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(54) Title: COMPLEXES OF SIROLIMUS AND ITS DERIVATIVES, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

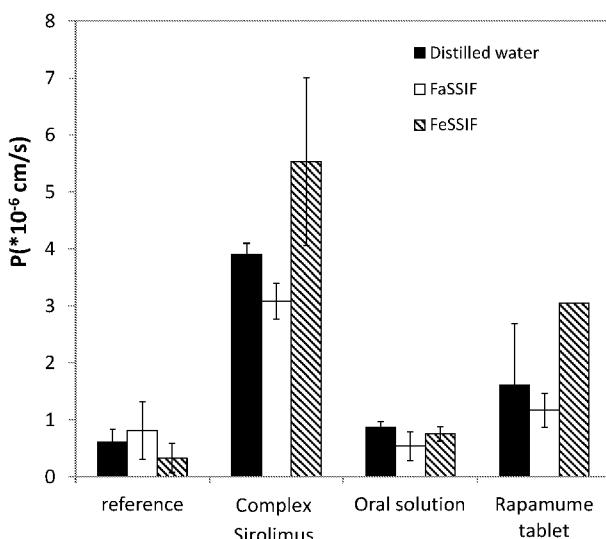


Figure 2

using the complex and its compositions.

(57) Abstract: The invention is directed to a stable complex with controlled particle size, increased apparent solubility and increased dissolution rate comprising as active compound Sirolimus or derivatives thereof, which is useful in the prophylaxis of organ rejection in patients receiving renal transplants, in the treatment of psoriasis, facial angiofibromas associated with tuberous sclerosis, fibrofolliculomas found in Birt-Hogg-Dubé Syndrome, chronic erosive oral lichen planus, Early Stage Cutaneous T-cell Lymphoma, Treatment of Autoimmune Active Anterior Uveitis, dry eye syndrome, age-related macular degeneration, diabetic macular edema, noninfectious uveitis, telangiectasia, inflammatory skin diseases (dermatitis, including psoriasis and lichen ruber planus), Pachyonychia Congenita and in the suppression of angiogenesis pathways. More specifically, the complex of the present invention possesses increased apparent solubility, permeability and enhanced biological performance including significantly improved exposure, earlier t_{max} , higher C_{max} and higher trough concentrations at 24 hours which will allow the reduction of the dose. Furthermore, the complex of the present invention possesses exceptional stability as a redispersed solution allowing the development of liquid based formulation for transdermal and other topical applications. The invention also relates to methods of formulating and manufacturing complex according to the invention, pharmaceutical compositions containing it, its uses and methods of treatment



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**COMPLEXES OF SIROLIMUS AND ITS DERIVATIVES, PROCESS FOR THE
PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS
CONTAINING THEM**

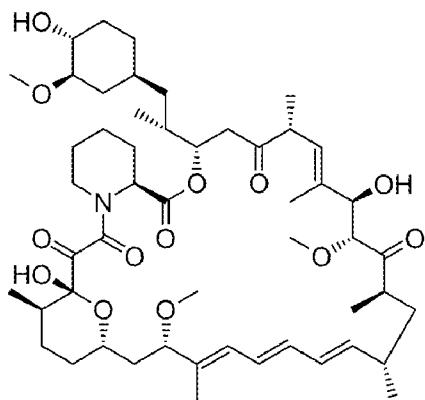
5 FIELD OF THE INVENTION

The invention is directed to a stable complex with controlled particle size, increased apparent solubility and increased dissolution rate comprising as active compound Sirolimus or derivatives thereof, which is useful in the prophylaxis of organ rejection in patients 10 receiving renal transplants, in the treatment of psoriasis, facial angiofibromas associated with tuberous sclerosis, fibrofolliculomas found in Birt-Hogg-Dubé Syndrome, chronic erosive oral lichen planus, Early Stage Cutaneous T-cell Lymphoma, Treatment of Autoimmune Active Anterior Uveitis, dry eye syndrome, age-related macular degeneration, diabetic macular edema, noninfectious uveitis, telangiectasia, inflammatory skin diseases (dermatitis, 15 including psoriasis and lichen ruber planus), Pachyonychia Congenita and in the suppression of angiogenesis pathways. More specifically, the complex of the present invention possesses increased apparent solubility, permeability and enhanced biological performance including significantly improved exposure, earlier t_{max} , higher C_{max} and higher trough concentrations at 24 hours which will allow the reduction of the dose. Furthermore, the complex of the present 20 invention possesses exceptional stability as a redispersed solution allowing the development of liquid based formulation for transdermal and other topical applications. The invention also relates to methods of formulating and manufacturing complex according to the invention, pharmaceutical compositions containing it, its uses and methods of treatment using the complex and its compositions.

25 BACKGROUND OF THE INVENTION

Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of Sirolimus (also known as Rapamycin) is (3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)9,10,12,13,14,21,22,23,24, 25,26,27,32,33,34, 34a-hexadecahydro-9,27-dihydroxy-3-[(1R)-2[(1S,3R,4R)-4-hydroxy-3-30 methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy6,8,12,14,20,26-hexamethyl-23,27- epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclohentriacantine1,5,11,28,29 (4H,6H,31H)-pentone.

Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.2. The structural formula of Sirolimus is illustrated as follows.



Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile.

Rapamune is available for administration as an oral solution containing 1 mg/mL Sirolimus. Rapamune is also available as a tan, triangular-shaped tablet containing 0.5 mg Sirolimus, as a white, triangular-shaped tablet containing 1 mg Sirolimus, and as a yellow-to-beige triangular-shaped tablet containing 2 mg Sirolimus.

10 The excipients in Rapamune Oral Solution are Phosal 50 PG® (phosphatidylcholine, propylene glycol, mono- and di-glycerides, ethanol, soy fatty acids, and ascorbyl palmitate) and polysorbate 80. Rapamune Oral Solution contains 1.5% - 2.5% ethanol.

15 The excipients in Rapamune Tablets include sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20,000, glyceryl monooleate, carnauba wax, dl-alpha tocopherol, and other ingredients. The 0.5 mg and 2 mg dosage strengths also contain yellow iron (ferric) oxide and brown iron (ferric) oxide.

20 Sirolimus inhibits T-lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, Sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The Sirolimus: FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian

Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G1 to the S phase of the cell cycle.

Studies in experimental models show that Sirolimus prolongs allograft (kidney, heart, skin,

5 islet, small bowel, pancreatico-duodenal and bone marrow) survival in mice, rats, pigs, and/or primates. Sirolimus reverses acute rejection of heart and kidney allografts in rats and prolongs the graft survival in presensitized rats. In some studies, the immunosuppressive effect of Sirolimus lasts up to 6 months after discontinuation of therapy. This tolerization effect is alloantigen-specific.

10 In rodent models of autoimmune disease, Sirolimus suppresses immune-mediated events associated with systemic lupus erythematosus, collagen-induced arthritis, autoimmune type I diabetes, autoimmune myocarditis, experimental allergic encephalomyelitis, graft-versus-host disease, and autoimmune uveoretinitis.

The use of topical Sirolimus in the treatment of psoriasis was published by AD Ormerod et.al

15 in Br J Dermatol, 152(4):758-64 (2005). It was a study published in 2005 that found a significant reduction in the clinical score but measurements of plaque thickness and erythema did not show significant improvement. It was concluded that topically applied Sirolimus penetrated normal skin and may have some antipsoriatic and immunosuppressive activity.

Numerous references such as B Madke, Indian Dermatol Online J., 4(1): 54–57 (2013) are

20 available to extemporaneous formulations used to treat facial angiofibromas associated with tuberous sclerosis. Various investigators have shown that topically applied Sirolimus causes regression of facial angiofibromas with acceptable cosmetic results. The tumors return when topical use is discontinued. No detectable systemic absorption of Sirolimus (>1.0 ng/mL) was found. A substantial placebo controlled phase 2 study is currently ongoing.

25 A study of the efficacy of topical Sirolimus vs. topical betamethasone in chronic erosive oral

lichen planus was terminated due to per protocol interim analyses of 76 patients and enrollment difficulties. A clinical trial to test whether topical Sirolimus is an effective treatment for the fibrofolliculomas found in Birt-Hogg-Dubé Syndrome (a rare genetic disorder) has been conducted and the results are currently under evaluation. There is a small

30 open label study of the use of topical Sirolimus in Early Stage Cutaneous T-cell Lymphoma (CTCL) which has not yet begun to recruit subjects. A small (5 subject) study of

subconjunctival Sirolimus for the treatment of autoimmune active anterior uveitis showed subconjunctival Sirolimus to be well tolerated and showed promise as a treatment for active inflammation in patients with chronic anterior uveitis. There are some promising publications on the topical delivery of Sirolimus to the eye for the treatment of retinal diseases. DE-109, an 5 intravitreal formulation of Sirolimus, has been studied in dry eye syndrome, age-related macular degeneration, and diabetic macular edema. DE-109 is currently being evaluated in a phase 3 trial in patients with active noninfectious uveitis (www.clinicaltrials.gov).

Topical application of 1% Sirolimus can suppress the angiogenesis pathways and, therefore, reduce the regeneration and revascularization of photocoagulated blood vessels as described 10 in *Lasers Surg Med.*, 44(10):796-804 (2012).

