dispersions prepared with high proportions of PVP tend to exhibit a higher drug solubility and release rate than those with high proportions of drug. For albendazole, for example, it has been shown that an increase in the %PVP in the dispersion leads to an increase in the release rate [76]. Doherty and York [77] studied the release behaviour of furosemide/PVP dispersions as a function of the degree of crystallinity of the preparation. When solid dispersions comprising 50% furosemide were prepared, crystalline regions could be detected by X-ray diffraction. In contrast, when the drug/carrier ratio was 2:3, the dispersion was amorphous. Dispersions containing crystalline areas exhibited biphasic release profiles, with the amorphous areas dissolving quickly and the crystalline areas more slowly. Similar behaviour was reported by Kearney et al. [45] for the experimental anti-inflammatory compound CI-987. When the carrier comprised 81% of the dispersion, no crystalline areas could be detected and the release rate of the compound was rapid. Interestingly, when the %carrier was further increased, the release rate became slower. In the case of piroxicam/PVP solid dispersions [78], the release rate increased with the %PVP up till a ratio of drug/carrier of 1:4, after which it fell again (at ratios of 1:5 and 1:6). These results were clarified with X-ray diffraction studies. Only the dispersion containing a 1:4 ratio was amorphous; at all other ratios semi-crystalline areas could be detected. In this case, the 1:4 ratio proved to be optimal for the formulation of piroxicam in PVP K30.

3.2.2.4. Drug/PVP systems Most studies of PVP solid dispersions reported in the literature have used PVPs of MW 2500–50 000 (K12 to K30). As in the case of PEGs, griseofulvin has been one of the most widely studied compounds. The first solid dispersions of griseofulvin in PVP were reported in 1966 by Mayersohn and Gibaldi [42]. Improved dissolution of the test compound from solid dispersions prepared with PVP K17 have been reported variously for sulphathiazole [44], hydrochlorothiazide [79], and piroxicam [80]. For a series of non-steroidal anti-inflammatory drugs (NSAIDs) including mefenamic acid, azapropazone, glafenin and flotafenin, it was shown that coevaporates prepared with PVP K25 improved the release and bioavailability of the drug more than those prepared with PEG 6000 [81]. Furthermore, it was shown in the same studies that the NSAIDs were less likely to cause ulceration in the GI tract when administered as a solid dispersion. In another study, the release rates from solid dispersions of etopiside in PEGs and PVPs were compared [50]. PVP K25 produced faster release than PEG 3400, 6000 or 8000. On the other hand, the release rate from PEG 3400 and 6000 was higher than from PVP K17. Using PVP K30 as the carrier, the release rate of the 5-lipoxygenase inhibitor SB 210661 [51], a weakly basic experimental compound, RS 8359 [82] and benidipine HCl [83] could all be improved. In the case of atenolol, the improvement in release rate using PVP K30 proved to be better than the release rate from other carriers tested [84].

3.2.2.5. Toxicity profile of PVP Polyvinylpyrrolidones found their first pharmaceutical application as plasma expanders in the 1940s. This role became less important with the advent of dextrans. However, PVPs are still widely used in the pharmaceutical sector as excipients. When given orally, they are regarded as not being toxic, partly because they have too high a MW to be absorbed from the GI tract. Reports of side effects are restricted to the formation of granulomas after intramuscular injection [72].

3.2.3. Polyvinylalcohol (PVA), crospovidone (PVP-CL), polvinylpyrrolidone-polyvinylacetate copolymer (PVP-PVA)

All three polymers belong to the polyvinyl group. Whereas polyvinylalcohol (PVA) and vinylpyrrolidone/vinylacetate (PVP-PVA) copolymers are both water soluble, crospovidone swells when dispersed in water. When solid dispersions of nifedipine were prepared with carrier mixtures consisting of nicotinamide and PVP, hydroxypropylmethylcellulose (HPMC) or PVA in a drug/nicotinamide/polymer ratio of 1:3:1, those prepared with PVA dissolved 20 times as fast as the drug alone [85]. However, the other carriers, HPMC and PVP, yielded even better results. The use of PVA/PVP copolymers as carriers in solid dispersions has been shown to lead to enormous increases in the drug release rate. Studies with the cytostatic drug HO-221 showed that the PVA/PVP solid dispersed not only dissolved 25 times faster than the drug powder, but also enhanced the bioavailability in beagles by a factor of 3.5 [86]. Moneghini et al. [84] reported that in the case of atenolol, too high a PVA/PVP content could lead to a decrease in the release rate of the drug. This observation was attributed to high viscosity in the diffusion boundary layer adjacent to the dissolving surface. Similar results were subsequently reported for PVA/PVP coevaporates of carbamazepine [87]. In this case the optimal drug/carrier ratio was 1:4; when the proportion of carrier was either lower or higher, the increase in the release rate was not as dramatic. The fall-off at higher carrier ratios could be attributed to gel formation in this case. Even though crospovidone does not dissolve in water, it can also be used as a carrier to improve drug release rates. For example, a 1:2 ratio of furosemide to crospovidone led to an increase in the dissolution rate by a factor of 5.8 [88] in comparison with either the drug powder or a physical mixture of furosemide with crospovidone. The mechanism of the increase in the release rate of furosemide proved to be the presentation of the drug in the amorphous form in the dispersion, as shown by X-ray diffraction studies.

3.2.4. Cellulose derivatives

3.2.4.1. General characteristics of cellulose derivatives - Celluloses are naturally occurring polysaccharides that are ubiquitous in the plant kingdom. They consist of high molecular weight unbranched chains, in which the saccharide units are linked by β-1,4-glycoside bonds. By appropriate alkylation, the cellulose can be derivatized to form methyl- (MC), hydroxypropyl- (HPC), hydroxypropylmethyl- (HPMC) and many other semi-synthetic celluloses. Since each glucose unit has three hydroxyl groups that can be derivatized, the average substitution grade (SG) cannot exceed three, unless of course the hydroxyl groups on the substituents themselves (e.g. in the case of HPMC) are also derivatized. A further possibility for derivatization is the esterification of the cellulose to form compounds such as cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HPMCP). The ethyl celluose (EC) is an other hydrophobic cellulose ether used also for controlled release dosage forms.

3.2.4.2. Hydroxypropylmethylcellulose (HMPC) HPMCs are mixed ethers of cellulose, in which 16.5–30% of the hydroxyl groups are methylated and 4–32% are derivatized with hydroxypropyl groups. For example, Type 2910 has an average methoxy content of 29% and an hydroxypropyl content of 10%. The molecular weight of the HPMCs ranges from about 10 000 to 1 500 000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane [89].

Studies with albendazole, a poorly soluble weak base with incomplete bioavailability, showed that the release rate and the bioavailability in beagles could be improved through preparation of a solid dispersion in HPMC [90]. It was further demonstrated that HPMC was able to inhibit the recrystallization of the albendazole, and that a further improvement in release characteristics could be achieved when a carrier mixture consisting of HPMC and HPMCP was employed. Other drugs which exhibit faster release from solid dispersion in HPMC include the poorly soluble weak acids nilvadipine [91] and benidipine [83]. In combination with nicotinamide as the carrier system, HPMCs produced the best increase in the release of nifedipine of the series PVP, PVA and HPMC [85].

3.2.4.3. Hydroxypropylcellulose (HPC) Hydroxypropylmethylcellulose (HPC) exhibits good solubility in a range of solvents, including water (up till 40°C), ethanol, methanol and chloroform. The average MW of the HPCs ranges from 37 000 (Type SSL) to 1 150 000 (Type H) [92]. Yuasa et al. [93] carried out extensive studies of the influence of the chain length and proportion of HPC in the solid dispersion on the release behaviour of flurbiprofen. The release rate improved as the proportion of HPC was increased and when lower MW HPCs were used as the carrier.

3.2.4.3. Hydroxypropylmethylcellulose phthalate (HPMCP) HPMCPs are cellulose esters which are often used as enteric coatings. Depending on the grade, they dissolve first at pH 5 (HP 50) or pH 5.5 (HP 55). Their solubility in organic solvents is also type-dependent. Their MWs range from 20 000 to 2 000 000 [96]. The dissolution rate of griseofulvin at pH 6.8 could be greatly enhanced by incorporating it in a coevaporate of HPMCP [94]. In this case it was shown that griseofulvin was present in the dispersion in the amorphous form. Using a spray-drying technique to form a solid dispersion in HP 55, the dissolution rate of the anti-fungal drug MFB-1041 could be increased by a factor of 12.5 as compared to the best possible dissolution achievable by micronizing the drug [95]. Furthermore, the oral bioavailability in beagles was almost 17 times better following administration of the drug in solid dispersion form. In studies of coevaporates of the poorly water soluble cytostatic drug HO-221, it was shown that, while at pH 1.2 the dispersion in HPMCP did not release the drug, at pH 6.5 it released the drug as well as dispersions in the pH-independent polymers PVP and PVP/PVA [86]. In this set of studies, the bioavailability of the various dispersions of HO-221 was assessed in beagles. The coevaporate in PVP/PVA led to an increase in bioavailability of 30–60%, whereas the coevaporate in HPMCP led to almost complete absorption of the drug. Since the intraduodenal application of the PVP/PVA coevaporate also led to virtually complete absorption, it was concluded that the incomplete absorption from PVP/PVA coevaporate after oral administration was due to precipitation of the drug following rapid dissolution and formation of a supersaturated solution in the gastric juice. These studies demonstrated the potential advantage of using a gastric juice resistant polymer as carriers for poorly soluble drugs.

3.2.4.4. *Ethylcellulose (EC)* is an ethyl ether of cellulose, is a long chain polymer of b-anhydroglucose units joined together by acetal linkages. It is a hydrophobic polymer and is used extensively as a coating material for the preparation of microcapsules, microspheres and tablets, a binder for the preparation of conventional as well as matrix type controlled release tablets, etc. It is also used in solid dispersion for water soluble drugs, or sparingly water soluble drugs. It has been observed that the amount of EC used for solid dispersion has a direct effect on the release rate of the drug.

3.2.5. Polyacrylates and polymethacrylates

Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. In pharmaceuticals they are mostly used as coatings to modify the release of the drug from the dosage form. Commonly they are referred to by the trade name Eudragit® [97]. Among the Eudragits,

Eudragit® E is often used to improve the release rate since it is soluble in buffer solutions at pH values up to 5 and swells at higher pHs, while Eudragit® L can be used when it is desirable to avoid release in the stomach. When benipidine was formulated as a coevaporate with Eudragit® E, the rate of dissolution was much higher than from the pure drug powder [83]. On the other hand, Eudragit® L has been successfully used to increase the dissolution of griseofulvin and spironolactone at a pH value of 6.8 [94].

3.2.6. Urea

Urea is the end product of human protein metabolism, has a light diuretic effect and is regarded as non-toxic. Its solubility in water is greater than 1 in 1 and it also exhibits good solubility in many common organic solvents. In one of the first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea [9]. Similarly, Goldberg et al. [21] reported faster dissolution rates of chloramphenicol when prepared with urea as the carrier. Although urea is not often used as a carrier these days, it has been recently shown that the dissolution rate of the poorly soluble compound ofloxacin can be improved by more than three-fold by incorporating it in a coevaporate with urea [98]. In the case of ursodeoxycholic acid the release rate from urea dispersions prepared by the hot melt method was faster than from other carriers studied, including PEG 6000 [70]. A two-fold increase in the dissolution rate of phenytoin has also been achieved with urea; however, in this case PEG 6000 was far more efficient [69].

3.2.7. Sugar, polyols and their polymers

Although sugars and related compounds are highly water soluble and have few, if any, toxicity issues, they are less suitable than other carriers for the manufacture of solid dispersions. The melting point of most sugars is high, making preparation by the hot melt method problematic, and their solubility in most organic solvents is poor, making it difficult to prepare coevaporates. Despite these drawbacks, several attempts to prepare solid dispersions using sugars and their derivatives have been reported. Mannitol, which has a melting point of 165–168°C and decomposes only above 250°C, can be employed in some cases to prepare dispersions by the hot melt method. Improved release characteristics have been reported for sorbitol dispersions of several compounds, including nitrofurantoin [63], prednisolone [30], ofloxacin [98] and ursodeoxycholic acid [70]. In most of these cases, other carriers produced better results. Interestingly, nitrofurantoin showed better release from sorbitol than mannitol dispersions (the two sugars are isomers) [63]. Indeed, a dispersion of prednisolone in sorbitol released the drug faster than all other carriers tested, including PEG, PVP, urea and mannitol [30]. Chitosan, a derivative of the polysaccharide chitin which is formed by deacetylation at the N position, has also been used as a carrier in solid dispersions. Both chitosan and its salt form, chitosan glutamate, were able to improve the release of nifedipine by a factor of two to three compared to the drug powder [99]. In these studies, the performance of the coevaporates was compared to that of physical dispersions prepared by co-grinding. The coevaporates produced faster release rates than co-ground mixtures.

