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(71) Applicant: **NATCO PHARMA LIMITED** [IN/IN]; Natco House, Road No: 2, Banjara Hills, Telangana, Hyderabad 500034 (IN).

(72) Inventors: **BHAVANASI, Krishna Murthy**; Natco Pharma Limited, Natco House, Road No.2, Banjara Hills, Telangana, India, Hyderabad 500034 (IN). **TRIPURANENI, Rama Swamy Chowdary**; Natco Pharma Limited, Natco House, Road No.2, Banjara Hills, Telangana, India, Hyderabad 500034 (IN). **BHIMAVARAPU, Rami Reddy**; Natco Pharma Limited, Natco House, Road No.2, Banjara Hills, Telangana, India, Hyderabad 500034 (IN). **NANNAPANENI, Venkaiah Chowdary**; Natco Pharma Limited, Natco House, Road No.2, Banjara Hills, Telangana, India, Hyderabad 500034 (IN).

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(54) **Title**: PROCESS FOR PREPARING STABLE ORAL COMPOSITIONS OF EVEROLIMUS

(57) **Abstract**: Process for preparing composition comprising Everolimus or its pharmaceutically acceptable salts and one or more pharmaceutically acceptable excipients by wet granulation by dissolving Everolimus in one or more pharmaceutically acceptable solvents.

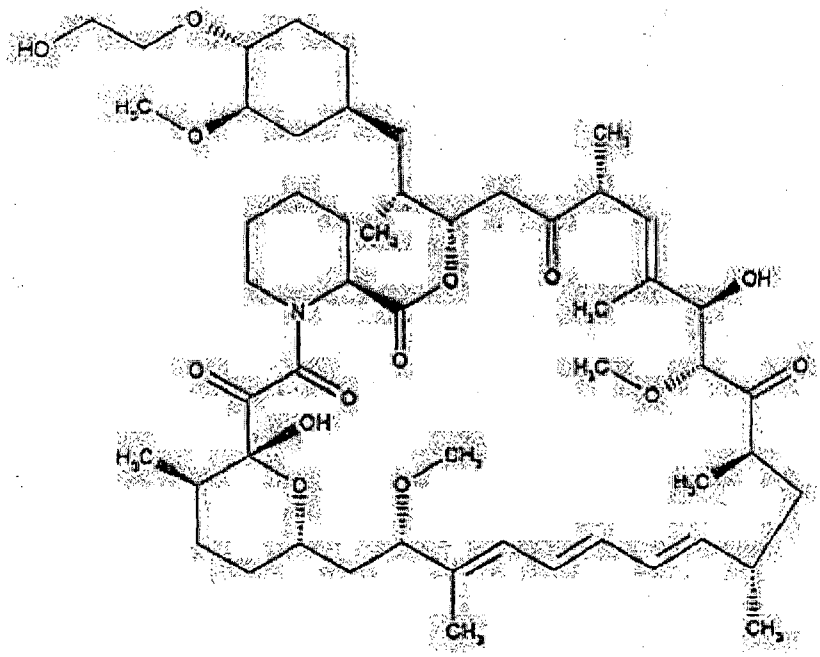
PROCESS FOR PREPARING STABLE ORAL COMPOSITIONS OF EVEROLIMUS

FIELD OF THE INVENTION:

The present invention relates to a process for preparing stable solid oral compositions comprising 40-O-(2- hydroxy) ethyl-Rapamycin or its pharmaceutically acceptable salts thereof:

BACKGROUND OF THE INVENTION:

Everolimus is chemically designated as (1R,9S,12S,15R,16E,18R,19R,21R, 23S,24E,26E, 28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxy cyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.04,9] hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone with structural formula as follows.



In the United States, Everolimus is available as oral tablets with the name of Afinitor® for the treatment of tumour diseases, and under the name of Zortress® for the prevention of organ rejection. U.S. Patent No. 5665772 disclose Everolimus.

U.S. Patent No. 6004973 disclosed pharmaceutical compositions in the form of solid dispersion comprising 40-O-(2-hydroxy) ethyl-Rapamycin (Everolimus, RAD001) and a carrier medium. These compositions provide high bioavailability of drug substance, convenient to administer and are stable.

U.S. Patent No. 8617598 disclosed oral pharmaceutical compositions comprising solid dispersion of 40-O-(2-hydroxy) ethyl-Rapamycin, a disintegrant comprising cross-linked polyvinyl pyrrolidone and colloidal silicon dioxide.

However Solid dispersion is complex process, involves higher quantity of solvents and higher cost for preparation, there is a need to develop alternative stable compositions of Everolimus using simplified and robust process, which is cost effective and having good dissolution rates and bioavailability.