Topical Sirolimus is being evaluated in Pachyonychia Congenita (a rare congenital disorder of the nails) in early phase trials. The topical formulation is being developed through an agreement with Pfizer and TransDerm, Inc to avoid the side effects found with oral Rapamycin in an earlier study.

15 The use of topical Sirolimus for treating inflammatory skin diseases (dermatitis, including psoriasis and lichen ruber planus) is described in CA2078379 patent application.

Following the administration of Rapamune Oral Solution, the mean times to peak concentration (t_{max}) of Sirolimus are approximately 1 hour and 2 hours in healthy subjects and renal transplant patients, respectively. The systemic availability of Sirolimus is low, and was 20 estimated to be approximately 14% after the administration of Rapamune Oral Solution. In healthy subjects, the mean bioavailability of Sirolimus after administration of the tablet is approximately 27% higher relative to the solution. Sirolimus tablets are not bioequivalent to the solution; however, clinical equivalence has been demonstrated at the 2 mg dose level. Sirolimus concentrations, following the administration of Rapamune Oral Solution to stable 25 renal transplant patients, are dose-proportional between 3 and 12 mg/m².

To minimize variability in Sirolimus concentrations, both Rapamune Oral Solution and Tablets should be taken consistently with or without food. In healthy subjects, a high-fat meal (861.8 kcal, 54.9% kcal from fat) increased the mean total exposure (AUC) of Sirolimus by 23 to 35%, compared with fasting. The effect of food on the mean Sirolimus C_{max} was 30 inconsistent depending on the Rapamune dosage form evaluated.

The mean (\pm SD) blood-to-plasma ratio of Sirolimus was 36 ± 18 in stable renal allograft patients, indicating that Sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution (V_{ss/F}) of Sirolimus is 12 ± 8 L/kg. Sirolimus is extensively bound (approximately 92%) to human plasma proteins, mainly serum albumin (97%), α 1-acid glycoprotein, and lipoproteins.

Sirolimus is a substrate for both CYP3A4 and P-gp. Sirolimus is extensively metabolized in the intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen. Inhibitors of CYP3A4 and P-gp increase Sirolimus concentrations. Inducers of CYP3A4 and P-gp decrease Sirolimus concentrations. Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation. Seven (7) major metabolites, including hydroxy, demethyl, and hydroxydemethyl, are identifiable in whole blood. Some of these metabolites are also detectable in plasma, fecal, and urine samples. Sirolimus is the major component in human whole blood and contributes to more than 90% of the immunosuppressive activity.

After a single dose of [¹⁴C] Sirolimus oral solution in healthy volunteers, the majority (91%) of radioactivity was recovered from the feces, and only a minor amount (2.2%) was excreted in urine. The mean \pm SD terminal elimination half-life (t_{1/2}) of Sirolimus after multiple dosing in stable renal transplant patients was estimated to be about 62 ± 16 hours.

Sirolimus was originally marketed as an oral suspension. It requires cold storage and before administration it required mixing with water or orange juice. In order to increase the patient compliance, a tablet formulation was developed containing drug nanocrystals. The particle size reduction of the drug resulted in 23-27 % higher bioavailability compared to the oral solution. In spite of the achieved benefits, the oral bioavailability of the tablet formulation is still low (14%). To minimize variability in Sirolimus concentrations, both Rapamune oral solution and tablets should be taken consistently with or without food. Moreover, current production method is complicated and expensive.

In order to overcome the problems associated with prior conventional Sirolimus formulations and available drug delivery systems, novel complex formulation of Sirolimus or its derivatives and complexing agents and pharmaceutically acceptable excipients characterized by increased apparent solubility, instantaneous dissolution, increased permeability and enhanced biological performance including significantly improved exposure, earlier t_{max},

higher C_{max} and higher trough concentrations at 24 hours which will allow the reduction of the dose was developed. Furthermore, the complex of the present invention possesses exceptional stability as a redispersed solution allowing the development of liquid based formulation for transdermal and other topical applications.

5 A variety of strategies have been used to attempt to overcome these issues, see for example US20100098770, WO2007091059, US20130150397, US20090068266, WO2010130982 WO2006101972, WO2007079560, EP2522338, US20100183728, US20080138405, US20130280336 US20130039951, US20090130210, WO2013022201 US20080176888 WO2008022557, US6565859, US6239102 WO2011135580, WO2006094507

10 WO2011128910, EP1781671, US20110009325, EP2575889, EP1273288, EP0650357, EP1670437 EP1871343, EP2480207, US20110076308, US20060251710, EP2402350 US20120022095, US20130225631, JP2005312967, WO2012142145, US20050025810, US20060263409, EP2402350, WO2006123226, US20050032680 and US20050239724.

DESCRIPTION OF THE INVENTION

15 Disclosed herein is a stable complex comprising as active compound chosen from Sirolimus, its salts or derivatives thereof; and at least one complexing agent chosen from polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers; poloxamers; polyvinylpyrrolidone; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether), preferably polyvinylpyrrolidone; said complex characterized in 20 that it possesses at least one of the following properties:

a) a particle size in the range between 50 nm and 600 nm, preferably 50 nm and 200 nm;

b) is instantaneously redispersable in physiological relevant media

c) is stable in solid form and in colloid solution and/or dispersion at least 3 months;

d) has a PAMPA permeability of at least 2.0*10⁻⁶ cm/s, which does not decrease in time 25 at least for 3 months;

e) has characteristic infrared (ATR) and or Raman absorption peaks/bands;

f) said complex has decreased fed/faasted effect;

g) said complex has significantly improved exposure, earlier t_{max}, higher C_{max} and higher trough concentrations at 24 hours which will allow the reduction of the dose,

30 h) said complex faster onset of action; and

i) said complex possibility of the development of liquid based formulation for transdermal and other topical applications based on stability of the formula in liquid form.

The invention is a complex Sirolimus formula having increased solubility, instantaneous dissolution, increased permeability, decreased fed/faasted effect, higher AUC, C_{max}, faster onset of action and higher trough concentrations at 24 hours which will allow the reduction of the dose compared to unformulated compound and/or to the marketed drugs such as Rapamune described in the present invention. The present invention satisfies this need. Furthermore, the complex of the present invention possesses exceptional stability as a 10 redispersed solution allowing the development of liquid based formulation for transdermal and other topical applications.

We have found that only the selected combinations of stabilizers and pharmaceutically acceptable excipients disclosed in the present invention result in a stable complex formulae having improved physicochemical characteristics and enhanced biological performance.

15 The expression Sirolimus is generally used for Sirolimus, or salts or its derivatives.

In an embodiment, said complexing agent is chosen from polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol (e.g.; Gelucire 44/14, Gelucire 50/13), hydroxypropylcellulose (e.g; Klucell EF, Klucell LF), poloxamers (copolymers of ethylene oxide and propylene oxide blocks) (e.g; Lutrol F127), 20 vinylpyrrolidone/vinyl acetate copolymer (e.g.; Luviskol VA64), Polyethylene glycol (e.g; PEG2000, PEG6000), poly(2-ethyl-2-oxazoline) (e.g; PEOX50, PEOX500), polyvinylpyrrolidone (e.g; Plasdone K-12, PVP 40, PVP K90, PVP 10), block copolymers based on ethylene oxide and propylene oxide (e.g; Pluronic PE10500, Pluronic PE6800, Pluronic F108), poly(maleic acid/methyl vinyl ether) (PMAMVE), (polyvinyl caprolactam-25 polyvinyl acetate-polyethylene glycol graft copolymer (e.g; Soluplus), polyoxyl 15 hydroxystearate (e.g; Solutol HS15), ethylene oxide/propylene oxide block copolymer (e.g.; Tetronic 1107), and d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS).

In an embodiment, said complexing agent is polyvinylpyrrolidone.

30 In an embodiment, said complex further comprises at least one pharmaceutically acceptable excipient selected from the group of sodium-lauryl-sulfate and sodium-acetate.

In an embodiment, said pharmaceutically acceptable excipient is sodium-lauryl-sulfate.

In an embodiment, said complex has a controlled particle size in the range between 50 nm and 600 nm. In an embodiment, said particle size is between 50 nm and 200 nm.

In an embodiment, said complex further comprises one or more additional active agents.

5 In an embodiment, said additional active agent is chosen from agents useful for the prophylaxis of organ rejection in patients receiving renal transplants, for the treatment of psoriasis, facial angiofibromas associated with tuberous sclerosis, fibrofolliculomas found in Birt-Hogg-Dubé Syndrome, chronic erosive oral lichen planus, Early Stage Cutaneous T-cell Lymphoma, Treatment of Autoimmune Active Anterior Uveitis, dry eye syndrome, age-related macular degeneration, diabetic macular edema, noninfectious uveitis, telangiectasia, inflammatory skin diseases (dermatitis, including psoriasis and lichen ruber planus), Pachyonychia Congenita and for the suppression angiogenesis pathways.

10

In an embodiment, said complex possesses at least two of the properties described in a) – i).

In an embodiment, said complex possesses at least three of the properties described in a) – i).

15 In an embodiment, said complex has an increased dissolution rate.

Further disclosed herein is a stable complex comprising an active compound selected from the group of Sirolimus, its salt, or derivatives thereof; at least one complexing agent chosen from polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers; poloxamers; polyvinylpyrrolidone; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether); and at least one pharmaceutically acceptable excipient chosen from sodium-lauryl-sulfate and sodium-acetate; wherein said complex obtained via a mixing process.

