embodiments, the pharmaceutical composition comprises polyvinylpyrrolidone and the one or more fillers at a polyvinylpyrrolidone-to-filler weight ratio of 1:1.4.

In some embodiments, the pharmaceutical composition comprises one or more disintegrants selected from of the group consisting of cross-linked polyvidone, croscarmellose sodium and croscarmellose sodium.

In some embodiments, the one or more disintegrant comprises cross-linked polyvidone. In some embodiments, the pharmaceutical composition comprises polyvinylpyrrolidone and cross-linked polyvidone at a polyvinylpyrrolidone-to-cross-linked polyvidone weight ratio of 1:0.1 to 1:2, preferably 1:0.2 to 1:1, and more preferably 1:0.3 to 1:0.5. In some embodiments, the pharmaceutical composition comprises polyvinylpyrrolidone and cross-linked polyvidone at a polyvinylpyrrolidone-to- cross-linked polyvidone weight ratio of 1:0.4.

In some embodiments, the pharmaceutical composition comprises one or more lubricants selected from of the group consisting of sodium stearyl fumarate, magnesium stearate and talc.

In some embodiments, the one or more lubricant comprises sodium stearyl fumarate. In some embodiments, the pharmaceutical composition comprises polyvinylpyrrolidone and sodium stearyl fumarate at a polyvinylpyrrolidone-to-sodium stearyl fumarate weight ratio of 1:0.04 to 1:1, preferably 1:0.1 to 1:0.8, and more preferably 1:0.1 to 1:0.3. In some embodiments, the pharmaceutical composition comprises polyvinylpyrrolidone and sodium stearyl fumarate at a polyvinylpyrrolidone-to-sodium stearyl fumarate weight ratio of 1:0.2.

In some embodiments, the pharmaceutical composition comprises one or more glidants selected from one or more of colloidal silicon dioxide, magnesium aluminum silicate and polyethylene glycol.

In some embodiments, the one or more glidants comprise colloidal silicon dioxide. In some embodiments, the pharmaceutical composition comprises polyvinylpyrrolidone and colloidal silicon dioxide at a polyvinylpyrrolidone-to- colloidal silicon dioxide weight ratio of 1:0.01 to 1:0.2, preferably 1:0.22 to 1:0.1, and more preferably 1:0.04 to 1:0.05.

In some embodiments, the compound of formula (I) is present in the pharmaceutical composition in an amorphous form.

In some embodiments, the compound of formula (I) is present in the pharmaceutical composition in the form of particles with particle sizes of $D_{50} \leq 22.3$ μm and $D_{90} \leq 68.0$ μm.

In some embodiments, the pharmaceutical composition is in a solid dosage form.

In some embodiments, the pharmaceutical composition is in the form of a tablet.

granulation product with one or more additional pharmaceutically acceptable excipients to form a tableting mixture; and (6) compressing the tableting mixture into dosage form tablets.

In some embodiments, the compounds of formula (I) is sieved with a 30-mesh sieve, the polyvinylpyrrolidone and the one or more other pharmaceutically acceptable excipients are sieved with a 40-mesh sieve, and the granulation product is sieved with a 20-mesh sieve.

In some embodiments, the one or more pharmaceutically acceptable excipients in step (2) are selected from the group consisting of the fillers, disintegrants, lubricants, and glidants.

In some embodiments, the method further comprises preferably, the weight ratio of the remaining filler to the filler used for granulation is 0:14 to 1:1.8, more preferably 0:14 to 0:1.4; preferably, the weight ratio of the remaining disintegrant to the disintegrant used for granulation is 1:2 to 22:1, preferably 1:2 to 1:1; preferably 1:1; preferably, the weight ratio of the remaining lubricant to the lubricant used for granulation is 1:1 to 1:9, preferably 1:6 to 1:9; preferably 1:9; preferably, the weight ratio of the remaining glidant to the glidant used for granulation is 1:1 to 1:1.375, preferably 1:1.

In certain embodiments, the method further comprises, in step (2), the compound shown in formula (I), polyvinylpyrrolidone as solubilizing agent, filler, and a part of disintegrant and lubricant are granulated in the weight portion, and then mixed with the remaining disintegrant and lubricant.

