SUSTAINED-RELEASE PREPARATION OF IVABRADINE OR PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

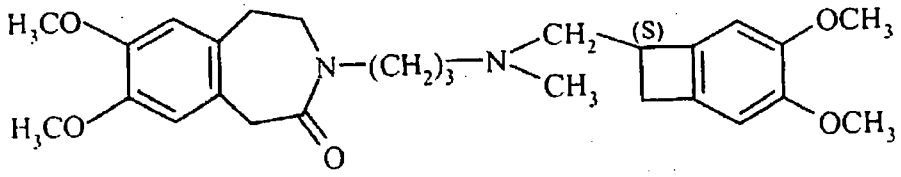
FIELD OF THE INVENTION

The present invention is related to a sustained-release preparation of ivabradine or pharmaceutical acceptable salts thereof.

BACKGROUND OF THE INVENTION

Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in the patients with normal sinus rhythm who have a contraindication or intolerance to beta-blockers.

Ivabradine ,7,8-dimethoxy-3-(3-[[(1S)(4,5-dimethoxybenzocyclobutan-1-yl)methyl]-methylamino]propyl)-1,3,4,5-tetrahydro-2H-benzazepin-2-one,with a formula of $C_{27}H_{36}N_2O_5$,can be represented by the following general formula.



Ivabradine is the first pure heart rate-lowering agent and acts by selective inhibition of the cardiac pacemaker IF current that controls the spontaneous diastolic depolarization in the sinus node and regulates heart rate. Ivabradine's effects are selective to the sinus node and the new agent has no effect on intracardiac conduction, myocardial contractility or ventricular repolarization .Unlike beta-blockers, the most common current treatment for angina, ivabradine is free from sexual disturbances, respiratory side effects caused by constriction or spasm of the airways, bradycardia or rebound phenomena. Now it is generally believed that the heart rate-lowering is an important way of prevention and treatment of angina, this product has opened up a promising new way for the treatment of angina. It is one of the most significant advances in the past 20 years in the treatment of cardiovascular disease.

This invention provides an effective and significant, dose-dependent reduction in heart rate, which is also reflected in a reduction in the rate pressure product leading to a myocardial oxygen consumption. A large clinical program including almost 5000 patients has demonstrated the efficacy and tolerability of ivabradine. The antiangina I and anti-ischemic efficacy of ivabradine was evaluated using a standardized exercise tolerance test in four double-blind randomized trials(two versus placebo, and one each

versus the beta-blocker atenolol and the calcium channel blocker amlodipine)involving 3222 patients with chronic stable angina. Ivabradine (5mg and 7.5mg twice daily) was associated with a significant decrease in angina attacks, and the twice-daily dosage regimen provided uniform efficacy over 24 hours. A sustained reduction in heart rate was demonstrated in patients for at least one year (n=713) and no rebound effected occurred following the withdrawal of treatment. Moreover, no influence on glucose or lipid metabolism was observed.

At present the rapid release preparations of ivabradine hydrochloride are for marketing. Ivabradine is rapidly and almost completely absorbed after oral administration with a peak plasma level reached in about 1 hour under fasting condition. Ivabradine is approximately 70% plasma protein bound and the volume of distribution at steady state is close to 100L in patients. The maximum plasma concentration following chronic administration at the recommended dose of 5mg twice daily is 22ng/ml (CV=29%), the average plasma concentration is 10ng/ml (CV=38%) at steady state. Ivabradine is extensively metabolized by the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4) only. The major active metabolite is N-demethylated derivative. Ivabradine is eliminated with a main half-life of 2 hours (70~75% of the AUC) in plasma and an effective half-life of 11 hours. The total clearance is about 400ml/min and the renal clearance is about 70ml/min. Excretion of metabolites occurs to a similar extent via faeces and urine. About 4% of an oral dose is excreted unchanged in urine.