3.2.8. Emulsifiers

The release behaviour of many drugs can also be improved through the use of emulsifying agents. Two mechanisms are possible here: improvement of wetting characteristics and solubilization of the drug. Owing to their potential toxicity problems, such as damage to mucosal surfaces, they are usually used in combination with another carrier. For example, the release of naproxen from solid dispersions in PEG 4000, 6000 and 20 000 could be further enhanced when either sodium lauryl sulphate (SLS) or Tween® 80 (a polyethylene sorbitan fatty acid ester) was added to the system [56]. Inclusion of alkali dodecylsulphate surfactants in carrier systems can lead to conversion of a solid dispersion to a solid solution. Melts of griseofulvin and PEG 6000 normally contain crystalline areas; in the presence of SLS a solid solution is formed [100].

Bile salts and their derivatives are natural surfactants that are built from a steroidal skeleton in the liver and which are important to the emulsification of fats and oils in the diet. As with other surfactants, they can enhance the wetting and solubility of many lipophilic substances, leading to an increase in the dissolution rate. Stoll et al. [27] demonstrated the ability of bile salts such as cholic acid, deoxycholic acid and lithocholic acid to improve not only the release but also the sedative effects of reserpine when given as a coevaporate. Likewise, the release of hydrocortisone can be enhanced by formulation as a solid dispersion in cholesterol and various cholesterol esters [28]. In recent times, however, there has been little activity in this area.

3.2.9. Organic acids and their derivatives

Organic acids such as succinic acid and citric acid have also been used as carriers in solid dispersions, originally to enhance the release rate of griseofulvin [16,20]. In more recent years, no further studies with these two acids have been published. Melts of nifedipine with nicotinamide, the amide of nicotinic acid, exhibited about a six-fold increase in the dissolution rate compared to the drug powder but even better results were obtained with PEG 6000 as the carrier [68]. By combining the nicotinamide with a polymeric carrier such as HPMC or PVP, the release of nifedipine could be further greatly improved [85]. The best results, a 20-fold increase, were obtained with a dispersion of nifedipine, nicotinamide and HPMC in a ratio of 1:3:1.

3.2.10. Other carriers

Many other substances have been tested as carriers for solid dispersions. A hydrolysis product of collagen, Gelita®

Collagel, was reported to improve the release rate of oxazepam by a factor of six when prepared as a solid dispersion by spray drying [67]. Even after tabletting, the solid dispersion displayed better release characteristics than the physical mixture or the drug powder alone [101]. Other materials tested include pentaerythritol [16] and phospholipids [46].

3.3. Characterization of solid dispersions

The methods that have been used to characterize solid dispersions are summarized in Table 3. Among these, the most important methods are thermoanalytical, X-ray diffraction, infrared spectroscopy and measurement of the release rate of the drug. In addition to characterizing the solid dispersion, these methods can be used to differentiate between solid solutions (molecularly dispersed drug), solid dispersions in which drug is only partly molecularly dispersed and physical mixtures of drug and carrier. Due to the complex composition of these preparations, it is often difficult to delineate precisely between molecularly dispersed and not molecularly dispersed systems and different analytical methods may yield disparate results. It is usually assumed that dispersions in which no crystallinity can be detected are molecularly dispersed and the absence of crystallinity is used as a criterion to differentiate between solid solutions and solid dispersions.

Thermoanalytical methods include all that examine a characteristic of the system as a function of temperature. Of these, differential scanning calorimetry (DSC) is the most highly regarded method. DSC enables the quantitative detection of all processes in which energy is required or produced (i.e. endothermic and exothermic phase transformations). The usual method of measurement is to heat the reference and test samples in such a way that the temperature of the two is kept identical. If an energy-requiring phase transition occurs in the test sample, extra heat is applied to this sample so that its temperature climbs at the same rate as in the reference. The additional heat required is recorded and used to quantitate the energy of the phase transition. Exothermic transitions, such as conversion of one polymorph to a more stable polymorph, can also be detected. Lack of a melting peak in the DSC of a solid dispersion indicates that the drug is present in an amorphous rather than a crystalline form. Since the method is quantitative in nature, the degree of crystallinity can also be calculated for systems in which the drug is partly amorphous and partly crystalline. However, crystallinities of under 2% cannot generally be detected with DSC [15].

Table 3
Methods for the characterization of solid dispersions

Dissolution testing
Thermoanalytical methods: differential thermoanalysis and hot stage microscopy
Calorimetric analysis of the solution or melting enthalpy for calculation of entropy change
X-Ray diffraction
Spectroscopic methods, e.g. IR spectroscopy
Microscopic methods including polarization microscopy and scanning electron microscopy

The principle behind X-ray diffraction is that when an X-ray beam is applied to the sample, interference bands can be detected. The angle at which the interference bands can be detected depends on the wavelength applied and the geometry of the sample with respect to periodicities in the structure. Crystallinity in the sample is reflected by a characteristic fingerprint region in the diffraction pattern. Owing to the specificity of the fingerprint, crystallinity in the drug can be separately identified from crystallinity in the carrier. Therefore, it is possible with X-ray diffraction to differentiate between solid solutions, in which the drug is amorphous, and solid dispersions, in which it is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline. However, crystallinities of under 5–10% cannot generally be detected with X-ray diffraction.

Structural changes and lack of a crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy. Since not all peaks in the IR spectrum are sensitive to crystalline changes, it is possible to differentiate between those that are sensitive to changes in crystallinity and those that are not [22].

Release rate experiments cannot be used on a stand-alone basis to determine whether a solid solution has been formed or not. However, in conjunction with other physicochemical data, they provide strong evidence for the formation of a molecularly dispersed or nearly molecularly dispersed system. When the goal of preparing a solid dispersion is to improve the dissolution characteristics of the drug in question, the results of the release rate experiments are obviously of prime importance in assessing the success of the approach. A well-designed release experiment will show whether the solubility of the drug and its dissolution rate has been enhanced, and also whether the resulting supersaturated solution is stable or tends to precipitate quickly. Comparison of results with those for pure drug powder and physical mixtures of the drug and carrier can help to indicate the mechanism by which the carrier improves dissolution: via solubilization and wetting effects which could be affected by a simple mixture of the components, or by formation of a solid dispersion/solution.

4. Summary and future perspectives

Experience with solid dispersions over the last 20–30 years indicates that this is a very fruitful approach to improving the release rate and oral bioavailability of poorly soluble drugs. The most frequent concerns with solid dispersions have been the ability to scale-up the manufacturing method, the physical stability of the dispersion, and the amount of carrier needed to facilitate the required increase in the release rate. When a high carrier/drug ratio must be

used, the amount of dispersion required to administer the usual dose of the drug may be too high to produce a tablet or capsule that can be easily swallowed. The higher the unit dose of the drug, the more likely this problem is to occur. Another aspect that must be considered is the correlation between in vitro and in vivo results. Dispersions with a rapid in vitro release rate may fail to improve the oral bioavailability if the in vitro test conditions do not adequately simulate the gastrointestinal conditions, or if there is some specific interaction between the carrier and a component of the GI fluids or a co-ingested foodstuff. Despite these concerns, several products containing solid dispersions are already on the market and the number is expected to increase dramatically in the next years.

Two trends strongly favour an increasing role for solid dispersions in pharmaceutical development: the increasing number of drug candidates which are poorly soluble, and the substantial improvements in the manufacturing methods for solid dispersions that have been made in the last few years. The application of hot melt extrusion to the production of solid dispersions is a particularly important breakthrough for scale-up of solid dispersion manufacture. Another advantage of solid dispersions over other approaches is that many of the carriers that can be applied are already extensively used in the pharmaceutical industry as excipients, so additional toxicity studies above and beyond what is required for the drug itself should not be required. The possibility of combining several carriers to produce an optimized product further extends the range of possibilities for formulation. Yet another advantage of solid dispersions over other approaches is that the increases in solubility and release rate that can be achieved are often much, much greater (up to orders of magnitude). This could potentially lead to an increase in bioavailability that is so great that the dose administered could be lowered.

Aspects that still need to be addressed in the next years include further improvements in manufacturing on a large scale, and better predictions of whether a particular drug/ carrier combination will lead to a true solid solution or to a partly crystalline dispersion as well as whether the dispersion will remain physically stable during further processing and storage. Last but not least, although this article has been devoted to the use of solid dispersions for the improvement of the release rate and oral bioavailability, by judicious choice of the carrier it is also possible to delay or slow down the release pattern of a drug by formulating it as a solid dispersion. The availability of a wide variety of polymers that are them- selves poorly soluble or which swell under aqueous conditions suggests that solid dispersions have tremendous potential in the area of controlled release dosage

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(54) **SUSTAINED RELEASE PREPARATION OF A MACROLIDE**

MAKROLID-FORMULIERUNG MIT VERZÖGERTER WIRKSTOFFABGABE

PREPARATIONS A LIBERATION PROLONGEE D'UN MACROLIDE

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Description

TECHNICAL FIELD

[0001] The present invention relates to a formulation containing a macrolide compound and being endowed with an ability of an excellent sustained-release, for use in a medical field.

BACKGROUND OF THE INVENTION

[0002] An oral formulation of one of macrolide compounds, namely benelimus with an useful immunosuppressive activity, has been prepared as a solid dispersion composition (SDC), which possesses a rapid-release characterization by using polymers such as hydroxypropylmethyl cellulose and disintegrator. Owing to the presence of disintegrator therein, it is a rapid-release formulation. It has been appraised highly in clinical field owing to its high absorbability. In clinical practice, alternatively, the emergence of an oral benelimus formulation with a sufficient long action and excellent oral absorbability has been expected.

[0003] However, it is the state of the art for a person skilled in the art that the absorbability of a pharmaceutically active agent given orally in a manner as sustained-release formulation is generally reduced and/or that a non-negligible variation of the absorbability is observed. The inventors of the invention have carried out a lot of investigations. Consequently, the inventors have invented sustained-release formulations of macrolide compounds, the representative of which benelimus, characterized in that macrolide compound is excellently absorbed orally and/or that variation of its absorbability is suppressed.

DISCLOSURE OF THE INVENTION

[0004] The present invention relates to a sustained-release formulation of a macrolide compound, wherein the dissolution of the macrolide compound is under sustained release.

[0005] It is an object of the invention to provide a sustained-release formulation of a macrolide compound, wherein the time (T63.2%) required for 63.2 % of the maximum amount of macrolide compound to be dissolved is 0.7 to 15 hours, as measured according to the Japanese Pharmacopoeia, the 13-th edition, Dissolution Test, No. 2 (Paddle method, 50 rpm) using a test solution which is an aqueous 0.005 % hydroxypropyl cellulose solution, adjusted to pH 4.5.

[0006] It is an object of the invention to provide a solid dispersion composition of macrolides compounds stable in the sustained-release formulation mentioned above, wherein the macrolide compound is present as an amorphous state in a solid base.

[0007] The T63.2% value as determined by the dissolution test in accordance with this invention can be estimated from the release curve constructed by plotting test data on graph paper. However, the release profile of a drug can be generally analyzed by fitting dissolution test data to a release model and such a method can-also be used in the computation of said T63.2% value. The model for fitting which can be used includes the first-order or linear model, zero-order model, cube-root model, etc.

[0008] Weibull function is a function such that the dissolution rate (%) in time (T) can be expressed by the following equation:

$$\text{Dissolution rate (\%)} = D_{max} \times \{1-\exp[-((T-Ti)^{n})/m]\}$$

where D_{max} represents the maximum dissolution rate at infinite time, m is a scale parameter representing the dissolution velocity, n is a shape parameter representing the shape of the dissolution curve, Ti is a position parameter representing the lag time till start of dissolution, and the dissolution characteristic of a pharmaceutical product can be expressed by using those parameters in combination.

[0009] In order to fit dissolution test data to Weibull function and calculate the respective parameters, the nonlinear least square method described in Yamaoka, K. & Yagahara, Y.: Introduction to Pharmacokinetics with a Microcomputer, Nankodo, p.40, mentioned above, is used. More particularly, the parameters are determined at the point of time where the sum of the squares of differences between the values calculated by the above equation and the measured values at each point of time is minimal and the dissolution curve calculated by means of the above equation using those parameters is the curve which dose most faithfully represent the measured values.

[0010] The meaning of each parameter of Weibull function is now explained.

