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(56) Related Art
WO 2014/097125 A1
EP 2742940 A1

Abstract

The present disclosure is directed to oral tablet of ribociclib including its salt(s). One embodiment of the present disclosure is directed to tablet of ribociclib with high drug load with an immediate release profile. One embodiment of the present disclosure is directed to coated tablet of ribociclib. Another embodiment of the present disclosure is directed to coated tablet of ribociclib where the coating is an advanced moisture barrier coating (e.g., Opadry® amb II coating where the coating is PVA based).

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Ribociclib Tablet

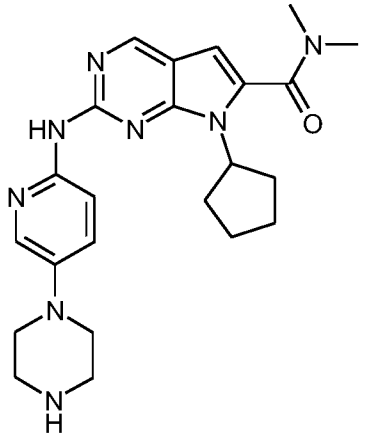
This is a divisional of Australian patent application No. 2020250190, the entire contents of which are incorporated herein by reference.

Field of the Invention

The present disclosure relates to tablet formulation of ribociclib and/or its pharmaceutically acceptable salts, as well as methods of treatment using the same.

Background Art

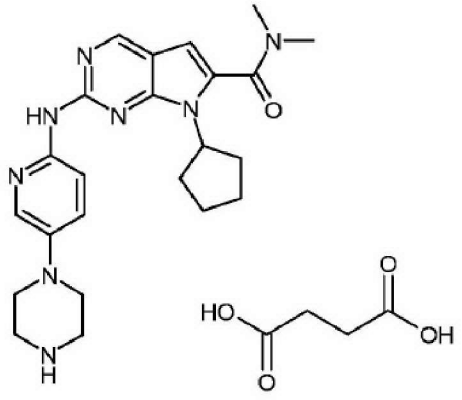
The compound of Formula (I)



(I)

is known as ribociclib. Its chemical name is 7-cyclopentyl-N,N-dimethyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide and its synthesis is specifically described in WO 2010/020675 A1, Example 74.

The succinate salt of ribociclib is described by Formula (II):



(II)

and is described in W02012/064805.

Ribociclib and its pharmaceutically acceptable salt(s) have valuable pharmacological properties and can be used, for example, (1) as inhibitors of cyclin dependent kinases, (in particular, cyclin dependent kinases selected from CDK1, CDK2, CDK3,.CDK4, CDK5, CDK6 and CDK9); and (2) as modulators and/or inhibitors of glycogen synthase kinase-3 (GSK-3).

Ribociclib is also known under the code name LEEO11.

Summary Of The Invention

The present disclosure is directed to oral formulations ofribociclib including its salt(s) and/or solvate(s). One embodiment of the present disclosure is directed to tablet formulations of ribociclib with high drug load with an immediate release profile. One embodiment of the present disclosure is directed to coated tablet formulations of ribociclib. Another embodiment of the present disclosure is directed to coated tablet formulations of ribociclib where the coating is an aqueous moisture barrier coating (e.g., Opadry@ amb II coating where the coating is PVA based). A further embodiment of the present disclosure is directed to a pharmaceutical oral tablet comprising ribociclib succinate, the pharmaceutical oral tablet comprising a tablet core and a coating, wherein the % of ribociclib succinate (w/w) is 50% to 65% of the tablet core, and the coating is a polyvinyl alcohol (PVA)-based aqueous moisture barrier coating.

Brief Description Of The Drawings

The invention is illustrated by reference to the accompanying drawing described below.

FIGS. 1A and 1B depict a process flow diagram for making ribociclib tablets. Uncoated tablets are made according to Steps 1-8. Coated tablets are made according to Steps 1-9.

FIG. 2 shows the images of the tablets manufactured with Opadry® (standard HPMC based) and with Opadry® amb II (advance moisture barrier (AMB) coating material with PVA based).

FIG. 3. shows the Dynamic Vapor Sorption (DVS) data of the ribociclib tablets coated with standard Opadry® and Opadry® amb II.