The kinetics of ivabradine is linear over an oral dose range of 0.5mg~24mg. The heart rate decreases almost linearly with increasing ivabradine and its main metabolite plasma concentration for dose of up to 15~20mg twice daily. At high doses, the decrease in heart rate is no longer proportional to ivabradine plasma concentrations. When ivabradine is given in combination with strong CYP3A4 inhibitors may results in an excessive decrease in heart rate although this risk reduced with moderate CYP3A4 inhibitor.

When the rapid release preparations of ivabradine hydrochloride are used clinically, the following phenomenons may occur, the blood medicine concentration increases so fast that the heart rate decreases too fast (heart rate decreases persistently below 50 beats per minute) or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension. When the plasma concentration is too high, there is side effects, while if it is too low, below the therapeutic concentration, there will be no therapeutic effects.

To reduce the peak-valley phenomenon of the blood medicine concentration of ivabradine, that causes the short increasing of the blood medicine concentration and

rapid elimination of that, the sustained release preparation of ivabradine or pharmaceutically acceptable salts thereof is needed clinically.

At present, Patent No.CN1482901A, the patent related to ivabradine sustained release preparation, discloses a solid pharmaceutical composition of controlled release of ivabradine, this patent is related to a solid pharmaceutical composition which could be obtained by thermoforming, but no specific pharmaceutical preparation is provided. Moreover, hot extrusion forming technology and hot injection molding technology are used in the patent, which are too complex to be applied in the industrialization. Besides, while using these two techniques, drugs and excipients have to be heated to 130°C, which will influence the stability of the drug.

The inventor has tried to use polymethacrylate Eudragit RL and RS to prepare sustained release skeleton tablets by the conventional methods of granulation compression, but superior sustained release effect can not be approached. This indicates that the sustained release materials used in Patent No. CN1482901A and the techniques of hot extrusion forming and hot injection molding must be used at the same time, otherwise even if using Eudragit RL and RS as skeleton materials. superior sustained release effect can not be approached via conventional method.

After researching large amount of sustained release materials, it is proved that using conventional sustained release materials such as hydropropylmethyl cellulose ,ethyl cellulose, sodium alginate, polymethacrylate, polyvinyl alcohol and the conventional preparation method such as granulation tableting or direct compression cannot prepare the sustained release preparation of ivabradine with superior sustained release effect. However, the inventor unexpectedly discovered that the polymers of polyoxyethylenes and polyvinyl acetates are appropriate for the sustained release skeleton materials of ivabradine or pharmaceutically acceptable salts thereof, and the sustained release preparation method of ivabradine or pharmaceutically acceptable salts thereof can be made by conventional methods such as granulation compression or direct compression. The product has better stability than the solid pharmaceutical composition in Patent No. CN 1482901A.

SUMMARY OF THE INVENTION

The object of the present invention is to provide a sustained-release preparation of ivabradine or pharmaceutically acceptable salts thereof, which can moderate the peak-valley phenomenon of blood medicinal concentration and improve the drug therapeutic effect and security as well as reduce the frequency of administration and improve the patient compliance.

The present invention provides a sustained-release preparation of ivabradine or pharmaceutically acceptable salts thereof comprising ivabradine or pharmaceutically acceptable salts thereof and sustained-release skeleton materials, wherein the one or more sustained-release skeleton materials are selected from polyoxyethylene, polyvinyl acetate-polyvinylpyrrolidone polymer.

In a preferred embodiment, the sustained-release skeleton material used in the present invention is polyoxyethylene. The polyoxyethylene is a kind of Polyox water-soluble resin, which has a large molecular weight distribution from 100,000 Da to 7,000,000 Da. The molecular weight of the Polyox water-soluble resin is preferably from 900,000 Da to 7,000,000 Da, more preferably from 1,000,000 Da to 7,000,000 Da, even more preferably from 4,000,000 Da to 7,000,000 Da, and most preferably from 5,000,000 Da to 7,000,000 Da.