[0011] D_{max} (maximum dissolution rate) is the maximum dissolution rate at infinity of time as mentioned above and generally the value of D_{max} is preferably as close to 100 (%) as possible.

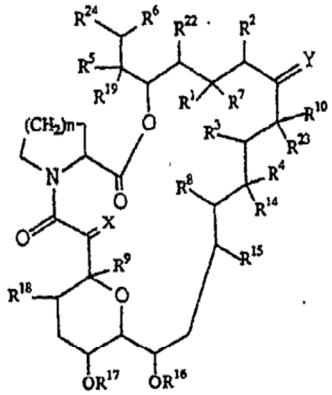
[0012] m (scale parameter) is a parameter representing the dissolution velocity of a pharmaceutical product, and the smaller the value of m is, the higher is the dissolution velocity and similarly the larger the value of m is, the lower is the dissolution velocity.

[0013] n (shape parameter) is a parameter representing the shape of a dissolution curve. When the value of n is 1, Weibull function can be written as dissolution rate (%) = D_{max} x {1-exp[-(T-Ti) /m]}, and since this is equivalent to first-order kinetics, the dissolution curve is linear. When the value of n is smaller than 1, the dissolution curve plateaus off. When the value of n is larger than 1, a sigmoid dissolution curve prevails.

[0014] Ti (position parameter) is a parameter representing the lag time till start of dissolution.

[0017] The term "macrolide compound" for use in accordance with the invention is the generic name of compounds with 12 members or more, which belong to large-ring lactones. Abundant macrolide compounds generated by microorganisms of the genus Streptomyces, such as rapamycin, benelimus (FK007), and ascomycin, and the analogs and derivatives thereof are included in the term macrolide compound.

[0018] The macrolide compound of the invention is a tricyclic compound of the following formula (I).



(I)

(wherein each of adjacent pairs of R^1 and R^2, R^3 and R^4 , and R^5 and R^6 independently

(a) is two adjacent hydrogen atoms, but R^2 may also be an alkyl group or
(b) may form another bond formed between the carbon atoms to which they are attached;

R^7	is a hydrogen atom, a hydroxy group, a protected hydroxy group, or an alkoxy group, or an oxo group together with R^1;
R^8 and R^9	are independently a hydrogen atom or a hydroxy group;
R^{10}	is a hydrogen atom, an alkyl group, an alkyl group substituted by one or more hydroxy groups, an alkenyl group, an alkenyl group substituted by one or more hydroxy groups, or an alkyl group substituted by an oxo group;
X	is an oxo group, (a hydrogen atom and a hydroxy group) , (a hydrogen atom and a hydrogen atom), or a group represented by the formula $-CH_2O-$;
Y	is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula $N-NR^{11}R^{12}$ or $N-OR^{13}$;
R^{11} and R^{12}	are independently a hydrogen atom, an alkyl group, an aryl group or a tosyl group;
R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23}	are independently a hydrogen atom or an alkyl group;
R^{24}	is an optionally substituted ring system which may contain one or more heteroatoms;
n	is an integer of 1 or 2; and

in addition to the above definitions, Y, R^{10} and R^{23}, together with the carbon atoms to which they are attached, may represent a saturated or unsaturated 5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring optionally substituted by one or more groups selected from the group consisting of an alkyl, a hydroxy, an alkoxy, a benzyl, a group of the formula $-CH_2Se(C_6H_5)$, and an alkyl substituted by one or more hydroxy groups.

[0019] Preferable R^{24} may be cyclo(C_{5-7})alkyl group, and the following ones can be exemplified.

(a) a 3,4-di-oxo-cyclohexyl group;
(b) a 3-R^{20}-4-R^{21}-cyclohexyl group,
in which

R^{20} is hydroxy, an alkoxy group, an oxo group, or a $-OCH_2OCH_2CH_2OCH_3$ group, and
R^{21} is hydroxy, -OCN, an alkoxy group, a heteroaryloxy which may be substituted by suitable substituents, a $-OCH_2OCH_2CH_2OCH_3$ group, a protected hydroxy group, chloro, bromo, iodo, aminooxalyloxy, an azido group, p-tolyloxythiocarbonyloxy, or $R^{25}R^{26}CHCOO-$,
in which

R^{25} is optionally protected hydroxy or protected amino, and
R^{26} is hydrogen or methyl, or

R^{20} and R^{21} together form an oxygen atom in an epoxide ring; or

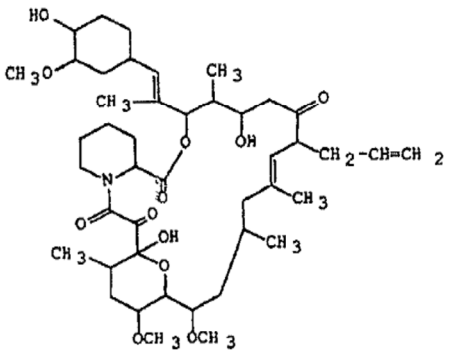
(c) cyclopentyl group substituted by methoxymethyl, optionally protected hydroxymethyl, acyloxymethyl (in which the acyl moiety optionally contains either a dimethylamino group which may be quaternized, or a carboxy group which may be esterified) , one or more amino and/or hydroxy groups which may be protected, or aminooxalyloxymethyl. A preferred example is a 2-formyl-cyclopentyl group.

[0020] The definitions used in the above general formula (I) and the specific and preferred examples thereof are now explained and set forth in detail.

[0021] The term "lower" means, unless otherwise indicated, a group having 1 to 6 carbon atoms.

[0022] Preferable examples of the "alkyl groups" and an alkyl moiety of the "alkoxy group" include a straight or branched chain aliphatic hydrocarbon residue, for example, a lower alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl and hexyl.

[0033] The FK007 (general name: benelimus) following chemical formula, is preferred and of particular interest according to the invention.



Chemical name: 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone

[0034] The preferred examples of the tricyclic compounds (I) are the ones, wherein each of adjacent pairs of R^3 and R^4 or R^5 and R^6 independently form another bond formed between the carbon atoms to which they are attached;
each of R^8 and R^{23} is independently a hydrogen atom;
R^9 is a hydroxy group;
R^{10} is a methyl group, an ethyl group, a propyl group or an allyl group;
X is (a hydrogen atom and a hydrogen atom) or an oxo group;
Y is an oxo group;
each of R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{22} is a methyl group;
R^{24} is a 3-R^{20}-4-R^{21}-cyclohexyl group, in which

R^{20} is hydroxy, an alkoxy group, an oxo group, or a $-OCH_2OCH_2CH_2OCH_3$ group, and
R^{23} is hydroxy, -OCN, an alkoxy group, a heteroaryloxy which may be substituted by suitable substituents, a $-OCH_2OCH_2CH_2OCH_3$ group, a protected hydroxy group, chloro, bromo, iodo, aminooxalyloxy, an azido group, p-tolyloxythiocarbonyloxy, or $R^{25}R^{26}CHCOO$-, in which

R^{25} is optionally protected hydroxy or protected amino, and
R^{26} is hydrogen or methyl, or

R^{20} and R^{21} together form an oxygen atom in an epoxide ring; and

n is an integer of 1 or 2.

[0035] The most preferable tricyclic compounds (I) are, in addition to FK007, ascomycin derivatives such as halogenated-ascomycin (e.g., 33-epi-chloro-33-desoxyascomycin), which is disclosed in EP 427,680, example 66a.

[0036] The tricyclic compounds (I) have a similar basic structure, i.e., tricyclic macrolide structure, and at least one of the similar biological properties (for example, immunosupressive activity).

[0037] The tricyclic compounds (I) may be in a form of its salt, which includes conventional non-toxic and pharmaceutically acceptable salt such as the salt with inorganic or organic bases, specifically, an alkali metal salt such as sodium salt and potassium salt, an alkali earth metal salt such as calcium salt and magnesium salt, an ammonium salt and an amine salt such as triethylamine salt and N-benzyl-N-methylamine salt.

[0038] With respect to the macrolide compound used in the present invention, it is to be understood that there may be conformers and one or more stereoisomers such as optical and geometrical isomers due to asymmetric carbon atom (s) or double bond(s) , and such conformers and isomers are also included within the scope of macrolide compound in the present invention. And further, the macrolide compounds can be in the form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

[0039] The sustained-release formulation in accordance with the present invention is a formulation comprising a solid dispersion composition, wherein the macrolide compound is present as an amorphous state in a solid base, which shows

its T 63.2% value is 0.7 to 15 hours. The presence or absence of a diffraction peak detected by X-ray crystallography, thermal analyses, and so on indicates whether or not a macrolide compound is present as an amorphous state in a solid base in the solid dispersion composition.

[0040] The solid base of the invention is a water-insoluble pharmaceutically acceptable bases capable of retaining the macrolide compound as an amorphous state and being at the solid state at ambient temperature, selected from, wax and water-insoluble polymers.

[0041] Specifically, preferable examples of wax include glycerin monostearate and sucrose fatty acid esters [for example, mono-, di- or triesters of sucrose with moderate to higher fatty acids, with 8 to 20 carbon atoms, for example caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachic acid, behenic acid, oleic acid, linoleic acid, etc.). Additional examples of wax include polyglycerin fatty acid ester. Any polyglycerin fatty acid ester including monoester, diester or polyester of polyglycerin with fatty acid is satisfactory. Specific examples of polyglycerin fatty acid ester include for example behenate hexa(tetra)glyceride, caprylate mono(deca)glyceride, caprylate di(tri)glyc-eride, caprate di(tri)glyceride, laurate mono(tetra)glyceride, laurate mono(hexa)glyceride, laurate mono(deca)glyceride, oleate mono(tetra)glyceride, oleate mono(hexa)glyceride, oleate mono(deca)glyceride, oleate di(tri)glyceride, oleate di (tetra)glyceride, oleate sesqui(deca)glyceride, oleate penta(tetra)glyceride, oleate penta (hexa) glyceride, oleate deca (deca)glyceride, linoleate mono(hepta)glyceride, linoleate di(tri)glyceride, linoleate di(tetra)glyceride, linoleate di(hexa) glyceride, stearate mono(di)glyceride, stearate mono(tetra)glyceride, stearate mono(hexa)glyceride, stearate mono(de-ca)glyceride, stearate tri(tetra)glyceride, stearate tri(hexa)glyceride, stearate sesqui (hexa)glyceride, stearate penta (tetra)glyceride, stearate penta(hexa)glyceride, stearate deca(deca)glyceride, palmitate mono(tetra)glyceride, palmitate mono(hexa)glyceride, palmitate mono(deca)glyceride, palmitate tri(tetra)glyceride, palmitate tri(hexa)glyceride, palmitate sesqui(hexa)glyceride, palmitate penta(tetra)glyceride, palmitate penta(hexa)glyceride, and palmitate deca(deca) glyceride. Preferable polyglycerin fatty acid esters are for example behenate hexa (tetra) glyceride [for example, Poem J-46B under a trade name, manufactured by Riken Vitamin Co., Ltd.], stearate penta(tetra)glyceride [for example, PS-310 under a trade name, manufactured by Sakamoto Yakuhin Kogyo Co., Ltd.], stearate mono (tetra) glyceride [for example, MS-310 under a trade name, manufactured by Sakamoto Yakuhin Kogyo Co., Ltd.], stearate penta(hexa) glyceride [PS-500 under a trade name, manufactured by Sakamoto Yakuhin Kogyo Co., Ltd.], stearate sesqui (hexa) glyceride [SS-500 under a trade name, manufactured by Sakamoto Yakuhin Kogyo Co., Ltd.], stearate mono(deca) glyceride and a mixture thereof. More preferable waxes are glycerin monostearate and low-HLB sucrose fatty acid ester [for example, F-50, F-20, F-10, etc., manufactured by Dai-ichi Kogyo Seiyaku, Co., Ltd.).

[0042] The weight ratio of the macrolide compound and wax is preferably 1 : 10 to 1 : 100, more preferably 1 : 40 to 1 : 60, when the wax is for example glycerin monostearate; the weight ratio thereof is preferably 1 : 0.2 to 1 : 20, more preferably 1 : 0. 5 to 1 : 5, when the wax is for example sucrose fatty acid ester; the weight ratio thereof is preferably 1 : 0.1 to 1 : 100, more preferably 1 : 0.5 to 1 : 50, when the wax is polyglycerin fatty acid ester.