FIG. 4 shows the dissolution profile of ribociclib (LEE011) tablets coated with Opadry® amb II obtained with the rotating basket at 100 rpm with dissolution media having different pH values, at 37 °C.

Detailed Description of The Invention

The present disclosure relates to a solid oral tablet dosage form of ribociclib or its pharmaceutically acceptable salt. Such formulation has very good process performance and high stability.

The tablet of the present disclosure has an immediate release profile. These tablets release at least 75%(Q) (where Q refers to the acceptance criteria defined by USP chapter <711>) of the active after 45 minutes under standard dissolution test. In embodiment, the tablets release at least 75% of the active after 45 minutes when using the rotating basket at 100 rpm, with 900 ml of HCl pH 1 as dissolution medium at 37 °C. In another embodiment, the tablets release at least 75% of the active after 45 minutes when using the rotating basket at 100 rpm, with 900 ml of HCl pH 2 as dissolution medium at 37 °C. In another embodiment, the tablets release at least 75% of the active after 45 minutes when using the rotating basket at 100 rpm, with 900 ml of acetate buffer pH 4.5 as dissolution medium at 37 °C. In another embodiment, the tablets release at least 75% of the active after 45 minutes when using the rotating basket at 100 rpm, with 900 ml of phosphate buffer pH 6.8 as dissolution medium at 37 °C.

The tablets of the present disclosure can be coated or uncoated.

The tablets of the present disclosure have high drug load of at least 40%, 45%, 50%, 55% or 60%, when measured in w/w percentage of the ribociclib succinate of the core tablet.

The tablets of the present disclosure have high drug load of at least 32%, 40%, 44%, 47% or 52%, when measured in w/w percentage of the ribociclib free base of the core tablet.

The % of ribociclib succinate (w/w) is at least 40% of the core tablet. In one embodiment, the % of ribociclib succinate (w/w) is at least 50% of the core tablet. In another embodiment, the % of ribociclib succinate (w/w) is at least 55% of the core tablet. In another embodiment, the % of ribociclib succinate (w/w) is at about 55% to 65% of the core tablet. In another embodiment, the % of ribociclib succinate (w/w) is at about 60% of the core tablet.

When measured in terms of ribociclib free base, the % of ribociclib (w/w) is at least 32% of the core tablet. In one embodiment, the % of ribociclib (w/w) is at least 40% of the core tablet. In another embodiment, the % of ribociclib (w/w) is at least 44% of the core tablet. In another embodiment, the % of ribociclib (w/w) is at about 44% to 52% of the core tablet. In another embodiment, the % of ribociclib (w/w) is at about 47% of the core tablet.

Core tablet is also referred to as "tablet core".

In an uncoated tablet, the tablet core is the whole tablet. In a coated tablet, the tablet core is the portion of the tablet excluding the coating.

The tablet formulation according to the disclosure may contain pharmaceutically acceptable excipients commonly used in pharmaceutical formulations, particularly those for oral administration for example, as fillers, binders, disintegrants and lubricants.

Fillers, for example, can be cellulose, mannitol, di-calcium phosphate, lactose, microcrytalline cellulose, alone or in combination thereof.

Binders, for example, can be hydroxypropyl cellulose, polyvinyl-pyrrolidone, alone or in combination thereof.

Disintegrants, for example, can be crosslinked polyvinyl-pyrrolidone, crosslinked sodium carboxymethyl cellulose, low substituted hydroxypropyl cellulose, sodium starch glycolate, alone or in combination thereof.

Lubricants, for example, can be magnesium stearate, stearic acid, talc, silicon dioxide, sodium stearyl fumarate, alone or in combination thereof.

As an example, FIGS. 1A and 1B show the process flow diagram of making ribociclib tablets. Uncoated tablets are made according to Steps 1-8. Coated tablets are made according to Steps 1-9.

In one embodiment, the core ribociclib tablets have an inner phase comprising ribociclib or salt(s) thereof, and an outer phase.

Coating material:

The ribociclib tablets of the present disclosure are immediate release tablets and can be coated with any immediate release coating materials. For example, the coating material can be Opadry®, Opadry® 200, Opadry® amb II, Opadry® fx™, Opadry® II, Opalux®, or mixtures thereof. Opadry®, Opadry® 200, Opadry® amb II, Opadry® fx™, Opadry® II, and Opalux® are all commercially available through Colorcon, Inc.