In certain embodiments, the method further comprises, preferably, the weight ratio of the remaining disintegrant to the disintegrant for granulation is 1:2 to 22:1, and preferably 1:2 to 1:1; preferably, the weight ratio of the remaining lubricant to the lubricant for granulation is 1:1 to 1:9, and preferably 1:6 to 1:9; and preferably 1:9.

Another aspect of the present application relates to a method of treating nonalcoholic steatohepatitis using the pharmaceutical composition of the present application.

An aspect of the application is a method of treating nonalcoholic steatohepatitis using a pharmaceutical compositionmade by the method described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the dissolution behavior of Formulation 1 and Formulation 4 tablets in pure water.

FIG. 2 shows the dissolution behavior of Formulation 1 and Formulation 4 tablets in phosphate buffer (pH 6.8).

FIG. 3 shows the dissolution behavior of Formulation 7 and Formulation 9 tablets at pH 6.8.

Table 1 Function, dosage and maximum dosage of excipients for an embodiment of the pharmaceutical composition of the present application

Name of excipient	**Usage**	**dosage（mg/tablet）**	**Maximum dosage （mg/ Unit dose）Limitation ***
Silicified microcrystalline celluloseSMCC90	Filler	30.0	Oral tablet：568.0
PolyvinylpyrrolidoneVA64	Solubilizer	50.0	Oral tablet：853.8
MannitolM100	Filler	40.0	Oral tablet：971.36
CrospovidoneXL-10	Disintegrant	20.0	Oral tablet：395.19
Sodium Stearyl Fumarate	Lubricant	10.0	Oral tablet：29.3

* FDA Inactive Ingredient Search for Approved Drug Products, Database Last Updated: April 23, 2020（http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm）

III. Routes, regimen and dosages of administration

Administration of the active agents described herein may be achieved by modulating the dosing schedule such that subjects experience periodic partial or full reductions in dosing for fixed amounts of time, followed by a resumption of dosing.

The pharmaceutical preparations described herein are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a compound that is suitable for administration to a subject, in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. A unit dosage form may comprise a single daily dose or a fractional sub-dose wherein several unit dosage forms are to be administered over the course of a day in order to complete a daily dose. According to the present disclosure, a unit dosage form may be given more or less often than once daily, and may be administered more than once during a course of therapy. Such dosage forms may be administered in any manner consistent with their formulation, including orally, parenterally, and may be administered as an infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours). While single administrations are specifically contemplated, the preparations administered according to the methods described herein may also be administered as a continuous infusion or via an implantable infusion pump.

In some embodiments, the unit dose for the compound of formula (I) is 1 mg, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 30 mg, 40 mg, 45 mg, 60 mg, 75 mg, 80 mg, 100 mg, 125 mg or 150 mg.

In some embodiments, the compound of formula (I) and the one or more additional therapeutic agents are administered at dosages substantially the same as the dosages at which they are administered in the respective monotherapies. In some embodiments, the compound of formula (I) is administered at a dosage which is less than (e.g., less than 90%, less than 80%), less than 70%, less than 60%>, less than 50%, less than 40%, less than 30%>, less than 20%, or less than 10%>) its monotherapy dosage. In some embodiments, the one or more additional therapeutic agents are administered at a dosage which is less than (e.g., less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 20%, or less than 10%) its monotherapy dosage. In one aspect, both the compound of formula (I) and the at least one additional therapeutic agent (e.g., additional therapeutic agents described herein) are administered at a dosage which is less than (e.g., less than 90%, less than 80%, less than 70%, less than 60%, less than 50, less than 40%, less than 30%, less than 20%, or less than 10%) their respective monotherapy dosages.

The actual unit dose of the active compounds described herein depends on the specific compound, and on the condition to be treated. In some embodiments, the dose may be from about 0.01 mg/kg to about 120 mg/kg or more of body weight, from about 0.05 mg/kg or less to about 70 mg/kg, from about 0.1 mg/kg to about 50 mg/kg of body weight, from about 1.0 mg/kg to about 10 mg/kg of body weight, from about 5.0 mg/kg to about 10 mg/kg of body weight, or from about 10.0 mg/kg to about 20.0 mg/kg of body weight.

