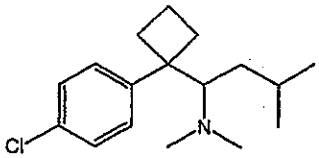
PHARMACEUTICAL COMPOSITION COMPRISING CRYSTALLINE SIBUTRAMINE METHANESULFONATE HEMIHYDRATE

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition for treating or preventing obesity, which comprises crystalline hemihydrate of sibutramine acid-addition salt.

BACKGROUND OF THE INVENTION

Sibutramine, N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine of formula (II);



(II)

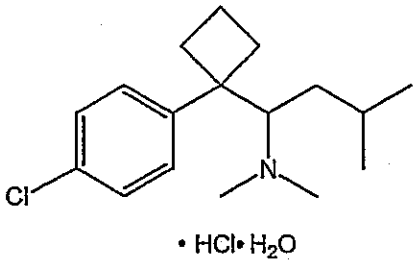
may be used for preventing or treating depression, Parkinson's disease and obesity (*see* GB Patent No. 2,098,602, Korean Patent Publication Nos. 90-00274 and 99-164435, and International Publication No. WO 88/06444). Further, sibutramine may be used for reducing the resistance to insulin or enhancing the resistance to sugar, and for preventing or treating such diseases as gout, hyperuricemia, hyperlipemia, osteoarthritis, anxiety disorder, somnipathy, sexual dysfunction, chronic fatigue syndrome and cholelithiasis (*see* US Patent Nos. 6,174,925, 5,459,164, 6,187,820, 6,162,831, 6,232,347, 6,355,685, 6,365,631, 6,376,554, 6,376,551 and 6,376,552).

However, since sibutramine has a low melting point, it is used as an acid-addition salt in the pharmaceutical application.

GB Patent No. 2,098,302 and Korean Patent Publication No. 90-00274

disclose methods for preparing sibutramine and an anhydrous hydrochloride form thereof as a pharmaceutically acceptable acid-addition salt. However, anhydrous sibutramine hydrochloride is highly hygroscopic. Accordingly, it is difficult to use anhydrous sibutramine hydrochloride in a pharmaceutical composition.

In order to solve the above problem, non-hygroscopic sibutramine hydrochloride monohydrate of formula (IV) was developed (*see* GB Patent No. 2,184,122 and Korean Patent Publication No. 94-08913), e.g., for treating obesity.



(IV)

However, sibutramine hydrochloride monohydrate of formula (IV) for treating obesity, e.g., Meridia and Reductil, has a relatively low solubility in water, for example 2.9 mg/ml at pH 5.2, which does not meet the lowest limit of the solubility desired of an active ingredient of a pharmaceutical composition *(see* Merck Index, 13th Ed, p1522).

Accordingly, there has been a need to develop a novel salt or hydrate of crystalline sibutramine, which is suitable for use in a pharmaceutical composition. The present inventors have therefore endeavored to develop sibutramine methanesulfonate hemihydrate, which has a high solubility in water and is non-hygroscopic, being stable under a high temperature/humidity condition.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a pharmaceutical composition for treating or preventing obesity, comprising an acid-addition salt of sibutramine which has a high solubility in water and are stable under a high humidity/temperature condition.

It is another object of the present invention to provide a method for the preparation thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

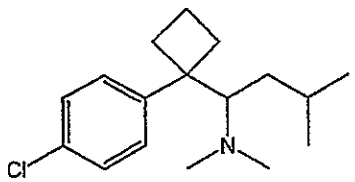
The above and other objects and features of the present invention will become apparent from the following description of the invention, when taken in conjunction with the accompanying drawings, which respectively show:

Figs. 1 to 3: Powder X-ray diffraction spectra of the crystalline sibutramine methanesulfonate hemihydrate of formula (I) according to the present invention, anhydrous sibutramine methanesulfonate of formula (II), and sibutramine methanesulfonate monohydrate of formula (IV), respectively;

Figs. 4 and 5: Differential scanning calorimeter thermograms of the crystalline sibutramine methanesulfonate hemihydrate of formula (I) in according to the present invention, and anhydrous sibutramine methanesulfonate of formula (II), respectively; and

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a pharmaceutical composition for treating or preventing obesity, comprising the novel crystalline sibutramine methanesulfonate hemihydrate of formula (I), which has a high solubility in water and high stability under a high humidity/temperature condition.



