therapeutic drugs include N-acetylcysteine, γ-interferon and pirfenidone (TNF-α inhibitor), colchicine, penicillamine, etc. The clinical efficacy of these drugs remains to be further validated. This technical solution provides an oral pharmaceutical composition of a phosphodiesterase (PDE) inhibitor compound and a preparation method therefor, which composition is intended for the treatment of idiopathic pulmonary fibrosis (IPF) and other related diseases.

[4] Phosphodiesterases (PDEs) are a family of hydrolases that hydrolyze cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), and serve as an important node regulating the levels of cAMP and cGMP. PDEs are classified into three categories: phosphodiesterases specifically hydrolyzing cAMP, including PDE4, PDE7 and PDE8; phosphodiesterases specifically hydrolyzing cGMP, including PDE5, PDE6 and PDE9; phosphodiesterases capable of hydrolyzing both cAMP and cGMP, including PDE1, PDE2, PDE3, PDE10 and PDE11.

[5] PDE4 enzymes are widely expressed in various tissues. They are generally divided into four subtypes: PDE4A, PDE4B, PDE4C and PDE4D, and have the functions including regulation of brain function, monocyte and macrophage function, and vascular smooth muscle cell proliferation. Although PDE4 is expressed in most cells, the catalytic hydrolysis of cAMP in immune cells is primarily dependent on PDE4. Therefore, PDE4 inhibitors may be used in the treatment of a variety of inflammatory diseases, including psoriasis, neuroinflammation, chronic obstructive pulmonary disease (COPD), asthma, ankylosing spondylitis (AS), inflammatory bowel disease (IBD), atopic dermatitis, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), etc.

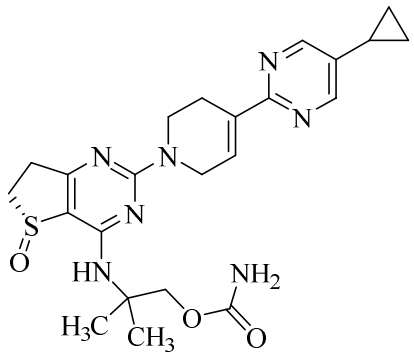
[6] The present invention relates to the field of pharmaceutical preparations, and in particular to an oral pharmaceutical composition of a small molecule phosphodiesterase (PDE) inhibitor compound (I). The present invention further relates to a method for preparing the pharmaceutical composition, and the use of the pharmaceutical composition in a drug for treating diseases or conditions associated with phosphodiesterases (PDEs). Specific solubilization techniques, compositions and preparation methods are used in the preparation technology to obtain a preparation with a high bioavailability, good content uniformity and good stability, which is suitable for industrial-scale production. The preparation is intended for the treatment of idiopathic pulmonary fibrosis and other related diseases, thereby enriching the existing therapeutic options available for such diseases.

[17]In some embodiments, the lubricant is present in the pharmaceutical composition at a mass percentage of 0.5% to 3%.

[18]In some embodiments, the glidant is present in the pharmaceutical composition at a mass percentage of 0% to 5%, preferably 0% to 1%.

[19]The present invention provides an oral pharmaceutical composition, comprising:

a) a compound of formula (I) or a pharmaceutically acceptable salt thereof,



(I)

and

b) a solubilizer and/or an acidity regulator.

[20]In some embodiments, the solubilizer is selected from an ionic surfactant, a nonionic surfactant or a combination thereof, and the nonionic surfactant does not comprise polyethylene glycol-15-hydroxystearate.

[21]In some embodiments, the ionic surfactant is selected from sulfonated castor oil, sodium dodecyl sulfate, sodium hexadecyl sulfate and sodium octadecyl sulfate.

[22]In some embodiments, the nonionic surfactant is selected from Spans (Span 20, Span 40, Span 60, etc.), Tweens (Tween 60, Tween 80, etc.), Myrjs (Myrj 40, Myrj 45, etc.), Brijs (Brij 35 etc.) and poloxamers (poloxamer 188, poloxamer 407, etc.).

[23]In some embodiments, the solubilizer is selected from at least one of sodium hexadecyl sulfate, sodium dodecyl sulfate, poloxamer 188, Tween 80 and Span 60.

[24]In some embodiments, the acidity regulator is selected from at least one of citric acid, fumaric acid, succinic acid, sorbic acid, oxalic acid and ascorbic acid.

[25]In some embodiments, the acidity regulator is selected from at least one of citric acid, fumaric acid, succinic acid, sorbic acid, oxalic acid and ascorbic acid.

[26]In some embodiments, the composition further comprises a filler, a disintegrant, an adhesive and a lubricant.

