(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 February 2013 (14.02.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/022458 Al

(51) International Patent Classification:
C07D 498/18 (2006.01)

(21) International Application Number:
PCT/US201 1/052935

(22) International Filing Date:
23 September 201 1 (23.09.201 1)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/5 15,500 5 August 201 1 (05.08.201 1) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2013/022458 A1

(54) Title: METHODS OF CONVERTING AMORPHOUS DRUG SUBSTANCE INTO CRYSTALLINE FORM

(57) Abstract: A method for converting an amorphous drug, such as everolimus, or other macrolide immunosuppressive drug, into a crystalline form. The method utilizes a slurry of the drug in organic liquid phase and ages the slurry to achieve the conversion.

Title

METHODS OF CONVERTING AMORPHOUS DRUG SUBSTANCE INTO CRYSTALLINE FORM

Cross-Reference To Related Applications

This application claims the benefit of U.S. Provisional Application No. 61/515500, entitled, "METHODS OF CONVERTING AMORPHOUS DRUG SUBSTANCE INTO CRYSTALLINE FORM," by Maggie Zeng, Yen-Lane Chen, Maura Romanshek, and Erin Meyer, and filed on August 5, 201 1, the entire contents of which being incorporated herein by reference.

Background of the Invention

Commercial everolimus, as supplied by the manufacturer Novartis, is an amorphous solid that has a high bioavailability. A crystalline form exists which has a lower water solubility.

US 7,232,486 describes a method for crystallizing tacrolimius that is said to work with everolimus as well. The method uses a polar solvent solution of the drug that is combined with a 2-phase hydrocarbon and aqueous system. The drug is entirely dissolved in the polar solvent. Controlled pH of the aqueous phase is understood to be important in this method.

Summary of the Invention

The present invention pertains to a method for converting an amorphous drug, such as everolimus, tacrolimus, sirolimus, zotarolimus, biolimus, rapamycin or other macrolide immunosuppressive drug, into a crystalline form. In some embodiments the invention pertains specifically to conversion of everolimus.

The method utilizes slurry of the drug in organic liquid to achieve conversion with high efficiency.

In some aspects the inventive method comprises the steps of

providing an amount of a drug in a solid amorphous form;

providing a volume of a solvent for the drug, the volume being insufficient to fully dissolve said amount of the drug;

forming a slurry with said volume of said solvent and said amount of said drug; and

aging the slurry for a time to allow substantial conversion of the solid amorphous drug into crystalline drug.

In some embodiments the slurry is continuously or intermittently subjected to agitation.

In some embodiments the solvent is cooled or partially evaporated after a period of time to form seed crystal.

Further aspects pertain to medical devices comprising polymer-free drug coating comprising a crystalline drug with or without a protective polymer layer thereover. In some embodiments no protective layer is needed. In some embodiments the drug is everolimus.

These and other aspects and embodiments of the invention are described in the Detailed Description, Claims and Figures which follow.

Brief Description of the Figures

Figure 1 is an XRPD scan of a sample of commercial everolimus converted to crystalline form.

Figure 2 is an X-ray powder(XRPD) scan of a sample of commercial everlolimus.

Figure 3 is a graph showing the relative water solubilities of the amorphous and crystalline forms of everolimus.

Detailed Description of the Invention

The invention provides a simple cost effective method of conversion from amorphous drug to crystalline drug.

Drug morphology has significant impact on drug release kinetics and bioavailability of the drug product. While drug in amorphous solid state may be desirable for some applications where high dissolution rates and quick adsorption are required, the amorphous materials tend to exist in metastable states that may be prone to chemical and physical instability. Previous work done on drug-eluting-balloons have demonstrated that a sustained paclitaxel tissue concentration can be achieved by controlling appropriate drug morphology between various polymorphs of that drug.

While the amorphous form of some drug substances such as everolimus are generally suited for conventional administration routes, and in some cases have also been successfully used in compositions with polymers on stents for prevention of restenosis, the crystalline forms of such drugs are of particular importance for use in anti-restenotic drug coatings, for instance, in coatings on stents that provide extended tissue residence times on the stent without using a polymer. The crystalline forms are also of interest for delivery from balloons or at the site of balloon deployment, and on other medical devices.

The inventors hereof have discovered, for instance, that amorphous everolimus can be readily converted into crystalline form in very high yield using single-phase organic solvent systems from slurries of the amorphous drug. Solubility of the crystalline everolimus is about 25 times lower than that of amorphous everolimus,

which confirms the suitability of using crystalline everolimus to achieve sustained tissue concentration in drug delivery products. This crystalline form is especially useful for achieving controlled and sustained drug release for polymer-free drug eluting stents and polymer-free drug eluting balloons, where no polymer matrix is present in the coating to modulate the drug release.