[0043] Preferable water-insoluble polymers include for example ethylcellulose , metacrylate copolymers (for example, Eudragits such as Eudragit E, R, S, RS, LD, etc.) . In case that the water-insoluble polymer is ethylcellulose, a pharmaceutically acceptable one can be used in the present invention. However, its preferable viscosity is 3 to 110 cps, more preferably 6 to 49 cps, most preferably 9 to 11 cps, when the viscosity of 5% ethylcellulose-toluene/ethanol (80/20) solution is measured by a viscosity test described in USP 23, NF18. For example, the preferable one is ETHOCELL (viscosity: 10) (trademark, Dow Chemical(US)).

[0044] The weight ratio of the macrolide compound and the water-insoluble polymer is preferably 1 : 0.01 to 1 : 10, more preferably 1 : 0.1 to 1 : 5; most preferably 1 0. 1 to 1 : 1, when the water-insoluble polymer is ethylcellulose; the weight ratio thereof is most preferably 1 : 0.5 to 1 : 5, when the water-insoluble polymer is a methacrylate copolymer.

[0045] The sustained-release formulation of the invention may further contain a water-soluble base; and more preferably, this added base is one of the following water-soluble polymers:

polyvinylpyrrolidone (PVP), cellulose polymer [hydroxypropylmethyl cellulose (HPMC), hydroxypropylmethyl cellu-lose phthalate, methyl cellulose (MC), carboxymethyl cellulose sodium (CMC-Na), hydroxyethyl cellulose, hydrox-ypropyl cellulose (HPC), etc.], pectin, cyclodextrins, galactomannan, polyethylene glycol (PEG) with a mean mo-lecular weight of 4000 or more, gelatin, etc.

[0046] For use, furthermore, the water-soluble polymers are added individually or in a mixture of two or more thereof. A more preferable water-soluble base is cellulose polymer or PVP; and the most preferable water-soluble base is HPMC, PVP or a combination thereof. In particular, HPMC of a type with a low viscosity can exert a more desirable sustained-release effect, when used; an aqueous 2% solution of the type of HPMC is at a viscosity of 1 to 4,000 cps, preferably 1 to 50 cps, more preferably 1 to 15 cps, as measured at 20 °C by a viscometer of Brookfield type; in particular, HPMC 2910 at a viscosity of 3 cps (TC-5E, EW, Shin-estu Chemical Co., Ltd.) is preferable.

[0047] The weight ratio of the macrolide compound and such water-soluble base is preferably 1 : 0.05 to 1 : 2, more preferably 1 : 0.1 to 2 : 1, most preferably 1 : 0.2 to 1 : 0.4.

[0048] When preparing the solid dispersion composition of the present invention, the above water-insoluble base, may be usable singly or in combination with the water-soluble base. Since the water-insoluble base is adopted as the essential solid base in the present invention, suitable dissolution profile of the solid dispersion composition can be achieved by mixing a suitable amount of water-soluble base, such as water-soluble polymer (e.g., HPMC). If desired, other than the solid base described above, suitable excipients (lactose, etc.), binders, coloring agents, sweeteners, flavor, diluents, antioxidants (vitamin E, etc.) and lubricants (for example, synthetic aluminium silicate, magnesium stearate, calcium hydrogen phosphate, calcium stearate, talc, etc.) for common use, are added to prepare a solid dispersion composition.

[0049] Depending on the type of the solid base, additionally, the dissolution rate of the macrolide compound from the solid dispersion composition is sometimes too slow or the initial dissolution rate thereof is sometimes required to be elevated. In that case, the dissolution rate of the macrolide compound from the solid dispersion composition can be adjusted, by adding appropriate disintegrators [for example, cross carmelose sodium (CC-Na), carboxymethyl cellulose, crosspovidone, etc.] or appropriate surfactants [for example, hardened polyoxyethylene castor oil, polyoxyl stearate 40, polysorbate 80, sodium lauryl sulfate, sucrose fatty acid ester (HLB is more than 10), etc] to the solid dispersion composition.

0050] The particule size of the solid dispersion composition where the macrolide compound is present as an amorphous state in the solid base is preferably equal to or smaller than 500 μm. More preferably, the composition is of a particle size passing through a 350-μm, most preferably 250-μm sieve.

[0051] Furthermore, the solid dispersion composition of a macrolide compound comprised in the sustained-release formulation in accordance with the invention can be produced by methods described EP 1123456 and the like; the methods are more specifically described below.

[0052] The macrolide compound is dissolved in an organic solvent (for example, ethanol, dichloromethane or an aqueous mixture thereof, etc.), followed by addition of an appropriate amount of a solid base, and the resulting mixture is sufficiently dissolved or suspended together or is allowed to swell. Then, the mixture is sufficiently kneaded together.

After removing the organic solvent from the mixture, the residue is dried and ground and is then subjected to size reduction, whereby a solid dispersion composition can be prepared, where the macrolide compound is present as an amorphous state in the solid base. During the kneading process, furthermore, lubricants such as calcium hydrogen phosphate, excipients such as lactose, and the like can further be added to the mixture, if necessary.

[0053] The sustained-release formulation comprising a macrolide compound in accordance with this invention can be manufactured by using a finely divided powder of the macrolide compound. The particle size control of the macrolide compound can be effected by means of milling machinery which is of routine use in pharmaceutical industry. The macrolide compound fine powder should have a particle diameter distribution within the range of 0.1~50 μm, preferably 0.2~20 μm, and more preferably 0.5~10 μm, and/or a mean particle diameter of 0.2~20 μm, preferably 0.5~10 μm, and more preferably 1~5μm.

[0055] If desired, then, the sustained-release formulation can be prepared by mixing the solid dispersion composition of macrolide compounds, with, for example, diluents or lubricants (such as sucrose, lactose, starch, crystal cellulose, synthetic aluminium silicate, magnesium stearate, calcium stearate, calcium hydrogen phosphate, and talc) and/or coloring agents, sweeteners, flavor and disintegrators for routine use. The resulting mixture is then thoroughly mixed together to prepare a sustained-release formulation.

[0056] The effective dose of the macrolide compound varies, depending on the type of the compound, the age of a patient, his (her) disease, the severity thereof, or other factors. Generally, the effective ingredient is used at a dose of about 0.001 to 1,000 mg, preferably 0.01 to 500 mg, more preferably 0.1 to 100 mg per day for the therapeutic treatment of the disease; generally, a mean single dose is about 0.01 mg, 0.1 mg, 0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg, and 500 mg.

[0057] After oral administration, the sustained-release formulation of the macrolide compound in accordance with the invention characteristically releases the macrolide compound in a sustained manner and the pharmaceutical activity maintains for a long period. In accordance with this invention, the frequency of administration of pharmacologically active macrolide compounds can be decreased. More particularly, it has become possible to provide a macrolide-containing pharmaceutical formulation which may be administered only once a day. Furthermore, it is by now possible to provide a pharmaceutical composition which is free from the risk for undisired effects caused by a transiently excessive con-centration and insures an expression of pharmacological efficacy over a sufficiently extended period of time.

[0058] The sustained-release formulation of the present invention is useful for treatment and/or prevention of the following diseases and conditions because of the pharmacological activities possessed by the said macrolide tricyclic compounds (I).

Rejection reactions by transplantation of organs or tissues such as the heart, kidney, liver, bone marrow, skin, cornea, lung, pancreas, small intestine, limb, muscle, nerve, intervertebral disc, trachea, myoblast, cartilage, etc.;

graft-versus-host reactions following bone marrow transplantation;

autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, etc.;

and infections caused by pathogenic microorganisms (e.g. Aspergillus fumigatus, Fusarium oxysporum, Trichophyton asteroides, etc.);

Inflammatory or hyperproliferative skin diseases or cutaneous manifestations of immunologically-mediated diseases (e.g. psoriasis, atopic dermatitis, contact dermatitis, eczematoid dermatitis, seborrheic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, erythema, dermal eosinophilia, lupus erythematosus, acne, and alopecia areata) ;

autoimmune diseases of the eye (e.g. keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical keratitis, corneal epithelial dystrophy, keratoleukoma, ocular premphigus, Mooren's ulcer, scleritis, Graves' ophthalmopathy, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca(dry eye), phlyctenule, iridocyclitis, sarcoidosis, endocrine ophthalmopathy, etc.);

reversible obstructive airways diseases [asthma (e.g. bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, and dust asthma), particularly chronic or inveterate asthma (e.g. late asthma and airway hyper-responsiveness) bronchitis, etc.];

mucosal or vascular inflammations (e.g. gastric ulcer, ischemic or thrombotic vascular injury, ischemic bowel diseases, enteritis, necrotizing enterocolitis, intestinal damages associated with thermal burns, leukotriene B4-mediated diseases);

intestinal inflammations / allergies (e.g. coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis);

food-related allergic diseases with symptomatic manifestation remote from the gastrointestinal tract (e.g. migrain, rhinitis and eczema);

renal diseases (e.g. intestitial nephritis, Goodpasture's syndrome, hemolytic uremic syndrome, and diabetic nephropathy);

nervous diseases (e.g. multiple myositis, Guillain-Barre syndrome, Meniere's disease, multiple neuritis, solitary neuritis, cerebral infarction, Alzheimer's disease, Parkinson's disease amyotrophic lateral sclerosis(ALS) and radiculopathy);

cerebral ischemic disease(e.g., head injury, hemorrhage in brain(e.g., subarachnoid hemorrhage, intracerebral hemorrhage), cerebral thrombosis, cerebral embolism, cardiac arrest, stroke, transient ischemic attack (TIA), hypertensive encephalopathy, cerebral infarction);

endocrine diseases (e.g. hyperthyroidism, and Basedow's disease);

hematic diseases (e.g. pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, and anerythroplasia);

bone diseases (e.g. osteoporosis);

respiratory diseases (e.g. sarcoidosis, pulmonary fibrosis, and idiopathic interstitial pneumonia);

skin diseases (e.g. dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photosensitivity, and cutaneous T-cell lymphoma);

circulatory diseases (e.g. arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, and myocardosis);

collagen diseases (e.g. scleroderma, Wegener's granuloma, and Sjogren's syndrome);

adiposis;

eosinophilic fasciitis;

periodontal diseases (e.g. damage to gingiva, periodontium, alveolar bone or substantia ossea dentis);

nephrotic syndrome (e.g. glomerulonephritis);

male pattern alopecia, alopecia senile;

muscular dystrophy;

pyoderma and Sezary syndrome;

chromosome abnormality-associated diseases (e.g. Down's syndrome);

Addison's disease;

active oxygen-mediated diseases [e.g. organ injury (e.g. ischemic circulation disorders of organs (e.g. heart, liver, kidney, digestive tract, etc.) associated with preservation, transplantation, or ischemic diseases (e.g. thrombosis, cardial infarction, etc.)):

intestinal diseases (e.g. endotoxin shock, pseudomembranous colitis, and drug- or radiation-induced colitis):

renal diseases (e.g. ischemic acute renal insufficiency, chronic renal failure):

pulmonary diseases (e.g. toxicosis caused by pulmonary oxygen or drugs (e.g. paracort, bleomycin, etc.), lung cancer,

and pulmonary emphysema):
ocular diseases (e.g. cataracta, iron-storage disease (siderosis bulbi), retinitis, pigmentosa, senile plaques, vitreous scarring, corneal alkali burn): dermatitis (e.g. erythema multiforme, linear immunoglobulin A bullous dermatitis, cement dermatitis): and other diseases (e.g. gingivitis, periodontitis, sepsis, pancreatitis, and diseases caused by environmental pollution (e.g. air pollution), aging, carcinogen, metastasis of carcinoma, and hypobaropathy)];
diseases caused by histamine release or leukotriene C4 release;
restenosis of coronary artery following angioplasty and prevention of postsurgical adhesions;
autoimmune diseases and inflammatory conditions (e.g., primary mucosal edema, autoimmune atrophic gastritis, lens-induced uveitis, idiopathic leukopenia, active chronic hepatitis, idiopathic cirrhosis, discoid lupus erythematosus, autoimmune orchitis,arthritis(e.g. arthritis deformans),or polychondritis);
Human Immunodeficiency Virus (HIV) infection, AIDS; allergic conjunctivitis; hypertrophic cicatrix and keloid due to trauma.

[0059] In addition, the said tricyclic macrolides have liver regenerating activity and/or activities of stimulating hypertrophy and hyperplasia of hepatocytes. Therefore, the pharmaceutical composition of the present invention is useful for increasing the effect of the therapy and/or prophylaxis of liver diseases.

[0060] And further, the present composition is also useful for increasing the effect of the prevention and/or treatment of various diseases because of the useful pharmacological activity of the said tricyclic macrolides, such as augmenting activity of chemotherapeutic effect, activity of cytomegalovirus infection, anti-inflammatory activity, against peptidyl-prolyl isomerase or rotamase, antimalarial activity, antitumor activity, and so on.

