

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 November 2010 (11.11.2010)

PCT

(10) International Publication Number
WO 2010/128525 A2

(51) International Patent Classification:
A61K 31/55 (2006.01)

(21) International Application Number:
PCT/IN2010/000288

(22) International Filing Date:
4 May 2010 (04.05.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1161/MUM/2009 4 May 2009 (04.05.2009) IN

(72) Inventors; and

(71) Applicants : PATEL, Dinesh, Shantilal [IN/IN]; 11/12 Udyog Nagar, S V Road, Goregaon (W), Mumbai 400 104 (IN). PATEL, Sachin, Dinesh [IN/IN]; 11/12 Udyog Nagar, S V Road, Goregaon (W), Mumbai 400 104 (IN). KURANI, Shashikant, Prabhudas [IN/IN]; 11/12 Udyog Nagar, S V Road, Goregaon (W), Mumbai 400 104 (IN).

(74) Agents: MAJUMDAR, Subhatosh et al.; S. Majumdar & Co., 5, Harish Mukherjee Road, Kolkata 700 025 (IN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: A FORMULATION OF IVABRADINE FOR TREATING THE CARDIOVASCULAR DISEASE

(57) Abstract: A sustained release composition of Ivabradine, which is capable of releasing at least 80% of active drug in 24 hours, said composition comprising Ivabradine as a base or salt thereof or suitable derivative thereof as active ingredient in therapeutically effective amount; release retarding polymers selected from the group comprising cellulose ethers in amount of about 30% to 90 % by weight; pharmaceutically acceptable excipients selected from the category of binders, diluents, lubricants, glidants, solvents, co solvents, preservatives, buffering agents, acidifiers, surfactant, channeling agents, release retardants, coating materials, colorants, and flavors. Also a process for preparation of said sustained release formulation comprising process comprising the steps of dispensing, sieving, sifting, lubrication, compression and optionally coating.



WO 2010/128525 A2

A FORMULATION OF IVABRADINE FOR
TREATING THE CARDIOVASCULAR DISEASE

Field of the Invention:

The present invention provides sustained release drug formulations of Ivabradine, salt thereof and its like substances which is successful in retarding the drug release for period of 24 hours. The invention also extends to the process for the preparation of such formulation. The preparation is for once a day administration which is beneficial in reducing the dose frequency and side effects associated with administration of conventional dosage forms of administration for the prevention of anginal attack during full day and thereby providing therapeutic and economic advantage over the current therapies. The stated release of drug is for 24 hours which is achieved by using either a single viscosity grade hydroxypropyl methylcellulose polymer or combination of two different viscosity grades of hydroxypropyl methylcellulose polymer in a particular concentration.

Background of the Invention:

Chronic stable angina pectoris affects 2–4 % of the population in Western countries, and is associated with an estimated annual risk of death and nonfatal myocardial infarction of 1–2% and around 3%, respectively. Approximately 50% of patients with coronary heart disease have stable angina pectoris as their first clinical presentation. (Nature Reviews Cardiology 6, 329-330, May 2009).

Chronic stable angina pectoris is a common disorder whose incidence varies between ~0.2% in southern European countries and > 0.6% in northern Europe. In countries with relatively high coronary heart disease rates, the prevalence may be 3–4% of the total population.

The most common symptom of angina is chest pain that occurs behind the breastbone or slightly to the left. It may feel like tightness, heavy pressure, squeezing, or crushing pain. The pain may spread to shoulder, arm, jaw, neck, back, or other areas. Some people say the pain feels like gas or indigestion. The stable angina may lead to several deadly complications like unstable angina, heart attack, sudden death caused by lethal arrhythmias. Moreover, patients with angina have a threefold risk of developing unstable

angina and myocardial infarction and, therefore, often require emergency admission to hospital.

Most common used approach in the management of angina pectoris is to achieve the
5 reduction in the heart rate which is the major parameter to be determined in angina. Heart rate is governed by the I_f current which controls the electrical pacemaker activity in the sinoatrial node.

Nitrates, β -blockers and calcium channel blockers are three classes of drugs which are
10 used to treat symptoms of angina.