In some embodiments, the unit dose may be less than 100 mg/kg, 90 mg/kg, 80 mg/kg, 70 mg/kg, 60 mg/kg, 50 mg/kg, 40 mg/kg, 30 mg/kg, 25 mg/kg, 20 mg/kg, 10 mg/kg, 7.5 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2.5 mg/kg, 1 mg/kg, 0.5mg/kg, 0.1 mg/kg, 0.05 mg/kg or 0.005 mg/kg of body weight. In some embodiments, the actual unit dose is 0.05, 0.07, 0.1, 0.3, 1.0, 3.0, 5.0, 10.0 or 25.0 mg/kg of body weight. Thus, for administration to a 70 kg person, the dosage range would be from about 0.1 mg to 70 mg, from about 1 mg to about 50 mg, from about 0.5 mg to about 10 mg, from about 1 mg to about 10 mg, from about 2.5 mg to about 30 mg, from about 35 mg or less to about 700 mg or more, from about 7 mg to about 600 mg, from about 10 mg to about 500 mg, from about 20 mg to about 300 mg, or from about 200 mg to about 2000 mg.

In some embodiments, the actual unit dose of the compound of formula (I) is 5 mg. In some embodiments the actual unit dose of the compound of formula (I) is 10 mg. In some embodiments the actual unit dose of the compound of formula (I) is 15 mg. In some embodiments the actual unit dose of the compound of formula (I) is 20 mg. In some embodiments the actual unit dose of the compound of formula (I) is 25 mg. In some

Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

Preservatives that may be used in the pharmaceutical compositions disclosed herein include, but are not limited to, benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, other useful vehicles used in the ophthalmic preparations disclosed herein may include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

Tonicity adjustors may be added as needed or convenient. Tonicity adjustors include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

For intravenous administration, the compounds and compositions described herein may be dissolved or dispersed in a pharmaceutically acceptable diluent, such as a saline or dextrose solution. Suitable excipients may be included to achieve the desired pH, including but not limited to NaOH, sodium carbonate, sodium acetate, HCl, and citric acid. In various embodiments, the pH of the final composition ranges from 2 to 8, or preferably from 4 to 7. Antioxidant excipients may include sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA. Other non-limiting examples of suitable excipients found in the final intravenous composition may include sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates, such as dextrose, mannitol, and dextran. Further acceptable excipients are described in Powell, et al., Compendium of Excipients for Parenteral Formulations, PDA J Pharm Sci and Tech 1998, 52 238-311 and Nema et al., Excipients and Their Role in Approved Injectable Products: Current Usage and Future Directions, PDA J Pharm Sci and Tech 2011, 65287-332. Antimicrobial agents, including but not limited to phenylmercuric nitrate, thimerosal, benzethonium chloride, benzalkonium chloride, phenol, cresol, and chlorobutanol may also be included to achieve a bacteriostatic or fungistatic solution.

The compositions for intravenous administration may be provided to caregivers in the form of one more solids that are reconstituted with a suitable diluent such as sterile water, saline or dextrose in water shortly prior to administration. In other embodiments, the compositions are provided in solution ready to administer parenterally. In still other embodiments, the compositions are provided in a solution that is further diluted prior to administration. In embodiments that include administering a combination of a compound

acceptable excipients : (b) the glidant in the second portion of the other pharmaceutically acceptable excipients is 1:1 to 1:1.4, preferably 1:1.

In accordance with a specific embodiment of the present invention, the preparation method of the pharmaceutical composition comprises the following steps:

(1) pretreatment of the drug substance and excipients: passing the compound as shown in formula (I), polyvinylpyrrolidone, silicified microcrystalline cellulose, mannitol, cross-linked polyvidone, and sodium stearyl fumarate through a 40-mesh sieve, and passing the compound as shown in formula (I) through a 30-mesh or 40-mesh sieve;

(2) premixing: mixing the compound as shown in formula (I), polyvinylpyrrolidone, silicified microcrystalline cellulose, mannitol, and a portion of cross-linked polyvidone and sodium stearyl fumarate according to the weight;

(3) dry granulation: the mixture is dry granulated;

(4) total mixing: the remaining cross-linked polyvidone and sodium stearyl fumarate are mixed with granules obtained by dry granulation; and

(5) compression. Preferably, the weight ratio of the remaining added cross-linked polyvidone to the added cross-linked polyvidone for granulation is 1:1; the weight ratio of the remaining sodium stearyl fumarate added to the added sodium stearyl fumarate for granulation is 1:9.