In an embodiment, said complexing agent is a polyvinylpyrrolidone.

In an embodiment, said pharmaceutically acceptable excipient is sodium-lauryl-sulfate.

25 In an embodiment, said complex is obtained via a continuous flow mixing process.

In an embodiment, a complex comprises a complexing agent which is a polyvinylpyrrolidone and a pharmaceutically acceptable excipient which is sodium-lauryl-sulfate, in a total amount

ranging from about 1.0 weight% to about 95.0 weight % based on the total weight of the complex.

In an embodiment, said complexing agent which is a polyvinylpyrrolidone and pharmaceutically acceptable excipient which is sodium-lauryl-sulfate comprise 50 weight% to 5 about 95 weight% of the total weight of the complex.

Further disclosed herein is a process for the preparation of the complex, comprising the steps of mixing a solution of Sirolimus, its salt, or derivatives thereof, and at least one complexing agent chosen from polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers; poloxamers; polyvinylpyrrolidone; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether) in a pharmaceutically acceptable solvent with an aqueous solution containing at least one pharmaceutically acceptable excipient chosen from sodium-lauryl-sulfate and sodium-acetate.

In an embodiment, said process is performed in a continuous flow instrument.

In an embodiment, said continuous flow instrument is a microfluidic flow instrument.

15 In an embodiment, said pharmaceutically acceptable solvent is chosen from methanol, ethanol, isopropanol, n-propanol, acetone, acetonitrile, dimethyl-sulfoxide, tetrahydrofuran, or combinations thereof.

In an embodiment, said pharmaceutically acceptable solvent is methanol.

20 In an embodiment, said pharmaceutically acceptable solvent and said aqueous solvent are miscible with each other.

In an embodiment, said aqueous solvent comprises 0.1 to 99.9% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 to 90% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 to 80% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 to 70% weight of the final solution.

25 In an embodiment, said aqueous solvent comprises 50 to 60% weight of the final solution.

In an embodiment, said aqueous solvent comprises 50 % weight of the final solution.

In an embodiment a pharmaceutical composition comprises the complex together with pharmaceutically acceptable carrier.

In an embodiment, said composition is suitable for oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, or 5 topical administration.

In an embodiment, said composition is suitable for oral administration.

In an embodiment, said composition is suitable for topical/dermal administration.

In an embodiment, said complex is for use in the manufacture of a medicament for the prophylaxis of organ rejection in patients receiving renal transplants, for the treatment of 10 psoriasis, facial angiofibromas associated with tuberous sclerosis, fibrofolliculomas found in Birt-Hogg-Dubé Syndrome, chronic erosive oral lichen planus, Early Stage Cutaneous T-cell Lymphoma, Treatment of Autoimmune Active Anterior Uveitis, dry eye syndrome, age-related macular degeneration, diabetic macular edema, noninfectious uveitis, telangiectasia, inflammatory skin diseases (dermatitis, including psoriasis and lichen ruber planus), 15 Pachyonychia Congenita and for the suppression angiogenesis pathways.

In an embodiment, said complex is used for the prophylaxis of organ rejection in patients receiving renal transplants, for the treatment of psoriasis, facial angiofibromas associated with tuberous sclerosis, fibrofolliculomas found in Birt-Hogg-Dubé Syndrome, chronic erosive oral lichen planus, Early Stage Cutaneous T-cell Lymphoma, Treatment of Autoimmune 20 Active Anterior Uveitis, dry eye syndrome, age-related macular degeneration, diabetic macular edema, noninfectious uveitis, telangiectasia, inflammatory skin diseases (dermatitis, including psoriasis and lichen ruber planus), Pachyonychia Congenita and for the suppression angiogenesis pathways.

In an embodiment, a method of prophylaxis of organ rejection in patients receiving renal 25 transplants, the treatment of psoriasis, facial angiofibromas associated with tuberous sclerosis, fibrofolliculomas found in Birt-Hogg-Dubé Syndrome, chronic erosive oral lichen planus, Early Stage Cutaneous T-cell Lymphoma, Treatment of Autoimmune Active Anterior Uveitis, dry eye syndrome, age-related macular degeneration, diabetic macular edema, noninfectious uveitis, telangiectasia, inflammatory skin diseases (dermatitis, including psoriasis and lichen 30 ruber planus), Pachyonychia Congenita and the suppression angiogenesis pathways comprises

administration of a therapeutically effective amount of a complex or a pharmaceutical composition as described herein.

In an embodiment, a method for reducing the therapeutically effective dosage of Sirolimus compared to orally available solid dosage forms and dosage forms for topical/dermal treatment comprises oral or topical/dermal administration of a pharmaceutical composition as described herein.

Further disclosed herein is a stable complex comprising

- a. 5 – 50% by weight of Sirolimus, its salt, or derivatives thereof;
- b. 10 – 80% by weight of a polyvinylpyrrolidone; and
- 10 c. 1 – 50 % by weight of sodium-lauryl sulfate.

wherein said complex has a controlled particle size in the range between 50 nm and 600 nm; and wherein said complex is not obtained via a milling process or by high pressure homogenization process, encapsulation process and solid dispersion process, but it is obtained by a mixing process, preferable continuous flow mixing process.

15 In an embodiment, said particle size is between 50 nm and 200 nm.

In an embodiment, said complex shows reduced fed/faasted effect based on *in vivo* studies.

In an embodiment, said complex shows significantly improved exposure, earlier t_{max} , higher C_{max} and higher trough concentrations at 24 hours which will allow the reduction of the dose.

20 In an embodiment, said complex has a faster onset of action compared to the existing oral formulations.

In an embodiment, said complex is instantaneously redispersable in physiological relevant media.

In an embodiment, said complex is stable in solid form and in colloid solution and/or dispersion.

25 In an embodiment, said complex has a PAMPA permeability of at least 2.0×10^{-6} cm/s, which does not decrease in time at least for 3 months.

In an embodiment, said complex a) has characteristic infrared (ATR) and or Raman absorption peaks/bands.

The complexing agents and pharmaceutically acceptable excipients of the Sirolimus complex formulae of the invention are selected from the group of pharmaceutically acceptable nonionic, anionic, cationic, ionic polymers, surfactants and other types of excipients. The complexing agents themselves or together with the pharmaceutically accepted excipients have the function to form a complex structure with an active pharmaceutical ingredient through non-covalent secondary interactions. The secondary interactions can form through electrostatic interactions such as ionic interactions, H-bonding, dipole-dipole interactions, dipole-induced dipole interactions, London dispersion forces, $\pi-\pi$ interactions, and hydrophobic interactions. The complexing agents, pharmaceutically accepted excipients and active ingredients are selected from the group of complexing agents, pharmaceutically accepted excipients and active ingredients which are able to form such complex structures through non-covalent secondary interactions.

In some embodiments, the compositions may additionally include one or more pharmaceutically acceptable excipients, auxiliary materials, carriers, active agents or combinations thereof. In some embodiments, active agents may include agents useful for the treatment hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

Another aspect of the invention is the complex formulae of the Sirolimus with complexing agents and pharmaceutically acceptable excipients in which the complexing agents and pharmaceutically acceptable excipients preferably are associated or interacted with the Sirolimus especially as the results of the mixing process, preferably continuous flow mixing process. In some embodiment, the structure of the complex Sirolimus formula is different from the core-shell type milled particle, precipitated encapsulated particles, micelles and solid dispersions.

The pharmaceutical composition of the invention can be formulated: (a) for administration selected from the group consisting of oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, and topical administration; (b) into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, lyophilized formulations, tablets, capsules; (c)

into a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations; or (d) any combination of (a), (b), and (c).

5 The compositions can be formulated by adding different types of excipients for oral administration in solid, liquid, local (powders, ointments or drops), or topical administration, and the like.

10 The compositions can be formulated by adding different types of pharmaceutically acceptable excipients for oral administration in solid, liquid, local (powders, ointments or drops), or topical administration, and the like.

Preferred dosage forms of the invention are solid dosage forms and topical dosage forms, although any pharmaceutically acceptable dosage form can be utilized.