$\cdot CH_3SO_3H \cdot 1/2H_2O$ (I)

Further, the present invention provides crystalline sibutramine methanesulfonate hemihydrate of formula (I) and a method for the preparation thereof.

Herein, the term "sibutramine" refers to racemic sibutramine, unless otherwise indicated.

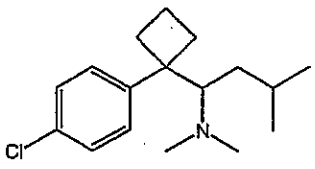
The crystalline sibutramine methanesulfonate hemihydrate of formula (I) has a high solubility in water, and is stable under a high humidity/temperature condition and non-hygroscopic, which is suitable for use in a pharmaceutical composition.

The 2θ values of major peaks observed in X-ray diffraction spectrum of the crystalline sibutramine methanesulfonate hemihydrate of formula (I) of the present invention are:

8.2±0.2, 10.8±0.2, 11.7±0.2, 12.0±0.2, 12.3±0.2, 15.8±0.2, 16.4±0.2, 17.4±0.2, 17.4±0.2, 17.8±0.2, 19.0±0.2, 21.2±0.2, 21.9±0.2, 22.2±0.2, 22.8±0.2, 23.3±0.2, 24.4±0.2, 24.9±0.2, 25.3±0.2, 25.6±0.2 and 26.8±0.2.

The present invention also provides two methods for preparing the crystalline sibutramine methanesulfonate hemihydrate of formula (I).

First, the crystalline sibutramine methanesulfonate hemihydrate of formula (I) may be prepared by reacting sibutramine of formula (II) with methanesulfonic acid in a mixture of an organic solvent and water (hereinafter, "the 1st method").



(II)

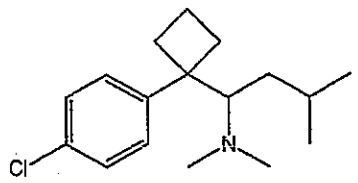
In the 1st method, methanesulfonic acid may be employed in an amount ranging from 1 to 2 mole equivalents, preferably from 1 to 1.2 mole equivalents, based on 1 mole of sibutramine of formula (II). Generally, methanesulfonic acid is dropwisely added to the substrate, which may be neat sibutramine or a solution thereof dissolved in an organic solvent.

The organic solvent may be an ester, an ether, a ketone, or a mixture thereof. The ester may be selected from the group consisting of ethyl acetate, n-

propyl acetate, isopropyl acetate and n-butyl acetate; the ether, from the group consisting of diethyl ether, diisopropyl ether and t-butyl methyl ether; and the ketone, from the group consisting of acetone, methyl ethyl ketone and methyl isobutyl ketone. When a mixture of a ketone and ether is used, the ketone to ether ratio is preferably in ranging of 1:0.5 to 1:1.5, more preferably 1:2 to 1:3.

In this method, water may be employed in an amount ranging from 0.5 to 5 mole equivalents, based on 1 mole of sibutramine of formula (II), and the reaction is performed at a reaction temperature ranging from 0℃ to the boiling point of the solvent, preferably from 15 to 35℃, for 0.5 to 5hrs after adding methanesulfonic acid.

Second, the crystalline sibutramine methanesulfonate hemihydrate of formula (I) may be prepared by (i) reacting sibutramine of formula (II) with methanesulfonic acid in an anhydrous organic solvent to obtain anhydrous sibutramine methanesulfonate of formula (III); and (ii) bringing the sibutramine methanesulfonate of formula (III) into contact with water in an organic solvent (hereinafter, "the 2nd method").



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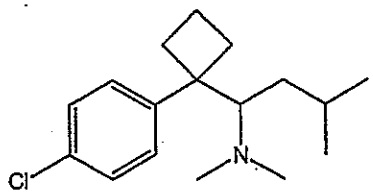


(III)

In the 2nd method, methanesulfonic acid may be employed in an amount ranging from 1 to 2 mole equivalents, preferably from 1 to 1.2 mole equivalents, based on 1 mole of the sibutramine of formula (II). Generally, methanesulfonic acid is dropwisely added to neat sibutramine of formula (II) or a solution thereof dissolved in an organic solvent.