[0061] This invention further provides a dissolution test method for oral solid formulation comprising macrolide compound which uses a test solution containing a suitable amount of cellulose polymer. In general, the dissolution test for testing a release characteristic of a medicinally active ingredient dissolved from a solid formulation containing it is carried out in accordance with Dissolution Test, Method 2 (Paddle method, 50 rpm), JP XIII, or Dissolution Test shown in USP 23. However, in conducting dissolution test of a formulation tesrt of a fromulation comprising macrolide compound a small amount of a macrolide compound, the release of the macrolide compound based on the intrinsic content thereof may not reach 100% even after several hours. This is because, when the amount of the macrolide compound is small, adsorption of the macrolide compound on surfaces of the test vessel, filter, etc. will exert an influence of increased magnitude. After much investigation, the present inventors found that by adding a suitable amount of cellulose polymer (such as HMPC, hydroxypropymethylcellulose or HPC, Hydroxypropylcellulose and so on) to the test solution and by, if necessary, adding phosphoric acid or the like to the test solution so as to bring its pH to not higher than 7 in order to avoid the adverse effect of the consequent increase in pH on the stability of the macrolide compound, the influence of adsorption of the macrolide compound on surfaces of the test apparatus can be inhibited to achieve a recovery rate of substantially 100%. Preferable cellulose polymer is hydroxypropyl cellulose or its equivalent, the viscosity of the solution is measured with a rotary viscometer at 25±0.1°C, the solution shows a viscosity of 75-150 cps.

[0062] The "suitable amount" of cellulose polymer to be added to the test solution is 0.001~0.1%, preferably 0.002~0.01%, and most preferably 0.005%, all based on the total amount of the test solution.

[0063] Where necessary, the test is performed with the test solution adjusted to a suitable pH. In the present invention, pH is preferably not higher than 7. In the present invention, "Dissolution Test, Method 2 (Paddle method, 50 rpm), JP XIII" means "Dissolution Test,Method 2 (Paddle method), JP XIII, which is carried out with stirring 50 revolutions per minute. The corresponding descriptions in JP XIII, USP 23 (NF18) and European Pharmacopoeia (3rd edition) is incorporated in this specification by reference.

[0064] The invention will now be described in the following examples. In the following examples, FK007 is admixed as its monohydrate when preparing compositions containing it, though its amount is expressed as the weight of FK007 not of its monohydrate.

Example 1 (Reference)

[0065]

FK007	1.0 mg
HPMC 2910	1.0 mg
total	2.0 mg

[0066] FK007 was dissolved in ethanol, and to the resulting solution was added HPMC 2910 for allowing FK007 to sufficiently swell. Thereafter, the mixture was kneaded together. The resulting kneaded mixture was transferred to a stainless tray, dried in vacuo, and ground with a coffee mill. Subsequently, the resulting powder was subjected to size reduction by the following processes, to prepare solid dispersion composition (hereinafter referred as SDC) 1-1) to 1-6).

(1) The ground powder was passed through a 250-μm sieve, and a fraction of those remaining on the sieve is designated as SDC 1-1) (> 250 μm).
(2) The fraction passing through the sieve at the process (1) was passed through a 180-μm sieve, and a fraction of those remaining on the sieve is designated as SDC 1-2) (180 - 250 μm).
(3) The fraction passing through the sieve at the process (2) was passed through a 150-μm sieve, and a fraction of those remaining on the sieve is designated as SDC 1-3) (150 - 180 μm).
(4) The fraction passing through the sieve at the process (3) was passed through a 106-μm sieve, and a fraction of those remaining on the sieve is designated as SDC 1-4) (106 - 150 μm).
(5) The fraction passing through the sieve at the process (4) was passed through a 75-μm sieve, and a fraction of those remaining on the sieve is designated as SDC 1-5) (75 - 106 μm).
(6) The fraction passing through the sieve at the process (5) is designated as SDC 1-6) (< 75 μm).

Example 2 (Reference)

[0067] The SDC 1-2), which was obtained in Example 1, was sufficiently mixed with lactose (58.0 mg), and the resulting mixture was encapsulated, to prepare a capsule.

Example 3 (Reference)

[0068] In a similar manner to that of Example 1, a ground powder of the following SDC of particle sizes of 180 to 250 μm was prepared.

SDC	Macrolide compound	Water-soluble base
3-1)	FK007 (1.0 mg)	HPMC 2910 (0.3 mg)
3-2)	FK007 (1.0 mg)	HPMC 2910 (0.1 mg)

[0069] Furthermore, the SDC 3-1) was sufficiently mixed with lactose (58.7 mg), and the resulting mixture was encapsulated, to prepare capsule 3-1). The SDC 3-2) was sufficiently mixed with lactose (58.9 mg), and the resulting mixture was encapsulated to prepare capsule 3-2).

Example 4 (Reference)

[0070] In a similar manner to that for SDC 1-2) of Example 1, the following SDCs were prepared.

SDC	Macrolide compound	Water-soluble base
4-1) (2.0 mg in total)	FK007 (1.0 mg)	MC (1.0 mg)
4-2) (2.0 mg in total)	FK007 (1.0 mg)	PVP (1.0 mg)
4-3)	FK007	HPMC 2910

(continued)

SDC	Macrolide compound	Water-soluble base
(2.0 mg in total)	(1.0 mg)	(1.0 mg)
4-4) (2.0 mg in total)	FK007 (1.0 mg)	HPC (1.0 mg)
4-5) (2.0 mg in total)	FK007 (1.0 mg)	PEG (1.0 mg)
4-6) (2.0 mg in total)	FK007 (1.0 mg)	HPMC 2910 (0.8mg) PVP (0.2 mg)

[0071] In a similar manner to that of Example 2, lactose (at an appropriate amount) and magnesium stearate (0.6 mg) were added to the respective SDCs to prepare respective capsules, each of 60.0 mg in total.

Example 5 (Reference)

[0072] In a similar manner to that of the SDC 1-2) in Example 1, a SDC was prepared by using FK007 (1.0 mg) and HPMC 2910 (1.0 mg). In a similar manner to that of Example 2, thereafter, the following additives were respectively added to the SDC to prepare capsules 5-1) to 5-4), each of 60.0 mg in total.

Capsule No.	Additive(s)	
5-1)	crystal cellulose magnesium stearate	(appropriate amount) (0.6 mg)
5-2)	calcium hydrogen phosphate magnesium stearate	(appropriate amount) (0.6 mg)
5-3)	lactose L-HPC magnesium stearate	(appropriate amount) (3.0 mg) (0.6 mg)
5-4)	corn starch calcium stearate	(appropriate amount) (0.6 mg)

Example 6 (Reference)

[0073]

FK007	1.0 g
HPMC 2910	0.3 g
total	1.3 g

[0074] FK007 was dissolved in ethanol, and to the resulting solution was added HPMC 2910 to allow to sufficiently swell. Subsequently, the mixture was kneaded together. The resulting kneaded substance was transferred onto a stain-less tray, dried in vacuo, and ground with a coffee mill. Subsequently, the resulting powder was subjected to size reduction by the following processes, to prepare SDCs 6-1) to 6-6).

(1) The ground powder was passed through a 250-μm sieve, and a fraction of those remaining on the sieve is designated as SDC 6-1) (> 250 μm).
(2) The fraction passing through the sieve at the process (1) was passed through a 180-μm sieve, and a fraction of those remaining on the sieve is designated as SDC 6-2) (180 - 250 μm).
(3) The fraction passing through the sieve at the process (2) was passed through a 150-μm sieve, and a fraction of those remaining on the sieve is designated as SDC 6-3) (150 - 180μ m).
(4) The fraction passing through the sieve at the process (3) was passed through a 106-μm sieve, and a fraction of

those remaining on the sieve is designated as SDC 6-4) (106 - 150 μm).
(5) The fraction passing through the sieve at the process (4) was passed through a 75-μm sieve, and a fraction of those remaining on the sieve is designated as SDC 6-5) (75 - 106 μm).
(6)The fraction passing through the sieve at the process (5) is designated as SDC 6-6).

Example 7 (Reference)

[0075] The SDC 6-4) (1.3 mg) which was obtained in Example 6 was mixed thoroughly with lactose (58.1 mg) and magnesium stearate (0.6 mg), and the resulting mixture was filled in capsules, which was defined as capsule 7.

Example 8 (Reference)

[0076] In a similar manner to that of Example 1, the following SDCs at particle sizes of 180-250 μm are prepared.

SDCs	Macrolide compound	Water-soluble base
8-1)	ascomycin (1.0 mg)	HPMC 2910 (0.3 mg)
8-2)	33-epi-chloro-33-desoxyascomycin (1.0 mg)	HPMC 2910 (0.3 mg)
8-3)	40-O-(2-hydroxy)-ethyl-rapamycin (1.0 mg)	HPMC 2910 (0.3 mg)

[0077] In a similar manner to that of Example 7, each capsule is prepared by adding lactose(58.1mg) and magnesium stearate (0.6mg).

Example 9 (Reference)

[0078]

SDC 9	
FK007	10 g
HPMC 2910	3 g
calcium hydrogen phosphate	3 g
total	16 g

Formulation 9	
SDC 9	16 g
lactose	qs
magnesium stearate	7 g
total	700 g

[0079] FK007 was dissolved in ethanol, and HPMC 2910 is added to and mixed sufficiently with the resulting solution, followed by further addition of calcium hydrogen phosphate. After drying in vacuo overnight, the resulting mixture was subjected to size reduction by using a speed mill and a roll granulator; the resulting powder was sieved with a sieve of 212 μm; a fraction of those passing through the sieve is designated as SDC 9. The SDC 9, lactose and magnesium stearate were mixed together, to prepare Formulation 9. The Formulation 9 was filled at 350 mg in No. 1 capsule and at 70 mg in No. 5 gelatin capsule, which were defined as Formulations A and B, respectively.

Example 10 (Reference)

[0080]

SDC 10	
FK007	10 g
HPMC 2910	3 g
Lactose	3 g
total	16 g

Formulation 10	
SDC 10	16 g
lactose	qs
magnesium stearate	7 g
total	700 g

[0081] In a similar manner to that of example 9, the SDC 10 and Formulation 10 were prepared respectively.

Example 11 (Reference)

[0082]

SDC 11	
FK007	10 g
HPMC 2910	3 g
calcium hydrogen phosphate	3 g
total	16 g

Formulation 11	
SDC 11	16 g
lactose	qs
magnesium stearate	7 g
total	700 g

FK007 was dissolved in ethanol, and HPMC 2910 was added to and mixed sufficiently with the resulting solution, followed by further addition of calcium hydrogen phosphate. After the resulting mixture was dried in vacuo overnight, the mixture was subjected to size reduction by using a speed mill and a roll granulator; the resulting powder was sieved with a sieve of 250 μm and a sieve of 180 μm; a fraction of 180 - 250 μm is defined as SDC 11. The SDC 11, lactose and magnesium stearate were mixed together, to prepare Formulation 11. The Formulation 11 was filled at 350 mg in No. 1 capsule and at 70 mg in No. 5 gelatin capsule, which were defined as Formulations C and D, respectively.

Example 12

[0083]

SDC 12	
FK007	2 g

(continued)

SDC 12	
glycerin monostearate	98 g
HPMC 2910	20 g
total	120 g

Formulation 12	
SDC 12	120 g
magnesium stearate	1.2 g
total	121.2 g

[0084] Glycerin monostearate was heated and melt at 80 °C, to which was added FK007 under agitation to dissolve FK007 therein. To the resulting mixture was added HPMC 2910 for sufficient mixing, and the resulting mixture was then transferred to a tray to stand alone for spontaneous cooling. The solid substance obtained by cooling was ground with a coffee mill and was then sieved with a sieve of 500 μm. A fraction of those passing through the sieve was defined as SDC 12. The SDC 12 was mixed with magnesium stearate, to prepare Formulation 12, which is then filled at 60.6 mg in No. 5 capsule. The resulting capsule is defined as Formulation E.

Example 13

[0085]

SDC 13	
FK007	2 g
Aminoalkyl methacrylate copolymer (Eudragit RL)	6 g
calcium hydrogen phosphate	2 g
total	10 g

Formulation 13	
SDC 13	10 g
lactose	130 g
total	140 g

[0086] In ethanol were dissolved FK007 and aminoalkyl methacrylate copolymer, followed by addition of calcium hydrogen phosphate, and the resulting mixture was sufficiently mixed together. The mixture was dried in vacuo overnight, ground in a mortar, and graded by using sieves of 150 μm and 106 μm, to prepare a fraction of 106 - 150 μm as SDC 13. The SDC 13 was mixed with lactose and prepared as Formulation 13, and was then filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation F.