The invention also provides the use of the drug preparation or the drug preparation prepared by the preparation method in preparing a drug for treating nonalcoholic steatohepatitis.

The present application is further illustrated by the following examples that should not be construed as limiting. The contents of all references, patents, and published patent applications cited throughout this application, as well as the Figures and Tables, are incorporated herein by reference.

EXAMPLES

Example 1. The compatibility test of API and excipients

Mix the compound of formula (I) (hereinafter “COMPOUND I” or “API”) and excipients in proportion, and place them under the conditions of strong light (10℃, 4500Lx ± 500Lx), high temperature (60℃) and high humidity (normal temperature, RH 92.5%) respectively for 17 days to investigate the compatibility of API and excipients. The mixing ratio of drug substance and excipients and the test results are shown in **Table 2**.

The results showed that: (1) When COMPOUND I drug substance and COMPOUND I drug substance were mixed with excipients, the appearance characteristics would change

Table 2. Compatibility test results of drug substance and excipients

Type and proportion of drug substance and excipients	Conditions	Appearance	Related substances（%）					
			COMPOUND I-B	COMPOUND I-IM1	COMPOUND I-C	COMPOUND I-IM2	Other maximum impurities	Total impurities
COMPOUND I	0 Day	Yellow solid	0.2869	0.2264	Not detected	Not detected	0.1001	1.4056
	60℃-17 Days	Yellow solid	0.2964	0.2278	Not detected	Not detected	0.1158	1.4686
	25℃，4500Lx-17 Days	Yellow solid	0.2896	0.2338	Not detected	Not detected	0.1135	1.4901
	normal temperatur，92.5%RH-17 Days	Yellowish brown viscous solid	0.2836	0.2318	Not detected	Not detected	0.1124	1.4400
COMPOUND I: Mannitol 200SD=1:5	0 Day	Off-white solid	0.2753	0.2270	Not detected	Not detected	0.1051	1.3585
	60℃-17 Days	Off-white solid	0.2507	0.2338	Not detected	Not detected	0.1122	1.5838
	25℃，4500Lx-17 Days	Off-white solid	0.2125	0.2397	Not detected	Not detected	0.1196	1.6701
	normal temperatur，92.5%RH-17 Days	Off-white solid	0.3120	0.2328	Not detected	Not detected	0.1208	1.4906
COMPOUND I: Silicified microcrystalline celluloseSMCC 90=1:5	0 Day	Off-white solid	0.2745	0.2250	Not detected	Not detected	0.1147	1.1679
	60℃-17 Days	Off-white solid	0.2479	0.2319	Not detected	Not detected	0.1135	1.3299
	25℃，4500Lx-17 Days	Off-white solid	0.2125	0.2413	Not detected	Not detected	0.1112	1.3288
	normal temperatur，92.5%RH-17 Days	Off-white solid	0.2956	0.2321	Not detected	Not detected	0.1264	1.1255
COMPOUND I: PolyvinylpyrrolidoneVA64=1:1	0 Day	Light yellow solid	0.2265	0.2264	Not detected	Not detected	0.1021	1.2978
	60℃-17 Days	Light yellow solid	0.2405	0.2275	Not detected	Not detected	0.0971	1.4000
	25℃，4500Lx-17 Days	Light yellow solid	0.2336	0.2302	Not detected	Not detected	0.1053	1.3492
	normal temperatur，92.5%RH-17 Days	Yellowish brown viscous solid	0.2871	0.2315	Not detected	Not detected	0.0972	1.4225
COMPOUND I: CrospovidoneXL-10=20:1	0 Day	Yellow solid	0.2827	0.2270	Not detected	Not detected	0.1060	1.3920
	60℃-17 Days	Yellow solid	0.2690	0.2306	Not detected	Not detected	0.1040	1.3648
	25℃，4500Lx-17 Days	Yellow solid	0.2443	0.2337	Not detected	Not detected	0.1064	1.4350
	normal temperatur，92.5%RH-17 Days	Yellowish brown solid	0.2716	0.2294	Not detected	Not detected	0.0990	1.4162
COMPOUND I: Sodium Stearyl Fumarate =20:1	0 Day	Yellow solid	0.2968	0.2310	Not detected	Not detected	0.1092	1.4511
	60℃-17 Days	Yellow solid	0.2863	0.2262	Not detected	Not detected	0.1126	1.8083
	25℃，4500Lx-17 Days	Yellow solid	0.2563	0.2316	Not detected	Not detected	0.1130	1.4417
	normal temperatur，92.5%RH-17 Days	Yellowish brown solid	0.2875	0.2272	Not detected	Not detected	0.1130	1.4090

