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(54) **PHARMACEUTICAL COMPOSITION COMPRISING SMALL MOLECULE EGFR INHIBITOR AND PREPARATION METHOD THEREFOR**

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(57) **ABSTRACT**

A pharmaceutical composition comprising a small molecule EGFR inhibitor and a preparation method therefor, the composition comprising N-(5-((4-(1-cyclopropyl-TH-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide, an isomer, solvate, hydrate, or pharmaceutically acceptable salt thereof, or a combination thereof that acts as an active ingredient, and at least one pharmaceutically acceptable excipient.

PHARMACEUTICAL COMPOSITION COMPRISING SMALL MOLECULE EGFR INHIBITOR AND PREPARATION METHOD THEREFOR

FIELD OF THE INVENTION

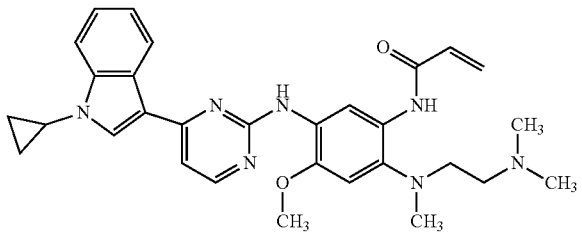
[0001] The present invention belongs to the field of pharmaceutical formulations, and specifically relates to a pharmaceutical composition comprising a third-generation small molecule EGFR inhibitor and a method for preparing the same.

BACKGROUND OF THE INVENTION

[0002] EGFR (Epidermal Growth Factor Receptor) is a member of the erbB receptor family, which includes transmembrane protein tyrosine kinase receptors. By binding to its ligand, such as epidermal growth factor (EGF), EGFR can form a homodimer on the cell membrane or form a heterodimer with other receptors in the family, such as erbB2, erbB3, or erbB4. The formation of these dimers can cause the phosphorylation of key tyrosine residues in EGFR cells, thereby activating a number of downstream signaling pathways in cells. These intracellular signaling pathways play an important role in cell proliferation, survival and anti-apoptosis. Disorders of EGFR signal transduction pathways, including increased expression of ligands and receptors, EGFR gene amplification and mutation and the like, can promote malignant transformation of cells, and play an important role in tumor cell proliferation, invasion, metastasis and angiogenesis. Therefore, EGFR is a reasonable target for the development of anticancer drugs.

[0003] N-(5-((4-(1-cyclopropyl-TH-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide, which belongs to the third-generation small molecule EGFR inhibitor, has high selectivity for inhibiting the EGFR T790M mutant, while has no or low activity on wild-type EGFR, therefore, it can be used in treating drug-resistant tumors caused by the secondary mutation of EGFR-T790M. This compound (hereinafter referred to as the compound of formula I) was first disclosed in the international patent application WO2016054987, and its structure is shown in the following formula I

(I)



SUMMARY OF THE INVENTION

[0004] The present invention provides a pharmaceutical composition comprising a third-generation small molecule EGFR inhibitor.

[0005] The pharmaceutical composition comprises a mesylate salt of N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide, a polymorph, solvate, hydrate, pharmaceutically acceptable salt thereof or a combination thereof as the active ingredient, and at least one pharmaceutically acceptable excipient.

[0006] In the pharmaceutical composition according to the present invention, the active ingredient is present in an amount of 1 to 60%.

[0007] In the pharmaceutical composition according to the present invention, the unit dose of the active ingredient is 10 to 200 mg, preferably 55 to 110 mg, and more preferably 55 mg or 110 mg.

[0008] In the pharmaceutical composition according to the present invention, the excipient comprises one or more filler(s), comprising at least one disaccharide or polysaccharide, such as glucan, starch, cellulose, lactose, maltose or sucrose. The starch can be selected from the group consisting of potato starch, corn starch, rice starch, wheat starch, amylopectin, pregelatinized starch and the like. The disaccharide or polysaccharide is present in an amount of 1 to 60%, preferably 5 to 55%, more preferably 5 to 30%, and further preferably 5 to 15%.

[0009] The filler is preferably a disaccharide, such as lactose, and it is present in an amount of 1 to 60%, preferably 5 to 55%, more preferably 5 to 30%, and further preferably 5 to 15%.

[0010] In the pharmaceutical composition according to the present invention, the excipient comprises one or more filler(s), disintegrant(s) or lubricant(s).

[0011] In the pharmaceutical composition according to the present invention, the weight percentage of each component is as follows:

active ingredient	1 to 60%
filler	20 to 80%
disintegrant	1 to 30%
lubricant	0.1 to 10%.

[0012] Preferably, the weight percentage of each component is as follows:

active ingredient	35 to 50%
filler	30 to 50%
disintegrant	10 to 20%
lubricant	0.5 to 5%.

[0013] More preferably, the weight percentage of each component is as follows:

active ingredient	43.3%
filler	40.2%
disintegrant	14%
lubricant	2.5%.

[0014] In the pharmaceutical composition according to the present invention, the filler comprises one or more of microcrystalline cellulose, lactose, anhydrous lactose, corn starch, pregelatinized starch, mannitol, sorbitol, calcium hydrophosphate and calcium sulfate, wherein the filler is present in an amount of 20 to 80%, and preferably 30 to

50%. Preferably, the filler comprises two of the above components, and the weight ratio of the two components is 1:3 to 3:1.

[0015] In the pharmaceutical composition according to the present invention, the filler is preferably microcrystalline cellulose and lactose. The microcrystalline cellulose is present in an amount of 1 to 60%, preferably 10 to 40%, and more preferably 20 to 40%, relative to the weight of the tablet core; and the lactose is present in an amount of 1 to 60%, preferably 5 to 30%, and more preferably 5 to 15%, relative to the weight of the tablet core. Optional technical solutions include, but are not limited to, the microcrystalline cellulose is present in an amount of 1 to 60%, and the lactose is present in an amount of 1 to 60%; the microcrystalline cellulose is present in an amount of 10 to 40%, and the lactose is present in an amount of 5 to 30%; and the microcrystalline cellulose is present in an amount of 20 to 40%, and the lactose is present in an amount of 5 to 15%.

[0016] Further preferably, the weight ratio of microcrystalline cellulose to lactose is 1:3 to 3:1, and more preferably 2-3:1.