Accordingly, inventors of the present invention have developed a simple process for preparing stable oral compositions of Everolimus.

SUMMARY OF THE INVENTION:

The present invention relates to a process for preparing stable oral compositions comprising Everolimus and one or more pharmaceutically acceptable excipients.

The present invention particularly relates to a wet granulation process for preparing stable oral compositions comprising Everolimus and one or more pharmaceutically acceptable excipients.

One embodiment of the present invention provides a process for preparing composition comprising Everolimus and one or more pharmaceutically acceptable excipients by wet granulation using drug solution.

Another embodiment of the present invention provides a process for preparing composition comprising Everolimus and one or more pharmaceutically acceptable excipients by wet granulation using drug solution obtained by dissolving Everolimus in one or more pharmaceutically acceptable solvents.

Another embodiment of the present invention provides a wet granulation process for preparing stable oral compositions of everolimus comprising the steps of: (a) sifting one or more pharmaceutically acceptable excipients, (b) dissolving Everolimus in solvent and (or) mixture of solvents to form drug solution, (c) granulating the dry mix of step (a) with the drug solution of step (b) to obtain wet mass, (d) drying and sieving the wet mass to obtain granules, (e) blending the granules with extra granular excipients followed by lubrication and (f) compressing the lubricated blend into tablets or filled into capsules.

Another embodiment of the present invention provides a process for preparation of stable oral compositions of everolimus comprising the steps of: (a) sifting one or more pharmaceutically acceptable excipients, (b) dissolving Everolimus in solvent and (or) mixture of solvents to form drug solution, (c) suspending one or more pharmaceutically acceptable excipients in to drug solution to form suspension, (d) granulating the dry mix of step (a) with the suspension of step (c) to obtain wet mass, (e) drying and sieving the wet mass to obtain granules, (f) blending the granules with extra granular excipients, followed by lubrication, and (g) compressing the lubricated blend into tablets or filled into capsules.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention relates to a process for preparing stable oral compositions comprising Everolimus and one or more pharmaceutically acceptable excipients.

Preferably, the present invention relates to a wet granulation process for preparing stable oral compositions comprising Everolimus and one or more pharmaceutically acceptable excipients.

More preferably the present invention relates to a wet granulation process for preparing stable oral compositions comprising Everolimus and one or more pharmaceutically acceptable excipients using drug solution.

The term "drug solution" as used herein according to the present invention includes solution obtained by dissolving Everolimus or its pharmaceutically acceptable salt thereof in solvent and (or) mixture of solvents.

One embodiment the present invention provides adding one or more pharmaceutically acceptable excipients in drug solution to form a suspension.

The term "Everolimus or 40-O-(2-hydroxy)ethyl-Rapamycin" as used herein according to the present invention includes, Everolimus in the form of free base, a pharmaceutically acceptable salt thereof, amorphous Everolimus, crystalline Everolimus, any isomer, derivative, hydrate, solvate or prodrug or a combination thereof.

The term "composition" or "solid oral composition" or "dosage form" or "pharmaceutical composition" as used herein synonymously include solid dosage forms such as tablets, capsules, powder, particles, granules, pellets, mini-tablets and the like meant for oral administration. A "composition" comprises an active pharmaceutical ingredient and at least one pharmaceutically acceptable excipient.

The term "drug" herein refers to Everolimus or a pharmaceutically acceptable salt thereof.

The term "pharmaceutically acceptable excipient" includes a pharmaceutically acceptable material such as diluents, disintegrates, binders, lubricants, antioxidants, and the like, suitable for administering an active pharmaceutical ingredient. Each excipient should be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient.

Another embodiment of the present invention provides a wet granulation process for preparing stable oral compositions of everolimus comprising the steps of: (a) sifting one or more pharmaceutically acceptable excipients, (b) dissolving Everolimus in solvent and (or) mixture of solvents to form drug solution, (c) granulating the dry mix of step (a) with the drug solution of step (b) to obtain wet mass, (d) drying and sieving the wet mass to obtain granules, (e) blending the granules of step (d) with extra granular excipients if any, followed by lubrication and (f) compressing the lubricated blend of step (e) into tablets or filled into capsules.

Another embodiment of the present invention provides a wet granulation process for preparing stable oral compositions of everolimus comprising the steps of: (a) sifting one or more pharmaceutically acceptable excipients, (b) dissolving Everolimus in solvent and (or) mixture of solvents to form drug solution, (c) suspending one or more pharmaceutically acceptable excipients in to drug solution to form a suspension, (d) granulating the dry mix of step (a) with the suspension of step (c) to obtain wet mass, (e) drying and sieving the wet mass to obtain granules, (f) blending the granules of step (e) with extra granular excipients if any, followed by lubrication, and (g) compressing the lubricated blend of step (f) into tablets or filled into capsules.