Everolimus is manufactured and supplied by Novartis as the amorphous form drug. It is the active agent used in the drug eluting stent coating of the PROMUS® Element® and Ion™ drug eluting stent systems sold by Boston Scientific Inc. It remains in amorphous state in that coating and the drug release from that stent is controlled by a polymer matrix.

Referring to Figures 1 and 2, it can be seen that the XRPD scans of the respective crystalline and amorphous forms of everolimus are distinctly different. The crystalline form provides sharp characteristic peaks whereas the amorphous form has very broad indistinct features. Crystalline everolimus also shows birefringence under optical microscope using polarized lighting.

The comparative aqueous solubilities of the two drug forms at body temperature (37 °C) is shown in Figure 3.

The solubility of the amorphous form contributes to its bioavailability. However, when deployed at a specific site for prevention of restenosis it would be advantageous to be in a form that provides extended release without having to add polymer or other excipients which can contribute to an inflammatory response in some individuals. The much lower solubility of the crystalline form may provide such benefits.

The inventive method can also be used for conversion between forms of other drugs that have amorphous and crystalline forms.

In some embodiments, the drug may be a macrolide immunosuppressive (limus) drug. In some embodiments, the macrolide immunosuppressive drug is rapamycin, biolimus (biolimus A9), 40-O-(2-Hydroxyethyl)rapamycin (everolimus), 40-O-Benzyl-rapamycin, 40-O-(4'-Hydroxymethyl)benzyl-rapamycin, 40-O-[4'-(l,2-Dihydroxyethyl)]benzyl-rapamycin, 40-O-Allyl-rapamycin, 40-O-[3'-(2,2-Dimethyl-l,3-dioxolan-4(S)-yl)-prop-2'-en-l'-yl]-rapamycin, (2':E,4'S)-40-O-(4',5'-Dihydroxypent-2'-en-1'-yl)-rapamycin 40-O-(2-Hydroxy)ethoxycar-bonylmethyl-rapamycin, 40-O-(3-Hydroxy)propyl-rapamycin 40-O-(6-Hydroxy)hexyl-rapamycin 40-0-[2-(2-Hydroxy)ethoxy]ethyl-rapamycin 40-O-[(3S)-2,2-Dimethyldioxolan-3-yl]methyl-rapamycin, 40-O-[(2S)-2,3-Dihydroxyprop-l-yl]-rapamycin, 40-O-(2-Acetoxy)ethyl-rapamycin 40-O-(2-Nicotinoyloxy)ethyl-rapamycin, 40-O-[2-(N-Morpholino)acetoxy]ethyl-rapamycin 40-O-(2-N-Imidazolylacetoxy)ethyl-rapamycin, 40-O-[2-(N-Methyl-N'-piperazinyl)acetoxy]ethyl-rapamycin, 39-O-Desmethyl-39,40-0,0-ethylene -rapamycin, (26R)-26-Dihydro-40-O-(2-hydroxy)ethyl-rapamycin, 28-0-Methyl-rapamycin, 40-O-(2-Aminoethyl)-rapamycin, 40-O-(2-Acetaminoethyl)-rapamycin 40-O-(2-Nicotinamidoethyl)-rapamycin, 40-O-(2-(N-Methyl-imidazo-2'-ylcarbethoxamido)ethyl)-rapamycin, 40-O-(2-Ethoxycarbonylaminoethyl)-rapamycin, 40-O-(2-Tolylsulfonamidoethyl)-rapamycin, 40-O-[2-(4',5'-Dicarboethoxy-1',2',3'-triazol-l'-yl)-ethyl] -rapamycin, 42-Epi-(tetrazolyl)rapamycin (tacrolimus), 42-[3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate]rapamycin (temsirolimus), (42S)-42-Deoxy-42-(lH-tetrazol-l-yl)-rapamycin (zotarolimus), or derivative, isomer, racemate, diastereoisomer, prodrug, hydrate, ester, or analog thereof, provided that the particular drug is one that has both an amorphous form and a crystalline form.

In some embodiments, the drug to be converted may be an amorphous form of everolimus, sirolimus, zotarolimus and biolimus. In some embodiments the drug is amorphous everolimus.

Other drugs for which the inventive conversion method that may be useful include antiinflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, and analogues thereof; antineoplastic/ antiproliferative/anti-miotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, thymidine kinase inhibitors, and analogues thereof; anesthetic agents such as lidocaine, bupivacaine, ropivacaine, and analogues thereof; anti-coagulants; and growth factors, again provided that the particular drug is one has an amorphous form and a crystalline form.

In some embodiments the invention is directed to slurry conversion of the drug from amorphous to crystalline form. Slurry conversion reduces the amount of solvent that is needed to obtain conversion of a given mass of the drug and reduces the energy budget for recovery of the crystalline drug, compared to a nucleated solution technique. To recover crystalline drug from solution one typically must induce nucleation, for instance by seeding, of a supersaturated solution, often requiring heating to fully dissolve the drug and then cooling the solution or evaporating the solvent. If the solvent is to be evaporated and recovered additional energy is needed for the recovery.