[0017] Further preferably, the lactose is anhydrous lactose. The microcrystalline cellulose is present in an amount of 1 to 60%, preferably 10 to 40%, and more preferably 20 to 40%, relative to the weight of the tablet core; and the anhydrous lactose is present in an amount of 1 to 60%, preferably 5 to 30%, and more preferably 5 to 15%, relative to the weight of the tablet core. Optional technical solutions include, but are not limited to, the microcrystalline cellulose is present in an amount of 1 to 60%, and the anhydrous lactose is present in an amount of 1 to 60%; the microcrystalline cellulose is present in an amount of 10 to 40%, and the anhydrous lactose is present in an amount of 5 to 30%; and the microcrystalline cellulose is present in an amount of 20 to 40%, and the anhydrous lactose is present in an amount of 5 to 15%.

[0018] Further preferably, the weight ratio of microcrystalline cellulose to anhydrous lactose is 1:3 to 3:1, more preferably 2-3:1.

[0019] Through the addition of lactose, the pharmaceutical composition with a high content of the compound of formula I can be prepared, and its drug loading capacity can reach more than 40%. At the same time, the resulting pharmaceutical composition has a good compressibility and uniform dissolution.

[0020] In the pharmaceutical composition according to the present invention, the disintegrant comprises one or more of low-substituted hydroxypropyl cellulose, croscarmellose sodium, carboxymethyl starch sodium and crospovidone, and preferably carboxymethyl starch sodium. The disintegrant is present in an amount of 1 to 30%, and preferably 10 to 20%. The disintegrant that is added in a totally intragranular manner can ensure good disintegration and preparation of the tablet. The addition of carboxymethyl starch sodium can further improve the stability of the formulation. Preferably, the disintegrant is added intragranularly.

[0021] In the pharmaceutical composition according to the present invention, the lubricant comprises one or more of talc, stearic acid, sodium stearyl fumarate, glyceryl behenate, magnesium stearate and micronized silica gel. The lubricant is present in an amount of 0.1 to 10%, and preferably 0.2 to 5%, relative to the weight of the tablet core.

[0022] Further, the lubricant is preferably sodium stearyl fumarate and magnesium stearate. The sodium stearyl fumarate is present in an amount of 0.1 to 5%, and preferably 0.3 to 3%, and the magnesium stearate is present in an amount of 0.1 to 5%, and preferably 0.2 to 2%. The combination of sodium stearyl fumarate and magnesium stearate can obviously improve the adhesion of raw materials on the surface of the equipment, ensure a smooth preparation process, and enable the finished product to have an excellent dissolution effect.

[0023] In the pharmaceutical composition according to the present invention, the amount refers to the percentage relative to the total weight of the drug, wherein the total weight of the drug does not include the weight of the coating. As for specific dosage forms, the amount refers to the percentage relative to the weight of the tablet core or granule.

[0024] The pharmaceutical composition according to the present invention comprises the following components:

active ingredient	35 to 50%
lactose	5 to 15%
microcrystalline cellulose	30 to 50%
carboxymethyl starch sodium	10 to 20%
lubricant	0.5 to 5%.

[0025] Preferably, it comprises the following components:

active ingredient	43.3%
lactose	10.2%
microcrystalline cellulose	30.0%
carboxymethyl starch sodium	10.4%
lubricant	0.5 to 5%.

[0026] More preferably, it comprises the following components:

active ingredient	43.3%
lactose	10.2%
microcrystalline cellulose	30.0%
carboxymethyl starch sodium	14%
lubricant	2.5%.

[0027] Most preferably, it comprises the following components:

active ingredient	43.3%
lactose	10.2%
microcrystalline cellulose	30.0%
carboxymethyl starch sodium	14%
magnesium stearate	1%
sodium stearyl fumarate	1.5%.

[0028] The pharmaceutical composition of the present invention is an oral formulation selected from the group consisting of tablet and capsule, preferably a film, and more preferably an immediate-release film-coated tablet. The coating agent is a gastric-soluble film coating premix, preferably Opadry 85F140124 (the main ingredients are polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, iron oxide red and iron oxide black), and Opadry 85F12300

(the main ingredients are polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide and iron oxide yellow).

[0029] The present invention further provides a method for preparing the pharmaceutical composition, mainly comprising the following steps of:

[0030] 1) pre-treatment of raw materials: sieving the filler, disintegrant and lubricant for later use;

[0031] 2) mixing: weighing the intragranular raw materials according to specified amounts and mixing them;

[0032] 3) dry granulation: granulating the above mixed powder by dry granulation;

[0033] 4) total mixing: mixing the resulting granules and extragranular lubricant;

[0034] 5) optionally, tableting: compressing the resulting mixture into tablets according to the theoretical tablet weight; and

[0035] 6) optionally, coating.

[0036] The above method comprises the specific steps of:

[0037] 1) pre-treatment of raw materials: sieving microcrystalline cellulose and anhydrous lactose with a 60-mesh sieve, and sieving sodium stearyl fumarate and carboxymethyl starch sodium with an 80-mesh sieve for later use;

[0038] 2) mixing: weighing the intragranular raw materials according to prescription amounts, and mixing microcrystalline cellulose, anhydrous lactose, carboxymethyl starch sodium, sodium stearyl fumarate, the active ingredient and magnesium stearate with a hopper mixer;

[0039] 3) dry granulation: granulating the above mixed powder with a dry granulator;

[0040] 4) total mixing: mixing the resulting fine granules and prescription amount of extragranular sodium stearyl fumarate with a hopper mixer;

[0041] 5) optionally, tableting: compressing the resulting mixture into tablets according to the theoretical tablet weight; and

[0042] 6) optionally, coating: i) formulation of a coating liquid, adding a prescription amount of Opadry to purified water under stirring to formulate a coating liquid with a solid content of 10%, stirring the coating liquid for 60 minutes after the completion of the addition of Opadry to make it evenly dispersed, and sieving the formulated coating liquid with a 100-mesh sieve for later use; and ii) setting the parameters according to the process requirements, and finishing the coating until the coating weight gain reaches about 2.0% to 4.0%.

[0043] The inventor finds through a large number of studies that N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl) amino)-4-methoxyphenyl)acrylamide, as third-generation small molecule EGFR inhibitor, is a drug with low permeability. Its solubility is greatly affected by pH, which is pH dependent. The pharmaceutical composition prepared according to the present invention has a good and uniform dissolution in different dissolution media.

DETAILED DESCRIPTION OF THE INVENTION

[0044] Regarding to the Filler:

[0045] It can be found from Table 1 that when the filler comprises lactose, a pharmaceutical composition with a high content of the compound of formula I can be prepared, and the resulting pharmaceutical composition has a good compressibility.