In one embodiment, the coating material is Opadry®. Opadry® is a HPMC (hydroxypropyl methylcellulose) coating material and has the following composition: HPMC (Pharmacoat 603) 71.4%, polyethylene glycol 7.15%, talc 7.15%, and iron oxide 14.3%.

In another embodiment, the coating material is Opadry® amb II. Opadry® amb II is a PVA (polyvinyl alcohol) based coating material and has the following composition: polyvinyl alcohol 45.52%, iron oxide 32%, talc 20%, lecithin (soya) 2%, and xanthan gum 0.48%.

When the ribociclib tablets are coated with Opadry® amb II, the tablets show improved appearances and are essentially free of cracking defects.

The present invention(s) is further described in the following example. The following non-limiting examples illustrate the invention(s) and are not to be construed as limiting the scope of the appended claims.

EXAMPLE 1 Uncoated 50 mg and 200mg ribociclib tablets

Table 1 below details the composition of uncoated 50 mg and 200mg ribociclib tablets. These tablets are made according to Steps 1-8 of the process flow diagram (FIGS. 1A-1B).

Table 1. Composition per dosage form unit

Ingredient	Composition per unit [mg/unit]	
	50mg of Ribociclib	200mg of Ribociclib
Inner phase		
Ribociclib (LEE011) succinate[1]	63.600	254.40
Microcrystalline cellulose/ Cellulose, microcrystalline	16.860	67.44
Hydroxypropylcellulose	12.030	48.12
Crospovidone	7.300	29.20
Colloidal silicon dioxide/ Silica, colloidal anhydrous	0.530	2.12
Magnesium stearate[2]	1.590	6.36
Outer phase		
Crospovidone	3.210	12.84
Colloidal silicon dioxide/ Silica, colloidal anhydrous	0.265	1.06
Magnesium stearate[2]	2.115	8.46
Tablet weight	107.500	430.00

[1] The salt factor is 1.272. The drug substance quantity is increased if the content is ≤ 99.5% with a corresponding reduction in the microcrystalline cellulose content.

[2] Vegetable origin

EXAMPLE 2 Uncoated 100 mg, 150 mg and 300 mg ribociclib tablets

Table 2 below details the composition of uncoated 100 mg, 150 mg, and 300mg ribociclib tablets. These tablets are made according to Steps 1-8 of the process flow diagram (FIGS. 1A-1B).

Table 2. Composition per dosage form unit

Ingredient	Composition per unit [mg/unit]		
	100mg of Ribociclib	150mg of Ribociclib	300 mg of Ribociclib
Inner phase			
Ribociclib (LEE011) succinate[1]	127.2	190.8	381.6
Microcrystalline cellulose/ Cellulose, microcrystalline	33.72	50.58	101.16
Hydroxypropylcellulose	24.06	36.09	72.18
Crospovidone	14.60	21.9	43.8
Colloidal silicon dioxide/ Silica, colloidal anhydrous	1.06	1.59	3.18
Magnesium stearate[2]	3.18	4.77	9.54
Outer phase			
Crospovidone	6.420	9.63	19.26
Colloidal silicon dioxide/ Silica, colloidal anhydrous	0.53	0.795	1.59
Magnesium stearate[2]	4.23	6.345	12.69
Tablet weight	215.00	322.5	645.00

[1] The salt factor is 1.272. The drug substance quantity is increased if the content is ≤ 99.5% with a corresponding reduction in the microcrystalline cellulose content.

[2] Vegetable origin

EXAMPLE 3 Coated (with Opadry@ amb II Coating) 50 mg and 200mg ribociclib tablets

Table 3 below details the composition of film-coated 50 mg and 200mg ribociclib tablets. These tablets were made according to Steps 1-9 of the process flow diagram (FIGS. 1A-1B). The coating material is Opadry@ ambII, which is commercially available and is an aqueous moisture barrier (AMB) coating, PVA based.