Example 14

[0087]

SDC 14	
FK007	2 g
Aminoalkyl methacrylate copolymer (Eudragit RL)	4.6 g
Aminoalkyl methacrylate copolymer (Eudragit RS)	1.4 g

(continued)

SDC 14	
calcium hydrogen phosphate	2 g
total	10 g

Formulation 14	
SDC 14	10 g
lactose	130 g
total	140 g

[0088] In a similar manner to that of Example 13, SDC 14 at particle sizes of 106 - 150 μm and Formulation 14 were prepared. And then Formulation 14 was filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation G.

Example 15

[0089]

SDC 15	
FK007	2 g
Aminoalkyl methacrylate copolymer (Eudragit RL)	3 g
AminoalkylmethacrylatecopolymerEudragitRS)	3 g
calcium hydrogen phosphate	2 g
total	10 g

Formulation 15	
SDC 15	10 g
lactose	130 g
total	140 g

In a similar manner to that of Example 13, SDC 15 at particle sizes of 106 - 150 μm and Formulation 15 were prepared. And then Formulation 15 was filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation H.

Example 16

[0090]

SDC 16	
FK007	2 g
Ethylcellulose	0.4 g
lactose	6 g
total	8.4 g

Formulation 16	
SDC 16	8.4 g

(continued)

Formulation 16	
lactose	131.6 g
total	140 g

[0091] In ethanol was dissolved FK007 and ethylcellulose, followed by addition of lactose, and the resulting mixture was sufficiently mixed together. The mixture was dried in vacuo overnight, ground in a mortar, and graded by using sieves of 150 μm and 106 μm, to prepare a fraction of 106 - 150 μm as SDC 16. The SDC 16 was mixed with lactose and prepared as Formulation 16, and was then filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation I.

Example 17

[0092]

SDC 17	
FK007	2 g
Ethylcellulose	1 g
lactose	6 g
total	9 g

Formulation 17	
SDC 17	9 g
lactose	131 g
total	140 g

[0093] In a similar manner to that of Example 16, SDC 17 at particle sizes of 106 - 150 μm and Formulation 17 were prepared. And then Formulation 17 was filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation J.

Example 18

[0094]

SDC 18	
FK007	2 g
Ethylcellulose	0.4 g
hydroxypropylmethyl cellulose	0.6 g
lactose	6 g
total	9 g

Formulation 18	
SDC 18	9 g
lactose	131 g
total	140 g

[0095] In a similar manner to that of Example 16, SDC 18 at particle sizes of 106 - 150 μm and Formulation 18 were prepared. And then Formulation 18 was filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation K.

Example 19

[0096]

SDC 19	
FK007	2 g
Ethylcellulose	0.6 g
HPMC 2910	0.6 g
lactose	6 g
total	9.2 g

Formulation 19	
SDC 19	9.2 g
lactose	130.8 g
total	140 g

[0097] In a similar manner to that of Example 16, SDC 19 at particle sizes of 106 - 150 μm and Formulation 19 were prepared. And then Formulation 19 was filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation L.

Example 20

[0098]

SDC 20	
FK007	10 g
Ethylcellulose	3 g
HPMC 2910	3 g
lactose	50 g
total	66 g

Formulation 20	
SDC 20	66 g
lactose	qs
magnesium stearate	7 g
total	700 g

[0099] FK007 was dissolved in ethanol, and ethylcellulose was added to and was solved. And HPMC 2910 and lactose were mixed sufficiently with the resulting solution. After drying in vacuo overnight, the resulting mixture was subjected to size reduction by using a power mill and a roll granulator; the resulting powder was sieved with a sieve of 250 μm; a fraction of those passing through the sieve is designated as SDC 20. The SDC 20, lactose and magnesium stearate were mixed together, to prepare Formulation 20. The Formulation 20 was filled at 350 mg in No. 1 capsule and at 70 mg in No. 5 gelatin capsule, which were defined as Formulations M and N, respectively.

Example 21

[0100]

SDC 21	
FK007	10 g
Ethylcellulose	3 g
HPMC 2910	3 g
lactose	20 g
total	36 g

Formulation 21	
SDC 21	36 g
lactose	qs
magnesium stearate	7 g
total	700 g

[0101] In a similar manner to that of Example 20, a fraction of those passing through the sieve 212 μm was designated as SDC 21 and Formulation 21 were prepared. And then Formulation 21 was filled at 350 mg in No. 1 gelatin capsule and at 70 mg in No. 5 gelatin capsule to be prepared as Formulation O and P, respectively.

Example 22

[0102]

SDC 22	
FK007	1 g
Sucrose fatty acid ester (HLB=6) (DK ester F-50)	1 g
total	2 g

Formulation 22	
SDC 22	2 g
lactose	68 g
total	70 g

[0103] In ethanol/acetone (1/1) was dissolved FK007. After heating its solution at 75°C, sucrose fatty acid ester was added to be solved and then cooled at room temperature. The mixture was dried in vacuo overnight, ground in a mortar, and graded by using sieves of 150 μm and 106 μm, to prepare a fraction of 106 - 150 μm as SDC 22. The SDC 22 was mixed with lactose and prepared as Formulation 22, and was then filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation Q.

Example 23

[0104]

SDC 23	
FK007	1 g
Sucrose fatty acid ester (HLB=6) (DK ester F-50)	0.75 g
Sucrose fatty acid ester (HLB=2) (DK ester F-20W)	0.25 g
total	2 g

Formulation 23	
SDC 23	2 g
lactose	68 g
total	70 g

[0105] In a similar mariner to that of Example 22, SDC 13 at particle sizes of 106 - 150 μm and Formulation 23 were prepared. And then Formulation 23 was filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation R.

Example 24

[0106]

SDC 24	
FK007	1 g
Sucrosefattyacidester(HLB=1) (DK ester F-10)	1 g
Lactose	1 g
total	3 g

Formulation 24	
SDC 24	3 g
lactose	67 g
total	70 g

[0107] In a similar manner to that of Example 22, SDC 24 at particle sizes of 106 - 150 μm and Formulation 24 were prepared. And then Formulation 24 was filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation S.

Example 25

[0108]

SDC 25	
FK007	1 g
Sucrosefattyacidester(HLB=1) (DK ester F-10)	1 g
Lactose	3 g
total	5 g

Formulation 24	
SDC 24	5 g
Lactose	65 g
total	70 g

[0109] In a similar manner to that of Example 22, SDC 25 at particle sizes of 106 - 150 μm and Formulation 25 were prepared. And then Formulation 25 was filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation T.

Example 26

[0110]

SDC 26	
FK007	1 g
Sucrose fatty acid ester (HLB=1) (DK ester F-10)	1 g
Lactose	5 g
total	7 g

Formulation 26	
SDC 26	7 g
Lactose	63 g
total	70 g

[0111] In a similar manner to that of Example 22, SDC 26 at particle sizes of 106 - 150 μm and Formulation 26 were prepared. And then Formulation 26 was filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation U.

Example 27

[0112]

SDC 27	
FK007	1 g
Tetraglycerine trifatty acid ester	30 g
Lactose	15 g
total	46 g

Formulation 27	
SDC 27	46 g
Lactose	24 g
total	70 g

[0113] In tetraglycerine trifatty acid ester melted by heating at 80 °C was added and solved FK007 with mixing. Lactose was added thereto, mixed and then cooled spontaneously in a tray. The resulting solid substance was ground by a coffee mill, and graded by using sieves of 150 μm and 106 μm, to prepare a fraction of 106 - 150 μm as SDC 27. The SDC 27 was mixed with lactose and prepared as Formulation 27, and then Formulation 27 was filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation V.

Example 28

[0114]

SDC 28	
FK007	1 g
Tetraglycerine trifatty acid ester	30 g
Polysolbate	0.3 g

(continued)

SDC 28	
total	31.3 g

Formulation 28	
SDC 28	31.3 g
Lactose	38.7 g
total	70 g

[0115] In a similar manner to that of Example 27, SDC 28 at particle sizes of 106 - 150 μm and Formulation 28 were prepared. And then Formulation 28 was filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation W.

Example 29

[0116]

SDC 29	
FK007	1 g
Tetraglycerine trifatty acid ester	1 g
Lactose	3 g
total	5 g

Formulation 29	
SDC 29	5 g
Lactose	65 g
total	70 g

[0117] Ethanol was added to tetraglycerine trifatty acid ester. The resulting mixture was melted by heating at 40° C and FK007 was added and melted with mixing. Lactose was added thereto, mixed and then cooled spontaneously in a tray The resulting solid substance was ground by a coffee mill, dried in vacuo overnight and graded by using sieves of 150 μm and 106 μm, to prepare a fraction of 106 - 150 μm as SDC 29. The SDC 29 was mixed with lactose and prepared as Formulation 29, and then Formulation 29 was filled at 70 mg in No. 5 gelatin capsule to be prepared as Formulation X.

Example 30 (Reference)

[0118]

Formulation 30	
FK007 fine powder	0.5 g
Lactose	29.2 g
Magnesium stearate	0.3 g
total	30 g

[0119] FK007 crystal was ground by a jet mill and was mixed with lactose and magnesium stearate to prepare For-mulation 30. Then Formulation 30 was filled at 60 mg in No. 5 gelatin capsule to be prepared as Formulation Z. The range of particle size of FK007 fine powder ground by a jet mill was 1-10 μm and its mean particle size was about 3 μm.

Example 31 (Reference)

Dissolution test

Test sample:

[0120] (1) Formulations A and C, which were prepared in Examples mentioned before.
(2) Control formulation (rapid realse formulation), which is a 1 mg capsule formulation comprising the following ingredients. It is prepared, in a similar manner to that of Examples 2 and 3 of EP 1 123 456, by mixing ingredients (e) and (f) with the solid dispersion composition composed of the following ingredients (a) to (d), and by being encapsulated.

(a)	benelimus (FK007)	1 mg
(b)	hydroxypropylmethyl cellulose	1 mg
(c)	lactose	2 mg
(d)	cross carmelose sodium	1 mg
(e)	lactose	59.35 mg
(f)	magnesium stearate	0.65 mg.

Test method:

[0121] According to the Japanese Pharmacopoeia, the 13-edition, Dissolution Test, No. 2 (Paddle method, 50 rpm) using an aqueous 0.005 % hydroxypropyl cellulose solution, adjusted to pH 4.5 as a test solution, a test was conducted. The obtained data were shown in the following.

Time (hr)	Formulation A (%)	Time (hr)	Formulation C (%)
0	0.0	0	0.0
0.5	17.4	1	12.1
1	35.6	2	30.9
2	57.6	4	55.9
3	71.9	6	71.3
4	80.9	8	81.6
6	89.7	10	87.0
9	95.2	12	90.4

Time (hr)	Control(%)
0	0.0
0.17	30.1
0.5	68.4
1	92.8
2	100.1

Example 32

[0122] In a similar manner to that of Example 31, dissolution test was carried out. And thereby various parameters in Weibull function and T63.2% were obtained by calculation.

Result

[0123]

Result					
Formulation	Dmax (%)	m	n	T i	$T_{63.2\%}$ (hr)
Capsule 7	101.7	2.69	1.18	0.0	2.3
A	95.9	2.24	1.03	0.0	2.2
C	92.5	6.14	1.24	0.0	4.3
E	101.6	1.93	0.60	0.0	3.0
F	95.6	2.51	1.00	0.0	2.5
G	99.0	3.69	0.91	0.0	4.2
H	88.8	6.34	0.88	0.0	8.2
I	95.6	2.51	1.00	0.0	2.5
J	99.0	3.69	0.91	0.0	4.2
K	101.2	1.69	0.80	0.0	1.9
L	91.4	2.48	0.75	0.0	3.3
M	90.4	1.61	0.62	0.0	2.1
O	83.9	2.5	0.67	0.0	3.9
Q	104.7	1.89	0.93	0.0	2.0
R	92.1	2.09	0.82	0.0	2.5
S	86.0	3.73	0.89	0.0	4.4
T	87.9	2.00	0.93	0.0	2.1
U	93.4	1.03	0.86	0.0	1.0
V	83.6	1.14	0.54	0.0	1.3
W	87.1	1.30	0.69	0.0	1.5
Z	85.7	1.98	0.75	0.0	2.5
Control	100.9	0.41	1.10	0.0	0.4

Example 33 (Reference)

Oral absorbability

Test sample:

[0124]

(1) Formulations B and D, which were prepared in the Examples mentioned before.
(2) Control formulation (the same as the control in Example 31)

Test Method:

[0125] The test samples were orally given to 6 cynomologus monkeys (at 1 mg/monkey as an FK007 dose), to assay the blood FK007 concentration after administration. Seventeen hours prior to the administration, feeds were withdrawn from a feed table for cynomologus monkeys of body weights around 6 kg. Then, the animals were starved until 12 hours passed after the administration. Water was fed ad libitum prior to the initiation of the test throughout the administration of the test samples and thereafter. At the dosing, water (20 ml) was simultaneously given to the animals. At predetermined intervals after dosing, 1 ml of blood was drawn from the forearm vein by using a sterile syringe into a plastic tube containing heparin and stored at about -80 °C until the assay of the drug concentration started. The whole blood drug concentration of FK007 was assayed by the FK007-specific enzyme immunoassay (EIA) known in JP-A-1-232323. The disclosure thereof is cited herein and encompassed within the description of the specification.