TABLE 1

Screening of the filler

Single-factor study	Sample 1	Sample 2	Sample 3
Active ingredient [1]	1.416	1.416	1.416
Microcrystalline cellulose	1.05	1.05	1.05
Anhydrous lactose	3.15	/	1.56
Mannitol	/	3.15	1.59
Croscarmellose sodium (added intragranularly)	0.18	0.18	0.18
Croscarmellose sodium (added extragranularly)	0.09	0.09	0.09
Magnesium stearate (added intragranularly)	0.09	0.09	0.09
Magnesium stearate (added extragranularly)	0.084	0.084	0.084
Process of compressing large tablets (called "slugs")	There was no punch sticking, and the large tablets were smooth and 100% qualified	There was punch sticking, and the large tablets were not smooth and does not meet the production requirement	There was punch sticking, and the large tablets were not smooth and does not meet the production requirement

Note:

[1] The active ingredient is calculated by mesylate salt, the same below.

[0046] The drug loading capacity of the active ingredient in the tablet was further increased. When the active ingredient was present in an amount of 43.3%, the tablet still had a very good compressibility. There was no punch sticking. The resulting uncoated tablets were smooth and 100% qualified, having a complete shape and good appearance.

TABLE 2

Type and dosage of the filler					
			Microcrystalline cellulose (PH102) + anhydrous lactose (21AN)		
Single-factor study			Ratio: 3:1	Ratio: 1:1	Ratio: 1:3
Batch			200 Tablets/g	200 Tablets/g	200 Tablets/g
Active ingredient[1]			25.96	25.96	25.96
Microcrystalline cellulose (PH102)			18.00	12.00	6.00
Anhydrous lactose (21AN)			6.14	12.14	18.14
Carboxymethyl starch sodium (Type A)			8.40	8.40	8.40
Sodium stearyl fumarate (added intragranularly)			0.3	0.3	0.3
Magnesium stearate (added intragranularly)			0.6	0.6	0.6
Sodium stearyl fumarate (added extragranularly)			0.6	0.6	0.6
Process of compressing large tablets (called "slugs")			There was no punch sticking, and the large tablets were smooth	There was no punch sticking, and the large tablets were smooth	There was no punch sticking, and the large tablets were smooth
Hardness of uncoated tablet (kgf)			6.60	6.67	6.89
Cumulative dissolution rate (%)	0.1M HCl	15 min	90	83	89

[0047] Moreover, the hardness of uncoated tablet is also one of the factors that affect the dissolution rate. Uneven hardness may lead to uneven dissolution, thereby affecting the efficacy. Table 3 below shows the corresponding dissolution profile of the prescription of the present invention at different hardnesses. It can be seen from the table that the prescription of the present invention can eliminate the effect of hardness changes on the dissolution result of the uncoated tablet under different hardness conditions, and enable the product to maintain a good dissolution rate. Therefore, the prescription of the present invention can overcome the adverse effect caused by the different hardness of uncoated tablets.

TABLE 3

Dissolution rate test of the prescription of the present invention at different hardnesses								
			Proportion (%)				Prescription amount (g)	
Active ingredient			43.27				25.96	
Microcrystalline cellulose			30.00				18.0	
Anhydrous lactose			10.23				6.14	
Carboxymethyl starch sodium			14.00				8.4	
Sodium stearyl fumarate (added intragranularly)			0.50				0.3	
Magnesium stearate (added intragranularly)			1.00				0.6	
Sodium stearyl fumarate (added extragranularly)			1.00				0.6	
Hardness range (kgf)			5.50		10.30		6.20	
Dissolution profile in 30 minutes			Almost no accumulation at the bottom of the bottle		Almost no accumulation at the bottom of the bottle		Almost no accumulation at the bottom of the bottle	
Cumulative dissolution rate (%)	0.1M hydrochloric acid	n = 6	Averange	RSD	Averange	RSD	Averange	RSD
		5 min	41	13.1	36	5.9	60	5.3
		15 min	88	2.7	88	1.4	91	3.4
		30 min	90	1.9	92	1.2	93	2.3

[0048] Regarding to the Disintegrant:

[0049] In the pharmaceutical composition system of the present invention, the addition of the disintegrant can also affect the dissolution rate of the tablet. The inventor finds that the dissolution rate is good when the disintegrant is present in an amount of 1 to 30%. See Table 4 for details. Carboxymethyl starch sodium used as the disintegrant can ensure a good disintegration and preparation of the tablet, and the preferred dosage is 10% to 20%.

[0051] The immediate-release film-coated tablets comprising the above components were prepared by the following preparation method:

[0052] (1) Pre-Treatment of Raw Materials

Material name	Treatment method
Microcrystalline cellulose (KG802)	Sieved with a 60-mesh sieve
Anhydrous lactose (21AN)	Sieved with a 60-mesh sieve

TABLE 4

	Dosage and adding method of the disintegrant					
Single-factor study	Carboxymethyl starch sodium (14%) added intragranularly	Carboxymethyl starch sodium (6%) added intragranularly	Carboxymethyl starch sodium (16%) added intragranularly	Carboxymethyl starch sodium (8%) added intragranularly	Carboxymethyl starch sodium (16%) added intragranularly:added extragranularly = 1:1	Carboxymethyl starch sodium (14%) added intragranularly:added extragranularly = 1:1
Batch	200 Tablets/g	200 Tablets/g	200 Tablets/g	200 Tablets/g	200 Tablets/g	200 Tablets/g
Active ingredient	25.96	25.96	25.96	25.96	25.96	25.96
Microcrystalline cellulose (PH102)	18.0	21.6	17.1	19.8	17.1	18.0
Anhydrous lactose (21AN)	6.14	7.34	5.84	6.74	5.84	6.14
Carboxymethyl starch sodium, Type A (added intragranularly)	8.4	3.6	9.6	6.0	4.8	4.2
Sodium stearyl fumarate (added intragranularly)	0.3	0.3	0.3	0.3	0.3	0.3
Magnesium stearate (added intragranularly)	0.6	0.6	0.6	0.6	0.6	0.6
Carboxymethyl starch sodium, Type A (added extragranularly)	/	/	/	/	4.8	4.2
Sodium stearyl fumarate (added extragranularly)	0.6	0.6	0.6	0.6	0.6	0.6
Hardness of uncoated tablet (kgf)	6.60	6.53	6.53	6.53	6.44	6.37
Cumulative dissolution rate (%) 0.1M HCl 15 min	90	74	88	72	86	82

Example 1

[0050] A pharmaceutical composition comprising the mesylate salt of N-(5+(4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide comprises the components of: 64.9 mg of the active ingredient (calculated by $C_{30}H_{35}N_7O_2.CH_3SO_3H$), 45.0 mg of microcrystalline cellulose (KG802), 15.3 mg of anhydrous lactose (21AN), 21.0 mg of carboxymethyl starch sodium (Type A), 0.8 mg of intragranular sodium stearyl fumarate, 1.5 mg of extragranular sodium stearyl fumarate and 1.5 mg of magnesium stearate. The prescription is as follows:

Mesylate salt of the compound of formula I	43.3%
Microcrystalline cellulose	30.0%
Anhydrous lactose	10.2%
Carboxymethyl starch sodium	14%
Sodium stearyl fumarate	0.5% + 1.0%
Magnesium stearate	1.0%

-continued

Material name	Treatment method
Carboxymethyl starch sodium (Type A)	Sieved with a 80-mesh sieve
Sodium stearyl fumarate	Sieved with a 80-mesh sieve

[0053] (2) Weighing

[0054] The raw materials were weighed according to the schedule list.