Table 3. Composition per dosage form unit

Ingredient	Composition per unit [mg/unit]	
	50mg of Ribociclib	200mg of Ribociclib
Inner phase		
Ribociclib (LEE011) succinate[1]	63.600	254.40
Microcrystalline cellulose/ Cellulose, microcrystalline	16.860	67.44
Hydroxypropylcellulose	12.030	48.12
Crospovidone	7.300	29.20
Colloidal silicon dioxide/ Silica, colloidal anhydrous	0.530	2.12
Magnesium stearate[2]	1.590	6.36
Outer phase		
Crospovidone	3.210	12.84
Colloidal silicon dioxide/ Silica, colloidal anhydrous	0.265	1.06
Magnesium stearate[2]	2.115	8.46
Core tablet weight	107.500	430.00
Coating[3]		
Coating premix, white[4]	0.774	3.096
Coating premix, yellow[4]	2.537	10.148
Coating premix, red[4]	0.774	3.096
Coating premix, black[4]	0.215	0.860
Purified water[5]	Qs	Qs
Film coated tablet weight	111.800	447.20

[1] The salt factor is 1.272. The drug substance quantity is increased if the content is ≤ 99.5% with a corresponding reduction in the microcrystalline cellulose content.
[2] Vegetable origin
[3] Excess coating is prepared to compensate for losses during the coating process
[4] The coating premix is a commercially available product
[5] Removed during processing

EXAMPLE 4 Coated (with Opadry@ amb II Coating) 100 mg, 150mg and 300mg ribociclib tablets

Table 4 below details the composition of film-coated 100 mg, 150 mg and 300mg ribociclib tablets. These tablets are made according to Steps 1-9 of the process flow diagram (FIGS. 1A-1B). The coating material is Opadry@ amb II, which is commercially available and is an aqueous moisture barrier (AMB) coating, PVA based.

Table 4. Composition per dosage form unit

Ingredient	Composition per unit [mg/unit]		
	100mg of Ribociclib	150mg of Ribociclib	300 mg of Ribociclib
Inner phase			
Ribociclib (LEE011) succinate[1]	127.2	190.8	381.6
Microcrystalline cellulose/ Cellulose, microcrystalline	33.72	50.58	101.16
Hydroxypropylcellulose	24.06	36.09	72.18
Crospovidone	14.60	21.9	43.8
Colloidal silicon dioxide/ Silica, colloidal anhydrous	1.06	1.59	3.18
Magnesium stearate[2]	3.18	4.77	9.54
Outer phase			
Crospovidone	6.420	9.63	19.26
Colloidal silicon dioxide/ Silica, colloidal anhydrous	0.53	0.795	1.59
Magnesium stearate[2]	4.23	6.345	12.69
Core tablet weight	215.00	322.5	645.00
Coating[3]			
Coating premix, white[4]	1.548	2.322	4.644
Coating premix, yellow[4]	5.074	7.611	15.222
Coating premix, red[4]	1.548	2.322	4.644
Coating premix, black[4]	0.43	0.645	1.29
Purified water[5]	Qs	qs	qs
Film coated tablet weight	223.6	335.4	670.8

[1] The salt factor is 1.272. The drug substance quantity is increased if the content is ≤ 99.5% with a corresponding reduction in the microcrystalline cellulose content.
[2] Vegetable origin
[3] Excess coating is prepared to compensate for losses during the coating process
[4] The coating premix is a commercially available product
[5] Removed during processing

EXAMPLE 5

Ribociclib tablets coated with different coatings (Opadry@ (standard HPMC based) vs. Opadry@ amb II (advance moisture barrier (AMB) coating material, PVA based)) were compared. Coating was carried out in Bohle coater 1 Kg scale with spray rate of 3g/ min. With standard Opadry@ coating, tablet logo bridging issue and tablet cracking defects were observed. In contrast, no cracking was observed with the PVA based Opadry@ amb II coated tablets. Fig. 2 shows the images of the tablets manufactured with Opadry@ (standard HPMC based) and with Opadry@ amb II (advance moisture barrier (AMB) coating material with PVA based).

EXAMPLE 6

Dynamic vapor sorption (DVS) data on the ribociclib tablets coated with standard Opadry@ and Opadry@ amb II are presented in FIG. 3. At both 50mg and 200 mg dosage unit, the tablets coated with the AMB coating (Opadry@ ambII) show better performance than the standard Opadry@ tablets.