According to the present invention, solvents suitable for processing the pharmaceutical compositions include one or more of organic solvents such as organic solvents such as an alcohol, for example methanol, ethanol, or isopropanol; an ester, e.g.

ethyl acetate; an ether, e.g. diethyl ether; a ketone, e.g. acetone; or a halogenated hydrocarbon, e.g. dichloroethane and mixtures thereof.

Various useful excipients include but are not limited to antioxidants, diluents, binders, disintegrants and lubricants.

Antioxidants include, but are not limited to butylated hydroxytoluene (BHT), Butylated hydroxy anisole, tocopherols, ascorbic acid derivatives, propyl gallate and fumaric acid and mixtures thereof.

Diluents, fillers, or bulking agents for this purpose include, but are not limited to lactose, microcrystalline cellulose, dibasic calcium phosphate, calcium phosphate, powdered cellulose, dextrates, isomalt, calcium carbonate, magnesium carbonate, starch, pre-gelatinized starch, and mixtures thereof.

Binders include, but are not limited to hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinylpyrrolidone (povidone), gum arabic and sugars such as sucrose, glucose, dextrose, lactose, polyvinyl alcohol and mixtures thereof.

Disintegrants include, but are not limited to crospovidone, croscarmellose sodium, starch, potato starch, pregelatinized starch, corn starch, sodium starch glycolate, microcrystalline cellulose, low substituted hydroxypropyl cellulose and mixtures thereof.

Suitable lubricants include but are not limited to fatty acids, fatty acid salts, and fatty acid esters such as magnesium stearate, calcium stearate, stearic acid, sodium stearyl fumarate, hydrogenated vegetable oil and mixtures thereof.

EXAMPLES

The following examples further describe and demonstrate particular embodiments within the scope of the present invention. The examples are given solely for illustration and are not to be construed as limitations as many variations are possible without departing from spirit and scope of the invention.

Example 1: Tablet compositions of Everolimus prepared by wet granulation method

S. No	Ingredient	mg/ tab
	Intra granular	
1	Everolimus	10.0
2	Butylated hydroxytoluene (BHT)	0.2
3	Hydroxypropyl methylcellulose	90.0
4	Acetone	qs
5	Dehydrated alcohol	qs
6	Anhydrous lactose	297.3
	Extra granular	
7	Crospovidone	100.0
8	Magnesium stearate	2.5
	Total	**500 mg**

*qs: quantity sufficient

Preparation method:

1. BHT, Everolimus in acetone were dissolved under stirring to form drug solution
2. Hydroxypropyl methylcellulose was dispersed in drug solution of step (1) under stirring to form a suspension
3. Dehydrated alcohol was added to suspension of step (2)
4. Obtained suspension of step (3) was added to anhydrous lactose in granulator bowl to obtain wet mass
5. Wet mass of step (4) was dried, sifted and milled to obtain granules
6. Obtained granules of step (5) were blended with extra granular crospovidone and lubricated with magnesium stearate

7. The lubricated blend of step (6) was finally filled into capsules or compressed into tablets.

Example 2: Tablet compositions of Everolimus prepared by wet granulation method

S. No	Ingredient	mg/ tab
	Intra granular	
1	Everolimus	10
2	Butylated hydroxytoluene	0.2
3	Hydroxypropyl methylcellulose	125
4	Lactose monohydrate	25
5	Acetone	qs
6	Dehydrated alcohol	qs
7	Anhydrous lactose	118.65
8	Crospovidone	50
	Extra granular	
9	Anhydrous lactose	118.65
10	Crospovidone	50
11	Magnesium stearate	2.5
	Total	**500 mg**

*qs: quantity sufficient

Preparation method:

1. Intra granular anhydrous lactose and crospovidone were mixed to form dry blend
2. BHT, Everolimus in acetone were dissolved under stirring to form drug solution
3. Hydroxypropyl methylcellulose and lactose monohydrate were dispersed in step (2) under stirring to form a suspension
4. Dehydrated alcohol was added to suspension of step (3)
5. Obtained suspension of step (4) was added to dry blend of step (1) in granulator bowl to obtain wet mass
6. Wet mass of step (5) was dried, sifted and milled to obtain granules
7. Obtained granules of step (6) were mixed with extra granular anhydrous lactose, crospovidone and lubricated with magnesium stearate
8. The lubricated blend of step (7) was finally filled into capsules or compressed into tablets.