Solubility test results				
Batch No.	Auxiliary material	Concentration	Solubility (mg/ml)	Fold increase
Y1	SDS	0.5%	0.307	34.1
Y2		1.0%	0.451	50.1
Y3	Fumaric acid	5%	0.217	24.1
Y4		10%	0.246	27.3
Y5	Citric acid	5%	0.454	50.4
Y6		10%	0.479	53.2
Y7	Purified water	/	0.009	1.0

[53]Fumaric acid was selected as the solubilizer to prepare samples, and the effect of the amount of fumaric acid on the preparation was investigated.

	Formulation 1			Formulation 2		
API/auxiliary materials	mg/tablet	Percentage/%	g/70 tablets	mg/tablet	Percentage/%	g/70 tablets
Compound of formula (I)	4.00	5.71	0.280	4.00	5.71	0.280
Mannitol	47.60	68.00	3.332	44.10	63.00	3.087
Microcrystalline cellulose	10.00	14.29	0.700	10.00	14.29	0.700
Fumaric acid	3.50	5.00	0.245	7.00	10.00	0.490
Crospovidone	2.10	3.00	0.147	2.10	3.00	0.147
Hydroxypropyl cellulose	2.10	3.00	0.147	2.10	3.00	0.147
Magnesium stearate	0.70	1.00	0.049	0.70	1.00	0.049
Total	70.00	100.00	4.90	70.00	100.00	4.90

[54]Sodium dodecyl sulfate was selected as the solubilizer to prepare samples, and the effect of the amount thereof on the preparation was investigated.

	Formulation 3			Formulation 4			Formulation 5 (without solubilizer)		
API/auxiliary materials	**mg/tablet**	**Percentage/%**	**g/70 tablets**	**mg/tablet**	**Percentage/%**	**g/70 tablets**	**mg/tablet**	**Percentage/%**	**g/70 tablets**
API	4.00	5.71	0.280	4.00	5.71	0.280	4.00	6.67	0.280
Mannitol	41.10	58.71	2.877	31.10	44.43	2.177	39.8	66.33	2.786
Microcrystalline cellulose	10.00	14.29	0.700	10.00	14.29	0.700	10.8	18	0.756
Sodium dodecyl sulfate	10.00	14.29	0.700	20.00	28.57	1.400	0	0	0
Crospovidone	2.10	3.00	0.147	2.10	3.00	0.147	3.0	5.00	0.21
Hydroxypropyl cellulose	2.10	3.00	0.147	2.10	3.00	0.147	1.80	3.00	0.126
Magnesium stearate	0.70	1.00	0.049	0.70	1.00	0.049	0.60	1.00	0.042
Total	70.00	100.00	4.90	70.00	100.00	4.90	60.00	100.00	4.20

[55]Dissolution profile data for formulation 1 to formulation 5

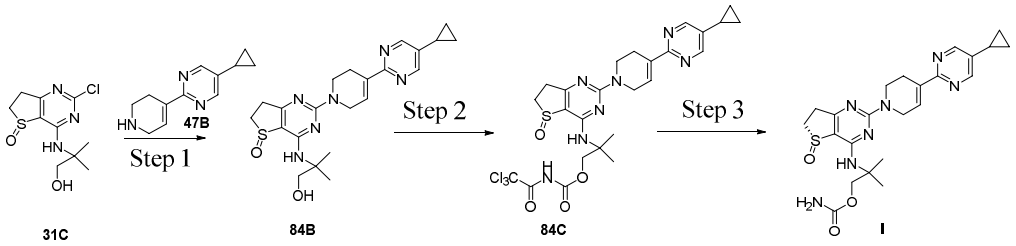
	Formulation 1		Formulation 2		Formulation 3		Formulation 4		Formulation 5	
Time	Dissolution rate	RSD /%	Dissolution rate	RSD /%	Dissolution rate	RSD /%	Dissolution rate	RSD /%	Dissolution rate	RSD /%
5	37.4	-12.1	68.7	-1.8	56.2	-0.6	64.9	0.5	28.0	-2.4
10	68.7	-7.9	80.6	1.0	83.3	-5.0	77.3	1.5	43.0	-1.5
15	84.4	-5.2	85.2	1.4	93.5	-2.4	84.5	3.0	51.0	-0.9
20	87.2	-3.2	86.0	0.0	92.5	-4.5	86.6	4.0	55.1	-1.3
30	89.2	-1.7	87.0	1.3	93.3	-3.1	90.9	1.5	59.9	-2.5
45	90.8	-2.2	87.9	1.2	96.9	-0.9	91.5	2.7	65.6	0.4
60	88.4	-4.8	90.2	2.2	96.5	-3.2	92.1	1.7	66.3	-1.6

[56]Conclusion: The solubilizer sodium dodecyl sulfate and the acidity regulator fumaric acid significantly improve the dissolution profile of the preparation, greatly increasing the dissolution rate thereof. The greater the amount of fumaric acid, the greater the dissolution rate thereof. Favorable dissolution rates are obtained when the amount ratio of sodium dodecyl sulfate to active pharmaceutical ingredient ranges from 2.5 : 1 to 5 : 1.