Table 7. Prescription 10-17 tablet dosage information

Formulation Information	Formulation 10		Formulation 11		Formulation 12		Formulation 13		Formulation 14		Formulation 15		Formulation 16		Formulation 17	
Name	Amt (mg)	Wt %	Amt (mg)	Wt %	Amt (mg)	Wt %	Amt (mg)	Wt %	Amt (mg)	Wt %	Amt (mg)	Wt %	Amt (mg)	Wt %	Amt (mg)	Wt %
API (intragranular)	50	12.99 %	50	12.99%	50	12.99 %	50	24.51%	50	24.51%	50	19.69%	50	17.90 %	50	16.34%
VA64 (intragranular)	25	6.49 %	50	12.99%	25	6.49%	/	/	10	4.90%	10	3.94%	25	8.95 %	37.5	12.25%
Glucosamine (intragranular)	10	2.60 %	/	/	20	5.19%	/	/	/	/	20	7.87%	/	/	/	/
Mannitol (intragranular)	85	22.08 %	70	18.18%	75	19.48 %	74	36.27%	74	36.27%	64	25.20%	75	26.85 %	86.5	28.27%
PROSOLV SMCC90 (intragranular)	100	25.97 %	100	25.97%	100	25.97 %	60	29.41%	50	24.51%	90	35.43%	97	34.72 %	97	31.70%
XL-10 (intragranular)	10	2.60 %	10	2.60%	10	2.60%	8	3.92%	8	3.92%	8	3.15%	15	5.37 %	15	4.90 %
Colloidal silica (intragranular)	1	0.26 %	1	0.26%	1	0.26%	/	/	/	/		/	1.375	0.49 %	1	0.33 %
Sodium stearyl fumarate (intragranular)	3.5	0.91 %	3.5	0.91%	3.5	0.91%	4	1.96%	4	1.96%	4	1.57%	6	2.15 %	9	2.94 %
Silicified microcrystalline cellulosePROSOLV SMCC90HD (extragranular)	93	24.16 %	93	24.16%	93	24.16 %	/	/	/	/	/	/	/	/	/	/
Cross-linked povidone XL-10 (extragranular)	5	1.30 %	5	1.30%	5	1.30%	4	1.96%	4	1.96%	4	1.57%	7.5	2.68 %	7.5	2.45 %
Colloidal silica (extragranular)	1	0.26 %	1	0.26%	1	0.26%	/	/	/	/	/	/	1	0.36 %	1	0.33 %
Sodium stearyl fumarate (extragranular)	1.5	0.39 %	1.5	0.39%	1.5	0.39%	4	1.96%	4	1.96%	4	1.57%	1.5	0.54 %	1.5	0.49 %
Total	385	100.00 %	385	100.00%	385	100.00%	204	100.00%	204	100.00%	254	100.00%	279.375	100.00 %	306	100.00 %

After stirring for 1 h in pH 1.0 hydrochloric acid solution using the 75 rpm paddle method, and found that the dissolution was <1% for all batches, which was consistent with the equilibrium solubility results in pH 1.0 hydrochloric acid solution. The dissolution solution was adjusted to pH 6.8 by continued addition of phosphate and dissolution curve studies were conducted to examine the amount of polyvinylpyrrolidone VA64 needed by Formulations 11, 13, 15, 16 and 17. The results are shown in **FIG. 6**.