Mean value			
Time (hr)	Formulation B	Formulation D	control
0	0.00	0.00	0.00
0.5	0.44	0.28	0.91
1	2.59	1.03	3.02
2	4.26	2.27	7.13
4	3.89	3.14	3.27
6	3.48	4.42	3.85
8	3.47	4.12	2.63
10	3.70	4.06	2.48
12	3.73	4.10	2.51
14	3.85	4.13	2.27
16	3.60	4.75	2.20
18	2.96	3.95	1.76
24	2.21	2.57	1.32

[0126] The maximum blood concentration (Cmax) is defined as the maximum value of the whole blood drug. Tmax is the time required for reaching the maximum blood concentration. MRT is defined as the mean retention time. The area under the blood concentration-time curve (AUC) was calculated by the trapezoid method. And as an indicator of the variation of oral absorbability, CV (standard deviation/mean in %) was calculated.

Test results				
Test Samples	Cmax(ng/mL)	Tmax (hr)	MRT (hr)	$AUC_{0\text{-}72hr}$ (ng·hr/mL)
(Formulation No.)	(C.V.(%))	(C.V.(%))	(C.V.(%))	(C.V.(%))
B	5.51±1.02 (45.4)	8.2±2.9 (87.8)	21.1±0.5 (5.5)	126.3±22.2 (43.1)
D	5.48±0.94 (41.8)	10.0±2.7 (66.9)	22.6±1.0 (11.2)	144.3±21.0 (35.7)
Control	8.41±1.46 (42.6)	3.3±0.8 (62.2)	17.6±0.9 (12.7)	91.1±20.4 (54.9)

Example 34

[0127] According to a similar manner to that of Example 33, the oral absorbability of the various formulations of the present invention was carried out.

Results				
Test samples	Cmax (ng/mL)	Tmax (hr)	MRT (hr)	$AUC_{0\text{-}72hr}$ (ng·hr/mL)
(Formulation No.)	[CV%]	[CV%]	[CV%]	[CV%]
E	9.36±1.08 [28.4]	6.3±1.7 [67.5]	20.0±0.4 [5.1]	186.6±18.5 [24.3]
L	6.16±0.57 [22.6]	4.3±1.1 [61.4]	19.3±0.5 [6.9]	135.5±17.7 [31.9]
Q	4.70±0.39 [20.2]	5.0±1.7 [83.0]	21.4±1.6 [7.0]	122.6±10.2 [20.3]
Z	5.72±0.92 [39.3)]	8.0±1.2 [35.4]	20.9±1.2 [13.7]	133.2±16.1 [29.6]

(continued)

Results				
Test samples (Formulation No.)	Cmax (ng/mL) [CV%]	Tmax (hr) [CV%]	MRT (hr) [CV%]	AUC $_{0\text{-}72hr}$ (ng·hr/mL) [CV%]
control	12.27± 2.60 [51.8]	1.4±0.3 [46.5]	14.3±1.0 [17.7]	80.8±15.1 [45.8]

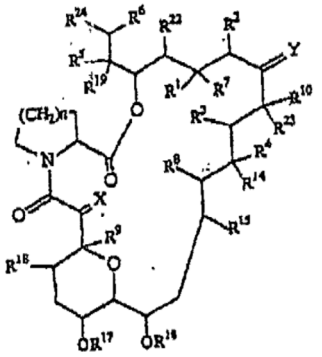
[0128] The above results show that the formulations adopted in the above experiments, after oral administration, have smaller Cmax, sufficiently prolonged Tmax and MRT than those of the rapid-release formulation (control). And compared with the rapid-release formulation, AUC shown by the above formulations are almost the same or more. Or the above sustained-release formulations have small variations in individuals of Cmax and/or AUC, compared with a rapid-release formulation.

[0129] In accordance with the invention of the present application, the small variation in individuals of the maximum blood concentration or area under the blood concentration time curve of the macrolide compound after oral dosing, compared with a rapid release formulation thereof can be determined, by using an indicator of the variation of the blood absorbability of the macrolide compound, namely standard deviation/mean (CV in %) of the maximum blood concentration or the area under the blood concentration time curve. The term "small variation" means a small CV value thereof; more specifically, the term means that the CV value is smaller than that of a rapid release formulation as described above.

[0130] The disclosure of the patents, patent application and references cited herein in the application is encompassed within the description of the specification.

Claims

1. A sustained-release formulation of a macrolide compound, wherein the time (T63.2%) required for 63.2 % of the maximum amount of macrolide compound to be dissolved is 0.7 to 15 hours, as measured according to the Japanese Pharmacopoeia, the 13-th edition, Dissolution Test, No. 2 (Paddle method, 50 rpm) using a test solution which is an aqueous 0.005 % hydroxypropyl cellulose solution adjusted to pH 4.5, in which the macrolide compound is a tricyclic compound represented by the general formula (I) and a pharmaceutically acceptable salt thereof,



(I)

wherein each of adjacent pairs of R^1 and R^2, R^3 and R^4, and R^5 and R^6 independently

(a) is two adjacent hydrogen atoms, but R^2 may also be an alkyl group or
(b) may form another bond formed between the carbon atoms to which they are attached;

R^7 is a hydrogen atom, a hydroxy group, a protected hydroxy group, or an alkoxy group, or an oxo group together with R^1;

R^8 and R^9 are independently a hydrogen atom or a hydroxy group;
R^{10} is a hydrogen atom, an alkyl group, an alkyl group substituted by one or more hydroxy groups, an alkenyl group, an alkenyl group substituted by one or more hydroxy groups, or an alkyl group substituted by an oxo group;
X is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula - CH_2O -;
Y is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula N-$NR^{11}R^{12}$ or N - OR^{13};
R^{11} and R^{12} are independently a hydrogen atom, an alkyl group, an aryl group or a tosyl group;
R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} are independently a hydrogen atom or an alkyl group;
R^{24} is an optionally substituted ring system which may contain one or more heteroatoms;
n is an integer of 1 or 2; and
in addition to the above definitions, Y, R^{10} and R^{23}, together with the carbon atom to which they are attached, may represent a saturated or unsaturated 5- or 6-membered nitrogen-, sulfur- and/or oxygen- containing heterocyclic ring optionally substituted by one or more groups selected from the group consisting of an alkyl, a hydroxy, an alkoxy, a benzyl, a group of the formula -$CH_2Se(C_6H_5)$, and an alkyl substituted by one or more hydroxy groups, which comprises a solid dispersion composition, wherein the macrolide compound (I) is present as an amorphous state in a water-insoluble base,
in which the water-insoluble base comprised in the solid dispersion composition is selected from water-insoluble polymer or wax.

2. The sustained-release formulation in Claim 1, wherein the water-insoluble base is a water-insoluble polymer,

3. The sustained-release formulation in Claim 1, in which the solid dispersion composition is **characterized by**

(1) lactose or calcium hydrogen phosphate being contained as an excipient and/or lubricant,
(2) no disintegrator being contained, and
(3) the particle size of said solid dispersion composition being equal to or smaller than 350 μm.

4. The sustained-release formulation in Claim 2, in which the solid dispersion composition is **characterized by** the water-insoluble polymer being present in an amount of 0.1 - 5 to the compound (I) (1 .0) by weight.

5. The sustained-release formulation in Claim 2, in which the water-insoluble polymer is ethylcellulose or methacrylate copolymer.

6. The sustained-release formulation in Claim 5, in which the water-insoluble polymer is ethylcellulose.

7. The sustained-release formulation in Claim 2, in which a water-soluble polymer is mixed with the water-Insoluble polymer.

8. The sustained-release formulation in Claim 7, in which the water-soluble polymer is hydroxypropylmethyl cellulose.

9. The sustained-release formulation in Claim 8, in which the solid dispersion composition is **characterized by**

(1) the macrolide compound (I) is present as an amorphous state in a mixture of ethylcellulose and hydroxy-propylmethyl cellulose,
(2) lactose is contained as an excipient,
(3) the particle size of said solid dispersion composition is equal to or smaller than 250 μm.

10. The sustained-release formulation in Claim 9, in which the weight ratio of the compound (I) to hydroxypropylmeth-ylcellulose is 1 to 0.2 - 0.4.

11. The sustained-release formulation in Claim 1, in which the water-insoluble base is wax.

12. The sustained-release formulation in Claim 11, in which the wax is glycerin monostearate, polyglycerin fatty acid ester or sucrose fatty acid ester.

13. The sustained-release formulation in Claim 11 or 12, in which the solid dispersion composition is **characterized by**

(1) lactose or calcium hydrogen phosphate is contained as an excipient,
(2) any disintegrators are not contained, and
(3) the particle size of said solid dispersion composition is equal to or smaller than 350 μm.

14. The sustained-release formulation In Claim 12, which comprises a solid dispersion composition which is **characterized by** the compound (I) being present as an amorphous state in sucrose fatty acid ester, in an amount of 0.2-20 to the compound (I) (1.0) by weight ratio.

15. The sustained-release formulation in Claim 12, which comprises α solid dispersion composition which is **characterized by** the compound (I) being present as an amorphous state In glycerin monostearate, in an amount of 10 - 100 to the compound (I) (1.0) by weight ratio.

16. The sustained-release formulation in Claim 12, which comprises a solid dispersion composition which is **characterized by** the compound (I) being present as an amorphous state in polyglycerin fatty acid ester, in an amount of 0.1-100 to the compound (I) (1 .0) by weight ratio.

17. The sustained-release formulation in Claim 1, in which the compounds (I) are the ones, wherein each of adjacent pairs of R^3 and R^4 or R^5 and R^6 independently form another bond formed between the carbon atoms to which they are attached; each of R^8 and R^{23} is independently a hydrogen atom:

R^9 is a hydroxy group;
R^{10} is a methyl group, an ethyl group, a propyl group or an allyl group;
X is a (hydrogen atom and a hydrogen atom) or an oxo group; Y is an oxo group;
each of R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{22} is a methyl group;
R^{24} is a 3-R^{20}-4-R^{21}-cyclohexyl group,
in which R^{20} is hydroxy, an alkoxy group, an oxo group, or a $-OCH_2OCH_2CH_2OCH_3$ group, and
R^{21} is hydroxy, -OCN, an alkoxy group, a heteroaryloxy which may be substituted by suitable substituents, a $-OCH_2OCH_2CH_2OCH_3$ group, a protected hydroxy group, chloro, bromo, iodo, aminooxalyloxy, an azido group, p-tolyloxythiocarbonyloxy, or $R^{25}R^{26}CHCOO$-,
in which R^{25} is optionally protected hydroxy or protected amino, and R^{26} is hydrogen or methyl, or
R^{20} and R^{21} together form an oxygen atom in an epoxide ring; and
n is an integer of 1 or 2.

18. The sustained-release formulation in any of Claims 1 to 17, in which the compound (I) is tacroli mus or its hydrate.

19. Thesustained-releaseformuiationinanyofClaims1to18,whichisinaformofpowder,finepowder,granule,tablet or capsule.

20. The sustained-release formulation in Claim 1, in which the time (T63.2%) is 1.0 to 12 hours.

21. The sustained-release formulation in Claim 1, in which the time (T63.2%) is 1.3 to 8.2 hours.

22. The sustained-release formulation in Claim 1, in which the time (T63.2%) is 2 to 5 hours.

23. A sustained-release formulation comprising a solid dispersion composition which is **characterized by**

(1) benelimus or its hydrate being present as an amorphous state in a mixiure of ethylcellulcse and hydroxy-propylmethyl cellulose In amount of 0.1 to 5 and 0.2 to 0.4 respectively to benelimus or its hydrate (1,0) by weight ratio,
(2) lactose is contained as an excipient,
(3) the particle size of said solid dispersion composition is equal to or smaller than 250 μm.

24. The sustained-release formulation in Claim 23, in which the amount of ethylcellulose is 0.1 - 1 to benelimus(1.0) by weight ratio.