EXAMPLE 7

The dissolution profiles of the Opadry@ amb II coated ribociclib tablets are evaluated in different pH media. Apparatus: basket, Rotation: 100 rpm, Volume: 900 mL, Media: HCl pH 1, HCl pH 2, acetate buffer pH 4.5, phosphate buffer pH 6.8. FIG. 4 shows the dissolution profile of the Opadry@ amb II film-coated ribociclib tablet in different pH media.

EXAMPLE 8 Coated (with Opadry@ amb II Coating) 50 mg and 200mg ribociclib tablets with different coating premix combination

Table 5 below details the composition of film-coated 50 mg and 200mg ribociclib tablets with different coating premix combination compared to Example 3. These tablets were made according to Steps 1-9 of the process flow diagram (FIGS. 1A-1B). The coating material is Opadry@ amb II, which is commercially available and is an aqueous moisture barrier (AMB) coating, PVA based.

Table 5. Composition per dosage form unit

Ingredient	Composition per unit [mg/unit]	
	50mg of Ribociclib	200mg of Ribociclib
Inner phase		
Ribociclib (LEE011) succinate[1]	63.600	254.40
Microcrystalline cellulose/ Cellulose, microcrystalline	16.860	67.44
Hydroxypropylcellulose	12.030	48.12
Crospovidone	7.300	29.20
Colloidal silicon dioxide/ Silica, colloidal anhydrous	0.530	2.12
Magnesium stearate[2]	1.590	6.36
Outer phase		
Crospovidone	3.210	12.84
Colloidal silicon dioxide/ Silica, colloidal anhydrous	0.265	1.06
Magnesium stearate[2]	2.115	8.46
Core tablet weight	107.500	430.00
Coating[3]		
Coating premix, white[4]	4.201	16.804
Coating premix, red[4]	0.037	0.146
Coating premix, black[4]	0.062	0.25
Purified water[5]	Qs	Qs
Film coated tablet weight	111.800	447.20

[1] The salt factor is 1.272. The drug substance quantity is increased if the content is ≤ 99.5% with a corresponding reduction in the microcrystalline cellulose content.
[2] Vegetable origin
[3] Excess coating is prepared to compensate for losses during the coating process
[4] The coating premix is a commercially available product
[5] Removed during processing

EXAMPLE 9 Coated (with Opadry@ amb II Coating) 100 mg, 150mg and 300mg ribociclib tablets with different coating premix combination

Table 6 below details the composition of film-coated 100 mg, 150 mg and 300mg ribociclib tablets with different coating premix combination compared to Example 4. These tablets are made according to Steps 1-9 of the process flow diagram (FIGS. 1A-1B). The coating material is Opadry@ amb II, which is commercially available and is an aqueous moisture barrier (AMB) coating, PVA based.

Table 6. Composition per dosage form unit

Ingredient	Composition per unit [mg/unit]		
	100mg of Ribociclib	150mg of Ribociclib	300 mg of Ribociclib
Inner phase			
Ribociclib (LEE011) succinate[1]	127.2	190.8	381.6
Microcrystalline cellulose/ Cellulose, microcrystalline	33.72	50.58	101.16
Hydroxypropylcellulose	24.06	36.09	72.18
Crospovidone	14.60	21.9	43.8
Colloidal silicon dioxide/ Silica, colloidal anhydrous	1.06	1.59	3.18
Magnesium stearate[2]	3.18	4.77	9.54
Outer phase			
Crospovidone	6.420	9.63	19.26
Colloidal silicon dioxide/ Silica, colloidal anhydrous	0.53	0.795	1.59
Magnesium stearate[2]	4.23	6.345	12.69
Core tablet weight	215.00	322.5	645.00
Coating[3]			
Coating premix, white[4]	8.402	12.603	25.206
Coating premix, red[4]	0.074	0.111	0.222
Coating premix, black[4]	0.124	0.186	0.372
Purified water[5]	Qs	qs	qs
Film coated tablet weight	223.6	335.4	670.8

[1] The salt factor is 1.272. The drug substance quantity is increased if the content is ≤ 99.5% with a corresponding reduction in the microcrystalline cellulose content.
[2] Vegetable origin
[3] Excess coating is prepared to compensate for losses during the coating process
[4] The coating premix is a commercially available product
[5] Removed during processing

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A pharmaceutical oral tablet comprising ribociclib succinate, the pharmaceutical oral tablet comprising a tablet core and a coating, wherein the % of ribociclib succinate (w/w) is 50% to 65% of the tablet core, and the coating is a polyvinyl alcohol (PVA)-based aqueous moisture barrier coating.