The organic solvent may be an ester, a ketone, an ether, toluene, or a mixture thereof. The ester may be selected from the group consisting of ethyl acetate, n-propyl acetate, isopropyl acetate and n-butyl acetate; the ketone, from the group consisting of acetone, methyl ethyl ketone and methyl isobutyl ketone; and the ether, from the group consisting of ethyl ether, isopropyl ether and t-butyl methyl ether.

When the organic solvent is a mixture of a ketone and ether, the ketone to ether ratio is preferably in the range of from 1:0.5 to 1:1.5, more preferably from 1:2 to 1:3.

In the 2nd method, water may be employed in an amount ranging from 0.5 to 5 mole equivalents, based on 1 mole of sibutramine of formula (II), and the reaction is performed at a temperature ranging from 0℃ to the boiling point of the solvent, preferably from 15 to 35℃, for 0.5 to 5hrs after adding methanesulfonic acid. It is preferred that anhydrous sibutramine methanesulfonate of formula (III) is brought into contact with water for 2 hrs to 5 days.

Crystalline sibutramine methanesulfonate hemihydrate of formula (I) prepared according to the 1st or the 2nd method has a high solubility in water, and is non-hygroscopic and highly stable under a high humidity/temperature condition.

Examined for a comparative purpose was whether crystalline sibutramine methanesulfonate hemihydrate can be prepared from either of the enantiomers of sibutramine, (+)- and (-)-sibutramine. However, crystalline sibutramine methanesulfonate hemihydrate failed to form from (+)- and (-)-sibutramine.

Specifically, examined was whether crystalline sibutramine methanesulfonate hemihydrate can be prepared from (+)- and (-)-sibutramine separated from racemic sibutramine. Racemic sibutramine was optically resolved to obtain (+)- and (-)-sibutramine, according to the method disclosed in US Patent Publication US No. 2002/0006963, US 2002/0006964 or International Patent publication No. WO 00/10551. Then, the (+)- and (-)-sibutramine were

each treated according to the method of the present invention to see whether crystalline methanesulfonate hemihydrate can be prepared therefrom.

However, the (-)- or (+)-sibutramine failed to give crystalline methanesulfonate hemihydrate when the method according to the present invention is employed. Accordingly, the crystalline sibutramine methanesulfonate hemihydrate of the present invention is not easily conceivable by those skilled in the art.

The present invention includes a pharmaceutical composition for treating obesity and diseases related therewith, which comprises the crystalline sibutramine methanesulfonate hemihydrate of formula (I) as an active ingredient, and a pharmaceutically acceptable carrier, diluent, excipient or other additive.

Preferably, the pharmaceutical composition of the present invention is administrated as an oral formulation in the form of a tablet or capsule.

Tablets may be prepared by mixing the active ingredient with a carrier, diluent or excipient. Examples of the carrier, excipient and diluent employed in the pharmaceutical composition of the present invention are a disintegrator (e.g., starch, sugar and mannitol); a filler and extender (e.g., calcium phosphate and silicate derivatives); a binder (e.g., carboxymethyl cellulose and a derivative thereof, gelatin, and polyvinyl pyrrolidone); and a lubricant (e.g., talc, calcium stearate and magnesium stearate, and polyethylene glycol(s)).

Hard or soft capsules containing the active ingredient may be prepared without or with an additive such as a carrier, diluent and excipient, according to a conventional method.

Preferably, the effective amount of the crystalline sibutramine methanesulfonate hemihydrate of formula (I) in the inventive pharmaceutical composition ranges from 1 to 50 weight part, based on 250 weight part of the composition.

For example, the pharmaceutical composition may be prepared to contain 10mg of crystalline sibutramine methanesulfonate hemihydrate of formula (I), 115mg of fine crystalline cellulose, 115mg of lactose, 5mg of silicon dioxide and

5mg of magnesium stearate. However, it should be understood that the amount of the active ingredient actually administered ought to be determined in light of various relevant factors including the condition of the patient to be treated, the age and weight, and the severity of the patient's symptom; and, therefore, the above composition ratio dose should not be intended to limit the scope of the invention in any way.

The crystalline sibutramine methanesulfonate hemihydrate of the present invention can be used for treating or preventing obesity.

The following Examples are intended to further illustrate the present invention without limiting its scope.