[0055] (3) Mixing

[0056] 1) Premixing I: the intragranular raw materials were mixed in a hopper mixer (speed: 15 rpm, time: 10 min). 2) Milling: sieve size: 1.0 mm, milling speed: 350 to 800 rpm. 3) Premixing II: the milled material and magnesium stearate were mixed in a hopper mixer (speed: 15 rpm, time: 10 min).

[0057] (4) Dry Granulation

[0058] Delivery frequency conversion (Hz): 7 to 13; tableting frequency conversion (Hz): 20 to 40; granulation frequency conversion (Hz): 30 to 50; granulation sieve size: 1.0 mm; powder mesh number: 60 mesh.

[0059] (5) Total Mixing

[0060] The fine granules obtained by dry granulation and a prescription amount of extragranular sodium stearyl fumarate were mixed in a hopper mixer for 10 min at a speed of 15 rpm.

[0061] (6) Tableting

[0062] The theoretical tablet weight was calculated according to the particle content. The mixture was compressed into tablets after adjusting the tablet weight and hardness.

[0063] (7) Coating

[0064] 1) Formulation of a coating liquid: a coating liquid with a solid content of 10% was formulated with a film-coating premix (gastric-soluble type) and a prescription amount of purified water. The coating liquid was stirred for 60 minutes, and filtered with a 100-mesh sieve for later use.

[0065] 2) Coating: the corresponding parameters were set according to the process requirements. During the coating process, the bed temperature was controlled at 30 to 40° C., and the coating weight gain was 2.0 to 4.0%.

[0066] (8) Packaging.

Example 2

[0067] A pharmaceutical composition comprising the mesylate salt of N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide comprises the components of: 129.8 mg of the active ingredient (calculated by $C_{30}H_{35}N_7O_2.CH_3SO_3H$), 90.0 mg of microcrystalline cellulose (KG802), 30.6 mg of anhydrous lactose (21AN), 42.0 mg of carboxymethyl starch sodium (Type A), 1.6 mg of intragranular sodium stearyl fumarate, 3.0 mg of extragranular sodium stearyl fumarate and 3.0 mg of magnesium stearate. The prescription is as follows:

Mesylate salt of the compound of formula I	43.3%
Microcrystalline cellulose	30.0%
Anhydrous lactose	10.2%
Carboxymethyl starch sodium	14%
Sodium stearyl fumarate	0.5% + 1.0%
Magnesium stearate	1.0%

[0068] The immediate-release film-coated tablets comprising the above components were prepared by the following preparation method:

[0069] (1) Pre-Treatment of Raw Materials

Material name	Treatment method
Microcrystalline cellulose (KG802)	Sieved with a 60-mesh sieve
Anhydrous lactose (21AN)	Sieved with a 60-mesh sieve
Carboxymethyl starch sodium (Type A)	Sieved with a 80-mesh sieve
Sodium stearyl fumarate	Sieved with a 80-mesh sieve

[0070] (2) Weighing

[0071] The raw materials were weighed according to the schedule list.

[0072] (3) Mixing

[0073] 1) Premixing I: the intragranular raw materials (microcrystalline cellulose (KG802), anhydrous lactose (21AN), carboxymethyl starch sodium (Type A), sodium stearyl fumarate, the active pharmaceutical ingredient) were mixed in a hopper mixer (speed: 15 rpm, time: 20 min). 2) Premixing II: after premixing I was completed, magnesium stearate (intragranular) was added to the hopper mixer for mixing (speed: 15 rpm, time: 10 min).

[0074] (4) Dry Granulation

[0075] HFS speed: 30 to 45 rpm, VFS speed: 200 to 240 rpm, pressure wheel speed: 3 to 7 rpm, pressure wheel pressure: 20 to 25 KN, crushing knife speed: 1000 to 1500 rpm, pressure wheel gap: 1.0 mm, granulation sieve size: 1.6 mm.

[0076] (5) Total Mixing

[0077] The fine granules obtained by dry granulation and a prescription amount of extragranular sodium stearyl fumarate were mixed in a hopper mixer for 10 min at a speed of 15 rpm.

[0078] (6) Tableting

[0079] The theoretical tablet weight was calculated according to the particle content. The mixture was compressed into tablets after adjusting the tablet weight and hardness.

[0080] (7) Coating

[0081] 1) Formulation of a coating liquid: a coating liquid with a solid content of 10% was formulated with a film-coating premix (gastric-soluble type) and a prescription amount of purified water. The coating liquid was stirred for 60 minutes, and filtered with an 80-mesh sieve for later use.

[0082] 2) Coating: the corresponding parameters were set according to the process requirements. During the coating process, the bed temperature was controlled at 30 to 40° C., and the coating weight gain was 2.0 to 4.0%.

[0083] (8) Packaging.

Example 3

[0084] A pharmaceutical composition comprising the mesylate salt of N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide comprises the components of: 5.9 mg of the active ingredient (calculated by $C_{30}H_{35}N_7O_2.CH_3SO_3H$), 25.0 mg of microcrystalline cellulose, 54.7 mg of anhydrous lactose, 15.0 mg of carboxymethyl starch sodium, 0.5 mg of intragranular sodium stearyl fumarate, 0.9 mg of extragranular sodium stearyl fumarate and 0.5 mg of magnesium stearate. The prescription is as follows:

Mesylate salt of the compound of formula I	5.8%
Microcrystalline cellulose	24.4%
Anhydrous lactose	53.4%
Carboxymethyl starch sodium	14.6%
Sodium stearyl fumarate	0.5% + 0.8%
Magnesium stearate	0.5%

[0085] The immediate-release film-coated tablets comprising the above components were prepared by the preparation method of Example 1.

Example 4

[0086] A pharmaceutical composition comprising the mesylate salt of N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide comprises the components of: 31.8 mg of the active ingredient (calculated by $C_{30}H_{35}N_7O_2.CH_3SO_3H$), 30.0 mg of microcrystalline cellulose, 89.4 mg of anhydrous lactose, 30.0 mg of carboxymethyl starch sodium, 1.0 mg of intragranular sodium stearyl

fumarate, 1.8 mg of extragranular sodium stearyl fumarate and 1.0 mg of magnesium stearate.