In another preferred embodiment, the sustained-release preparation of the present invention use polyvinyl acetate-polyvinylpyrrolidone polymer (Kollidon SR) as sustained-release skeleton material.

In another preferred embodiment, the sustained-release preparation of the present invention use the mixture of the two polymers aforementioned as the sustained-release skeleton material, that is use polyoxyethylene and polyvinyl acetate-polyvinylpyrrolidone polymer simultaneously. There is no limitation to the ratio of the two. The polyoxyethylene is a kind of Polyox water-soluble resin, the molecular weight of which is preferably from 900,000 Da to 7,000,000 Da , more preferably from 1,000,000 Da to 7,000,000 Da, even more preferably from 4,000,000 to 7,000,000 Da, most preferably from 5,000,000 Da to 7,000,000 Da.

The sustained-released preparation of the present invention contains 5mg~20mg ivabradine in each unit (based of the weight of ivabradine for the ivabradine pharmaceutically acceptable salts). The range of the proportion by weight of the skeleton materials in the sustained-release preparation can be very broad. Superior sustained-release preparation can be formulated as long as the proportion is more than 30%. Theoretically, the higher the proportion of the skeleton materials in the sustained-released preparation, the better the sustained-release effects are, but other pharmaceutically factors should be considered during the preparation. The preferred proportion is 30% to 95%, more preferably 50% to 95%, most preferably 50% to 90%.

As a preferred embodiment of the present invention, the sustained-release preparation of the present invention may also comprise other excipients such as diluents, adhesives, and lubricants, wherein the diluents may be pre-gelatinized starch, microcrystalline

cellulose, calcium hydrogen phosphate or other pharmaceutically acceptable auxiliary; the adhesives may be polyvinylpyrrolidone, starch, carboxymethylcellulose, hydropropylmethyl cellulose or other pharmaceutically acceptable auxiliary; the lubricants may be magnesium stearate, glyceryl behenate, hydrogenated vegetable oil or other pharmaceutically acceptable auxiliary.

In a particular preferred embodiment, the sustained-release preparation of the present invention is consist of ivabradine or pharmaceutically acceptable salts thereof, Polyox water-soluble resins, magnesium stearate and glyceryl behenate. In a further preferred embodiment, the molecular weight of the Polyox water-soluble resins is preferably from 900,000 Da to 7,000,000 Da, more preferably from 1,000,000 Da to 7,000,000, even more preferably from 4,000,000 Da to 7,000,000 Da, most preferably from 5,000,000 Da to 7,000,000 Da.

In another particular preferred embodiment, the present sustained-release preparation is consist of ivabradine or pharmaceutically acceptable salts thereof, polyvinyl acetate-polyvinylpyrrolidone polymer, magnesium stearate, and glyceryl behenate; or microcrystalline cellulose can be included otherwise.

In another particular preferred embodiment, the present sustained-release preparation is consist of ivabradine or pharmaceutically acceptable salts thereof, Polyox water-soluble resin, polyvinyl acetate-polyvinylpyrrolidone polymer, magnesium stearate and glyceryl behenate; or calcium hydrogen phosphate can be included otherwise. In a further preferred embodiment, the molecular weight of the Polyox water soluble resin used is preferably from 900,000 Da to 7,000,000 Da, more preferably from 1,000,000 Da to 7,000,000 Da , even more preferably from 4,000,000 Da to 7,000,000 Da, most preferably from 5,000,000 Da to 7,000,000 Da.

The pharmaceutically acceptable salts of ivabradine can be in the form of the hydrochloride, hydrosulfate, sulfate, phosphate, citrate and on the like.

The preferred dosage form of the present sustained-release preparation is tablets.

The present sustained-release preparation can be prepared by conventional techniques, such as granulation compression techniques or direct compression techniques, preferably direct compression techniques. A sustained-release preparation with superior sustained-release effects can be prepared by simple direct compression technique, with using together with some excipients, such as pre-gelatinized starch, microcrystalline cellulose, calcium hydrogen phosphate, glyceryl behenate, magnesium stearate and the like.

