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(54) Benævnelse: **RIBOCICLIB-TABLET**

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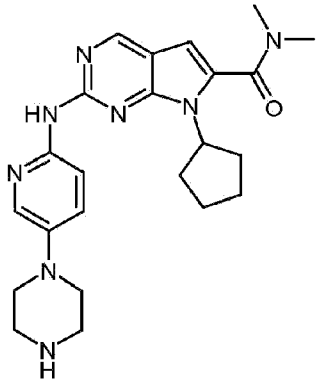
DESCRIPTION

Field of the Invention

[0001] 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

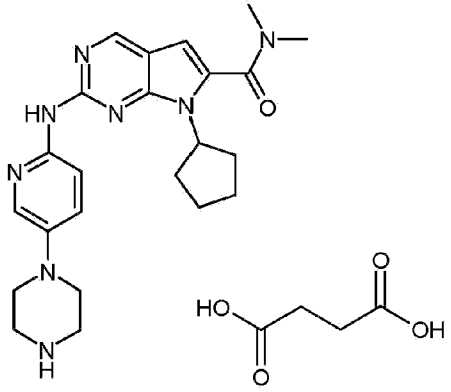
[0002] The compound of Formula (I)



(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.

[0003] The succinate salt of ribociclib is described by Formula (II):



(II)

and is described in WO2012/064805.

[0004] 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).

[0005] Ribociclib is also known under the code name LEE011.

[0006] WO2014/097125 relates to a combination therapy with a CDK4/6 inhibitor compound and a MEK inhibitor compound. A preferred CDK4/6 inhibitor compound is ribocidib succinate. According to D1, the CDK4/6 inhibitor compound and the MEK inhibitor compound can be either found in a single galenical composition or as separate compositions. The active agents in the compositions are present together or singly from about 0.1 % to about 99.9%. The compositions can be sugar-coated tablets, tablets, capsules or suppositories or ampoules.

Summary Of The Invention

[0007] The present invention provides a coated pharmaceutical oral tablet comprising ribociclib succinate, the coated pharmaceutical oral tablet comprising a tablet core and a coating, wherein the % of ribociclib succinate (w/w) is at least 50% of the core tablet, and the coating is a polyvinyl alcohol-based advanced moisture barrier coating.

[0008] The present invention also provides other embodiments as described in the claims.

[0009] The present disclosure is directed to oral formulations of ribociclib sucinate. The present disclosure is directed to tablet formulations of ribociclib with high drug load with an immediate release profile. The present disclosure is directed to coated tablet formulations of ribociclib as described in the claims. The present disclosure is directed to coated tablet formulations of ribociclib where the coating is a PVA-based advanced moisture barrier coating (e.g., Opadry® amb II coating where the coating is PVA based).

Brief Description Of The Drawings

[0010] 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

[0011] The present disclosure relates to a solid oral tablet dosage form of ribociclib salt which is as described in the claims. Such a formulation has very good process performance and high stability.

[0012] 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 one 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.

[0013] The tablets of the present disclosure are coated.

[0014] The tablets of the present disclosure have a high drug load of at least 50%, 55% or 60%, when measured in w/w percentage of the ribociclib succinate of the core tablet.

[0015] 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.

[0016] Core tablet is also referred to as "tablet core".

[0017] In the coated tablet, the tablet core is the portion of the tablet excluding the coating.

[0018] 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.

[0019] Fillers, for example, can be cellulose, mannitol, di-calcium phosphate, lactose, microcrytalline cellulose, alone or in combination thereof.

[0020] Binders, for example, can be hydroxypropyl cellulose, polyvinyl-pyrrolidone, alone or in

combination thereof.

[0021] Disintegrants, for example, can be crosslinked polyvinyl-pyrrolidone, crosslinked sodium carboxymethyl cellulose, low substituted hydroxypropyl cellulose, sodium starch glycolate, alone or in combination thereof.

[0022] Lubricants, for example, can be magnesium stearate, stearic acid, talc, silicon dioxide, sodium stearyl fumarate, alone or in combination thereof.

[0023] As an example, FIGS. 1A and 1B show the process flow diagram of making ribociclib tablets. Reference uncoated tablets are made according to Steps 1-8. Coated tablets are made according to Steps 1-9.

[0024] In one embodiment, the core ribociclib tablets have an inner phase comprising ribociclib or salt(s) thereof, and an outer phase.