The results showed that the higher the dosage of polyvinylpyrrolidone VA64 in 50 mg size COMPOUND I tablets, the better the dissolution effect. 50 mg of polyvinylpyrrolidone VA64 can make the dissolution of 50 mg tablets greater than 90%.

Example 6. The effect of glucosamine

The examination of glucosamine dosage in COMPOUND I tablet formulations was carried out, and the results are shown in **Table 7**, and the glucosamine dosage was examined by Formulations 10, 12, 15 and 16. The dissolution behavior of the above tablets under dissolution conditions (dissolution method of pH 1.0 then pH 6.8) is shown in **FIG. 7**.

Table 9. Investigation of internal and external dosage of crospovidone XL-10

47 Disintegrant	Formulation	Intragranular and extragranular dosages	Dissolution status of tablets at pH 1.0	Dissolution status of tablets at pH 4.5/6.8
Crospovidone XL-10	Formulation 10	Intragranular 10 mg + extragranular 5 mg	Tablets were still intact but cracked by gently touch after 1 h of dissolution.	Very slow dissolved during dissolution
	Formulation 11			
	Formulation 12			
	Formulation 13	Intragranular 8 mg + extragranular 4 mg		
	Formulation 15	Intragranular 8 mg + extragranular 5 mg		
	Formulation 16	Intragranular 15 mg + extragranular 7.5 mg		
	Formulation 17			
	Formulation 21	Intragranular 1 mg + extragranular 22 mg		
	Formulation 24	Intragranular 10 mg + extragranular 10 mg		

Table 10. Composition of Formulation 21 and Formulation 24 Tablets

	Formulation 21		Formulation 24	
Name of drug substance and excipients	**Dosage (mg)**	**Ratio**	**Dosage (mg)**	**Ratio**
Drug substance (intragranular)	50	21.46%	50	25.00%
Polyvinylpyrrolidone VA64 (intragranular)	50	21.46%	50	25.00%
Mannitol (intragranular)	50	21.46%	40	20.00%
PROSOLV SMCC90 (intragranular)	50	21.46%	30	15.00%
Crospovidone XL-10 (intragranular)	1	0.43%	10	5.00%
Sodium stearyl fumarate (intragranular)	9	3.86%	9	4.50%
Crospovidone XL-10 (extragranular)	22	9.44%	10	5.00%
Sodium stearyl fumarate (extragranular)	1	0.43%	1	0.50%
Total	233	100.00%	200	100.00%

The dissolution behavior of Formulation 21 and Formulation 24 tablets was investigated under more stringent dissolution conditions (dissolution method at pH 1.0 followed by pH 6.8), and the results are shown in **FIG. 8**.

The results showed that (1) the amount of disintegrant reached a higher level, but still did not achieve the effect of faster disintegration, which may be related to the properties of COMPOUND I; (2) higher dissolution rate is achieved by adding disintegrant both before and after granulation; and (3) tablets with cross-linked polyvidone XL-10 was more stable in the one-month pilot stability study.

Example 8. Selection of lubricant dosage

In the early study, the target tablet weight was designed as 385 mg (such as in Formulation 10, Formulation 11, and Formulation 12). Due to the large dosage of filler, even if the dosage of sodium stearyl fumarate was controlled at a low level, the dry granulation

Table 12. The raw material and particle size information for a larger proportion of excipients and API size

Name	Manufacturer	Size	Function
API（Intragranular）	Gannex	D90≈42.0 μ M	API
Polyvinylpyrrolidone VA64（Intragranular）	BASF	D90≈100 μ M	Solubilizing effector
Mannitol（200SD）（Intragranular）	Roget, France	Average particle size：approximate 200 μ m	Filler
Mannitol（M100）（Intragranular）	Merck, Germany	Average particle size：approximate 100 μ m	Filler
PROSOLV SMCC90（Intragranular）	JRS	Average particle size：125 μ m	Filler

Example 10. Determination of tablet formulation processes

On the basis of development of the formulation process, the 50 mg and 5 mg COMPOUND I tablets were developed and determined using the dissolution profiles and stability as parameters. The optimized lab-scale formulations of 50 mg and 5 mg are shown in **Table 13-1** and **Table 13-2**. The process control is shown in **Table 14-1** and **Table 14-2**. The difference between 5 mg tablets and 50 mg tablets was only the difference of API dosage. The types and dosage of other excipients were consistent with those of 50 mg tablets, and the process of both were consistent.