15 Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following excipients: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, microcrystalline cellulose and silicic acid; (c) binders, such as cellulose derivatives, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as crospovidon, sodium starch 20 glycolate, effervescent compositions, croscarmellose sodium, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate; (f) solution retarders, such as acrylates, cellulose derivatives, paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as polysorbates, cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as 25 talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Topical dosage forms include, but are not limited to powders, aerosols, plasters, lotions, liniments, solutions, emulsions, suspensions, ointments, creams, pastes, gels, jellies, suppositories. Compositions suitable for the topical, including transdermal, administration may comprise pharmaceutically acceptable topical ingredients, such as hydrophobic vehicle, 5 water-miscible vehicle, co-solvent, structural matrix former, suspending, jelling, or viscosity inducing agents, water-in-oil(w/o) emulsifier, preservative, chelating agents, citric acid, edetic acid, sequestering antioxidant. Examples of pharmaceutically acceptable topical ingredients include *hydrocarbons* such as liquid petrolatum (mineral oil, liquid paraffin, paraffin oil), white petrolatum (petroleum jelly, Vaseline), yellow petrolatum (petroleum jelly), squalane 10 (perhydrosqualene, spinacane), paraffin (paraffin wax, hard paraffin), microcrystalline wax, ceresin (mineral wax, purified ozokerite); *silicones* such as liquid polydimethylsiloxanes (dimethicone, silastic, medical grade silicone oil), fumed silica (cab-O-sil), bentonite (colloidal aluminum silicate), veegum (colloidal magnesium aluminum silicate); *alcohols* such as lauryl alcohols (1-dodecanol, dodecyl alcohols), myristyl alcohols (tetradecanol, 15 tetradecyl alcohols), cetyl alcohols (hexadecanol, ethyl, palmityl alcohols), stearyl alcohols (stenol, cetosteryl alcohols), oleyl alcohols (ocenol); *sterols and sterol esters* such as lanolin (hydrated wool fat, lanum), anhydrous lanolin (wool fat, anhydrous lanum, agnin), semi synthetic lanolin's; *carboxylic acids* such as lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid; *esters and polyesters* such as cholesterol esters (stearate), ethylene glycol 20 monoesters, propylene glycol monoesters, glyceryl monoesters, glyceryl monostearate, sorbitol monoesters, sorbitan monoesters, sorbitol diesters, sorbitan polyesters (spans, arlacels), glyceryl tristearate, lard, almond oil, corn oil, caster oil, cottonseed oil, olive oil, soyabean oil, hydrogenated oils, sulfated oils, isopropyl myristate, isopropyl palmitate, polyoxyethylene sorbitan monoesters (stearate-tweens), polyoxyethylene sorbitan polyesters 25 (tweens), ethers and polyethers such as polyethylene glycol monocetyl ether (cetomacrogol 1000), polyethylene-polypropylene glycols (pluronics), polyoxyethylene esters (stearate-polyethylene glycol monoesters, Myrij); bees wax, white bees wax (bleached bees wax), carnauba wax; *polyols and polyglycols* such as propylene glycol (1,2-propanediol), glycerin (glycerol), liquid polyethylene glycol, solid polyethylene glycol (hard macrogol, carbowax), 30 1,2, phenols-hexanetriol, sorbitol solution; *polycarboxylates, polysulfates and polysaccharides* such as agar, alginates, carragen, acacia, tragacanth, methylcellulose, carboxy methylcellulose, hydroxy ethyl cellulose, carboxy vinyl polymer, gelatin, pectin, xanthan, polyacrylic acid; *antioxidants* such as a-Tocopherol, ascorbic acid, ascorbyl

palmitate, butylated hydroxyanisole, sodium ascorbate, sodium metabisulfite; buffers citric acid and salts, phosphoric acid and salts, H_3PO_4 / NaH_2PO_4 , glycine, acetic acid, triethanolamine, boric acid, Ethylenediaminetetraacetic acid (Versene, EDTA); *humectant* such as glycerin (glycerol), propylene glycol (E 1520), glyceryl triacetate (E1518), sorbitol (E420), xylitol and maltitol (E965), polydextrose (E1200), quillaia (E999), lactic acid, urea, lithium chloride, *others* such as ethanolamin, riethanolamin, sodium lauryl sulfate, borax (sodium borate); presevatives such as benzalkonium chloride, benzoic acid, benzyl alcohol, bronopol, chlorhexidine, chlorocresol, imidazolidinyl urea, paraben esters, phenol, phenoxyethanol, potassium sorbate, sorbic acid and the like.

10 Advantages of the complex Sirolimus formulae of the invention include, but are not limited to (1) long term physical and chemical stability in solid form and in colloid solution and/or dispersion, (2) instantaneous redispersibility of the solid form, (3) stability in colloid solution or dispersion in the therapeutic time window, (4) increased solubility compared to the conventional Sirolimus formulation, (5) increased permeability, (6) increased C_{max} , AUC and

15 earlier t_{max} compared to the conventional Sirolimus formulations, (7) decreased fed/fasted effect, increased trough concentrations at 24 hours which will allow the reduction of the dose (8) and (9) good processability.

Beneficial features of the present invention are as follows: the good/instantaneous redispersibility of solid complex formulae of Sirolimus in water, biologically relevant media, e.g.; physiological saline solution, pH=2.5 HCl solution, FessiF and FassiF media and gastro intestinal fluids and long term stability in colloid solutions and/or dispersion in the therapeutic time window.

One of the preferred characteristics of the complex Sirolimus formulae of the present invention is their increased apparent solubility and permeability. In some embodiments, the 25 permeability of the complex Sirolimus formulae is at least 2.0×10^{-6} cm/s and maintains it for at least 3 months.

Another preferred characteristic of the complex Sirolimus formulae of the present invention relates to the enhanced pharmacokinetic performance including significantly improved exposure, earlier t_{max} , higher C_{max} and higher trough concentrations at 24 hours which will 30 allow the reduction of the dose. Furthermore, the complex of the present invention possesses

exceptional stability as a redispersed solution allowing the development of liquid based formulation for transdermal and other topical applications.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. shows the complexing agent screening for formula selection in order to select the

5 formulae having instantaneous redispersibility

Figure 2. shows Comparative PAMPA assays of the unformulated compound, complex Sirolimus formula, marketed oral solution and marketed tablet form dispersed in different media

Figure 3. shows PAMPA permeability of solid complex Sirolimus formula stored at 4⁰C,

10 room temperature or 40⁰C 75% relative humidity right after redispersion and at different time points (1, 7, 14, 34 and 95 days after the production)

Figure 4. shows PAMPA permeability of colloid solution of complex Sirolimus formula

stored at 4⁰C, room temperature or 40⁰C 75% relative humidity and at different time points (1, 7, 14, 34 and 95 days after the production)

15 **Figure 5.** shows plasma concentration of Sirolimus following the oral administration of the marketed drug (Rapamune tablet) and Sirolimus complex to rats under the fasting conditions (n=4, dose: 1.0 mg/kg)

Figure 6. shows pharmacokinetic parameters following the oral administration of the

marketed drug (Rapamune tablet) and the Sirolimus complex to rats under the fasting

20 conditions (n=4, dose: 1.0 mg/kg)

Figure 7. shows dissolution test of capsule containing complex Sirolimus

EXAMPLES

Several pharmaceutically accepted complexing agents and pharmaceutically accepted

excipients and their combinations were tested in order to select the formulae having

25 instantaneous redispersibility as shown in Figure 1. One of the examples that displayed an acceptable level of redispersibility was selected for further analysis.

Polyvinylpyrrolidone as complexing agent and sodium-lauryl sulfate as pharmaceutically accepted excipient were selected to form complex Sirolimus formulation having improved material characteristics.

The ratio of the selected complexing agent and pharmaceutically accepted excipient (polyvinylpyrrolidone and sodium-lauryl sulfate) was optimized making some slight differences in the preparation process to modify some characteristics of the product.

Colloid solution of Sirolimus complex formula of the present invention was prepared by continuous flow precipitation in a flow instrument. As a starting solution, 100 mg Sirolimus and 300 mg polyvinylpyrrolidone (PVP K90) dissolved in 100 mL methanol was used. The prepared solution was passed into the instrument with 5 mL/min flow rate. Meanwhile, antisolvent containing 250 mg sodium-lauryl sulfate in 500 mL water was passed into the instrument with 20 mL/min flow rate, where Sirolimus was precipitated to form complex Sirolimus composition. The colloid solution of the complex Sirolimus is continuously produced at atmospheric pressure. The produced colloid solution was frozen on dry-ice and then it was lyophilized using Scavac CoolSafe 110-8 freeze drier equipped with -110°C ice condenser, with a Vacuubrand RZ6 vacuum pump.

In order to make the production process industrially feasible, process intensification was performed by increasing the concentrations of the starting solution. A colloid solution of Sirolimus complex formula of the present invention was prepared by continuous flow mixing in a flow instrument using the intensified process parameters. As a starting solution, 1000 mg Sirolimus and 3000 mg polyvinylpyrrolidone (PVP K90) dissolved in 100 mL methanol was used. The prepared solution was passed into the instrument with 10 mL/min flow rate. Meanwhile, aqueous solvent containing 2500 mg sodium-lauryl sulfate in 500 mL water was passed into the instrument with 40 mL/min flow rate, where Sirolimus formed complex Sirolimus composition.

Comparative *in vitro* PAMPA assays

PAMPA permeability measurements were performed as described by M. Kansi et al. (Journal of medicinal chemistry, 41, (1998) pp 1007) with modifications based on S. Bendels et al (Pharmaceutical research, 23 (2006) pp 2525). Sample containing the reference compound or the marketed drug were a suspension of crystals visible by the naked eye, while samples of the novel complex were opalescent colloid solutions. Permeability was measured in a 96-well

plate assay across an artificial membrane composed of dodecane with 20% soy lecithin supported by a PVDF membrane (Millipore, USA). The receiver compartment was phosphate buffered saline (pH 7.0) supplemented with 1% sodium dodecyl sulfate. The assay was performed at room temperature; incubation time was 1-24 hours. The concentration in the 5 receiver compartment was determined by UV-VIS spectrophotometry (Thermo Scientific Genesys S10).

PAMPA permeability of complex Sirolimus formula of the present invention and the marketed drug was in the $2-6 \times 10^{-6}$ cm/s range, while marketed Rapamune tablet exhibited at least 50% lower permeability when dispersed in water or in biorelevant media. The oral 10 solution and the reference compound exhibited lower than 1×10^{-6} cm/s permeability in all dispersing media tested (Figure 2).