In the inventive conversion method some of the same factors in the solvent handling are still involved. However, because the mass of drug is never fully dissolved the energy budget for solvent heating, cooling and recovery can be proportionally reduced. Further, if evaporation is used in the course of the process, the lower amount of solvent evaporated can significantly reduce the potential for environmental disruption and/or worker exposure to the solvent.

The choice of solvent or solvent mixture is not particularly critical. The solubility should not be so high that substantial amount of the drug is substantially all dissolved before the slurry is formed. If most of the drug is dissolved there may be little benefit to the slurry conversion process. Typical techniques for crystallization from a solution will have to be utilized for recovery of the dissolved drug. In at least some embodiments the amount of solvent used will be an amount that will dissolve no more than about 50%, of the saturation amount, that is the amount of solvent needed to dissolve the mass of drug employed in any particular batch being converted. In some embodiments the amount of solvent used will be no more than about 30% of the saturation amount. For instance the amount may be from about 0.5% to about 25%, or from about 1% to about 20%, or from about 5% to about 15% of the saturation amount. In some embodiments no more than 30%, no more than 25%, no more than 20% or no more than 10% of the amorphous drug is soluble in the amount of solvent provided at the temperature of aging. In some embodiments from about 0.5% to about 50%, from about 1% to about 30‰ or from about 2% to about 20‰ of the drug is soluble in the volume of solvent provided at the temperature of aging.

The solubility should not be so low that the conversion rate is impractical. Slurry conversion is a process that depends on exchange of drug molecules between solid and liquid solution phases. In some cases solvent blends can be used to provide a suitable balance between conversion speed and saturation excess. Examples of solvents that may be used include alcohols such as methanol, ethanol (EtOH), isopropanol (IPA), n-butanol, isobutyl alcohol or t-butyl alcohol; acetonitrile (ACN); ethers such as tetrahydrofuran (THF) isopropyl ether (IPE), diethyl ether (DEE); ketone solvents such as acetone, 2-butanone (MEK), or methyl isobutyl ketone (MIBK); halogenated solvents such as dichloromethane (DCM), monofluorobenzene (MFB),

α,α,α-trifluorotoluene (TFT), nitromethane (NM), ethyl trifluroacetate (ETFA); aliphatic hydrocarbons such as hexane, heptane, or the like; aromatic hydrocarbons, such as toluene or xylenes; and ester solvents such as ethyl acetate. Mixed solvents, for instance heptane/ethyl acetate, acetone/water, IPA/water, or IPA/THF, THF/heptane can also be used. In some embodiments the solvent is a mixture of an aliphatic hydrocarbon and an ether or ester cosolvent having a volume ratio in the range of from about 40:1 to about 5:1.

The temperature range for conducting the conversion can be any temperature below the boiling point of the solvent or temperature at which the drug begins to show thermal degradation. For instance, for a drug such as everolimus, a suitable temperature may be in the range of from about -30°C to about 60°C, or from 4°C to 50°C. In some cases it may accelerate conversion to initially supersaturate the slurry, by cooling a solution after it has been saturated at or above ambient. In other cases effective conversion can be accomplished with an ambient temperature aging.

To accelerate the conversion, the saturated slurry may be cooled or some of the solvent evaporated to force formation of seed crystals in of the drug. In some cases seed crystals of the crystalline drug form may be added to the slurry to speed initiation of conversion. Without being bound thereto, it is believed the seed crystals will grow over time as amorphous drug is dissolved and then is removed from the solution by addition to the existing seed crystals. Over time substantially all of the solid amorphous drug is replaced with crystalline drug.

In the case of a drug that has more than one crystalline form, the addition of seed crystals of a desired crystalline form may allow better control of the crystalline form obtained by the inventive process

In some embodiments intermittent or continuous agitation may accelerate the conversion process by breaking crystals to form more seed area and by maximizing the efficiency of dissolution of the amorphous drug as crystal formation removes the drug from solution. Agitation may be accomplished by sonication, stirring, shaking or the like. Particular conditions of agitation may also provide a specific particle size range of the crystalline drug product.

The skilled person can determine a suitable aging time taking into account the particular combination of drug and solvent used, the relative amounts of those ingredients, the temperature(s) employed and the other conditions employed, as well as the desired degree of conversion. In at least some embodiments the aging time will be sufficient to provide conversion of the amorphous drug to at least 50%, at least 75%, at least 80%, at least 85%, or at least 90% of the mass to crystalline form. Aging times for instance may be from about 1 day to about 15 days or more, or from about 2 to about 7 days, or from about 4-6 days.

At the end of the conversion the solids may be separated from the solvent, for instance by filtration, centrifuging or decanting, and then the solids dried. In some cases separate solvent/drug solution may be combined with additional amorphous drug in a semi-continuous or sequential batch conversion process. Alternatively all of the solvent may be removed by evaporation or heating, optionally with solvent recovery for instance by cooling the solvent vapor downstream of the slurry.