Preparation Example 1: Preparation of sibutramine hydrochloride monohydrate of formula (IV)

Anhydrous sibutramine hydrochloride was prepared according to the method disclosed in GB Patent No. 2,098,602 or Korean Patent Publication No. 90-00274, and 10g thereof was dissolved in a boiling mixture of acetone (110ml) and water (1.2ml), hot-filtered, and distillated to concentrate the filtrate, according to the method disclosed in GB Patent No. 2,184,122 or Korean Patent Publication No. 94-08913.

The concentrate was cooled and filtered to obtain crystals, and the crystals were dried under a vacuum to obtain 9.2g of the title compound (Yield: 87%).

Example 1: Preparation of sibutramine methanesulfonate hemihydrate of formula (I) by the 1st method

1-1) Procedure 1

30.0g of sibutramine of formula (II) was dissolved in 120ml of isopropyl acetate, 1.94ml of water was added, and then 10.9g of methanesulfonic acid was dropwisely added thereto. The reaction mixture was stirred for 1hr, cooled to 0℃, again stirred for about 2hrs, and then filtered to obtain crystals. The crystals

were sequentially washed with 30ml of isopropyl acetate and 30ml of isopropyl ether, and then dried at 50℃ to obtain 38.46g of the title compound as a white solid (Yield: 92.5%).

Melting point: 164~165℃ (shrunk at about 130℃);

Water content: 2.35% (Theoretical value: 2.34%); and

^{1}H-NMR (δ, DMSO-d6): 8.5(1H, br. s), 7.7~7.2(4H, dd), 3.7(1H, t), 2.8(3H, d), 2.5(2H, d), 2.4(3H, s), 2.3(2H, d), 2.1(3H, d), 1.9(1H, m), 1.7~1.6(2H, m), 1.3(2H, t), 1.0(6H, t).

1-2) Procedure 2

10.0g of sibutramine of formula (II) was dissolved in a mixture of 40ml of ethyl acetate and 40ml of t-butyl methyl ether, 0.97ml of water was added, and then 3.8g of methanesulfonic acid was dropwisely added thereto. The reaction mixture was stirred for 1hr, cooled to 0℃, again stirred for about 2hrs, and then filtered to obtain crystals. The crystals were sequentially washed with a mixture of 30ml of isopropyl acetate and 30ml of isopropyl ether, and then dried at 50℃ to obtain 12.1g of the title compound as a white solid (Yield: 88%). The water content of the title compound was 2.38% (Theoretical value: 2.34%), and the melting point and the ^{1}H-NMR data thereof were the same as those observed in 1-1).

1-3) Procedure 3

11.7g of the title compound was prepared by repeating the procedure of the above 1-2) (Yield: 85%), except for employing 30ml of acetone and 60ml of t-butyl methyl ether, instead of 40ml of ethyl acetate and 40ml of t-butyl methyl ether. The water content of the title compound was 2.27% (Theoretical value: 2.34%), and the melting point and the ^{1}H-NMR data thereof were the same as those observed in 1-1).

Example 2: Preparation of sibutramine methanesulfonate hemihydrate of formula (I) by 2nd method

2-1) Preparation of anhydrous sibutramine methanesulfonate of formula (III) (step 1 of the 2nd method)

2-1-1) Procedure 1

10.0g of sibutramine of formula (II) was dissolved in 70ml of acetone, and then 3.75g of methanesulfonic acid was dropwisely added at room temperature. The reaction suspension was stirred for 1hr, cooled to 0℃, again stirred for about 2hrs, and then filtered to obtain crystals. The crystals were washed with 30ml of ether, and then dried at 50℃ to obtain 11.7g of the title compound as a white solid (Yield: 88%).

Melting point: 164~165℃;

Water content: 0.2%; and

^{1}H-NMR (δ, DMSO-d6): 8.5(1H, br. s), 7.5(4H, dd), 3.7(1H, t), 2.8(3H, d), 2.5(2H, d), 2.4(3H, s), 2.3(2H, d), 2.1(3H, d), 1.9(1H, m), 1.7~1.6(2H, m), 1.4(2H, t), 1.0(6H, t).