Stability of the complex Sirolimus

The solid forms and the redispersed colloid solutions were subjected to stability tests at 4^0C , room temperature or 40^0C 75% relative humidity for up to three months. The solids 15 redispersed at the indicated time points exhibited no change in PAMPA permeability under any of the storage conditions (Figure 3). The redispersed colloids did not show significant change in PAMPA permeability for up to a month under all conditions, while no change was observed at 4^0C or room temperature for up to 3 months (Figure 4).

In-vivo pharmacokinetics

20 *In-vivo PK test in small animals*

Male Wistar rats (250-270 g) were treated orally with either the test article or the reference article (1.0 mg/kg) one time via esophageal gavage technique following overnight fasting. Whole blood was sampled from the saphenous vein into heparinized tubes (approx. 0.2 mL to 25 each tube) before and at 0.5, 1, 2, 3, 4, 6, 8, 24, and 48 hours after the oral administration of the test or reference articles. Whole blood samples were stored at minus 20^0C until analysis. Sirolimus concentrations were determined from whole blood samples by an LC-MS/MS technique.

Pharmacokinetic data were expressed as measured values and as normalized values. Measured values were normalized to the extraction recovery of the standard solution from whole blood. 30 Extraction recovery of the standard solution from whole blood varied between 94.0 and

114.7%. Following oral administration of Sirolimus as Sirolimus complex formula, t_{max} was significantly decreased whilst C_{max} and AUC values increased when compared to the marketed tablet form, Rapamune. The trough concentrations measured as blood Sirolimus levels at 24 hours were also increased over 2-fold when compared to Rapamune (Figure 5-6).

5 Pharmaceutical development

Production of intermediate drug product of complex Sirolimus formula

Intermediate drug product was produced by mixing solid complex Sirolimus formula and commercially available excipient, Cellactose® 80 composing of 75% wt% lactose monohydrate and 25 wt% microcrystalline cellulose in the bracketing range of 0.5 and 2.0 mg strengths. For the

10 production of intermediate drug product with 0.5 mg strength 9.23% wt% solid complex Sirolimus formula and 89.77% wt% Cellactose® 80 were mixed, while for 2.0 mg strength 1.67% wt% solid complex Sirolimus formula and 97.33% wt% Cellactose® 80 were mixed, respectively. Both powder mixtures were lubricated with 1% wt% magnesium stearate and filled into "1" size hard gelatin capsules. The powder mixture showed good flowability (USP <1174> and Ph.Eur.

15 2.9.16).

In-vitro dissolution tests

Dissolution test was performed by paddle method (Vankel VK7000) at 120 rpm and 37 °C.

20 Dissolution media was distilled water with 0.4% SLS (recommended by FDA). The concentration of Sirolimus was detected by UV-VIS spectrophotometry after filtration with a 1 µm pore size syringe filter at 279 nm wavelength. Complete dissolution of complex Sirolimus from the intermediate drug product was observed within 10 minutes (Figure 7).

Preparation of topical gel formulation of complex Sirolimus formula

A gel formula for topical administration was developed using the novel complex Sirolimus

25 formula. The gel was prepared by the sequential addition of the following components under continuous stirring: 1.800 g glycerol, 2.250 g 1 mg/ml sorbic acid solution, 3.828 g distilled water, 0.045 g Carbopol CP980 (as solid), 0.180 g 1 M sodium hydroxide solution and 0.900 g of the novel complex Sirolimus formula redispersed in distilled water at 10 mg/g concentration for active content.

Claims

What is claimed is:

1. A stable complex comprising as active compound selected from the group of Sirolimus, its salts or derivatives thereof; and at least one complexing agent selected from the group of polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers; poloxamers; polyvinylpyrrolidone; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether); said complex characterized in that it possesses at least one of the following properties:
 - a) has a particle size in the range between 50 nm and 600 nm, preferably 50 nm and 200 nm
 - b) is instantaneously redispersable in physiological relevant media;
 - c) has increased dissolution rate;
 - d) is stable in solid form and in colloid solution and/or dispersion;
 - e) has a PAMPA permeability of at least 2.0×10^{-6} cm/s, which does not decrease in time at least for 1 month;
 - f) has characteristic infrared (ATR) and or Raman absorption peaks/bands;
 - g) said complex has decreased fed/faasted effect;
 - h) said complex has significantly improved exposure, earlier t_{max} , higher C_{max} and higher trough concentrations at 24 hours which will allow the reduction of the dose,
 - i) said complex faster onset of action; and
 - j) said complex possibility of the development of liquid based formulation for transdermal and other topical applications based on stability of the formula in liquid form.
2. The complex according to Claim 1, wherein said complexing agent is selected from the group of polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol, hydroxypropylcellulose, poloxamers (copolymers of ethylene oxide and propylene oxide blocks), vinylpyrrolidone/vinyl acetate copolymer, Polyethylene glycol, poly(2-ethyl-2-oxazoline), polyvinylpyrrolidone, block copolymers based on ethylene oxide and propylene oxide, poly(maleic acid/methyl vinyl ether), (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, polyoxyl 15 hydroxystearate, ethylene

oxide/propylene oxide block copolymer, and d-alpha tocopheryl polyethylene glycol 1000 succinate, preferable the complexing agent is a polyvinylpyrrolidone.

3. The complex according to Claims 1 or 2, wherein said complex further comprises at least one pharmaceutically acceptable excipient selected from the group of sodium-lauryl-sulfate and sodium-acetate, preferable the pharmaceutically acceptable excipient is sodium-lauryl-sulfate.
4. The complex according to any of Claims 1 to 3, wherein said complex further comprises one or more additional active agents, preferable the additional active agent is selected from the group of agents useful for the prophylaxis of organ rejection in patients receiving renal transplants, for the treatment of psoriasis, facial angiofibromas associated with tuberous sclerosis, fibrofolliculomas found in Birt-Hogg-Dubé Syndrome, chronic erosive oral lichen planus, Early Stage Cutaneous T-cell Lymphoma, Treatment of Autoimmune Active Anterior Uveitis, dry eye syndrome, age-related macular degeneration, diabetic macular edema, noninfectious uveitis, telangiectasia, inflammatory skin diseases (dermatitis, including psoriasis and lichen ruber planus), Pachyonychia Congenita and for the suppression angiogenesis pathways.
5. A stable complex according to any of Claims 1 to 4 comprising an active compound selected from the group of Sirolimus, its salt, or derivatives thereof; at least one complexing agent selected from the group of polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers; poloxamers; polyvinylpyrrolidone; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether); and at least one pharmaceutically acceptable excipient chosen from sodium-lauryl-sulfate and sodium-acetate; wherein said complex obtained via a mixing process, preferable continuous flow mixing process, more preferable microfluidic flow mixing process.
6. A complex according to any of Claims 1 to 5 comprising a complexing agent which is a polyvinylpyrrolidone and a pharmaceutically acceptable excipient which is sodium-acetate, in a total amount ranging from about 1.0 weight% to about 95.0 weight % based on the total weight of the complex.

7. A process for the preparation of the complex according to any of Claims 1 to 6, comprising the steps of mixing a solution of Sirolimus, its salt, or derivatives thereof, and at least one complexing agent selected from the group of polyvinylcaprolactam-polyvinyl acetate-polyethylene-glycol graft copolymers; poloxamers; polyvinylpyrrolidone; copolymers of vinylpyrrolidone and vinyl-acetate; and poly(maleic acid-co-methyl-vinyl-ether) in a pharmaceutically acceptable solvent with an aqueous solution containing at least one pharmaceutically accepted excipient chosen from sodium-lauryl-sulfate and sodium-acetate.
- 5 8. The process according to Claim 7, wherein said process is performed in a continuous flow instrument, preferable in microfluidic instrument.
- 10 9. The process according to Claims 7 or 8, wherein said pharmaceutically acceptable solvent is selected from the group of methanol, ethanol, isopropanol, n-propanol, acetone, acetonitrile, dimethyl-sulfoxide, tetrahydrofuran, and combinations thereof, preferable the solvent is methanol.
- 15 10. The process according to any of Claims 7 to 9, wherein the solvent and the aqueous solvent are miscible with each other and the aqueous solvent comprises 0.1 to 99.9% weight of the final solution.
11. A pharmaceutical composition comprising the complex according to any of Claims 1 to 6 together with pharmaceutically acceptable carrier.
- 20 12. A pharmaceutical composition according to Claim 11, wherein said composition is suitable for oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, or topical administration, preferable the composition is suitable for oral and topical administration.
- 25 13. A complex according to any of Claims 1 to 6 for use in the manufacture of a medicament for the prophylaxis of organ rejection in patients receiving renal transplants, for the treatment of psoriasis, facial angiofibromas associated with tuberous sclerosis, fibrofolliculomas found in Birt-Hogg-Dubé Syndrome, chronic erosive oral lichen planus, Early Stage Cutaneous T-cell Lymphoma, Treatment of Autoimmune Active Anterior Uveitis, dry eye syndrome, age-related macular degeneration, diabetic macular edema, noninfectious uveitis, telangiectasia,
- 30

inflammatory skin diseases (dermatitis, including psoriasis and lichen ruber planus), Pachyonychia Congenita and for the suppression angiogenesis pathways.