A particular preparation method comprises the following steps:

i. ivabradine or its pharmaceutically acceptable salts is premixed with the sustained release skeleton materials after crushing;

ii. the mixture of ivabradine or its pharmaceutically accaptable salts and the sustained release skeleton materials obtained from Step 1 is mixed with reminder excipients;

iii. the mixture obtained from Step 2 is compressed and coated to give the matrix tablets.

The pharmaceutically acceptable salts of ivabradine can be in the form of hydrochloride, hydrosulfate, sulfate, phosphate, citrate and the like, preferably in the form of hydrochloride and hydrosulfate.

By researching the in vitro release rate and pharmacokinetics of the present sustained release preparation, and comparing to the pharmacokinetics of the normal rapid release preparation, the present invention has the following advantages:

i. effective drug blood concentration can be maintained for a longer time, the peak-valley phenomenon caused by frequent administration of normal preparation can be avoided, and the security, effectiveness and adaptability of drug can be improved;

ii the effect time of the medicine can be extended by different releasing mechanism, the frequency of administration can be reduced and the patient compliance can be improved;

iii. the product has good stabilities and the preparation technique is simple and has good reappearance, the industrialization degree is high, large scale production can be approached with conventional production equipments.

By performing the stability comparison experiments between the thermoforming mixture of ivabradine or its pharmaceutically acceptable salts and polymethacrylate disclosed by CN1482901A and the present sustained release preparation of ivabradine or its pharmaceutically acceptable salts thereof, the results indicates that the present preparation has better stability.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the release profiles of the different formulas in Example 1.

Figure 2 shows the release profiles of the different formulas in Example 2.

Figure 3 shows the release profiles of the different formulas in Example 3.

Figure 4 shows the release profiles of the different formulas in Example 4.

Figure 5 shows the pharmacokinetics profiles of Beagle dog in prescription 13, prescription 19 and ivabradine hydrochloride rapid release tablets (15mg).

DETAILED DESCRIPTION OF THE INVENTION

The present invention will be further illustrated by the following examples without any limitation of the present invention.

In the examples of the present invention, the addition amount of ivabradine pharmaceutically acceptable salts are all calculated by the ivabradine free base.

The chromatographic condition for the dissolution rate determination: C18 column and mobile phase is (0.01mol/l KH_2PO_4 (adding 0.5% triethylamine, adjusted to pH 6.0 with phosphric acid): methanol =80:20): methanol=60:40, the detect wavelength is 230nm; the temperature of the column is 30oC, the flow rate is 0.65ml/min.

The chromatographic condition for the related substances determination: C18 column and mobile phase A is 0.01mol/l KH_2PO_4 (adding 0.5% triethylamine, adjusted to pH 6.0 with phosphoric acid): methanol =80:20, mobile phase B is methanol, the gradient elution is shown in the following table, the detect wavelength is 230nm, the temperature of the column is 30°C, the flow rate is 0.75ml/min.

The gradient elution condition

t(min)	A(%)	B(%)
0	90	10
10	70	30
15	55	45
35	55	45

Example 1 Comparison Example

The ivabradine hydrochoride extrudate were prepared according to the method of hot melt extrusion at 120°C in Patent No. CN1482901A.

Formula:

Component	Formula 1	Formula 2
Ivabradine hydrochloride	15mg	15mg
Eudragit RLPO	150mg	75mg
Eudragit RSPO	-	75mg

The dissolution rate of the sustained release tablets in 900ml water was determined by HPLC. The results are shown in Table 1. The release profiles are shown in Figure 1.