[0087] The immediate-release film-coated tablets comprising the above components were prepared by the preparation method of Example 2.

Mesylate salt of the compound of formula I	17.2%
Microcrystalline cellulose	16.2%
Anhydrous lactose	48.3%
Carboxymethyl starch sodium	16.2%
Sodium stearyl fumarate	0.5% + 1.0%
Magnesium stearate	0.5%

Example 5

[0088] A pharmaceutical composition comprising the mesylate salt of N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide comprises the components of: 47.2 mg of the active ingredient (calculated by $C_{30}H_{35}N_7O_2.CH_3SO_3H$), 30.0 mg of microcrystalline cellulose, 93 mg of anhydrous lactose, 30.0 mg of carboxymethyl starch sodium, 1.0 mg of intragranular sodium stearyl fumarate, 1.8 mg of extragranular sodium stearyl fumarate and 2.0 mg of magnesium stearate.

Mesylate salt of the compound of formula I	23.0%
Microcrystalline cellulose	14.6%
Anhydrous lactose	45.4%
Carboxymethyl starch sodium	14.6%
Sodium stearyl fumarate	0.5% + 0.9%
Magnesium stearate	1.0%

[0089] The immediate-release film-coated tablets comprising the above components were prepared by the preparation method of Example 1.

Example 6

[0090] A pharmaceutical composition comprising the mesylate salt of N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide comprises the components of 97.35 g of the active ingredient (calculated by $C_{30}H_{35}N_7O_2.CH_3SO_3H$), 67.5 g of microcrystalline cellulose, 22.95 g of anhydrous lactose, 31.5 g of carboxymethyl starch sodium, 1.2 g of intragranular sodium stearyl fumarate, 2.25 g of extragranular sodium stearyl fumarate and 2.25 g of magnesium stearate.

Mesylate salt of the compound of formula I	43.3%
Microcrystalline cellulose	30.0%
Anhydrous lactose	10.2%
Carboxymethyl starch sodium	14.0%
Sodium stearyl fumarate	0.5% + 1.0%
Magnesium stearate	1.0%

[0091] The immediate-release film-coated tablets comprising the above components were prepared by the preparation method of Example 2.

Example 7

[0092] A pharmaceutical composition comprising the mesylate salt of N-(5-((4-(1-cyclopropyl-TH-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide comprises the components of 259.6 g of the active ingredient (calculated by $C_{30}H_{35}N_7O_2.CH_3SO_3H$), 180.0 g of microcrystalline cellulose, 61.2 g of anhydrous lactose, 84.0 g of carboxymethyl starch sodium, 3.2 g of intragranular sodium stearyl fumarate, 6.0 g of extragranular sodium stearyl fumarate and 6.0 g of magnesium stearate.

Mesylate salt of the compound of formula I	43.3%
Microcrystalline cellulose	30.0%
Anhydrous lactose	10.2%
Carboxymethyl starch sodium	14.0%
Sodium stearyl fumarate	0.5% + 1.0%
Magnesium stearate	1.0%

[0093] The immediate-release film-coated tablets comprising the above components were prepared by the preparation method of Example 1.

Example 8

[0094] A pharmaceutical composition comprising the mesylate salt of N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide comprises the components of 97.35 g of the active ingredient (calculated by $C_{30}H_{35}N_7O_2.CH_3SO_3H$), 67.5 g of microcrystalline cellulose, 22.95 g of anhydrous lactose, 31.5 g of carboxymethyl starch sodium, 1.2 g of intragranular sodium stearyl fumarate, 2.25 g of extragranular sodium stearyl fumarate and 2.25 g of magnesium stearate.

Mesylate salt of the compound of formula I	43.3%
Microcrystalline cellulose	30.0%
Anhydrous lactose	10.2%
Carboxymethyl starch sodium	14.0%
Sodium stearyl fumarate	0.5% + 1.0%
Magnesium stearate	1.0%

[0095] The immediate-release film-coated tablets comprising the above components were prepared by the preparation method of Example 2.

Example 9

[0096] A pharmaceutical composition comprising the mesylate salt of N-(5-((4-(1-cyclopropyl-TH-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide comprises the components of 47.2 mg of the active ingredient (calculated by $C_{30}H_{35}N_7O_2.CH_3SO_3H$), 30.0 mg of sorbitol, 93 mg of calcium hydrophosphate, 30.0 mg of crospovidone XL, 1.0 mg of intragranular sodium stearyl fumarate, 1.8 mg of extragranular stearic acid and 2.0 mg of talc.

Mesylate salt of the compound of formula I	23.0%
Sorbitol	14.6%
Calcium hydrophosphate	45.4%
Crospovidone	14.6%
Sodium stearyl fumarate	0.5%
Stearic acid	0.9%
Talc	1.0%

[0097] The immediate-release film-coated tablets comprising the above components were prepared by the preparation method of Example 1.

Example 10

[0098] A pharmaceutical composition comprising the mesylate salt of N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide comprises the components of: 47.2 mg of the active ingredient (calculated by $C_{30}H_{35}N_7O_2.CH_3SO_3H$), 30.0 mg of sucrose, 93 mg of calcium hydrophosphate, 30.0 mg of crospovidone XL, 1.0 mg of intragranular sodium stearyl fumarate, 1.8 mg of extragranular stearic acid and 2.0 mg of talc.

Mesylate salt of the compound of formula I	23.0%
Sucrose	14.6%
Calcium hydrophosphate	45.4%
Crospovidone	14.6%
Sodium stearyl fumarate	0.5%
Stearic acid	0.9%
Talc	1.0%

[0099] The immediate-release film-coated tablets comprising the above components were prepared by the preparation method of Example 1.

Example 11

[0100] A pharmaceutical composition comprising the mesylate salt of N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide comprises the components of: 97.35 g of the active ingredient (calculated by $C_{30}H_{35}N_7O_2.CH_3SO_3H$), 67.5 g of microcrystalline cellulose, 22.95 g of maltose, 31.5 g of carboxymethyl starch sodium, 1.2 g of intragranular sodium stearyl fumarate, 2.25 g of extragranular sodium stearyl fumarate and 2.25 g of magnesium stearate.

Mesylate salt of the compound of formula I	43.3%
Microcrystalline cellulose	30.0%
Maltose	10.2%
Carboxymethyl starch sodium	14.0%
Sodium stearyl fumarate	0.5% + 1.0%
Magnesium stearate	1.0%

[0101] The immediate-release film-coated tablets comprising the above components were prepared by the preparation method of Example 2.