In embodiments using amorphous everolimus, conversion of the amorphous drug to a 85-98% crystalline form drug is obtained with little or no change in drug purity. If the solvent is fully removed from the mass by evaporation, the purity

generally should not be affected. If the solvent is separated before drying there may be some increase in purity over the starting drug.

If the drug includes a stabilizer component, in some case the minor amount of the stabilizer in the drug may change enough to influence the stability of the crystalline drug. Consequently stabilizer retention in the crystalline product should be separately confirmed and adjusted if needed.

In some embodiments a stabilizer component provided in the amorphous drug, such as butylated hydroxy toluene (BHT) or another antioxidant stabilizer, may be substantially removed by the conversion process of the invention, e.g. if the crystalline drug is separated from the solvent by filtration, decanting, centrifugation or the like. This may be desirable for drug coated medical devices since a stabilizer itself may be a source of tissue inflammation on the device. If the coating process and coated devices are protected from oxygen until the time of use adequate shelf life can be achieved without stabilizer. This may be accomplished for instance, by processing crystalline everolimus under nitrogen or another inert gas during isolation and coating process, and then packaging the coated device in an air-tight enclosure that has been filled with inert gas. In some embodiments therefore the invention pertains to a medical device coated with a crystalline drug, such as crystalline everolimus, that is substantially free (e.g. less than 0.1 %, or less than 0.01%) of antioxidant stabilizer, or one in which the amount of stabilizer has been reduced by more than 50%, for instance more than 70%, more than 80% or more than 90% from a commercial amorphous form of the drug.

In some embodiments for applying a crystalline drug to a medical device, a suspension of crystalline particles is applied, optionally with a non-polymeric excipient that facilitates bonding or film formation, without dissolving the drug, and the suspension vehicle evaporated to provide a polymer-free crystalline drug coating.

Exemplary non-polymeric excipients include citrate esters, such as acetyl tributyl citrate or other acetylated trialkyl citrates, trialkyl citrates, and trialkyl citrates that have been etherified at the hydroxyl group on citric acid. Other non-polymeric excipients that may be useful include surfactants such as described in US 2008/01 18544 A1; oils; esters of fatty acids and C_1-C_6 alcohols such as isopropyl myristate; triacetin; and the like. Other documents in which describe non-polymeric excipients that may be useful include US 2005/0101522 A1; US 2006/0020243 A1; US 2008/0255509 A1; US 201 0/0063585 A1; US 201 0/01 79475 A1; and US 201 0/0272773 A1. In at least some embodiments the excipient is selected to be one in which the drug is substantially undissolved, so that the major portion of the drug remains in the crystalline form.

The medical devices used in conjunction with the present invention include any device amenable to the coating processes described herein. The medical device, or portion of the medical device, to be coated or surface modified may be made of metal, polymers, ceramics, composites or combinations thereof. Whereas the present invention is described herein with specific reference to a vascular stent, or balloon other medical devices within the scope of the present invention include any devices which are used, at least in part, to penetrate the body of a patient. Non-limiting examples of medical devices according to the present invention include catheters, guide wires, balloons, filters (e.g., vena cava filters), stents, stent grafts, vascular grafts, intraluminal paving systems, soft tissue and hard tissue implants, such as orthopedic repair plates and rods, joint implants, tooth and jaw implants, metallic alloy ligatures, vascular access ports, artificial heart housings, artificial heart valves, aneurysm filling coils and other coiled coil devices, trans myocardial revascularization ("TMR") devices, percutaneous myocardial revascularization ("PMR") devices, hypodermic needles, soft tissue clips, holding devices, and other types of medically useful needles and closures, and other

devices used in connection with drug-loaded polymer coatings. Such medical devices may be implanted or otherwise utilized in body lumina and organs such as the coronary vasculature, esophagus, trachea, colon, biliary tract, urinary tract, prostate, brain, lung, liver, heart, skeletal muscle, kidney, bladder, intestines, stomach, pancreas, ovary, cartilage, eye, bone, and the like. Any exposed surface of these medical devices may be coated with the methods and apparatus of the present invention.

In at least some embodiments the drug crystals in such a coating have a mean particle size of less than about 100 μιη as measured by dynamic light scattering methods, for instance using photo correlation spectroscopy, laser diffraction, low angle laser light scattering (LALLS), medium-angle laser light scattering (MALLS), light obscuration methods (Coulter method, for example), rheology, or microscopy (light or electron). The particles can be prepared in a wide range of sizes, such as from about 20 μιη to about 10 nm, from about 10 μιη to about 10 nm, from about 2 μιη to about 10 nm, from about 1 μιη to about 10 nm, from about 400 nm to about 50 nm, from about 200 nm to about 50 nm or any range or combination of ranges therein. The crystalline particle size in some cases may be sized to a desired distribution using agitation methods such as sonication during slurry aging. Alternatively a desired particle size may be obtained by mechanical grinding techniques such as pearl milling, a ball milling, hammer milling, fluid energy milling or wet grinding techniques or the like after the drug has been converted to crystalline form.