Table 1 The results of the dissolution rates of different formulas in Example 1

t (h)	Dissolution rate (%)	
	Formula 1	Formula 2
1	20	10
2	35	20
4	55	37
8	80	60
12	97	80
18	98	92

Table 1 and Figure 1 indicate that the ivabradine hydrochloride prepared by the method of Patent No.CN1482901A shows superior sustained release effect which can last 16 to 18 hours.

Example 2

Sustained release tablets were prepared respectively with hydropropylmethyl cellulose, ethyl cellulose, polymethacrylate (Eudragit RLPO, Eudragit RSPO), polyvinyl alcohol as the skeleton material.

Formula:

Component	Formula 3	Formula 4	Formula 5	Formula 6	Formula 7	Formula 8
Ivabradine hydrochloride	15mg	15 mg	15 mg	15 mg	15 mg	15 mg
Hydropropylmethyl cellulose (K100M)	150 mg	-	120mg	-	-	-
Ethyl cellulose (100cp)	-	150mg	50 mg	-	-	-
Eudragit RLPO	-	-	-	150mg	-	-
Eudragit RSPO	-	-	-	-	150mg	-
Polyvinyl acohol	-	-	-	-	-	150mg
Microcrystalline cellulose	50 mg	50mg	30 mg	50 mg	50mg	50mg
Magnesium stearate	2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Hydropropylmethyl cellulose (E15)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Preparation method:

The crude materials were sifted through a 80-mesh sieve (pre-crushed if necessary). Each skeleton materials were weighed according to the formula and mixed well. Then ivabradine hydrosulfate were added to the mixture and mixed well. Hydropropylmethyl cellulose (E5) water solution was added to prepare soft materials and granulated through

20-mesh sieve. The granule was dried at 50°C for 2 hours, and granulated by a 18-mesh sieve. Magnesium stearate was added at the same weight as the dry granule and mixed well. The mixture was compressed into tablets and coated.

The dissolution rate of the sustained release tablets in 900ml water was determined by HPLC. The results are shown in Table 2. The release profiles are shown in Figure 2.

Table 2 The results of the dissolution rates of different formulas in Example 2

t (h)	Dissolution rate (%)					
	Formula 3	Formula 4	Formula 5	Formula 6	Formula 7	Formula 8
1	38	55	48	68	61	67
2	51	75	65	80	77	79
4	72	95	82	96	97	98
8	96	96	97	97	98	98
12	98	97	98	97	98	98
18	98	98	98	97	98	98

From the research of the different formulas in Example 2, it indicates that the sustained release tablets prepared with the conventional material or the sustained release materials disclosed in Patent No.CN1482901A and by the conventional techniques does not show good sustained release effect. When using hydropropylmethyl cellulose (K100M) as the skeleton materials, it shows the most obvious sustained release effect, but it only can last for 8 hours.

Example 3

The sustained release tablets were prepared with polyoxyethylene (Polyox) as the skeleton materials.

Formula:

Component	Formula 9	Formula 10	Formula 11	Formula 12	Formula 13	Formula 14	Formula 15	Formula 16
Ivabradine hydrochloride	15 mg	15 mg	15mg	15mg	-	-	-	-
Ivabradine hydrosulfate	-	-	-	-	15mg	15mg	15mg	5mg
Polyox N-750 (m.w. 300000 Da)	150mg	-	-	-	-	-	-	-
Polyox 205 (m.w. 600000Da)	-	150mg	-	-	-	-	-	-
Polyox N-12K (m.w. 1000000Da)	-	-	150mg	-	-	-	-	-
Polyox 303 (m.w. 7000000Da)	-	-	-	150mg	180mg	150mg	60mg	160mg
Microcrystalline cellulose	30mg	30mg	30mg		-	30mg	80mg	20mg
Calcium hydrogen	-	-	-	30mg	-	-	20mg	-

phosphate								
Glyceryl behenate	10mg	10mg	10mg	10mg	20mg	10mg	20mg	-
Magnesium stearate	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg

Preparation method:

The raw materials and the excipients were mixed well and pressed directly into sustained release tablets. The dissolution rate of the sustained release tablets in 900ml water was determined by HPLC. The results are shown in Table 3. The release profiles are shown in Figure 3.