2-1-2) Procedure 2

10.0g of sibutramine of formula (II) was dissolved in 80ml of toluene, and then 3.75g of methanesulfonic acid was dropwisely added at room temperature. The reaction suspension was stirred for 2hrs, cooled to 0℃, stirred for about 2hrs, and then filtered to obtain crystals. The crystals were washed with 20ml of ether and then dried at 50℃ to obtain 12.8g of the title compound as a white solid (Yield: 95). The water content of the title compound was 0.1%, and the melting point and the ^{1}H-NMR data thereof were the same as those observed in 2-1-1).

2-1-3) Procedure 3

12.5g of the title compound as a white solid was prepared by repeating the procedure of the above 2-1-2) (Yield: 93%), except for using isopropyl acetate instead of toluene. The water content of the product was 2.27% (Theoretical value: 2.34%), and the melting point and the ^{1}H-NMR data thereof were the same as those observed in 2-1-1).

2-2) Preparation of sibutramine methanesulfonate hemihydrate of formula (I) (step 2 of the 2nd method)

2-2-1) Procedure 1

5.0g of anhydrous sibutramine methanesulfonate of formula (III) prepared in any one of 2-1-1) to 2-1-3) was dissolved in a mixture of 50ml of ether and 25ml of acetone, and then 0.72ml of water was added thereto. The reaction mixture was stirred for 18hrs at room temperature, and then filtered to obtain crystals. The crystals were washed with 10ml of a mixture of ether and acetone (2:1 v/v), dried at 50℃ to obtain 3.89g of the title compound as a white solid (Yield: 76%). The water content of the obtained compound was 2.30% (Theoretical value: 2.34%), and the melting point and the ^{1}H-NMR data thereof was the same as those observed in 1-1).

2-2-2) Procedure 2

10.0g of anhydrous sibutramine methanesulfonate of formula (III) prepared in any one of 2-1-1) to 2-1-3) was dissolved in a mixture of 100ml of ether and 40ml of methyl isobutyl ketone, and then 1.44ml of water was added thereto. The reaction mixture was stirred for 24hrs at room temperature and then filtered to obtain crystals. The crystals were washed with 30ml of a mixture of ether and methyl ethyl ketone (2:1 v/v), dried at 50℃ under warm wind to obtain 7.5g of the title compound as a white solid (Yield: 73%). The water content of the obtained

compound was 2.32% (Theoretical value: 2.34%), and the melting point and the ^{1}H-NMR data thereof were the same as those observed in 1-1).

Example 3: Qualitative analysis of the structure of crystalline sibutramine methanesulfonate hemihydrate of formula (I)

Powder X-ray diffraction data and a differential scanning calorimeter thermogram showed that crystal shape of sibutramine methanesulfonate hemihydrate of formula (I) was different from either anhydrous sibutramine methanesulfonate of formula (II) or sibutramine hydrochloride monohydrate of formula (IV) (*see* Figs. 1 to 5).

The powder X-ray diffraction spectrum of sibutramine methanesulfonate hemihydrate of formula (I) showed characteristic peaks (Fig. 1), which are represented in Table 1. In table 1, "2Θ ", "d" and "I/I_o" mean the diffraction angel, the distance between crystal facets, and the relative peak intensity, respectively.

Table 1

2θ(±0.2)	d	I/I_o	2θ	d	I/I_o
8.2	10.8	868	21.2	4.19	785
10.8	8.17	218	21.9	4.06	646
11.7	7.53	210	22.2	4.00	315
12.0	7.36	276	22.8	3.90	286
12.3	7.19	661	23.3	3.81	456
15.8	5.61	716	24.4	3.65	537
16.4	5.39	725	24.9	3.58	596
17.4	5.10	792	25.3	3.52	322
17.8	4.97	498	25.6	3.47	351
19.0	4.68	556	26.8	3.33	1000

Experimental Example 1: Solubility in water

Sibutramine methanesulfonate hemihydrate of formula (I) and sibutramine hydrochloride monohydrate were each dissolved to the saturation point at pH 5.2,

and then subjected to high performance liquid chromatography (HPLC) to determine the dissolved amount (based on water-free of sibutramine). The results are shown in Table 2.

Table 2.

Compound	Solubility in water (mg/ml, pH5.2)
Sibutramine hydrochloride monohydrate of formula (VI)	2.8
Sibutramine methanesulfonate hemihydrate of formula (I)	2,500

As can be seen in Table 2, sibutramine methanesulfonate hemihydrate of formula (I) had a markedly higher solubility in water than that of sibutramine hydrochloride monohydrate of formula (IV).