[0025] Coating material:
The ribociclib tablets of the present disclosure are immediate release tablets and are coated with aimmediate release coating material as described in the claims. Coating materials such as Opadry®, Opadry® 200, Opadry® amb II. Opadry®, Opadry® 200, Opadry® amb II, Opadry® fx™, Opadry® II, and Opalux® are all commercially available through Colorcon, Inc.

[0026] 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%.

[0027] 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%.

[0028] When the ribociclib tablets are coated with Opadry® amb II, the tablets show improved appearances and are essentially free of cracking defects.

[0029] The present invention(s) is further described in the following examples.

Reference EXAMPLE 1 Uncoated 50 mg and 200mg ribociclib tablets

[0030] 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

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

[0031] 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 (LEE01) 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

Ingredient	Composition per unit [mg/unit]		
	100mg of Ribociclib	**150mg of Ribociclib**	**300 mg of Ribociclib**
Inner phase			
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

[0032] 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® amb II, which is commercially available and is an advanced 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

Ingredient	Composition per unit [mg/unit]	
	50mg of Ribociclib	**200mg of Ribociclib**
Inner phase		
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

[0033] 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 advanced 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 (LEE01) 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

[0034] 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.

[0035] 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

[0036] 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® amb II) show better performance than the standard Opadry® tablets.

EXAMPLE 7

[0037] 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

[0038] 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 advanced 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

[0039] 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 advanced 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 (LEE01) 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

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

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- WO2012064805A **[0003]**
- WO2014097125A **[0006]**

Patentkrav

1. Overtrukket farmaceutisk oral tablet, som omfatter ribociclibsuccinat,

hvilken overtrukket farmaceutisk oral tablet omfatter en tabletkerne og et overtræk,

hvor ribociclibsuccinat i % (vægt/vægt) er mindst 50 % af kernetabletten,

og overtrækket er et polyvinylalkohol (PVA)-baseret overtræk med avanceret fugtbarriere.

2. Overtrukket farmaceutisk oral tablet ifølge krav 1, hvor overtrækket indeholder 45,52 % polyvinylalkohol, 32 % jernoxid, 20 % talkum, 2 % lecithin (soja) og 0,48 % xanthangummi.

3. Overtrukket farmaceutisk oral tablet ifølge krav 1 eller 2, hvor ribociclibsuccinat i % (vægt/vægt) er mindst 55 % af kernetabletten.

4. Overtrukket farmaceutisk oral tablet ifølge krav 1 eller 2, hvor ribociclibsuccinat i % (vægt/vægt) er ca. 55 % til 65 % af kernetabletten.

5. Overtrukket farmaceutisk oral tablet ifølge krav 1 eller 2, hvor ribociclibsuccinat i % (vægt/vægt) er ca. 60 % af kernetabletten.

6. Overtrukket farmaceutisk oral tablet ifølge krav 1 eller 2, hvor ribociclibsuccinat i % (vægt/vægt) er ca. 65 % af kernetabletten.

7. Overtrukket farmaceutisk oral tablet ifølge et hvilket som helst af de foregående krav, hvor tabletkernen har en indre fase, som omfatter ribociclibsuccinat, og en ydre fase.

8. Overtrukket farmaceutisk oral tablet ifølge krav 7 med følgende sammensætning:

Bestanddel	**Sammensætning pr. enhed [mg/enhed]**	
	50 mg ribociclib	**200 mg ribociclib**
Indre fase		
Ribociclib(LEE011)-succinat[1]	63.600	254.40
Mikrokrystallinsk cellulose/Cellulose, mikrokrystallinsk	16.860	67.44
Hydroxypropylcellulose	12.030	48.12
Crospovidon	7.300	29.20
Kolloid silica/Silica, kolloid vandfri	0.530	2.12
Magnesiumstearat[2]	1.590	6.36
Ydre fase		
Crospovidon	3.210	12.84
Kolloid silica/Silica, kolloid vandfri	0.265	1.06
Magnesiumstearat[2]	2.115	8.46
Vægt af kernetablet	107.500	430.00

Overtræk[3]		
Overtrækspremix, hvid[4]	0.774	3.096
Overtrækspremix, gul[4]	2.537	10.148
Overtrækspremix, rød[4]	0.774	3.096
Overtrækspremix, sort[4]	0.215	0.860
Renset vand[5]	q.s.	q.s.
Vægt af filmovertrukket tablet	111.800	447.20