14. The use of the complex according to any of Claims 1 to 6 for the prophylaxis of organ rejection in patients receiving renal transplants, for the treatment of psoriasis, facial angiofibromas associated with tuberous sclerosis, fibrofolliculomas found in Birt-Hogg-Dubé Syndrome, chronic erosive oral lichen planus, Early Stage Cutaneous T-cell Lymphoma, Treatment of Autoimmune Active Anterior Uveitis, dry eye syndrome, age-related macular degeneration, diabetic macular edema, noninfectious uveitis, telangiectasia, inflammatory skin diseases (dermatitis, including psoriasis and lichen ruber planus), Pachyonychia Congenita and for the suppression angiogenesis pathways.

5 15. A method of prophylaxis of organ rejection in patients receiving renal transplants, treatment of psoriasis, facial angiofibromas associated with tuberous sclerosis, fibrofolliculomas found in Birt-Hogg-Dubé Syndrome, chronic erosive oral lichen planus, Early Stage Cutaneous T-cell Lymphoma, Treatment of Autoimmune Active Anterior Uveitis, dry eye syndrome, age-related macular degeneration, diabetic macular edema, noninfectious uveitis, telangiectasia, inflammatory skin diseases (dermatitis, including psoriasis and lichen ruber planus), Pachyonychia Congenita and for the suppression angiogenesis pathways.

10 16. A method of prophylaxis of organ rejection in patients receiving renal transplants, treatment of psoriasis, facial angiofibromas associated with tuberous sclerosis, fibrofolliculomas found in Birt-Hogg-Dubé Syndrome, chronic erosive oral lichen planus, Early Stage Cutaneous T-cell Lymphoma, Treatment of Autoimmune Active Anterior Uveitis, dry eye syndrome, age-related macular degeneration, diabetic macular edema, noninfectious uveitis, telangiectasia, inflammatory skin diseases (dermatitis, including psoriasis and lichen ruber planus), Pachyonychia Congenita and for the suppression angiogenesis pathways comprising administration of a therapeutically effective amount of the complex according to any of Claims 1 to 6 or the pharmaceutical composition according to Claim 11 or 12.

15 17. A method for reducing the therapeutically effective dosage of Sirolimus compared to commercially available oral dosage forms, said method comprising oral administration of a pharmaceutical composition according to Claims 11 or 12.

20 25 17. A stable complex comprising

- a) 10 – 40% by weight of Sirolimus, its salt, or derivatives thereof;
- b) 20 – 80% by weight of a polyvinylpyrrolidone; and
- c) 5 – 50 % by weight of sodium-lauryl-sulfate

30 wherein said complex has a controlled particle size in the range between 50 nm and 600 nm, preferable the particle size is between 50 nm and 200 nm; and wherein said complex is obtained according to any of claims 7 to 10.

Excipient 2:	Citric Acid	D-Mannitol	DSS	Kollicoat-IR	NaOAc	NONE	Plur PE10500	SDC	SLS	Solutol HS15	Labrasol
Excipient 1:										-	+
Gelucire 44/14	-	-	+	-	+	-	-	-	+	+	+
Gelucire 50/13	+	-	+	+	+	+	+	+	+	-	+
Klucell EF	+	+	+	-	+	+	-	+	+	-	+
Klucell LF	-	-	+	+	-	-	+	-	+	-	+
Lutrol F127	+	+	+	+	+	+	+	+	+	-	-
Luviskol VA64	-	-	+	+	-	-	-	+	+	-	-
PEG2000	-	-	-	-	-	-	-	-	-	-	-
PEG6000	-	-	-	-	-	-	-	-	-	-	-
PEOX50	-	-	+	-	-	-	-	-	+	-	+
PEOX500	-	-	+	-	+	-	-	+	+	-	-
Plasdone K-12	+	-	-	-	+	-	-	-	+	+	+
Plur PE10500	+	+	+	+	+	+	+	+	+	-	-
Plur PE6800	+	-	-	+	-	-	-	+	+	-	-
Pluronic F108	-	-	+	+	-	+	+	+	+	+	+
PMAMVE	+	+	+	+	+	-	+	+	+	-	-
PVP 40	-	-	+	-	-	-	-	+	+	-	-
PVP K90	-	-	+	+	-	-	-	-	+	-	-
PVP10	-	-	+	-	-	-	-	+	+	-	-
Soluplus	-	-	+	-	-	-	-	-	+	+	+
Solutol HS15	+	+	+	+	+	+	+	+	+	-	-
Tetronic 1107	+	-	-	-	-	-	-	+	+	+	+
TPGS	+	+	+	+	+	+	+	+	+	-	+