Example 12

[0102] A pharmaceutical composition comprising the mesylate salt of N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl)acrylamide comprises the components of: 64.9 mg of the active ingredient (calculated by $C_{30}H_{35}N_7O_2.CH_3SO_3H$), 45.0 mg of microcrystalline cellulose (KG802), 15.3 mg of corn starch, 21.0 mg of carboxymethyl starch sodium (Type A), 0.8 mg of intragranular sodium stearyl fumarate, 1.5 mg of extragranular sodium stearyl fumarate and 1.5 mg of magnesium stearate. The prescription is as follows:

Mesylate salt of the compound of formula I	43.3%
Microcrystalline cellulose	30.0%
Corn starch	10.2%
Carboxymethyl starch sodium	14%
Sodium stearyl fumarate	0.5% + 1.0%
Magnesium stearate	1.0%

[0103] The immediate-release film-coated tablets comprising the above components were prepared by the preparation method of Example 1.

[0104] Stability Test and Result Analysis

[0105] 1. Stability of the Product in Different Dissolution Media

[0106] Chromatography Condition:

[0107] Instruments and reagents High performance liquid chromatograph, electronic analytical balance, potassium dihydrogen phosphate (chromatographically pure), acetonitrile (chromatographically pure), reference substance for system suitability of related substance

[0108] Chromatography CONDITION Octadecylsilane bonded silica gel as the filler (Waters XBridge C18, 4.6 mm×150 mm, 3.5 μm or a column with equivalent performance); flow rate: 1.0 ml/min; detection wavelength: 220 nm; column temperature: 35° C.; injection volume: 10 μl.

[0109] Mobile phase A 2.72 g of potassium dihydrogen phosphate was dissolved in about 900 ml of water, the pH was adjusted to 6.0 with sodium hydroxide solution, water was added until the volume reached 1000 ml, and then the solution was mixed well, filtrated and degased.

[0110] Mobile phase B Acetonitrile

[0111] Gradient elution was carried out according to the following table (the amount of mobile phase is scalable)

Time (min)	0	20	30	40	42	50
Mobile phase A (%)	80	60	30	30	80	80
Mobile phase B (%)	20	40	70	70	20	20

[0112] 0.05% phosphoric acid solution 0.5 ml of phosphoric acid was added to 1000 ml of water and mixed well.

[0113] Diluent 800 ml of 0.05% phosphoric acid solution and 200 ml of acetonitrile were mixed well.

TABLE 5

Results of the stability study of the product in different media

Dissolution medium		Time (hour) 0 hour	1 hour	2 hours	4 hours	8 hours	24 hours
0.1 mol/L hydrochloric acid solution	Peak area	5817.502	5724.833	5715.132	5709.908	5691.358	5709.127
	Relative content	100.0%	98.4%	98.2%	98.2%	97.8%	98.1%

TABLE 5-continued

Results of the stability study of the product in different media

Dissolution medium		Time (hour) 0 hour	1 hour	2 hours	4 hours	8 hours	24 hours
Acetate buffer, pH 4.5	Peak area	5388.433	5313.248	5301.212	5294.096	5282.456	5308.160
	Relative content	100.0%	98.6%	98.4%	98.2%	98.0%	98.5%
Phosphate buffer, pH 6.8	Peak area	3364.067	3310.739	3294.386	3270.577	3264.820	3236.565
	Relative content	100.0%	98.4%	97.9%	97.2%	97.0%	96.2%
Phosphate buffer, pH 6.8 (containing 0.1% SDS)	Peak area	4868.623	4864.179	4861.332	4865.548	4853.247	4837.464
	Relative content	100.0%	99.9%	99.9%	99.9%	99.7%	99.4%
Water	Peak area	3627.570	3623.876	3610.467	3602.525	3592.348	3590.479
	Relative content	100.0%	99.9%	99.5%	99.3%	99.0%	99.0%
Water (containing 0.1% SDS)	Peak area	5456.676	5443.102	5433.346	5430.342	5421.376	5422.712
	Relative content	100.0%	99.8%	99.6%	99.5%	99.4%	99.4%

[0114] The inventor studied the solution stability of the tablet prepared in Example 1 as example in 0.1 mol/L hydrochloric acid solution, acetate buffer (pH 4.5), phosphate buffer (pH 6.8), phosphate buffer containing 0.1% SDS (pH 6.8), water and water containing 0.1% SDS. According to the dissolution and release rate test (the second method described in general rule 0931 of volume IV of the Chinese Pharmacopoeia 2015 Edition) under a condition of 50 rpm, an eluate was taken at 30 minutes, and then filtered. The filtrate was used as the test solution to study the solution stability at room temperature within 24 hours. The solution stability data is shown in Table 4.

[0115] The results showed that the tablet prepared in the present invention was stable within 24 hours in 0.1 mol/L hydrochloric acid solution, acetate buffer (pH 4.5), phosphate buffer containing 0.1% SDS (pH 6.8), water and water containing 0.1% SDS; and the tablet degraded slightly in phosphate buffer (pH 6.8).

[0116] 2. Stability Under Light, High Temperature or High Humidity Conditions

TABLE 6

Results of influencing factor study (study condition: high temperature)

			Storage condition							
			40° C. Amount for quality study at each storage point				60° C. Amount for quality study at each storage point			
			63 tablets	25 tablets	25 tablets	25 tablets	63 tablets	25 tablets	25 tablets	25 tablets
Study item		Standard requirement	Storage time 0 d	5d	10 d	30 d	0 d	5d	10 d	30 d
Liquid chromatography identification		The retention time should be the same	Same	Same	Same	Same	Same	Same	Same	Same
Dissolution rate (%) 15 min		Should be ≥80	98	98	94	95	98	99	99	97
Related substance (%)	Impurity A[2]	Should be ≤2.0	0.10	0.14	0.11	0.21	0.10	0.11	0.07	0.10
	Other maximum single impurity	Should be ≤0.2	0.04	0.04	0.05	0.01	0.04	0.02	0.03	0.04
	Total impurity	Should be ≤3.0	0.15	0.19	0.17	0.24	0.15	0.16	0.14	0.19
Moisture (%)		Should be ≤3.0	2.3	2.4	2.4	1.6	2.3	2.5	2.4	1.6
Crystal form		Should be the same as that at Day 0	Meet the requirement	/	Meet the requirement	Meet the requirement	Meet the requirement	/	Meet the requirement	Meet the requirement
Content (%)		Should be 90.0 to 110.0	99.6	101.1	98.8	99.3	99.6	100.0	99.5	99.1

Note:

[2]the RRT of impurity A is about 1.23.