9. Overtrukket farmaceutisk oral tablet ifølge krav 7 med følgende sammensætning:

Bestanddel	**Sammensætning pr. enhed [mg/enhed]**		
	100 mg ribociclib	**150 mg ribociclib**	**300 mg ribociclib**
Indre fase			
Ribociclib(LEE011)-succinat[1]	127.2	190.8	381.6
Mikrokrystallinsk cellulose/Cellulose, mikrokrystallinsk	33.72	50.58	101.16
Hydroxypropylcellulose	24.06	36.09	72.18
Crospovidon	14.60	21.9	43.8
Kolloid silica/Silica, kolloid vandfri	1.06	1.59	**3.18**
Magnesiumstearat[2]	3.18	4.77	9.54
Ydre fase			
Crospovidon	6.420	9.63	19.26
Kolloid silica/Silica, kolloid vandfri	0.53	0.795	1.59
Magnesiumstearat[2]	4.23	6.345	12.69
Vægt af kernetablet	215.00	322.5	645.00

Overtræk[3]			
Overtrækspremix, hvid[4]	1.548	2.322	4.644
Overtrækspremix, gul[4]	5.074	7.611	15.222
Overtrækspremix, rød[4]	1.548	2.322	4.644
Overtrækspremix, sort[4]	0.43	0.645	1.29
Renset vand[5]	q.s.	q.s.	q.s.
Vægt af filmovertrukket tablet	223.6	335.4	670.8

10. Overtrukket farmaceutisk oral tablet ifølge krav 7 med følgende sammensætning:

Bestanddel	**Sammensætning pr. enhed [mg/enhed]**	
	50 mg ribociclib	**200 mg ribociclib**
Indre fase		
Ribociclib(LEE011)-succinat[1]	63.600	254.40
Mikrokrystallinsk cellulose/Cellulose, mikrokrystallinsk	16.860	67.44
Hydroxypropylcellulose	12.030	48.12
Crospovidon	7.300	29.20
Kolloid silica/Silica, kolloid vandfri	0.530	2.12
Magnesiumstearat[2]	1.590	6.36
Ydre fase		
Crospovidon	3.210	12.84
Kolloid silica/Silica, kolloid vandfri	0.265	1.06
Magnesiumstearat[2]	2.115	8.46
Vægt af kernetablet	107.500	430.00

Overtræk[3]		
Overtrækspremix, hvid[4]	4.201	16.804
Overtrækspremix, rød[4]	0.037	0.146
Overtrækspremix, sort[4]	0.062	0.25
Renset vand[5]	q.s.	q.s.
Vægt af filmovertrukket tablet	111.800	447.20

11. Overtrukket farmaceutisk oral tablet ifølge krav 7 med følgende sammensætning:

Bestanddel	**Sammensætning pr. enhed [mg/enhed]**		
	100 mg ribociclib	**150 mg ribociclib**	**300 mg ribociclib**
	Indre fase		
Ribociclib(LEE011)-succinat[1]	127.2	190.8	381.6
Mikrokrystallinsk cellulose/Cellulose, mikrokrystallinsk	33.72	50.58	101.16
Hydroxypropylcellulose	24.06	36.09	72.18
Crospovidon	14.60	21.9	43.8
Kolloid silica/Silica, kolloid vandfri	1.06	1.59	3.18
Magnesiumstearat[2]	3.18	4.77	9.54
	Ydre fase		
	Crospovidon	6.420	9.63	19.26
	Kolloid silica/Silica, kolloid vandfri	0.53	0.795	1.59
	Magnesiumstearat[2]	4.23	6.345	12.69
	Vægt af kernetablet	215.00	322.5	645.00

Overtræk[3]			
Overtrækspremix, hvid[4]	8.402	12.603	25.206
Overtrækspremix, rød[4]	0.074	0.111	0.222
Overtrækspremix, sort[4]	0.124	0.186	0.372
Renset vand[5]	q.s.	q.s.	q.s.
Vægt af filmovertrukket tablet	223.6	335.4	670.8

12. Overtrukket farmaceutisk tablet ifølge et hvilket som helst af kravene 1 til 11, hvor tabletten frigiver mindst 75 % af ribociclibsuccinatet efter 45 minutter ved test med den roterende kurv ved 100 r/min med 900 ml opløsningsmedium pH 2 eller pH 4,5 ved 37 °C i henhold til United States Pharmacopeia (USP) <711>.