25. The sustained-release formulation in Claim 23, in which the amount of lactose is 2, 3 or 5 to benelimus (1.0) by weight ratio.

26. The sustained-release formulation in Claim 23, in which any disintegrators are not contained in the solid dispersion composition.

27. The sustained-release formulation in Claim 23, in which the particle size of said solid dispersion composition is equal to or smaller than 212 μm.

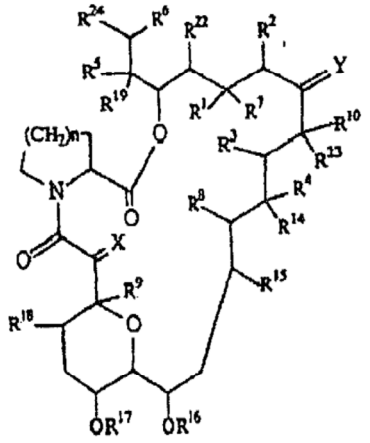
28. A sustained-release formulation comprising a solid dispersion composition which is **characterized by**

(1) benelimus or its hydrate being present as an amorphous state in a mixture of ethylcellulose and hydroxy-propylmethyl cellulose in an amount of 0.3 and 0.3 respectively to benelimus or its hydrate (1.0) by weight ratio,
(2) lactose is contained as an excipient,
(3) the particle size of said solid dispersion composition is equal to or smaller than 21 2 μm.

29. The sustained-release formulation in any of Claims 23 to 26, which is in a form of powder, fine powder, granule, tablet or capsule,

Revendications

1. Formulation à libération prolongée d'un composé de macrolide, dans laquelle le temps (T63,2%) nécessaire pour que 63,2 % de la quantité maximum du composé de macrolide soit dissous est de 0,7 à 15 heures, tel que mesuré selon la pharmacopée japonaise, 13ème édition, Test de Dissolution, No. 2 (Palette tournante, 50 tpm) en utilisant une solution de test qui est une solution aqueuse d'hydroxypropylcellulose 0,005 % ajustée à pH 4,5, dans laquelle le composé de macrolide est un composé tricyclique représenté par la formule générale (I) et un sel pharmaceutiquement açceptable de celui-ci,



(I)

où chacune des paires adjacentes de R^1 et R^2, R^3 et R^4, et R^5 et R^6 indépendamment

(a) est deux atomes d'hydrogène adjacents, mais R^2 peut aussi être un groupe alkyle ou
(b) peut former une autre liaison formée entre les atomes de carbone auxquels ils sont liés,

R^7 est un atome d'hydrogène, un groupe hydroxy, un groupe hydroxy protégé, ou un groupe alcoxy, ou un groupe oxo ensemble avec R^1;
R^8 et R^9 sont indépendamment un atome d'hydrogène ou un groupe hydroxy;
R^{10} est un atome d'hydrogène, un groupe alkyle, un groupe alkyle substitué par un ou plusieurs groupes hydroxy, un groupe alcényle, un groupe alcényle substitué par un ou plusieurs groupes hydroxy, ou un groupe alkyle substitué par un groupe oxo;
X est un groupe oxo, (un atome d'hydrogène et un groupe hydroxy), (un atome d'hydrogène et un atome d'hydrogène), ou un groupe représenté par la formule $-CH_2O-$;
Y est un groupe oxo, (un atome d'hydrogène et un groupe hydroxy), (un atome d'hydrogène et un atome d'hydrogène), ou un groupe représenté par la formule $N-NR^{11}R^{12}$ ou $N-OR^{13}$;
R^{11} et R^{12} sont indépendamment un atome d'hydrogène, un groupe alkyle, un groupe aryle, ou un groupe tosyle;
R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} et R^{23} sont indépendamment un atome d'hydrogène ou un groupe alkyle;
R^{24} est un système cyclique éventuellement substitué qui peut contenir un ou plusieurs hétéroatomes;
n est un nombre entier de 1 ou 2; et

en plus des définitions ci-dessus, Y, R^{10} et R^{23}, ensemble avec l'atome de carbone auquel ils sont liés, peuvent représenter un hétérocycle contenant de l'azote, du soufre et/ou de l'oxygène, à 5 ou 6 membres saturé ou insaturé éventuellement substitué par un ou plusieurs groupes choisis dans le groupe constitué par un alkyle, un hydroxy, un alcoxy, un benzyle, un groupe de formule $-CH_2Se(C_6H_5)$, et un alkyle substitué par un ou plusieurs groupes hydroxy, qui comprend une composition de dispersion solide, dans laquelle le composé de macrolide (I) est présent dans un état amorphe dans une base insoluble dans l'eau, dans laquelle la base insoluble dans l'eau comprise dans la composition de dispersion solide est choisie parmi un polymère ou cire insoluble dans l'eau.

2. Formulation à libération prolongée selon la revendication 1, dans laquelle la base insoluble dans l'eau est un polymère insoluble dans l'eau.

3. Formulation à libération prolongée selon la. revendication 1, dans laquelle la composition de dispersion solide est **caractérisée par le fait que**

(1) un lactose ou hydrogénophosphate de sodium est contenu en tant qu'excipient et/ou lubrifiant,
(2) aucun délitant n'est contenu, et
(3) la taille des particules de ladite composition de dispersion solide est égale à ou plus petite que 350 µm.

4. Formulation à libération prolongée selon la revendication 2, dans laquelle la composition de dispersion solide est **caractérisée par** le polymère insoluble dans l'eau qui est présent dans une quantité de 0,1 à 5 par rapport au composé (1) (1,0) en poids.

5. Formulation à libération prolongée selon la revendication 2, dans laquelle le polymère insoluble dans l'eau est une éthylcellulose ou un copolymère de méthacrylate.

6. Formulation à libération prolongée selon la revendication 5, dans laquelle le polymère insoluble dans l'eau est une éthylcellulose.

7. Formulation à libération prolongée selon la revendication 2, dans laquelle un polymère soluble dans l'eau est mélangé avec le polymère insoluble dans l'eau.

8. Formulation à libération prolongée selon la revendication 7, dans laquelle le polymère soluble dans l'eau est une hydroxypropylméthylcellulose.

9. Formulation à libération prolongée selon la revendication 8, dans laquelle la composition de dispersion solide est **caractérisée par le fait que**

(1) le composé de macrolide (I) est présent dans un état amorphe dans un mélange d'éthylcellulose et d'hydroxypropylméthylcellulose,
(2) un lactose est contenu en tant qu'excipient,
(3) la taille des particules de ladite composition de dispersion solide est égale à ou plus petite que 250 µm.

10. Formulation à libération prolongée selon la revendication 9, dans laquelle le rapport en poids du composé (I) sur l'hydroxypropylméthylcellulose est de 1 sur 0,2-0,4.

11. Formulation à libération prolongée selon la revendication 1, dans laquelle la base insoluble dans l'eau est une cire.

12. Formulation à libération prolongée selon la revendication 11, dans laquelle la cire est un monostéarate de glycérine, un ester d'acide gras de polyglycérine ou un ester d'acide gras de saccharose.

13. Formulation à libération prolongée selon la revendication 11 ou 12, dans laquelle la composition de dispersion solide est **caractérisée par le fait que**

(1) un lactose ou hydrogénophosphate de calcium est contenu en tant qu'excipient,
(2) des quelconques délitants ne sont pas contenus, et
(3) la taille des particules de ladite composition de dispersion solide est égale à ou plus petite que 350 pm.

14. Formulation à libération prolongée selon la revendication 12, qui comprend une composition de dispersion solide qui est **caractérisée par le fait que** le composé (I) est présent dans un état amorphe dans un ester d'acide gras de saccharose, dans une quantité de 0,2 à 20 par rapport au composé (1) (1,0) en rapport en poids.

15. Formulation à libération prolongée selon la revendication 12, qui comprend une composition de dispersion solide qui est **caractérisée par le fait que** le composé (I) est présent dans un état amorphe dans un monostérarate de glycérine, dans une quantité de 10 à 100 par rapport au composé (I) (1,0) en rapport en poids.

16. Formulation à libération prolongée selon la revendication 13, qui comprend une composition de dispersion solide qui est **caractérisée par le fait que** le composé (I) est présent dans un état amorphe dans un ester d'acide gras de polyglycérine, dans une quantité de 0,1 à 100 par rapport au composé (1) (1,0) en rapport en poids.

17. Formulation à libération prolongée selon la revendication 1, dans laquelle les composés (I) sont ceux dans lesquels chacune des paires adjacentes de R^3 et R^4 ou R^5 et R^6 forment une autre liaison formée entre les atomes de carbone auxquels ils sont liés; chacun de R^8 et R^{23} est indépendamment un atome d'hydrogène;

R^9 est un groupe hydroxy;
R^{10} est un groupe méthyle, un groupe éthyle, un groupe propyle ou un groupe allyle;
X est un (atome d'hydrogène et un atome d'hydrogène) ou un groupe oxo;
Y est un groupe oxo; chacun de R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} et R^{22} est un groupe méthyle;
R^{24} est un groupe 3-R^{20}-4-R^{21}-cyclohexyle, dans lequel
R^{20} est un hydroxy, un groupe alcoxy, un groupe oxo, ou un groupe $-OCH_2OCH_2CH_2OCH_3$, et
R^{21} est un hydroxy, -OCN, un groupe alcoxy, un hétéroaryloxy qui peut être substitué par des substituants appropriés, un groupe $-OCH_2OCH_2CH_2OCH_3$, un groupe hydroxy protégé, un chloro, un bromo, un iodo, un aminooxalyloxy, un groupe azido, un p-tolyloxythiocarbonyloxy, ou $R^{25}R^{26}CHCOO-$, dans lequel R^{25} est un hydroxy éventuellement protégé ou amino éventuellement protégé, et R^{26} est un hydrogène ou un méthyle, ou
R^{20} et R^{21} ensemble forment un atome d'oxygène dans un cycle époxyde; et
n est un nombre entier de 1 ou 2.

18. Formulation à libération prolongée selon l'une quelconque des revendications 1 à 17, dans laquelle le composé (I) est le benelimus ou son hydrate.

19. Formulation à libération prolongée selon l'une quelconque des revendications 1 à 18, qui est sous la forme d'une poudre, d'une poudre fine, d'un granulé, d'un comprimé ou d'une capsule.

20. Formulation à libération prolongée selon la revendication 1, dans laquelle le temps (T63,2%) est de 1,0 à 12 heures.

21. Formulation à libération prolongée selon la revendication 1., dans laquelle le temps (T63,2%) est de 1,3 à 8,2 heures.

22. Formulation à libération prolongée selon la revendication 1, dans laquelle le temps (T63,2%) est de 2 à 5 heures.

23. Formulation à libération prolongée comprenant une composition de dispersion solide qui est **caractérisée par le fait que**

(1) le benelimus ou son hydrate est présent dans un état amorphe dans un mélange d'éthylcellulose et d'hy-droxypropylméthylcellulose dans une quantité de 0,1 à 5 et 0,2 à 0,4 respectivement par rapport au benelimus ou son hydrate (1,0) en rapport en poids,
(2) un lactose est contenu en tant qu'excipient,
(3) la taille des particules de ladite composition de dispersion solide est égale à ou plus petite que 250 pm.

24. Formulation à libération prolongée selon la revendication 23, dans laquelle la quantité d'éthylcellulose est de 0,1 à 1 par rapport au benelimus (1,0) en rapport en poids.

25. Formulation à libération prolongée selon la revendication 23, dans laquelle la quantité de lactose est de 2, 3 ou 5 par rapport au benelimus (1,0) en rapport en poids.

26. Formulation à libération prolongée selon la revendication 23, dans laquelle des quelconques délitants ne sont pas contenus dans la composition de dispersion solide.

27. Formulation à libération prolongée selon la revendication 23, dans laquelle la taille des particules de ladite composition de dispersion solide est égale à ou plus petite que 212 μm.

28. Formulation à libération prolongée comprenant une composition de dispersion solide qui est **caractérisée par le fait que**

(1) le benelimus ou son hydrate est présent dans un état amorphe dans un mélange d'éthylcellulose et d'hy-droxypropylméthylcellulose dans une quantité de 0,3 et 0,3 respectivement par rapport au benelimus ou son hydrate (1,0) en rapport en poids,
(2) un lactose est contenu en tant qu'excipient,
(3) la taille des particules de ladite composition de dispersion solide est égale à ou plus petite que 212 pm.

29. Formulation à libération prolongée selon l'une quelconque des revendications 23 à 26, qui est sous la forme d'une poudre, d'une poudre fine, d'un granulé, d'un comprimé ou d'une capsule.