[0117] The structure of impurity A is as follows:

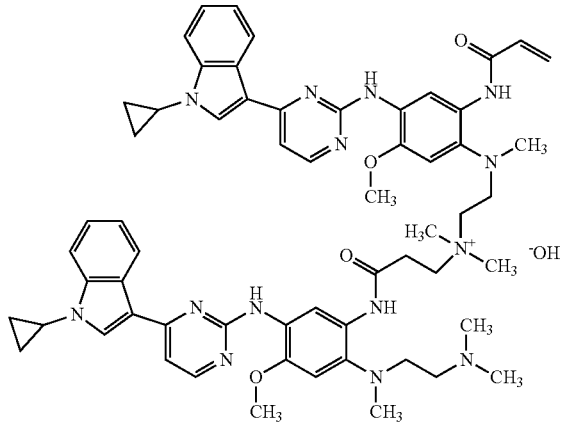


TABLE 7

Results of influencing factor study (study condition: high humidity)

			Storage condition			
			25° C./RH75% (saturated sodium chloride solution) Amount for quality study at each storage point			
			63 tablets	25 tablets	25 tablets	25 tablets
			Storage time			
Study item		Standard requirement	0 d	5 d	10 d	30 d
Liquid chromatography identification		The retention time should be the same	Same	Same	Same	Same
Dissolution rate (%)		Should be ≥80	98	98	97	95
Related substance (%)	Impurity A	Should be ≤2.0	0.10	0.16	0.09	0.21
	Other maximum single impurity	Should be ≤0.2	0.04	0.04	0.04	0.01
	Total impurity	Should be ≤3.0	0.15	0.19	0.13	0.25
Moisture (%)		Should be ≤3.0	2.3	3.7	3.5	3.9
Crystal form		Should be the same as that at Day 0	Meet the requirement	/	Meet the requirement	Meet the requirement
Content (%)		Should be 90.0 to 110.0	99.6	101.3	99.6	99.6

TABLE 8

Results of influencing factor study (study condition: light)

		Storage condition		
		Light Amount for quality test at each storage point		
		310 tablets	25 tablets	25 tablets
		Storage time		
Study item	Standard requirement	0 d	5 d	10 d
Liquid chromatography identification	The retention time should be the same	Same	Same	Same

TABLE 8-continued

Results of influencing factor study (study condition: light)

Study item		Standard requirement	Storage condition: Light; Amount for quality test at each storage point: 310 tablets; 25 tablets; 25 tablets; Storage time: 0 d	5 d	10 d
Dissolution rate (%)		Should be ≥80	98	98	97
Related substance (%)	Impurity A	Should be ≤2.0	0.10	0.13	0.10
	Other maximum single impurity	Should be ≤0.2	0.04	0.04	0.04
	Total impurity	Should be ≤3.0	0.15	0.17	0.16
Moisture (%)		Should be ≤3.0	2.3	2.7	2.4
Crystal form		Should be the same as that at Day 0	Meet the requirement	/	Meet the requirement
Content (%)		Should be 90.0 to 110.0	99.6	101.2	98.7

[0118] The results are shown in Tables 6 to 8. The influencing factor study was conducted for 30 days (the study under light condition was conducted for 10 days, the total illumination was not less than 1.2×106 lux·hr). The results showed that the product was stable under light condition (total illuminance 1.2×106 lux/hr) without degradation, and there was no obvious change in various quality indicators. Under high temperature (40° C.), high temperature (60° C.) and 25° C./RH75% conditions, the related substance slightly degraded, but there was no obvious change in other quality indicators, and the sample had a good stability.

[0119] 3. Product Stability

TABLE 9

Results of product quality study in the stability test (product of Example 1)

Study item		Limit requirement	Time: 0 day	1 month	2 months	3 months
Appearance		A light yellow film-coated tablet, being off-white to light yellow after removing the coating	A Light yellow film-coated tablet, being off-white after removing the coating	A Light yellow film-coated tablet, being off-white after removing the coating	A Light yellow film-coated tablet, being off-white after removing the coating	A Light yellow film-coated tablet, being off-white after removing the coating
Dissolution rate (%)		Should be ≥80	97	98	96	99
Related substance (%)	Impurity A	Should be ≤2.0	0.11	0.17	0.19	0.18
	Other maximum single impurity	Should be ≤0.2	0.08	0.06	0.06	0.06
	Total impurity	Should be ≤3.0	0.44	0.38	0.45	0.46
Content (%)		Should be 90.0 to 110.0	98.6	100.1	98.8	99.0

TABLE 10

Results of product quality study in the stability test (product of Example 2)

Study item	Limit requirement	Time: 0 day	1 month	2 month	3 month
Appearance	A pink film-coated tablet, being off-white to light yellow after removing the coating	A pink film-coated tablet, being off-white after removing the coating	A pink film-coated tablet, being off-white after removing the coating	A pink film-coated tablet, being off-white after removing the coating	A pink film-coated tablet, being off-white after removing the coating

TABLE 10-continued

Results of product quality study in the stability test (product of Example 2)

Study item		Limit requirement	Time 0 day	1 month	2 month	3 month
Dissolution rate (%)		Should be ≥80	98	99	97	99
Related substance (%)	Impurity A	Should be ≤2.0	0.10	0.18	0.27	0.21
	Other maximum single impurity	Should be ≤0.2	0.04	0.02	0.01	0.01
	Total impurity	Should be ≤3.0	0.15	0.22	0.29	0.25
Content (%)		Should be 90.0 to 110.0	99.6	99.7	100.9	100.6

[0120] It can be seen from Tables 9 and 10 that the tablet prepared in the present invention had a good quality, the product quality was stable in the stability test. The prescription and process of the product were stable, and the reproducibility was good.

[0121] The samples prepared in other Examples all had similar stability results to those of the samples of Examples 1 and 2.

[0122] Dissolution Test and Result Analysis

[0123] 1. Four batches of the product prepared in Example 1 were randomly selected for testing. The results are shown in Table 10.

TABLE 11

Dissolution curve of the product in 0.1M hydrochloric acid medium (product of Example 1)

Product of Example 1		Sample 1	Sample 2	Sample 3	Sample 4
Cumulative dissolution rate (%)	5 min	51	47	57	76
	10 min	94	88	97	97
	15 min	98	94	99	100
	30 min	99	97	100	101
	45 min	100	98	100	102

[0124] The results showed that the obtained samples all had good dissolution uniformity.

[0125] 2. The dissolution test of the product prepared in Example 2 in different media was carried out. The results are shown in Table 12.