DRAWINGS

FIG. 1A Process flow diagram

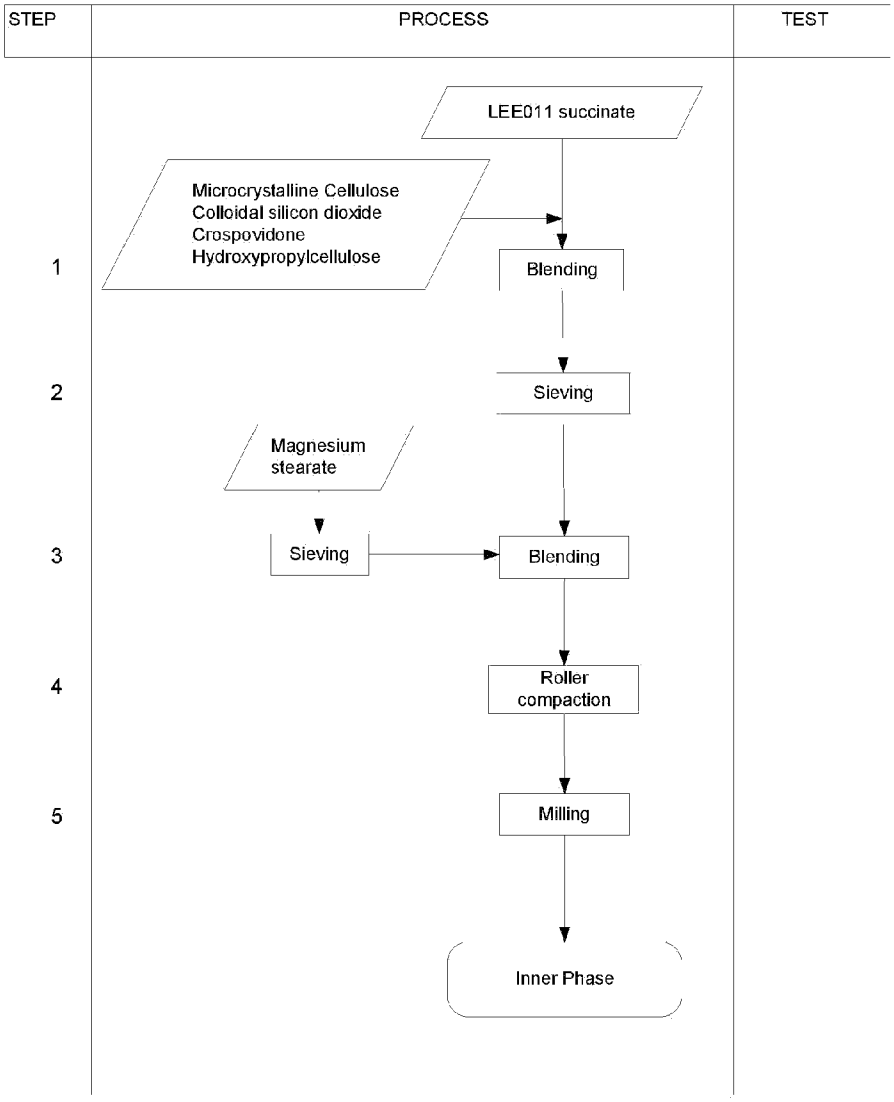


FIG. 1B **Process flow diagram (Continued)**

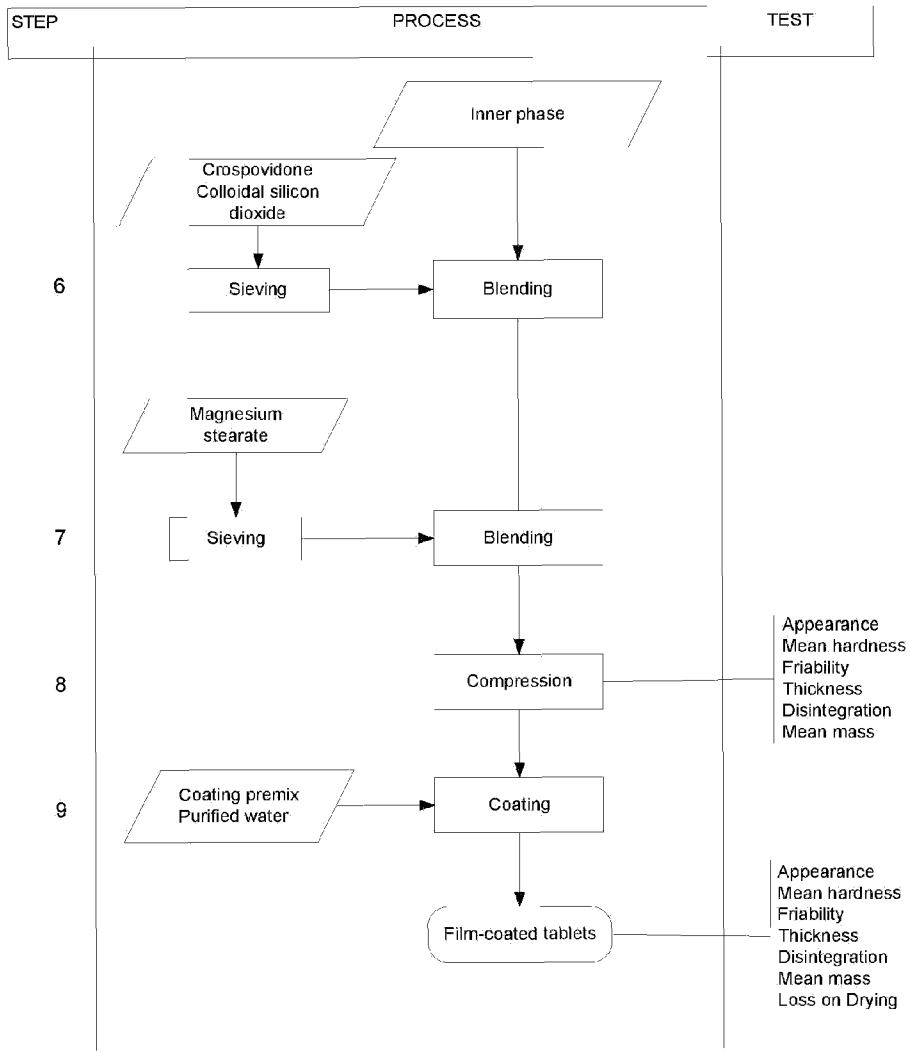
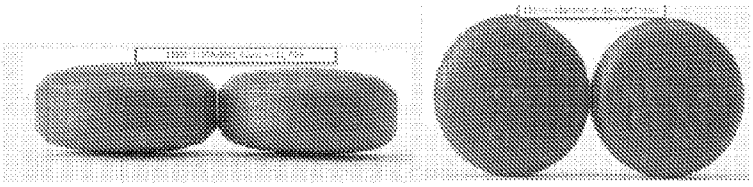