In specific examples slurries of everolimus may be prepared by adding enough solids to a given solvent at ambient conditions so that undissolved solids are present. The mixture may then be loaded onto a digital oscillator, stir plate or rotating wheel in a sealed vial at ambient or elevated temperature for an extended period of time, typically from 1 to 7 days. The solids may be isolated by vacuum filtration or by

decanting the liquid phase and allowing the solid to air dry in an open vial at ambient conditions, or drying under nitrogen at ambient or another suitable temperature.

In other examples, mixtures with undissolved solids of solvent and everolimus may be left to stand under ambient conditions. Solids are collected by vacuum filtration or by decanting the solvent and air drying at ambient conditions or under nitrogen.

The invention is illustrated by the following non-limiting examples.

Examples

Approximate solubilities of amorphous everolimus were determined by adding the drug gradually with stirring at room temperature to a fixed volume of the solvent until solid remained visible. Results are shown in Table 1.

Table 1

Solvent(s)	Amorphous Everolimus Solubilities mg/mL
Acetone	~ 100
ACN	~ 100
DCM	~ 46
DMF	~ 49
p-dioxane	~ 58
EtOH	~ 100
ethyl acetate	~ 100
n-heptane	~ 0.5
hexanes	not measured
IPA	~15
MEK	~ 70
MTBE	~ 62
THF	~ 67
water	~ 0.1
m-xylene	~ 76
ACN/water 3:2 *v/v*	~ 52
DMF/DCM *w/w*	~ 142
DMF/EtOAc *w/w*	~ 119
DMF/THF *w/w*	~ 112

Typically the solubility can be expected to increase from these values at higher than ambient temperatures and decrease at lower than ambient temperatures. The rates of change with temperature, however, may be quite different between different solvent systems.

Examples 1-3 and 5

A supersaturated slurry suspension of amorphous everolimus in an organic cosolvent solution was prepared. The slurry was aged at 50°C while agitating in

an orbital shaker set to 120 rpm for a couple of days. Some solvent evaporated under these conditions. The slurry is then placed at 4°C for several days to allow for crystal growth as well as additional solvent evaporation.

Example 4

Another everolimus crystalline sample was prepared by adding to approximately 500 mg of purified amorphous everolimus, 500 μL of a 1:20 ethyl acetate/heptane solvent solution. A slurry suspension was generated. The slurry was incubated uncovered at ambient conditions overnight to allow for complete solvent evaporation. The product had a crystalline habit that was seen to be a combination of larger needles and plate like crystals when observed under the polarized light microscope

Example 6

Approximately 200 mg of amorphous everolimus was added to 500 μL of isopropanol. The slurry solution was then briefly vortexed and incubated, with the crystallization vessel covered, at ambient conditions for two days. The solvent was then allowed to completely evaporate. The product had a needle-like crystalline habit when observed under a polarized light microscope. Analysis by HPLC of the purity of the recovered crystalline everolimus was 91.4%.

Example 7

Crystals of sample everolimus were generated dissolving approximately 100 mg of amorphous everolimus in 500 μL of p-xylene. A slurry suspension was then generated by adding additional everolimus. The slurry suspension was vortexed and incubated at ambient conditions for an extended period of time. The slurry was allowed

to evaporate for several days the following incubation period. Microscopic inspection of the product showed a micro-crystalline structure exhibiting a needle-like habit when observed under a polarized light.

Table 2 contains further details of these examples and the products obtained. "EvRL" designates everolimus.

Table 2

Summary of Solvent Systems Used to Generate Crystalline Everoliumus

Example No.	Solvent System	Weight of EvRL per volume solvent solution (w/v)	EvRL Conc. (mg/mL)	Conditions	Total mix/dry time	Birefringence Observed
1	1:20 EtOAc:Heptane slurry	97 mg in 500 µL solution	194 mg/mL	1) 50°C orbital shaker (120 rpm) for 2 days 2) Store at 4°C for 4 days 3) Left uncovered overnight for additional solvent evaporation	~6 days	Yes
2	1:20 EtOAc:Heptane slurry	92 mg in 500 µL solution	184 mg/mL	1) 50°C orbital shaker (120 rpm) for 6 days [note: solvent had fully evaporated within 6 day shaking time]	~6 days	Yes
3	1:10 EtOAc:Heptane slurry	109 mg in 1000 µL solution	109 mg/mL	1) 50°C orbital shaker (120 rpm) for 2 days 2) Store at 4°C for 4 days 3) Left uncovered overnight for additional solvent evaporation	~6 days	Yes
4	20:1 EtOAc:Heptane slurry	496 mg EvRL in 500 µL solution	992 mg/mL	1) Fast evaporation (allowed to dry uncovered) 2) Left uncovered overnight for additional solvent evaporation	~1 day	Yes
5	1:40 THF:Heptane slurry	95 mg EvRL in 500 µL solution	190 mg/mL	1) 50°C orbital shaker (120 rpm) for 2 days 2) Store at 4°C for 4 days 3) Left uncovered overnight for additional solvent evaporation	~6 days	Yes
6	IPA slurry	192 mg EvRL in 500 µL solution	384 mg/mL	1) Room temperature slurry for 2 days (no shaking)	~2 days	Yes
7	p-xylene slurry	411 mg EvRL in 500 µL solution	822 mg/mL	1) Slow evaporation (leave cover on, but unscrewed) 2) Left uncovered overnight for additional solvent evaporation	~2 days	Yes