Table 3 The results of the dissolution rates of different formulas in Example 3

t (h)	Dissolution rate (%)							
	Formula9	Formula10	Formula11	Formula 12	Formula 13	Formula 14	Formula 15	Formula16
1	58	37	23	16	14	15	25	14
2	75	53	36	28	25	30	37	24
4	92	74	58	45	41	46	59	39
8	97	94	84	70	65	71	85	59
12	98	98	96	87	83	88	98	76
18	98	98	98	97	98	98	98	92

Table 3 and Figure 3 indicate that superior sustained release effect can be obtained when the sustained release tablets were prepared with polyoxyethylene of high molecular weight (Polyox, the molecular weight is greater than 1,000,000 Da) by direct compression. The sustained release tablets prepared with polyoxyethylene of low molecular weight (formula 9 and 10) release too fast to meet the required sustained release effect. Moreover, it also proves that, the higher the proportion of the skeleton material and the active component, the better the sustained released effect is (formula 13 and 16).

Example 4

The sustained release tablets were prepared by the skeleton material mixture composed of polyoxyethylene, polyvinyl acetate and polyvinylpyrrolidone(PVP).

Formula:

Component	Formula 17	Formula 18	Formula 19	Formula 20
Ivabradine hydrochloride	15mg	15mg	-	-
Ivabradien hydrosulfate	-	-	15mg	15mg
Polyox 303 (m.w. 7000000Da)	-	50mg	-	-

The mixture of polyvinyl acetate and PVP (Kollidon SR)	150mg	100mg	180mg	-
The water dispersion of polyvinyl acetate (Kollicoat SR 30D)	-		-	500mg
Microcrystalline cellulose	30mg		-	50mg
Calcium hydrogen phosphate	-	30mg	-	-
Glyceyl behenate	10mg	10mg	20mg	10mg
Magnesium stearate	2mg	2mg	2mg	2mg

The preparation method:

The sustained release tablets of formula 17, 18, 19 were prepared by direct compression. The sustained release tablets of formula 20 were prepared by fluidized bed granulation compression. The dissolution rate of the sustained release tablets in 900ml water was determined by HPLC. The results are shown in Table 4. The release profiles are shown in Figure 4.

Table 4 The results of the dissolution rates of different formulas in Example 4

t (h)	Dissolurion rate (%)			
	Formula17	Formula18	Formula19	Formula20
1	22	18	19	15
2	37	29	34	29
4	58	48	53	50
8	80	70	75	72
12	92	85	89	88
18	98	97	98	98

From Table 4 and Figure 4 indicates that superior sustained release effect can be approached when using the combination of polyoxyethylene, polyvinyl acetate and polyvinylpyrrolidone (PVP) as the skeleton materials (formula 18).

Example 5 Stability Experiment

The prodocud from formula 1,2,3,19 were packaged with aluminum foil bags and stability tests were carried out in the condition of 40°C/RH75% and 30°C/RH65%. The results are shown in Table 5.

Table 5 The results of the stability comparison experiments

Experimental conditions	t	Related substance (%)			
		Formula 1	Formula 2	Formula 13	Formula 19
	Initial	0.67	0.87	0.14	0.15
30°C	1 month	0.95	1.12	0.15	0.15

RH65%	3 month	1.06	1.35	0.17	0.18
	6 month	1.23	1.56	0.17	0.18
40°C RH75%	1 month	1.08	1.23	0.17	0.18
	3 month	2.08	2.37	0.19	0.20
	6 month	4.05	4.53	0.77	0.73

It is indicated that the related substances increases obviously in the stability experiments of the composition prepared by the existing technology, and the present sustained-release preparationshows better stability than the composition prepared by the existing technology.