2. The tablet of claim 1, wherein the coating comprises polyvinyl alcohol and lacks hydroxypropyl methylcellulose

3. The tablet of claim 1 or claim 2, wherein the tablet releases 75%-100% of the ribociclib succinate after 45 minutes when tested with the rotating basket at 100 rpm with 900 ml of dissolution media pH 2 or pH 4.5, at 37 °C, according to United States Pharmacopeia (USP) <711>.

4. The tablet of any one of claims 1-3, wherein the % of ribociclib succinate (w/w) is 55% to 65% of the tablet core.

5. The tablet of claim 4, wherein the % of ribociclib succinate (w/w) is 60% of the tablet core.

6. The tablet of any one of claims 1 to 5, wherein the tablet core has an inner phase and an outer phase, and wherein the inner phase comprises ribociclib succinate.

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FIG. 1A Process flow diagram

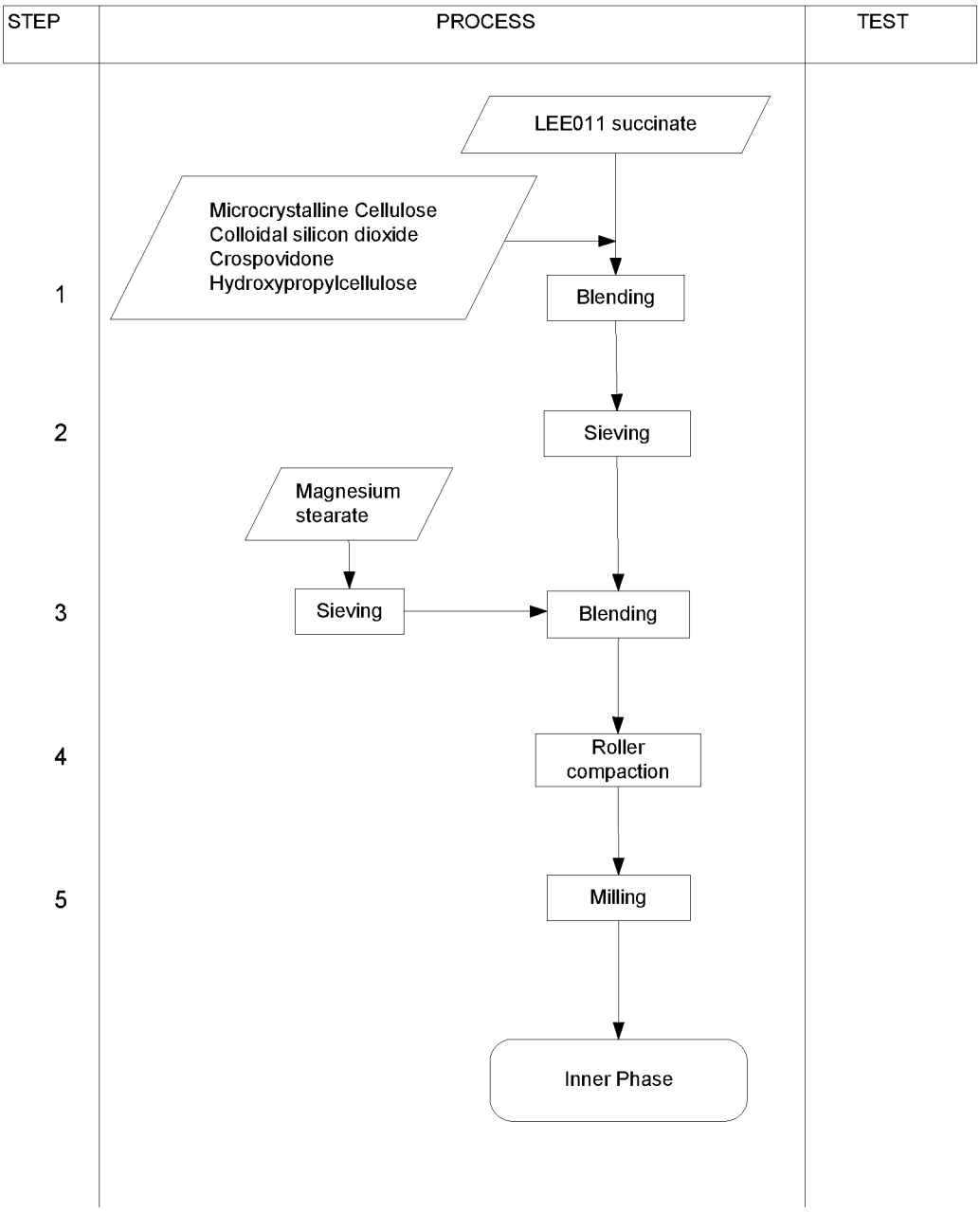

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FIG. 1B Process flow diagram (Continued)

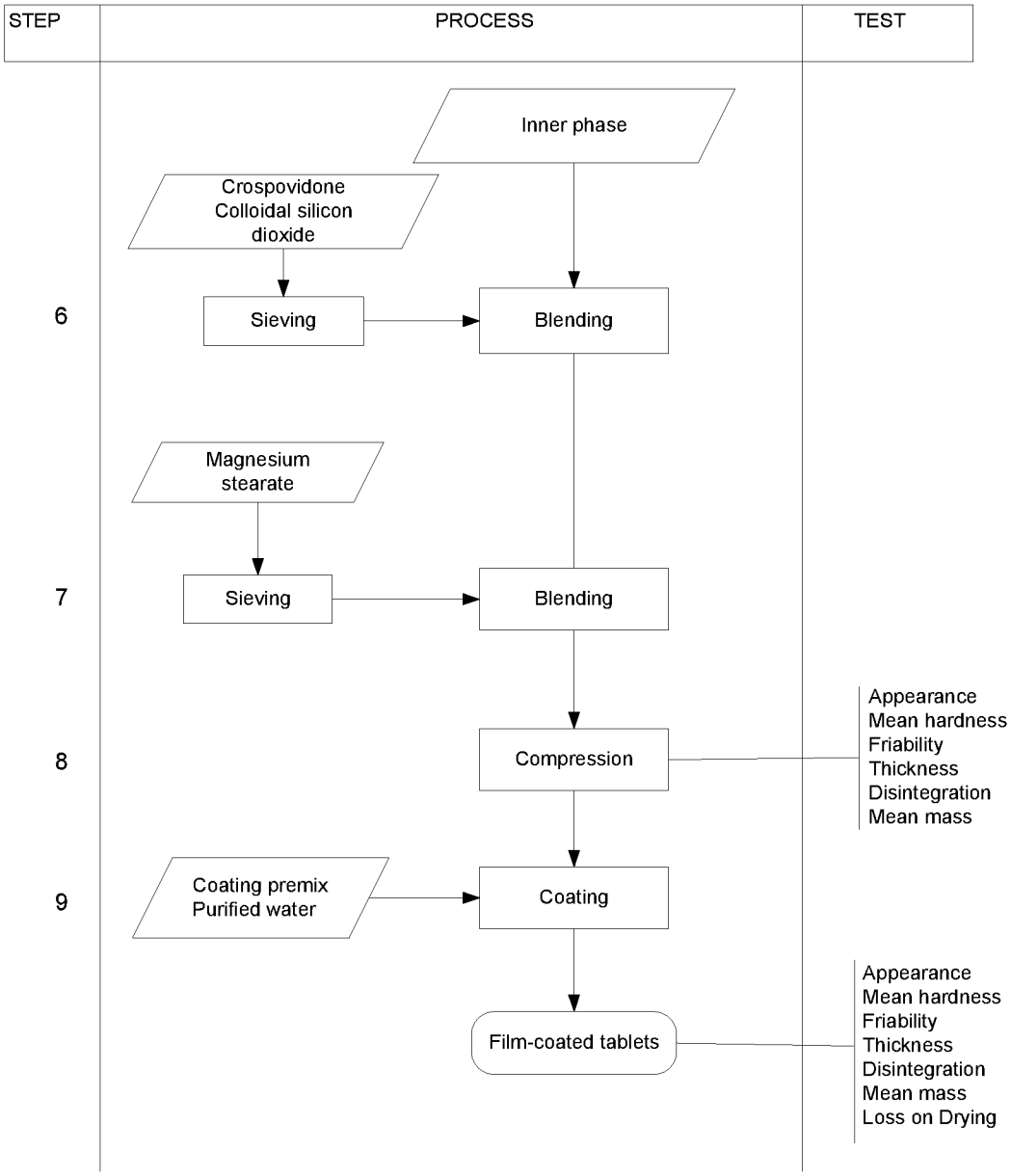
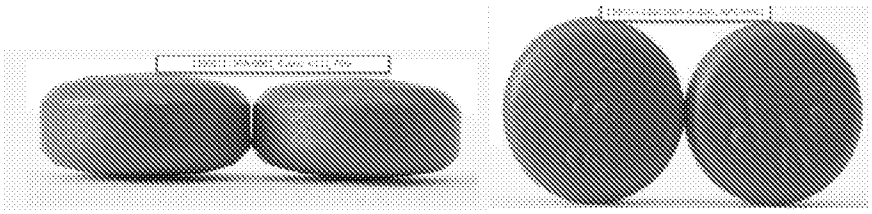
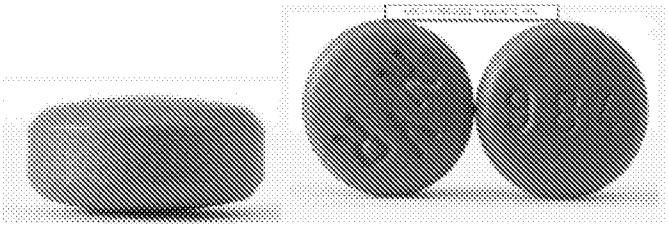