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In addition to the inventions recited in the claims other subject matter considered to be inventive disclosed herein includes the following items:

A. A medical device having a polymer-free coating comprising crystalline everolimus.

B. A medical device having a drug coating comprising crystalline everolimus which is substantially free of an antioxidant.

C. A medical device as in item A or B wherein the crystalline form everolimus comprises at least 85% by weight of the drug.

D. A medical device as in claim Item B wherein the crystalline form everolimus comprises at least 90% by weight of the drug.

E. A medical device as in item A or B wherein the polymer-free coating comprises a mixture of crystalline and amorphous everolimus, the mixture comprising from 15% to 90%> by weight of said crystalline everolimus.

F. A medical device as in one of items A-E wherein the device is stent, a catheter balloon, guide wire, heart valve, catheter, vena cava filter, vascular graft or a stent graft.

All published documents, including all US patent documents, mentioned anywhere in this application are hereby expressly incorporated herein by reference in their entirety. Any copending patent applications, mentioned anywhere in this application are also hereby expressly incorporated herein by reference in their entirety.

The above examples and disclosure are intended to be illustrative and not exhaustive. These examples and description will suggest many variations and alternatives to one of ordinary skill in this art. All these alternatives and variations are intended to be included within the scope of the claims, where the term "comprising" means "including, but not limited to". Those familiar with the art may recognize other

equivalents to the specific embodiments described herein which equivalents are also intended to be encompassed by the claims. Further, the particular features presented in the dependent claims can be combined with each other in other manners within the scope of the invention such that the invention should be recognized as also specifically directed to other embodiments having any other possible combination of the features of the dependent claims. For instance, for purposes of claim publication, any dependent claim which follows should be taken as alternatively written in a multiple dependent form from all claims which possess all antecedents referenced in such dependent claim if such multiple dependent format is an accepted format within the jurisdiction. In jurisdictions where multiple dependent claim formats are restricted, the following dependent claims should each be also taken as alternatively written in each singly dependent claim format which creates a dependency from an antecedent-possessing claim other than the specific claim listed in such dependent claim.

Claims

1. A method of converting an amorphous form of a drug to a crystalline form of said drug comprising the steps of

providing an amount of said drug in a solid amorphous form;

providing a volume of a solvent for the drug, the volume being insufficient to fully dissolve said amount of the drug;

forming a slurry with said volume of said solvent and said amount of said drug; and

aging the slurry for a time to allow substantial conversion of the solid amorphous drug into crystalline drug.

2. A method as in claim 1 wherein the drug is a macrolide immunosuppressive drug.

3. A method as in claim 1 wherein the drug is a member of the group consisting of everolimus, rapamycin, zotarolimus and biolimus.

4. A method as in claim 3 wherein the drug the drug is everolimus.

5. A method as in claim 1 wherein during at least a portion of the aging time the slurry is subjected to agitation.

6. A method as in claim 1 wherein the volume of said solvent is no more than 50%, the amount of solvent needed to fully dissolve said amount of the drug at the temperature of aging.

7. A method as in claim 6 wherein the volume of said solvent is no more than 30% of the amount of solvent needed to fully dissolve said amount of the drug at the temperature of aging.

8. A method as in claim 6 wherein the volume of said solvent is from about 2% to about 20% of the amount of solvent needed to fully dissolve said amount of the drug at the temperature of aging.

9. A method as in claim 1 wherein seed crystals of the crystalline drug form are be added to the slurry.

10. A method as in claim 1 wherein during said aging step the slurry is agitated in a manner that breaks formed crystals of the drug into a predetermined size distribution.

11. A method as in claim 1 wherein the solvent is selected from the group consisting of alcohols, acetonitrile, ethers, ketones, halogenated solvents, hydrocarbon solvents, and mixtures thereof.

12. A method as in claim 11 wherein the solvent is a mixture of an aliphatic hydrocarbon with an ether or ester co-solvent having a volume ratio of 40:1 to 5:1.