Experimental Example 2: Stability under a high humidity/temperature condition

The thermal stability of crystalline methanesulfonate hemihydrate of formula (I) during a long term storage was compared with that of the sibutramine hydrochloride monohydrate of formula (IV). The amounts of unchanged crystalline methanesulfonate hemihydrate of formula (I) and sibutramine hydrochloride monohydrate of formula (IV) at 60℃ after 1, 2, 3 and 6 months are shown in Table 3.

Table 3.

Compound	Initial	Residual rate after 1 month	Residual rate after 2 months	Residual rate after 3 months	Residual rate after 6 months
Sibutramine hydrochloride monohydrate of formula (IV)	1.000	1.000	0.999	0.999	0.992
Sibutramine methanesulfonate hemihydrate of formula (I)	1.000	1.001	0.999	0.999	1.000

The above result shows that crystalline sibutramine hemihydrate is as stable as sibutramine hydrochloride monohydrate.

Experimental Example 3: Non-hydroscopic test

Crystalline sibutramine methanesulfonate hemihydrate of formula (I), sibutramine hydrochloride monohydrate (IV) and anhydrous sibutramine methanesulfonate were each exposed to a high temperature/humidity condition of 40℃ and 75% relative humidity for 1, 2, and 5 days, and the water content thereof was measured by employing Kaal-Fisher moisture analyzer. The results are shown in Table 4.

A similar series of experiments were conducted at 40℃ and 10% relative humidity, in order to examine whether the respective compounds are stable under a relatively dry condition.

Table 4: water-content (% by weight)

Temperature(℃) Relative humidity (℃)	Storage time (day)	Sibutramine methanesulfonate of formula (I)	Sibutramine hydrochloride monohydrate of formula (IV)	Anhydrous sibutramine methanesulfonate of formula (II)
40℃ 75%	1	2.27	5.40	0.60
	2	2.30	5.45	2.20
	5	2.30	5.48	2.25
40℃ 10%	1	2.27	5.40	0.60
	2	2.25	5.36	0.71
	5	2.26	5.36	0.70

As can be seen in Table 4, crystalline sibutramine methanesulfonate hemihydrate of formula (I) is non-hygroscopic under a high humidity condition, while it does not release the water of crystallization under a dry condition.

Experimental Example 4: Weight loss effect

16 each of overweight Zuker rats (fa/fa) and thin Zuker rats (Fa/Fa) were

divided into drug-administrating and control groups (8 rats per group), and the weight of each rat was measured prior to the test. A 3mg/kg dose of crystalline sibutramine methanesulfonate hemihydrate was administrated to each rat of the drug-administrating groups, whiling the vehicle was administrated to those of the control groups, everyday for 21days. During the period, rats were allowed free access to high-fat food, and the average weights of the drug-administrating and control groups were determined in order to calculate the weight gain and loss.

Table 5

	Overweight Zuker rats		Thin Zuker rats	
	the drug-administrating group	the control group	the drug-administrating group	the control group
The average weigh before test (g: A)	332.2	333.2	245.0	244.8
The average weight after test (g: B)	455.6	486.2	303.4	323.6
Weight gain (g: B-A)	123.4	153.0	58.4	78.8
Weight loss effect (g: (Gain in weight of the control group)-(Gain in weight of the drug-administrating group))	29.6		20.4	

As can be shown in Table 5, the group administrated with crystalline methanesulfonate hemihydrate of formula (I) showed a remarkable weight loss effect, as compared with the control group. Accordingly, it was demonstrated that crystalline methanesulfonate hemihydrate of formula (I) is available for treating or preventing obesity.

Comparative Example: Attempted preparation of (+)- and (-)-sibutramine methanesulfonate hemihydrate

(1) Optical resolution of sibutramine of formula (II) (preparation of (+)- and

(-)-sibutramine of formula (II))

12.3g of racemic sibutramine was dissolved in 85ml of ethyl acetate, L-DBTA dissolved in 85ml of ethyl acetate was added thereto. The reaction mixture was heated under reflux, cooled to room temperature and then filtered to obtain crystals (ee: about 85%). And then, the crystals were suspended in 220ml of ethyl acetate, and heated under reflux to obtain solids. The solids were recrystallized from 450ml of isopropyl alcohol to obtain L-DBTA salt of (-)-sibutramine (ee: ≥ 99.3%). The L-DBTA salt of (-)-sibutramine was neutralized with saturated sodium bicarbonate, and then extracted with chloroform to obtain (-)-sibutramine free base.