Example 2 Pharmacokinetic study in dogs

Formulation information:

Capsule	**Formulation 6**		**Formulation 7**		**Formulation 8**	
API/auxiliary materials	mg/tablet	Percentage/%	mg/tablet	Percentage/%	mg/tablet	Percentage/%
API	4.00	4.00	4.00	4.00	4.00	4.00
Mannitol 160C	96.00	96.00	56.00	56.00	16.00	16.00
SDS	0.00	0.00	40.00	40.00	80.00	80.00
Total	100.00	100.00	100.00	100.00	100.00	100.00



[66]Step 1: Compound **31C** (1.0 g, 3.63 mmol) was dissolved in 1,4-dioxane (30 mL), and compound **47B** (880 mg, 4.36 mmol) and N,N-diisopropylethylamine (1.40 g, 10.86 mmol) were added. The mixture was stirred at 90°C overnight under nitrogen atmosphere. After the reaction was completed, the reaction solution was concentrated and subjected to silica gel column chromatography (dichloromethane/methanol (v/v) = 95/5) to obtain compound **84B** (1.6 g, 94%).

[67]LC-MS (ESI): m/z = 441.6 $[M+H]^+$

[68]Step 2: Compound **84B** (1.6 g, 3.63 mmol) was dissolved in dichloromethane (5 mL), and trichloroacetyl isocyanate (820 mg, 4.36 mmol) was added in an ice bath. The mixture was stirred in the ice bath for one hour. The reaction solution was concentrated to obtain compound **84C** (2.28 g, 100%).

[69]Step 3: Compound **84C** (2.28 g, 3.63 mmol) was dissolved in methanol (20 mL), and potassium carbonate (1.51 g, 10.89 mmol) and water (20 mL) were added in an ice bath. The mixture was stirred at room temperature for 2.5 hours. The reaction solution was diluted with water and extracted with dichloromethane. The organic phases were combined, dried, filtered, concentrated, and subjected to SFC chiral resolution to obtain compound (I) (1.3 g, 74%).

[70]Preparation method: instrument: Waters 150 Prep-SFC E, column: Chiralcel OX column (250 mm × 30 mm, 10 μm), mobile phase: (phase A: CO_2, phase B: EtOH (0.1%NH_3•H_2O)); 50% mobile phase B, isocratic elution; flow rate: 100 mL/min, back pressure: 100 bar, column temperature: 25°C, wavelength: 220 nm, cycle time: 7.0 min, sample preparation: sample concentration 10 mg/ml, acetonitrile solution injection: 8 ml each time. Retention time: 1.499 min. After separation, the fraction was dried in a water bath at 35°C using a rotary evaporator to obtain a product. The solvent was dried by a lyophilizer at -80°C to obtain the final product, the compound of formula (I).

[71]^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 2H), 7.19 (d, 1H), 6.70 – 6.40 (m, 3H), 4.46 (s, 2H), 4.30 (s, 2H), 4.00 (t, 2H), 3.48 – 3.38 (m, 1H), 3.28 – 3.23 (m, 1H), 3.01 – 2.92 (m, 1H), 2.92 – 2.82 (m, 1H), 2.67 (s, 2H), 1.98 – 1.88 (m, 1H), 1.46 (d, 6H), 1.10 – 0.96 (m, 2H), 0.91 – 0.77 (m, 2H).

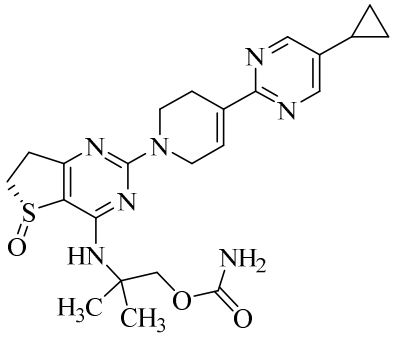
-: not applicable.

[92]Conclusion: The compound as shown in formula (I) of the present invention exhibits excellent pharmacokinetic properties in the PK test in rats.

Claims

1. An oral pharmaceutical composition, comprising:

   an active ingredient, wherein the active ingredient is a compound of formula (I) or a pharmaceutically acceptable salt thereof,



(I)

   wherein the active ingredient is present in the pharmaceutical composition at a mass percentage of 0.1% to 10%, preferably 0.5% to 6.5%.

2. The composition according to claim 1, wherein the composition further comprises at least one of a filler, a disintegrant, an adhesive and a lubricant; optionally, the composition also further comprises a glidant.