13. A method as in claim 1 wherein a mixture of two or more organic solvents are used as the solvent for the drug.

14. A method as in claim 1 wherein the slurry is aged at a temperature of from about 4 °C to about 80°C.

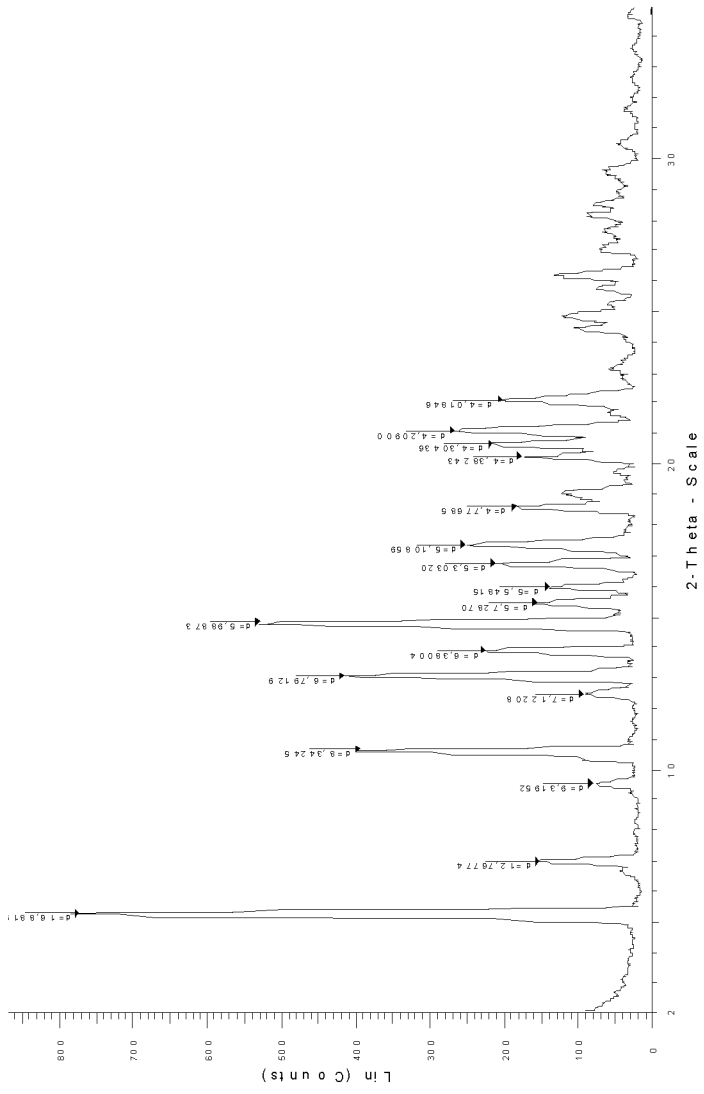
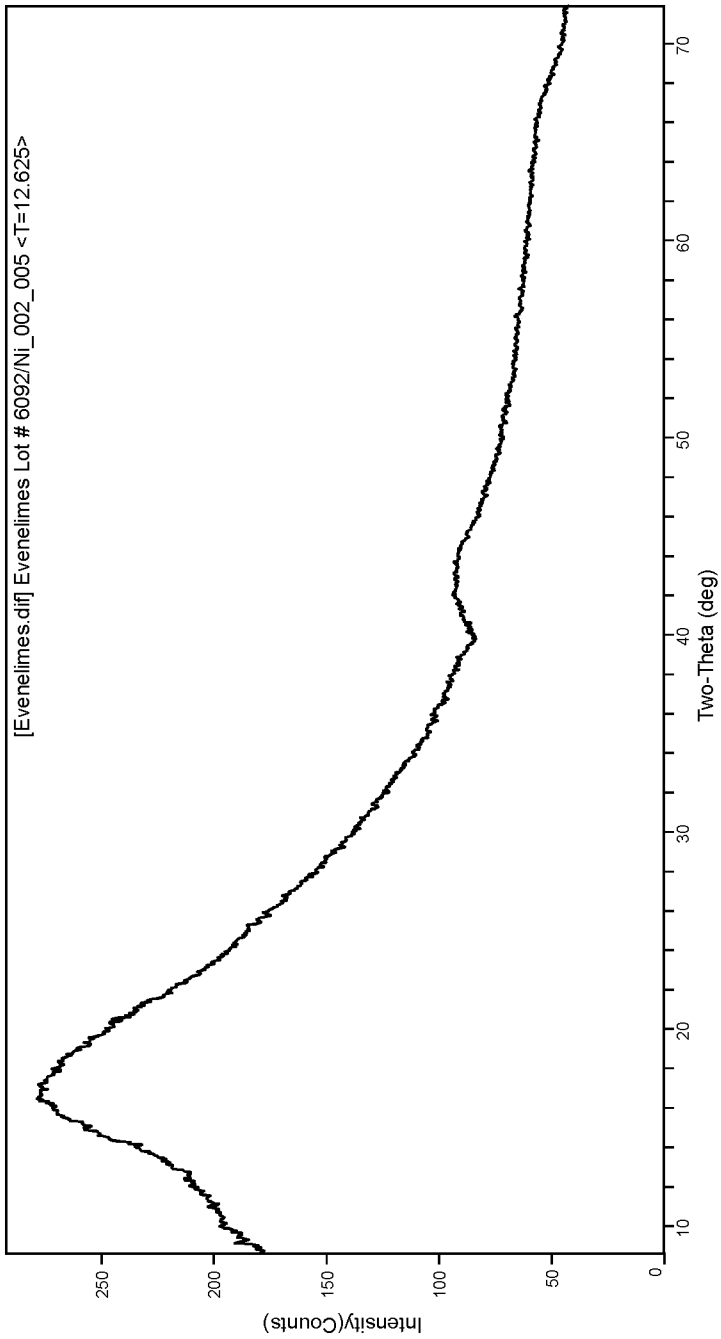