The filtrate obtained by filtration after reacting with L-DBTA was neutralized to pH 8.5 with sodium hydroxide, and then extracted with chloroform to obtain (+)-sibutramine, which was nearly pure (+)-isomer. D-DBTA was added thereto to obtain crystals and the crystals were recrystallized from 450ml of isopropyl alcohol to obtain D-DBTA salt of (+)-sibutramine (ee: ≥ 99.3%). The D-DBTA salt of (-)-sibutramine was neutralized to pH 8.5 with saturated sodium bicarbonate, and then extracted with chloroform to obtain (+)-sibutramine free base.

(2) Preparation of (+) and (-)-sibutramine methanesulfonate

(+)- and (-)-sibutramine free bases prepared in above (1) were treated according to the same method as that described in 2-1-2) of Example 2 to prepare the respective anhydrous methanesulfonate.

(+)-sibutramine methanesulfonate: m.p. 156.5~157.5℃, water-content 0.30%;
(-)-sibutramine methanesulfonate: m.p. 156.5~157.5℃, water-content 0.05%.

(3) Attempt to prepare (+)- and (-)-sibutramine methanesulfonate hemihydrate

Anhydrous (+)- and (-)-sibutramine methanesulfonate prepared in (2) were each treated according to the same method as that described in 2-2) of Example 2. However, no crystal formation was observed.

Accordingly, the solvent of (+)- or (-)-sibutramine methanesulfonate was replaced with toluene to induce crystal formulation. However, the crystals obtained had the same melting points/water-contents as those of anhydrous (+)- and (-)-sibutramine methanesulfonate prepared in above (2), respectively.

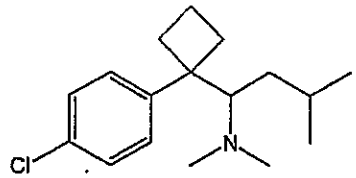
Further, anhydrous (+)- and (-)-sibutramine methanesulfonate were each placed for 1 day at room temperature under 75% relative humidity. Each melted within 2 hours, and became a transparent liquid in 1 day.

The above results showed that sibutramine methanesulfonate hemihydrate of formula (I) cannot be prepared from either enantiomer.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for treating or preventing obesity, comprising the crystalline sibutramine methanesulfonate hemihydrate of formula (I).



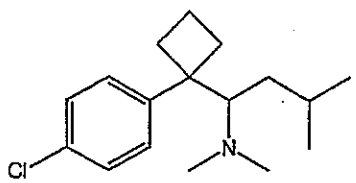
• CH_3SO_3H• 1/2H_2O (I)

2. The pharmaceutical composition of claim 1, wherein the 2θ values of the major peaks in the X-ray diffraction spectrum of the crystalline sibutramine methanesulfonate hemihydrate are:
8.2±0.2, 10.8±0.2, 11.7±0.2, 12.0±0.2, 12.3±0.2, 15.8±0.2, 16.4±0.2, 17.4±0.2, 17.4±0.2, 17.8±0.2, 19.0±0.2, 21.2±0.2, 21.9±0.2, 22.2±0.2, 22.8±0.2, 23.3±0.2, 24.4±0.2, 24.9±0.2, 25.3±0.2, 25.6±0.2 and 26.8±0.2.

3. The pharmaceutical composition of claim 1 or 2, further comprising a pharmaceutically acceptable carrier, diluent or excipient.

4. The pharmaceutical composition of claim 1, wherein the crystalline sibutramine methanesulfonate hemihydrate of formula (I) is present in an amount ranging form 1 to 50mg.

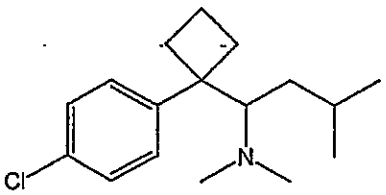
5. The crystalline sibutramine methanesulfonate hemihydrate of formula (I).