Fig. 2:

A)



(B)



(A) Tablet with Opadry® (Standard HPMC);

(B) Tablet with Opadry® amb II (with AMB coating, PVA based)

FIG. 3 **DVS data on the Ribociclib Tablets with standard Opadry® (aka Opadry 1, HMPC coating) and Opadry® amb II (aka Opadry 2, AMB functional coating)**

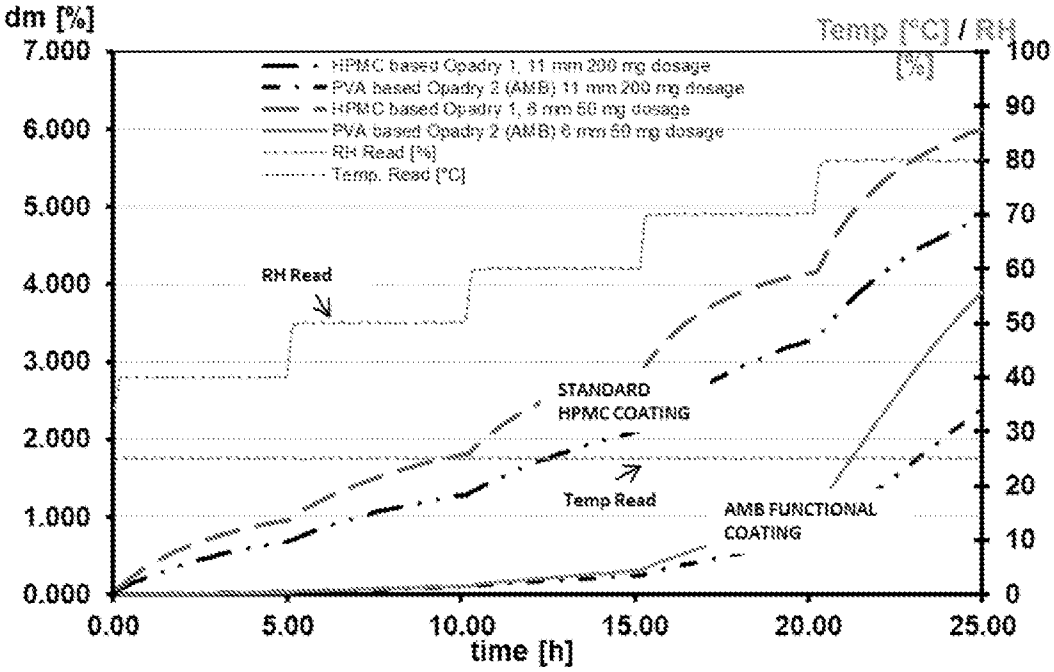


FIG. 4 Dissolution profile of Ribociclib (LEE011) tablets coated with Opadry® amb II