+ redispersable solid Sirolimus complex

- non-redispersable solid Sirolimus complex

Figure 1

2/6

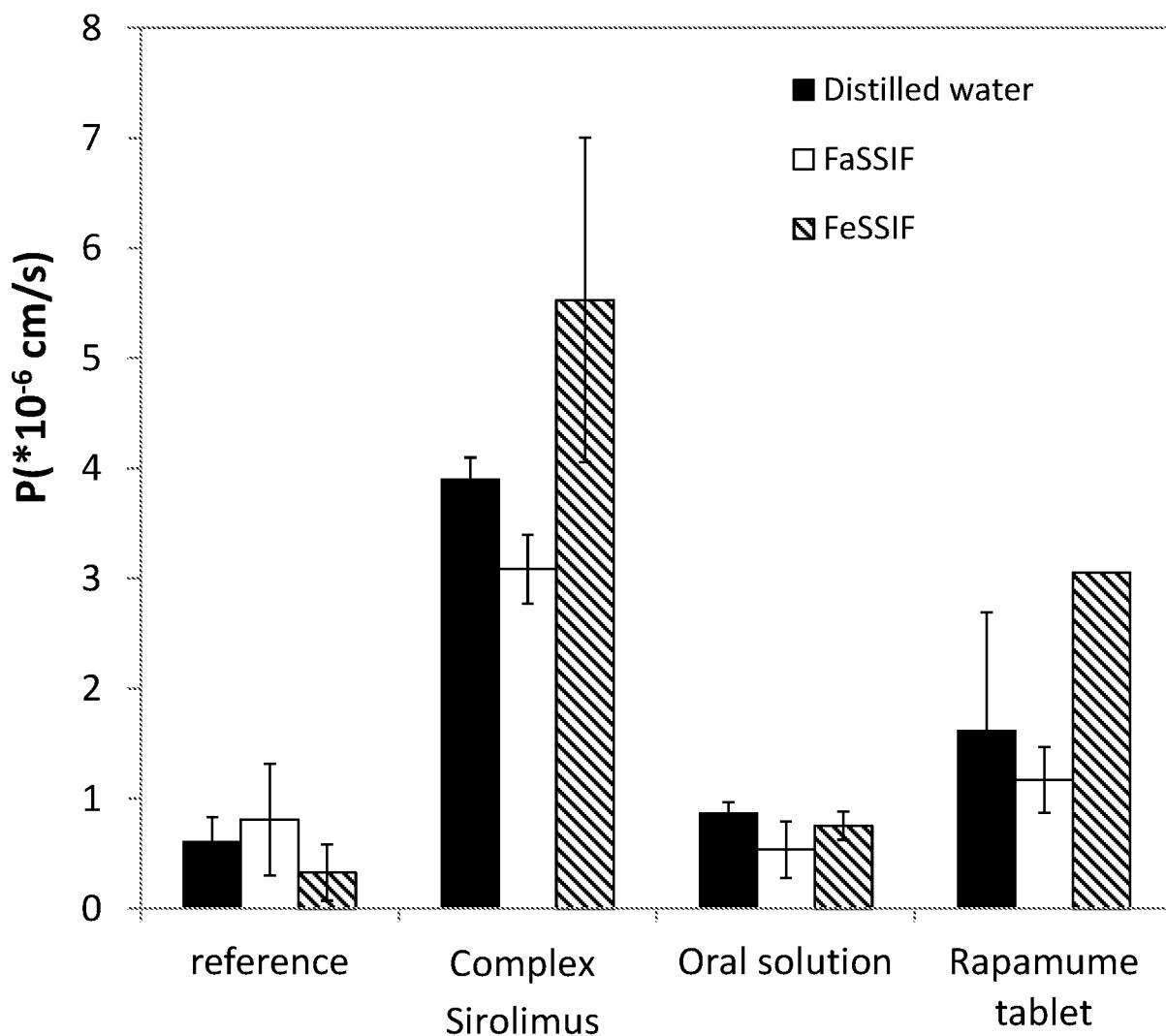


Figure 2

3/6

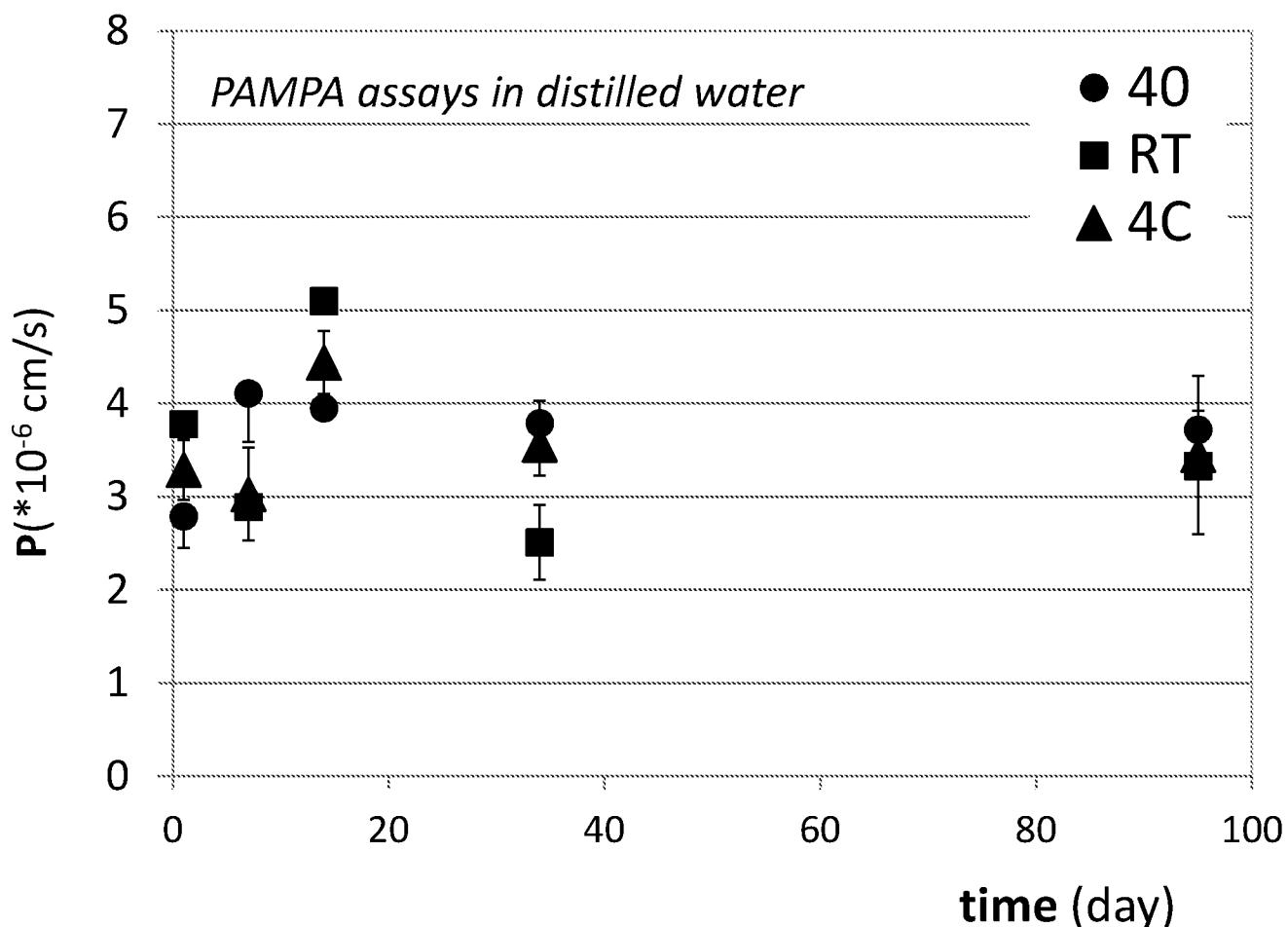


Figure 3

4/6

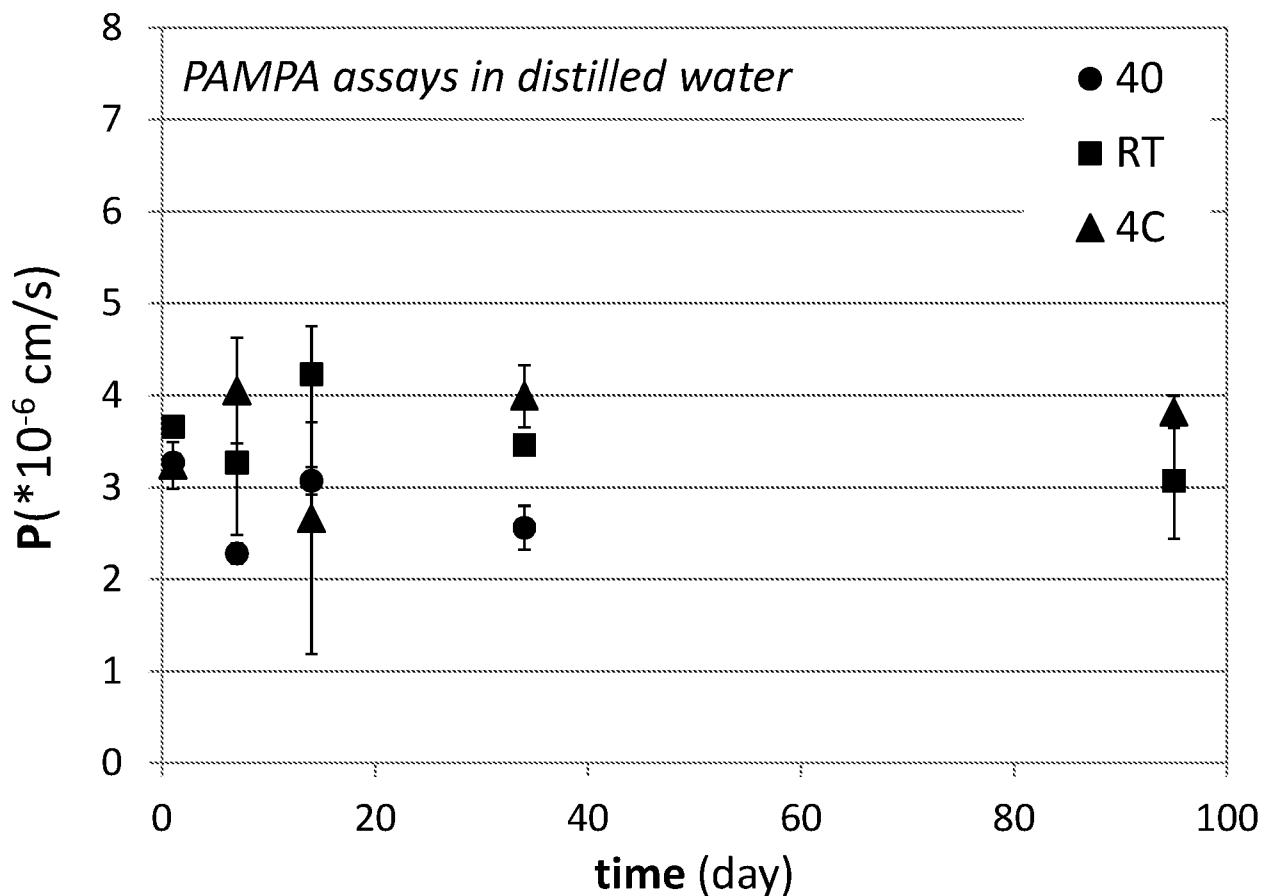


Figure 4

5/6

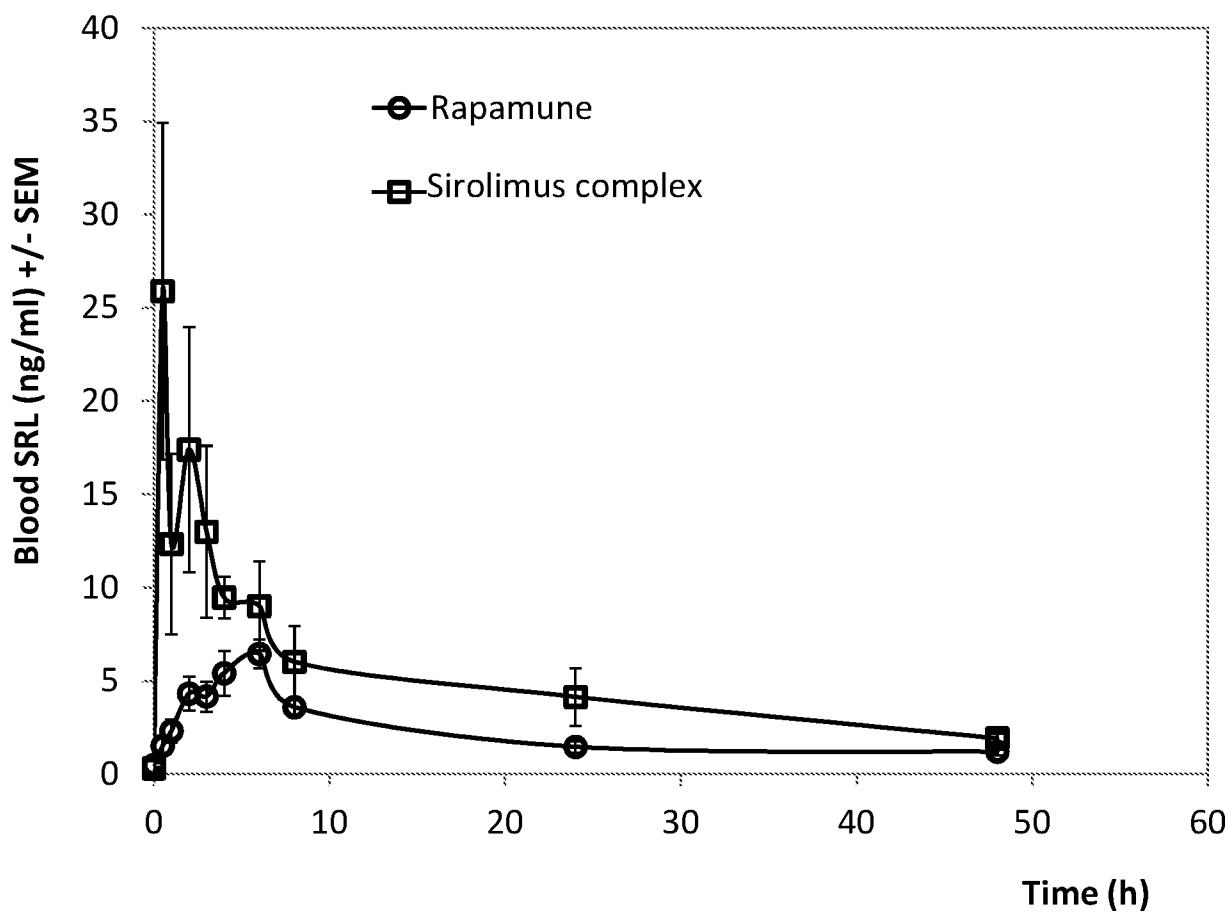


Figure 5

	AUC_{0-72} (ng/ml/h)	$AUC_{0-\infty}$ (ng/ml/h)	C_{\max} (ng/ml)	t_{\max} (h)
Rapamune	109	147	7.24	4.8
Sirolimus complex	243	308	25.9	0.5