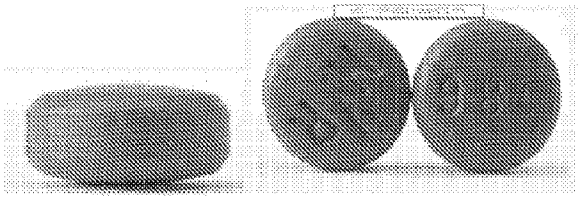


Fig. 2:

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)**

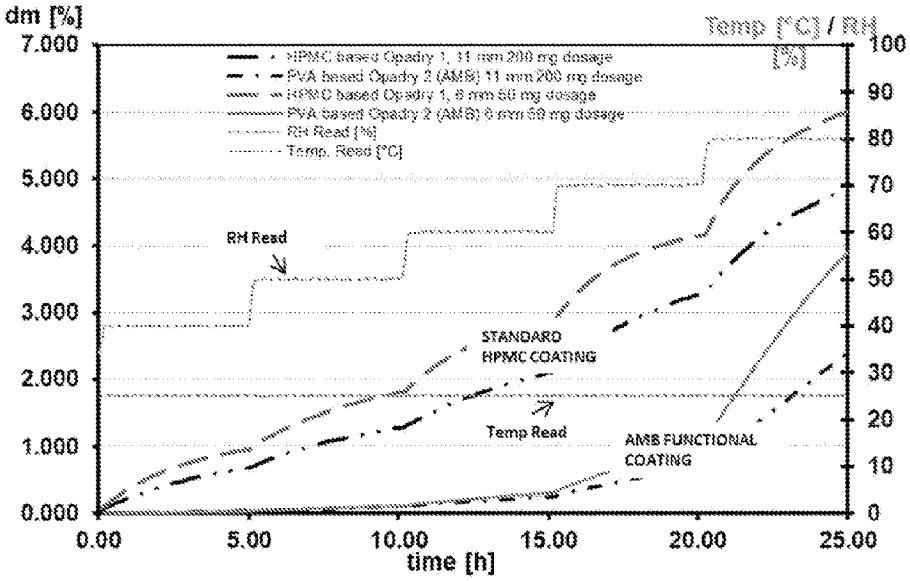


FIG. 4 Dissolution profile of Ribociclib (LEE011) tablets coated with Opadry® amb II