3. The composition according to claim 2, wherein the filler is selected from at least one of lactose, microcrystalline cellulose, mannitol, starch, sucrose, dextrin, dicalcium phosphate, calcium sulfate and calcium carbonate;

   the disintegrant is selected from at least one of croscarmellose sodium, crospovidone, sodium carboxymethyl starch and low-substituted hydroxypropyl cellulose;

   the adhesive is selected from at least one of hydroxypropyl cellulose, hypromellose, copovidone, povidone, ethyl cellulose and methyl cellulose;

   the lubricant is selected from at least one of magnesium stearate, calcium stearate, sodium stearyl fumarate and glyceryl behenate;

   the glidant is selected from at least one of silicon dioxide, talc and colloidal silicon dioxide.

4. The composition according to any one of claims 2-3, wherein the disintegrant is present in the pharmaceutical composition at a mass percentage of 1% to 15%, preferably 2% to 5%;

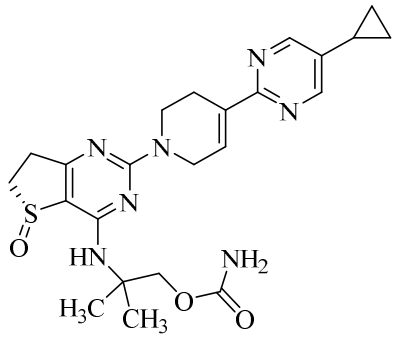
   the adhesive is present in the pharmaceutical composition at a mass percentage of 1% to 20%, preferably 2% to 5%;

   the lubricant is present in the pharmaceutical composition at a mass percentage of 0.5% to 3%;

the glidant is present in the pharmaceutical composition at a mass percentage of 0% to 5%, preferably 0% to 1%.

5. An oral pharmaceutical composition, comprising:

   a) a compound of formula (I) or a pharmaceutically acceptable salt thereof,



(I)

   and

   b) a solubilizer and/or an acidity regulator.

6. The composition according to claim 5, wherein the solubilizer is selected from an ionic surfactant, a nonionic surfactant or a combination thereof, and the nonionic surfactant does not comprise polyethylene glycol-15-hydroxystearate; optionally, the ionic surfactant is selected from sulfonated castor oil, sodium dodecyl sulfate, sodium hexadecyl sulfate and sodium octadecyl sulfate; the nonionic surfactant is selected from Spans, Tweens, Myrjs, Brijs and poloxamers; further, the solubilizer is selected from at least one of sodium hexadecyl sulfate, sodium dodecyl sulfate, poloxamer 188, Tween 80 and Span 60;
   optionally, the acidity regulator is selected from at least one of citric acid, fumaric acid, succinic acid, sorbic acid, oxalic acid and ascorbic acid.

7. The composition according to any one of claims 5-6, wherein the composition further comprises at least one of a filler, a disintegrant, an adhesive and a lubricant; optionally, the composition also further comprises a glidant.

8. The composition according to claim 7, wherein the filler is selected from at least one of lactose, microcrystalline cellulose, mannitol, starch, sucrose, dextrin, dicalcium phosphate, calcium sulfate and calcium carbonate;
   the disintegrant is selected from at least one of croscarmellose sodium, crospovidone, sodium carboxymethyl starch and low-substituted hydroxypropyl cellulose;
   the adhesive is selected from at least one of hydroxypropyl cellulose, hypromellose, copovidone, povidone, ethyl cellulose and methyl cellulose;

the lubricant is selected from at least one of magnesium stearate, calcium stearate, sodium stearyl fumarate and glyceryl behenate;

the glidant is selected from at least one of silicon dioxide, talc and colloidal silicon dioxide.

9. The composition according to any one of claims 5-8, wherein the compound of formula (I) is present in the pharmaceutical composition at a mass percentage of 0.1% to 10%, preferably 0.5% to 6.5%;

the mass ratio of the solubilizer to the compound of formula (I) is 1 : 1 to 50 : 1, preferably 1 : 1 to 20 : 1;

the acidity regulator is present in the pharmaceutical composition at a mass percentage of 1% to 20%;

the disintegrant is present in the pharmaceutical composition at a mass percentage of 1% to 15%, preferably 2% to 5%;

the adhesive is present in the pharmaceutical composition at a mass percentage of 1% to 20%, preferably 2% to 5%;

the lubricant is present in the pharmaceutical composition at a mass percentage of 0.5% to 3%;

the glidant is present in the pharmaceutical composition at a mass percentage of 0% to 5%, preferably 0% to 1%.

10. A pharmaceutical preparation prepared from the oral pharmaceutical composition according to any one of claims 1-9, wherein optionally, the compound of formula (I) is present in a unit preparation thereof in an amount from 0.1 mg to 100 mg, for example, in an amount selected from 0.5 mg, 1 mg, 2 mg, 4 mg, 8 mg or 10 mg.