Example 3: Tablet compositions of Everolimus prepared by wet granulation method

S. No	Ingredient	mg/ tab
Intra granular		
1	Everolimus	10
2	Butylated hydroxytoluene	0.2
3	Acetone	qs
4	Hydroxypropyl methylcellulose	150
5	Anhydrous lactose	118.65
Extra granular		
6	Anhydrous lactose	118.65
7	Crospovidone	100
8	Magnesium stearate	2.5
Total		**500 mg**

*qs: quantity sufficient

Preparation method:

1. BHT, Everolimus in acetone were dissolved under stirring to form drug solution
2. Intragranular anhydrous lactose and Hydroxypropyl methylcellulose were transferred in to granulator bowl and blended
3. Blend of step (2) was granulated with drug solution of step (1) to form granules which are dried and milled
4. Milled Granules of step (3) were blended with extra granular anhydrous lactose, crospovidone and lubricated with magnesium stearate
5. The lubricated blend of step (4) was finally filled into capsules or compressed into tablets.

Comparative study on dissolution time:

Dissolution test was performed for tablets prepared as per the Examples 1, 2, 3 and Comparative reference (Afinitor), using USP apparatus type II, at 50 rpm, in 500 ml of purified water with 0.4 % sodium lauryl sulphate.

(Cumulative % drug dissolved)				
Time in min	**Afinitor**	**Example 1**	**Example 2**	**Example 3**
10	96.6	93.1	80.0	86
20	100.5	101.1	93.0	97.1
30	100.0	103.6	96.0	100.4
45	99.1	105.1	97.0	102.2

Based on the dissolution data, tablets prepared according to the present invention were acceptable.

We Claim:

1. A process for preparing stable oral composition comprising Everolimus or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient, wherein the process is wet granulation.

2. The process according to claim 1, wherein the process comprises wet granulation using drug solution.

3. The drug solution according to claim 1, is prepared by dissolving drug in one or more pharmaceutically acceptable solvents.

4. The solvents according to claim 3, includes organic solvents such as an alcohol, for example methanol, ethanol, or isopropanol; an ester, e.g. ethyl acetate; an ether, e.g. diethyl ether; a ketone, e.g. acetone; or a halogenated hydrocarbon, e.g. dichloroethane and mixtures thereof.

5. The pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable excipients are selected from antioxidants, diluents, binders, disintegrants, lubricants or a mixture thereof.

6. The process according to claim 1, wherein the composition is in the form of capsules, tablets, MUPS, granules, pellets, solid dispersions, beads, particles, mini- tablets, and the like.

7. Wet granulation process for preparing stable oral compositions of everolimus comprising the steps of: (a) sifting one or more pharmaceutically acceptable excipients, (b) dissolving Everolimus in solvent and (or) mixture of solvents to form drug solution, (c) granulating the dry mix of step (a) with the drug solution of step (b) to obtain wet mass, (d) drying and sieving the wet mass to obtain

granules, (e) blending the granules of step (d) with extra granular excipients if any, followed by lubrication and (f) compressing the lubricated blend of step (e) into tablets or filled into capsules.

8. Wet granulation process for preparing stable oral compositions of everolimus comprising the steps of: (a) sifting one or more pharmaceutically acceptable excipients, (b) dissolving Everolimus in solvent and (or) mixture of solvents to form drug solution, (c) suspending one or more pharmaceutically acceptable excipients in to drug solution to form a suspension, (d) granulating the dry mix of step (a) with the suspension of step (c) to obtain wet mass, (e) drying and sieving the wet mass to obtain granules, (f) blending the granules of step (e) with extra granular excipients if any, followed by lubrication, and (g) compressing the lubricated blend of step (f) into tablets or filled into capsules.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2015/000182

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K31/436
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, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/022201 A1 (DONG A PHARM CO LTD [KR]; KIM SOON-HOE [KR]; SON MI-WON [KR]; JANG SUN) 14 February 2013 (2013-02-14) claims; examples	1-8
X	CN 102 138 903 B (SUZHOU TERUI PHARMACEUTICAL CO LTD) 12 December 2012 (2012-12-12) claims; examples	1-8
X	WO 2014/186581 A1 (TOBIRA THERAPEUTICS INC [US]) 20 November 2014 (2014-11-20) claims; examples	1-8
X	CN 103 610 646 A (JIANGSU AOSAIKANG PHARM CO LTD) 5 March 2014 (2014-03-05) the whole document	1-8

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

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
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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	Ceyte, Mathilde

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2015/000182

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013022201 A1	14-02-2013	NONE	
CN 102138903 B	12-12-2012	NONE	
WO 2014186581 A1	20-11-2014	NONE	
CN 103610646 A	05-03-2014	NONE	