Example 6 Pharmacokinetic Studies

The pharmacokinetic comparison experiment of Beagle dog was performed for the preparation of formula 13,19 and the ivabradine hydrochloride rapid release tablets (15mg) (7.5mg, 2 pieces, Servier, France). The results are shown in Figure 5.

Comparing the pharmacoinetic results in Beagle dogs of the present sustained release preparation and the rapid release preparation, the C_{max} of the present preparation is obviously lower than that of the rapid release preparation, and the present preparation overcomes the side effects of the rapid decreasing of heart rate caused by the rapid increasing of C_{max} after administration. Furthermore, the present sustained-release preparation prolongs the in vivo drug retention time up to 12 hours, which exhibits superior sustained release effect.

Due to the detailed description of the particular embodiments of the present invention, some modifications and variants are obvious for the person skilled in the art and will be included in the scope of the present invention.

What is claimed is:

1. A sustained release preparation of ivabradine or pharmaceutically acceptable salts thereof, comprising ivabradine or pharmaceutically acceptable salts thereof and the sustained release skeleton materials, wherein the one or more sustained release skeleton materials are selected from the group consisting of polyoxyethylene, polyvinyl acetate –polyvinylpyrrolidone polymer.

2. The sustained release preparation according to claim 1, wherein the polyoxyethylene is Polyox water soluble resin.

3. The sustained release preparaion according to claim 2, wherein the molecular weight of the Polyox water soluble resins is 900,000 Da to 7,000,000 Da, preferably1,000,000 Da to 7,000,000 Da, more preferably 4,000,000 Da to 7,000,000 Da, most preferably 5,000,000 Da to 7,000,000 Da.

4. The sustained release preparation according to any one of claims 1 to 3, wherein the proportion of the sustained release skeleton materials by weight of the preparation is 30% to 95%, preferably 50% to 95%, more preferably 50% to 90%.

5. The sustained release preparation according to any one of claims 1 to 4, wherein the content of ivabradine or pharmaceutically acceptable salts thereof calculated by ivabradine is 5mg-50mg.

6. The sustained release preparation according to any one of claims 1 to 5, wherein the preparation comprises pharmaceutically acceptable excipients.

7. The sustained release preparation according to claim 6, wherein the excipients comprises one of diluents, adhesives, lubricants or the combination of them.

8. The sustained release preparation according to claim 7, wherein one or more diluents are selected from the group consisting of pre-gelatinized starch, microcrystalline cellulose, and Calcium hydrogen phosphate.

9. The sustained release preparation according to claim 7, wherein one or more adhesives are selected from the group consisting of polyvinylpyrrolidone, starch, carboxymethyl cellulose, hydropropylmethyl cellulose.

10. The sustained release preparation according to claim 7, wherein the one or more lubricants are selected from the group consisting of magnesium stearate, glyceryl

behenate, hydrogenated vegetable oil, preferably selected from magnesium stearate and glyceryl behenate.

11. The sustained release preparation according to claim 6, wherein the sustained release preparation is consisted of ivabradine or pharmaceutically acceptable thereof, Polyox water soluble resin, magnesium stearate, and glyceryl behenate.

12. The sustained release preparation according to claim 6, wherein the sustained release preparation is consisted of ivabradine or pharmaceutically acceptable salts thereof, Polyox water soluble resin, polyvinyl acetate-polyvinylpyrrolidone polymer, magnesium stearate and glyceryl behenate.

13. The sustained release preparation according to any one of claims 1 to 12, wherein the one or more ivabradine pharmaceutically acceptable salts are selected from the group of hydrochloride, hydrosulfate, sulfate, phosphate and citrate.

14. The sustained release preparation according to any one of claims 1 to 13, wherein the sustained release preparation is tablet,

15. The preparation method of sustained release preparation according to claim 14, wherein the method is direct compression or granulation compression, preferably direct compression.

16. The preparation methods according to claim 15, wherein the granulation compression is fluidized bed granulation compression.