Table 13-1 Optimized lab-scale formulation of 50 mg COMPOUND I tablets (Formulation 24)

Ingredient	Theoretical Dosage (g) (1000 Tablets)	Overage	Function
COMPOUND I	50	N/A	Active pharmaceutical ingredient
Silicified microcrystalline cellulose SMCC90	30	N/A	Filler
Polyvinylpyrrolidone VA64	50	N/A	Solubilizer
Mannitol M100	40	N/A	Filler
Crospovidone XL-10	10	N/A	Disintegrant
Sodium stearyl fumarate	9	N/A	Lubricant
Crospovidone XL-10	10	N/A	Disintegrant
Sodium stearyl fumarate	1	N/A	Lubricant
Total weight	200		

Table 13-2 Optimized lab-scale formulation of 5 mg COMPOUND I tablets (Formulation 26)

Ingredient	Theoretical Dosage (g) (1000 Tablets)	Overage	Function
COMPOUND I	5	N/A	Active pharmaceutical ingredient
Silicified microcrystalline cellulose SMCC90	30	N/A	Filler
Polyvinylpyrrolidone VA64	50	N/A	Solubilizer
Mannitol M100	40	N/A	Filler
Crospovidone XL-10	10	N/A	Disintegrant
Sodium stearyl fumarate	9	N/A	Lubricant
Crospovidone XL-10	10	N/A	Disintegrant
Sodium stearyl fumarate	1	N/A	Lubricant
Total weight	155		

Table 14-1 Lab-scale process of 50 mg COMPOUND I tablets (Formulation 24)

Process Step	Process Description
Pretreatment of drug substance and excipients	Silicified microcrystalline cellulose SMCC90, Polyvinylpyrrolidone VA64, mannitol M100, crospovidone XL-10, and sodium stearyl fumarate were all sifted through a 40-mesh sieve and COMPOUND I was sifted through a 30-mesh sieve to remove the possible agglomerates of materials generated during storage.
Pre-blending	The materials were blended manually in a ziplock bag for 10 min.
Dry granulation	A TF-MINI_ITN dry granulator was used for granulation. The roller speed and feed screw speed were adjusted.
Final blending	The materials were blended manually in a ziplock bag for 10 min.
Tableting	A high-speed tablet press machine was used for tableting. The target weight of COMPOUND I tablet was controlled at 200 mg. The weight difference of single COMPOUND I tablets was controlled within ± 7.5%, the average tablet weight difference was controlled within ± 5.0%.

Table 14-2 Lab-scale process of 5 mg COMPOUND I tablets (Formulation 26)

Process Step	Process Description
Pretreatment of drug substance and excipients	Silicified microcrystalline cellulose SMCC90, Polyvinylpyrrolidone VA64, mannitol M100, crospovidone XL-10, and sodium stearyl fumarate were all sifted through a 40-mesh sieve and COMPOUND I was sifted through a 30-mesh sieve to remove the possible agglomerates of materials generated during storage.
Pre-blending	The materials were blended manually in a ziplock bag for 10 min.
Dry granulation	A TF-MINI_ITN dry granulator was used for granulation. The roller speed and feed screw speed were adjusted.
Final blending	The materials were blended manually in a ziplock bag for 10 min.
Tableting	A high-speed tablet press machine was used for tableting. The target weight of COMPOUND I tablet was controlled at 155 mg. The weight difference of single COMPOUND I tablets was controlled within ± 7.5%, the average tablet weight difference was controlled within ± 5.0%.

1. Dissolution study of 50 mg tablets by verified formulation processes

Dissolution profile of 50 mg tablets prepared by optimized formulation (Formulation 24) process was studied in dissolution medium under more stringent dissolution conditions (dissolution method at pH 1.0 followed by pH 6.8) and dissolution method at pH 6.8. The results are shown in **FIGS. 9-10**.