Lin (Counts)
0
10.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
2
10
20
30
2-Theta - Scale
d = 16.8817
d = 12.7677 4
d = 9.3198 52
d = 8.3424 5
d = 7.1 2 20 8
d = 6.78 12 9
d = 6.3800 4
d= 5.98 87 3
d = 5.7 28 70
d =5 .5 48 15
d = 5.3 03 20
d = 5 .10 8 59
d=4 .7 7 68 5
d =4 .38 2 43
d =4 .30 4 36
d = 4.2 09 8 0
d = 4 .0 1 8 4 6

Fig. 1


[Evenelimes.dif] Evenelimes Lot # 6092/Ni_002_005 <T=12.625>
Intensity(Counts)
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50
100
150
200
250
Two-Theta (deg)
10
20
30
40
50
60
70

Fig. 2

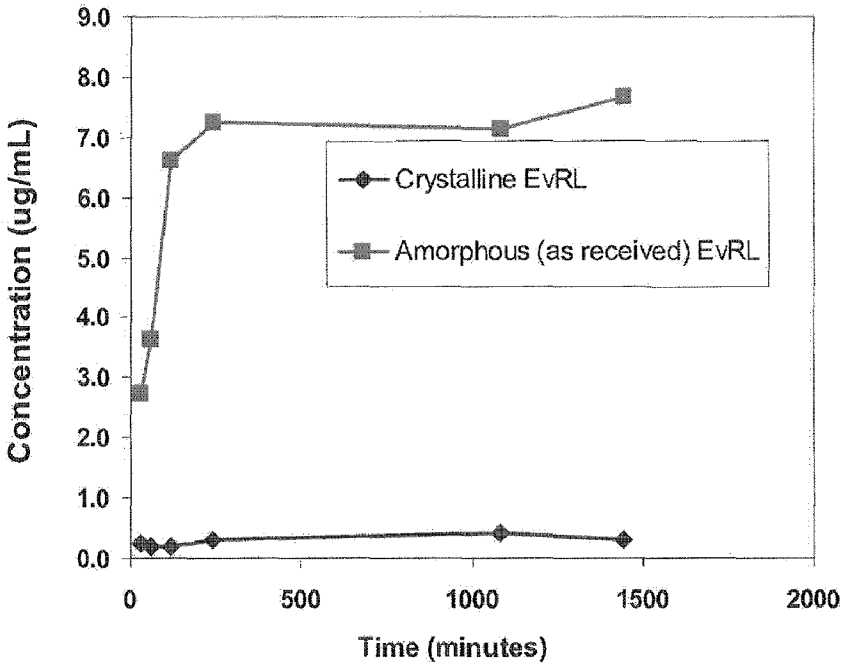
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Concentration (ug/mL)
0
500
1000
1500
2000
Time (minutes)
Crystalline EvRL
Amorphous (as received) EvRL

Fig. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/052935

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D498/18
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)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/014222 A1 (ABBOTT LAB [US] ; VISWANATH SHEKHAR [US] ; BARTELT LARRY [US] ; LEANNA R0) 31 January 2008 (2008-01-31) claims 80, 88, 89, 92, 93	1-3 ,5 , 11 , 13
X	WO 99/01458 A1 (N0VARTIS AG [CH] ; N0VARTIS ERFIND VERWALT GMBH [AT] ; D0SENBACH C0RNELI) 14 January 1999 (1999-01-14) page 5, final paragraph to page 6 first paragraph	1,2,5,9, 14
A	WO 2004/089958 A2 (BI0GAL GYOGYSZERGYAR [HU] ; TEVA PHARMA [US] ; KERI VI LM0S [HU] ; CS0RVAS) 21 October 2004 (2004-10-21) claims 1, 14	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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

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

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

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu¬ments, 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
13 January 2012	01/02/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bakboord, Joan

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/052935

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