Figure 6

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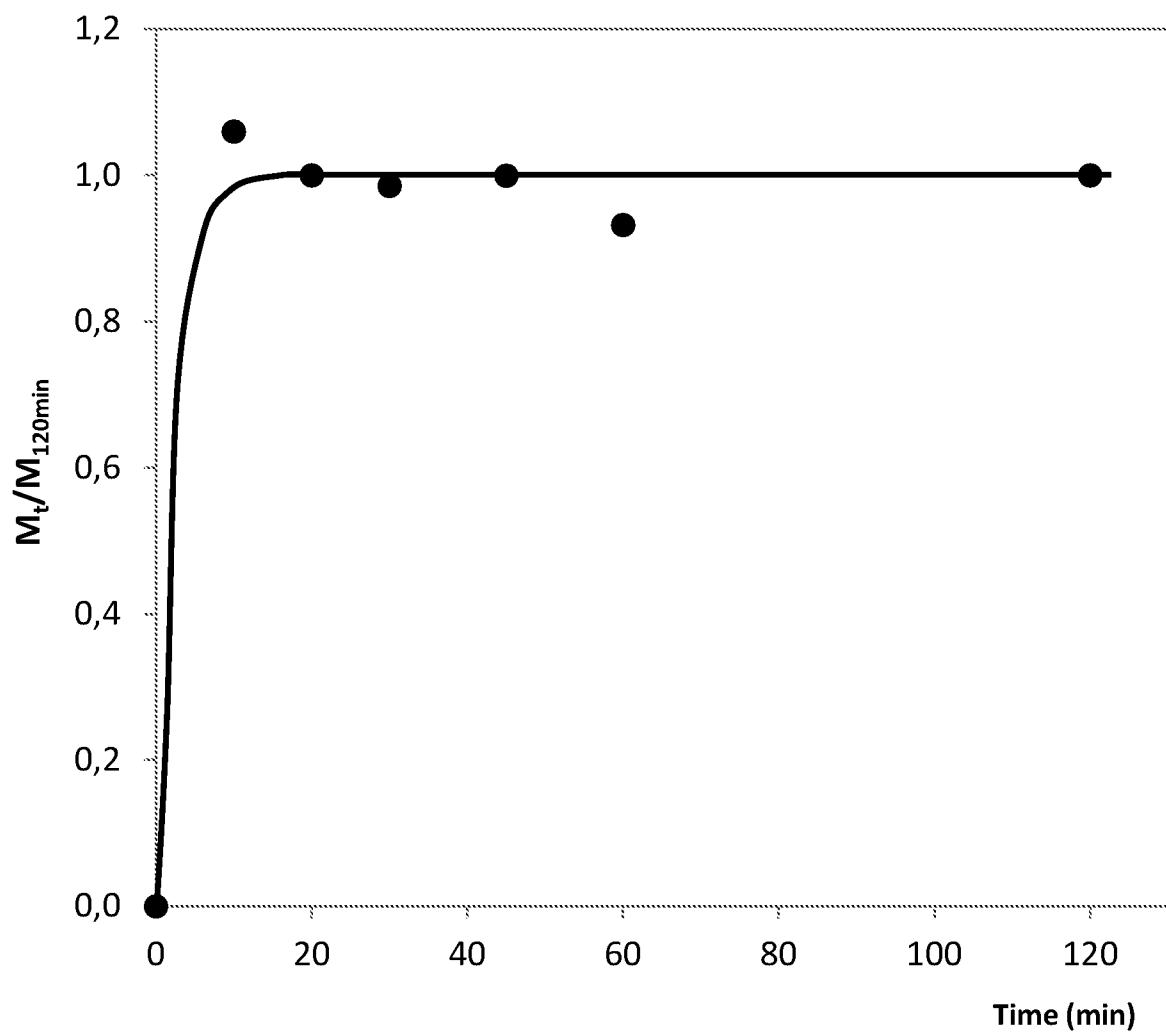


Figure 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/051086

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K47/10 A61K47/20
ADD.

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/094507 A1 (LIFECYCLE PHARMA AS [DK]; HOLM PER [DK]; NORLING TOMAS [DK]) 14 September 2006 (2006-09-14) page 23, line 23 - line 27 page 28, line 7 - page 29, line 20 page 31, line 10 - page 32, line 4; claims 1,10,45-48; examples -----	1-3,5-7, 11-16
A	page 23, line 23 - line 27 page 28, line 7 - page 29, line 20 page 31, line 10 - page 32, line 4; claims 1,10,45-48; examples -----	8-10,17
X	US 2013/150397 A1 (PIETRZYNSKI GRZEGORZ [CA] ET AL) 13 June 2013 (2013-06-13) cited in the application paragraph [0038] - paragraph [0053] paragraph [0081]; claim 13 ----- -/-	1,2,4,6, 11,12

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search Date of mailing of the international search report

12 June 2015

18/06/2015

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2013/039951 A1 (KIM SOON-HOE [KR] ET AL) 14 February 2013 (2013-02-14) cited in the application paragraph [0036] - paragraph [0053]; claims -----	1,2,4, 11-16
X	EP 1 759 724 A1 (CORDIS CORP [US]) 7 March 2007 (2007-03-07) paragraph [0427] - paragraph [0429] -----	1,2,11, 12
X	EP 1 952 807 A1 (LEK PHARMACEUTICALS [SI]) 6 August 2008 (2008-08-06) paragraph [0027] - paragraph [0030]; claims 1, 5; examples 4-6 -----	1,2,11, 12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/IB2015/051086

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 2006094507	A1 14-09-2006	AU 2006222409	A1 14-09-2006	CA 2599758	A1 14-09-2006
		CN 101137365	A 05-03-2008	EP 1858511	A1 28-11-2007
		JP 2008532953	A 21-08-2008	US 2008275076	A1 06-11-2008
		WO 2006094507	A1 14-09-2006		
<hr style="border-top: 1px dashed black;"/>					
US 2013150397	A1 13-06-2013	CN 104379215	A 25-02-2015	EP 2790700	A2 22-10-2014
		JP 2015513311	A 07-05-2015	US 2013150397	A1 13-06-2013
		WO 2013090602	A2 20-06-2013		
<hr style="border-top: 1px dashed black;"/>					
US 2013039951	A1 14-02-2013	KR 101151890	B1 31-05-2012	US 2013039951	A1 14-02-2013
<hr style="border-top: 1px dashed black;"/>					
EP 1759724	A1 07-03-2007	CA 2557437	A1 28-02-2007	EP 1759724	A1 07-03-2007
		JP 4990583	B2 01-08-2012	JP 2007061632	A 15-03-2007
		US 2007048350	A1 01-03-2007	US 2009311299	A1 17-12-2009
<hr style="border-top: 1px dashed black;"/>					
EP 1952807	A1 06-08-2008	EP 1952807	A1 06-08-2008	EP 1982702	A1 22-10-2008
		SI 1982702	T1 30-08-2013	US 2008176888	A1 24-07-2008

摘要

本发明涉及具有受控的粒径、增加的表观溶解度和增加的溶出率的稳定的络合物，其包含活性化合物西罗莫司或其衍生物，其用于在接受肾移植的患者中预防器官排斥反应，用于治疗银屑病、结节性硬化症相关的面部血管纤维瘤、在 Birt-Hogg-Dubé 综合征中发现的纤维毛囊瘤、慢性糜烂性口腔扁平苔癣、早期皮肤 T 细胞淋巴瘤，治疗自身免疫性活动性前葡萄膜炎、干眼综合征、年龄相关的黄斑变性、糖尿病黄斑水肿、非感染性葡萄膜炎、毛细血管扩张、炎症性皮肤病（皮炎，包括银屑病和扁平红苔癣）、先天性甲肥厚，以及用于抑制血管发生通路。更具体地，本发明的络合物具有增加的表观溶解度、渗透性和增强的生物学性能，包括显著改进的暴露、更早的 t_{max} 、更高的 C_{max} 和在 24 小时内更高的谷浓度，这将允许减少剂量。此外，本发明的络合物作为再分散溶液具有优异的稳定性，这使得能够开发用于经皮给药和其他局部给药的基于液体的制剂。本发明还涉及制备和生产本发明的络合物的方法，含有其的药物组合物，其用途和使用该络合物及其组合物的治疗方法。