TABLE 12

Dissolution data of the product in different media (product of Example 2)

Dissolution medium		0.1 mol/L hydrochloric acid	Buffer, pH 4.5	Buffer containing 0.1% SDS, pH 6.8	Water containing 0.1% SDS
Cumulative dissolution rate (%)	5 min	34	30	66	41
	10 min	84	76	86	75
	15 min	97	92	90	87
	30 min	101	96	91	93
	45 min	101	96	92	90
	60 min	101	97	92	94

[0126] The results showed that the product prepared in the present invention had good dissolution rate in different media.

[0127] The samples prepared in other Examples had similar dissolution profile to those of the samples of Examples 1 and 2.

1. A pharmaceutical composition, comprising N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl) acrylamide, an isomer, solvate, hydrate, pharmaceutically acceptable salt thereof or a combination thereof as the active ingredient, and at least one pharmaceutically acceptable excipient.

2. The pharmaceutical composition according to claim **1**, wherein the active ingredient is a mesylate salt of N-(5-((4-(1-cyclopropyl-1H-indol-3-yl)pyrimidin-2-yl)amino)-2-((2-(dimethylamino)ethyl)(methyl)amino)-4-methoxyphenyl) acrylamide.

3. The pharmaceutical composition according to claim **1**, wherein the active ingredient is present in an amount of 1 to 60%.

4. The pharmaceutical composition according to claim **3**, wherein the unit dose of the active ingredient is 10 to 200 mg.

5. The pharmaceutical composition according to claim **1**, wherein the excipient comprises one or more filler(s), comprising at least one disaccharide or polysaccharide, such as glucan, starch, cellulose, lactose, maltose or sucrose.

6. The pharmaceutical composition according to claim **5**, wherein the disaccharide or polysaccharide is present in an amount of 1 to 60%; and wherein the filler is a disaccharide.

7. The pharmaceutical composition according to claim **5**, wherein the filler also comprises one or more of microcrystalline cellulose, mannitol, sorbitol, calcium hydrophosphate and calcium sulfate.

8. The pharmaceutical composition according to claim **5**, wherein the filler is selected from the group consisting of microcrystalline cellulose and lactose.

9. The pharmaceutical composition according to claim **8**, wherein the microcrystalline cellulose is present in an amount of 1 to 60%; and the lactose is present in an amount of 1 to 60%.

10. The pharmaceutical composition according to claim **8**, wherein the weight ratio of microcrystalline cellulose to lactose is 1:3 to 3:1.

11. The pharmaceutical composition according to claim **5**, wherein the filler is selected from the group consisting of microcrystalline cellulose and anhydrous lactose.

12. The pharmaceutical composition according to claim **11**, wherein the microcrystalline cellulose is present in an amount of 1 to 60%; and the anhydrous lactose is present in an amount of 1 to 60%.

13. The pharmaceutical composition according to claim **11**, wherein the weight ratio of microcrystalline cellulose to anhydrous lactose is 1:3 to 3:1.

14. The pharmaceutical composition according to claim **5**, wherein the filler is present in an amount of 20 to 80%.

15. The pharmaceutical composition according to claim **1**, wherein the excipient comprises one or more disintegrant(s).

16. The pharmaceutical composition according to claim **15**, wherein the disintegrant is one or more selected from the group consisting of low-substituted hydroxypropyl cellulose, croscarmellose sodium, carboxymethyl starch sodium and crospovidone.

17. The pharmaceutical composition according to claim **15**, wherein the disintegrant is present in an amount of 1 to 30%.

18. The pharmaceutical composition according to claim **15**, wherein the disintegrant is added intragranularly.

19. The pharmaceutical composition according to claim **1**, wherein the excipient comprises one or more lubricant(s).

20. The pharmaceutical composition according to claim **19**, wherein the lubricant is one or more selected from the group consisting of talc, stearic acid, sodium stearyl fumarate, glyceryl behenate, magnesium stearate and micronized silica gel.

21. The pharmaceutical composition according to claim **19**, wherein the lubricant is present in an amount of 0.1 to 10%.

22. The pharmaceutical composition according to claim **19**, wherein the lubricant is selected from the group consisting of sodium stearyl fumarate and magnesium stearate, the sodium stearyl fumarate is present in an amount of 0.1 to 5%.

23. The pharmaceutical composition according to claim **1**, characterized by comprising the following components:

active ingredient	35 to 50%
lactose	5 to 15%
microcrystalline cellulose	30 to 50%
carboxymethyl starch sodium	10 to 20%
lubricant	0.5 to 5%.

24. The pharmaceutical composition according to claim **23**, characterized by comprising the following components:

active ingredient	43.3%
lactose	10.2%
microcrystalline cellulose	30.0%
carboxymethyl starch sodium	14%
lubricant	0.5 to 5%.

25. The pharmaceutical composition according to claim **1**, wherein the pharmaceutical composition is an oral formulation.

26. (canceled)

27. A method for preparing the pharmaceutical composition according to claim **1**, the method comprising:

1) pre-treatment of raw materials: sieving the filler, disintegrant and intragranular lubricant for later use;
2) mixing: weighing the intragranular raw materials according to specified amounts and mixing them;
3) dry granulation: granulating the above mixed powder by dry granulation;
4) total mixing: mixing the resulting granules and extragranular lubricant;
5) optionally, tableting; and
6) optionally, coating.

28. The method according to claim **27**, comprising:

1) pre-treatment of raw materials: sieving microcrystalline cellulose, lactose, sodium stearyl fumarate and carboxymethyl starch sodium for later use;
2) mixing: weighing the intragranular raw materials according to prescription amounts, and mixing microcrystalline cellulose, lactose, carboxymethyl starch sodium, sodium stearyl fumarate, the active ingredient and magnesium stearate with a hopper mixer;
3) dry granulation: granulating the above mixed powder with a dry granulator;
4) total mixing: mixing the resulting fine granules and prescription amount of extragranular sodium stearyl fumarate with a hopper mixer;
5) optionally, tableting; and
6) optionally, coating: i) formulation of a coating liquid, adding a prescription amount of Opadry to purified water under stirring to formulate a coating liquid with a solid content of 10%, stirring the coating liquid evenly, and sieving the coating liquid for later use; and ii) finishing the coating until the coating weight gain reaches about 2.0% to 4.0%.

29. The pharmaceutical composition according to claim **6**, wherein the disaccharide or polysaccharide is present in an amount of 5 to 15%.

30. The pharmaceutical composition according to claim **6**, wherein the filler is lactose.

31. The pharmaceutical composition according to claim **11**, wherein the microcrystalline cellulose is present in an amount of 20 to 40%, and the lactose is present in an amount of 5 to 15%.

32. The pharmaceutical composition according to claim **20**, wherein the disintegrant is present in an amount of 10 to 20%.

* * * * *