• CH_3SO_3H• 1/2H_2O (I)

6. The crystalline sibutramine methanesulfonate hemihydrate of formula (I) of claim 5, of which the 2θ values of the major peaks in the X-ray diffraction spectrum are:
8.2±0.2, 10.8±0.2, 11.7±0.2, 12.0±0.2, 12.3±0.2, 15.8±0.2, 16.4±0.2, 17.4±0.2, 17.4±0.2, 17.8±0.2, 19.0±0.2, 21.2±0.2, 21.9±0.2, 22.2±0.2, 22.8±0.2, 23.3±0.2, 24.4±0.2, 24.9±0.2, 25.3±0.2, 25.6±0.2 and 26.8±0.2.

7. A method of preparing the crystalline sibutramine methanesulfonate hemihydrate according to claim 5 or 6, which comprises reacting sibutramine of formula (II) with methanesulfonic acid dissolved in a mixture of an organic solvent and water.



(II)

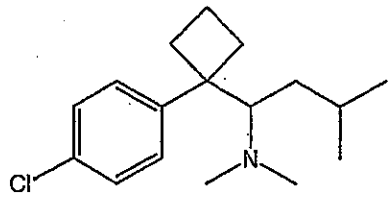
8. The method of claim 7, wherein methanesulfonic acid is employed in an amount ranging from 1 to 2 mole equivalents, based on 1 mole of sibutramine of formula (II).

9. The method of claim 7, wherein water is employed in an amount ranging from 0.5 to 5 mole equivalents, based on 1 mole of sibutramine of formula (II).

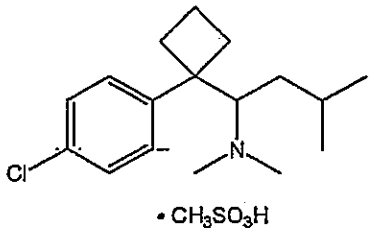
10. The method of claim 7, wherein the organic solvent is an ester selected from the group consisting of ethyl acetate, n-propyl acetate, isopropyl acetate and n-butyl acetate; an ether selected from the group consisting of diethyl ether, diisopropyl ether and t-butyl methyl ether; a ketone selected from the group consisting of acetone, methyl ethyl ketone; or a mixture thereof.

11. A method of preparing the crystalline sibutramine methanesulfonate

hemihydrate according to claim 5 or 6, which comprises (i) reacting sibutramine of formula (II) with methanesulfonic acid in an anhydrous organic solvent to obtain anhydrous sibutramine methanesulfonate of formula (III); and (ii) bringing the sibutramine methanesulfonate of formula (III) into contact with water in an organic solvent.



(II)



(III)

12. The method of claim 11, wherein methanesulfonic acid is employed in an amount ranging from 1 to 2 mole equivalents, based on 1 mole of sibutramine of formula (II).

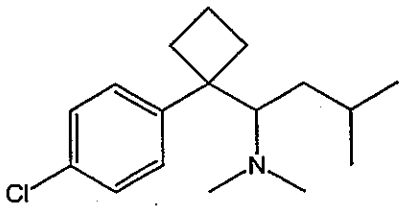
13. The method of claim 11, wherein water is employed in an amount ranging from 0.5 to 5 mole equivalents, based on 1 mole of anhydrous sibutramine methanesulfonate of formula (III).

14. The method of claim 11, wherein the anhydrous organic solvent of step (i) is an ester selected from the group consisting of ethyl acetate, n-propyl acetate, isopropyl acetate and n-butyl acetate; a ketone solvent selected from the group consisting of acetone, methyl ethyl ketone and methyl isobutyl ketone; an ether selected from the group consisting of ethyl ether, isopropyl ether and t-butyl methyl ether; toluene; or a mixture thereof.

15. The method of claim 11, wherein the organic solvent of step (ii) is an ester

selected from the group consisting of ethyl acetate, n-propyl acetate, isopropyl acetate and n-butyl acetate; an ether selected from the group consisting of diethyl ether, diisopropyl ether and t-butyl methyl ether; a ketone selected from the group consisting of acetone, methyl ethyl ketone and methyl isobutyl ketone; or a mixture thereof.

16. (New) A use of the crystalline sibutramine methanesulfonate hemihydrate of formula (I) in the manufacture of a medicament for treating or preventing obesity.



$\cdot CH_3SO_3H \cdot 1/2H_2O$ (I)