Nitrates are oldest drugs for angina and they have potent vasodilating effect directly on coronary arteries thereby leading to improved perfusion to ischemic myocardium but these drugs bear demerits of having some deleterious adverse effects like reflex
15 tachycardia and reflex increase in contractility resulting in increased myocardial oxygen requirement, syncope, facial flushing, and headaches.

Some β -blockers are approved for the treatment of angina pectoris but they are less frequently used for treating angina due to their unfavorable side effects which includes
20 negative inotropes, lethargy, exercise tolerance, sexual dysfunction, bronchospasm, peripheral vasoconstriction of the extremities and exacerbation of Raynaud's phenomenon.

Calcium channel blockers are usually preferred drugs after nitrates and are mostly a second-line choice when beta-blockers are contraindicated or ineffective. Generally
25 Nifedipine, Verapamil, Diltiazem are preferred among the calcium channel blockers for the treatment of angina but some adverse effects such as flushing, swelling of the abdomen, ankles, or feet and heartburns are associated with administration of these drugs.

Beta blockers and calcium channel blockers have some contraindications and adverse
30 actions which limit their use. In particular, the negative inotropic and hypotensive effects of these agents may exacerbate heart failure in patients with associated impaired ventricular function. Furthermore, around 20% of patients with chronic stable angina fail

to respond to beta blockers. This underlines the need for new classes of agents which act to reduce heart rate without impairing cardiac function. Recently, a new class of selective heart rate-reducing agents have been discovered, the I_f channel inhibitors. Such agents were developed to selectively inhibit cardiac pacemaker activity, thus allowing heart rate reduction without affecting myocardial contractility, conduction velocity and refractoriness, or arterial blood pressure. (Michael Shattock, A John Camm. Pure heart rate reduction: the I_f channels from discovery to therapeutic target. *Br J Cardiol* 2006; 13; 27–35)

Ivabradine is such a new I_f Channel inhibitors class drug which selectively inhibits the I_f channel and significantly reduces heart rate and may represent a real therapeutic innovation in the treatment of patients with ischaemic heart disease. Ivabradine has shown good heart rate reduction activity compared to Betablockers and calcium channel blockers.

Chemically Ivabradine hydrochloride is 3-(3-{[[(7*S*)-3,4-Dimethoxybicyclo [4.2.0]octa-1,3,5-trien-7-yl)methyl] methyl amino} propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one, hydrochloride.

Ivabradine is also known to reduce myocardial infarction and to have a good tolerability profile even when used in combination with other drugs. Ivabradine also has potential utility in atherosclerosis, primitive and dilatative cardiomyopathy, and arrhythmias but the main advantages of Ivabradine HCl in stable angina pectoris are exclusive heart rate reduction, proven anti-ischaemic and anti-anginal properties, absence of negative inotropic effects, preservation of left ventricular relaxation, absence of coronary vasoconstriction, preserved atrioventricular and ventricular conduction, preservation of blood pressure and absence of bronchospasm associated with β -blockers. (Jean-Claude Tardif, *European Heart Journal Supplements* (2005) 7 (Supplement H), H29–H32)

Followings are some of the prior arts related to Ivabradine.

EP1345594 describes thermoformable solid pharmaceutical composition for controlled release of ivabradine using polymethacrylates polymers. The specified dosage form are formulated by extrusion and injection technology at specified range of temperature. The invention uses the thermal process to formulate a dosage form. This invention does not hint about tablets dosage forms and moreover it involves expensive technology.

EP 1917979 relates to the use of Ivabradine for the treatment of atrial fibrillation. This inventions does not claim about the dosage forms comprising Ivabradine as it does not provide method of preparation of any dosage form.

US 7361650 relates to gamma crystalline form of Ivabradine hydrochloride, a process for its preperation and pharmaceutical composition containinig it. This invention does not relate to sustained release preparations of Ivabradine but it only deals with preparing conventional dosage form of gamma crystalline form of the drug.

US Patent Application 20050106238 relates to a oro-dispersible pharmaceutical composition comprising ivabradine which disintegrates in mouth in less than three minutes. This invention is not meant for sustained release preparations of Ivabradine.

WO/2008/065681 discloses the process for preparation of salts of ivabradine hydrochloride by suitable method in presence of base in suitable solvent to provide Ivabradine of specific formula. This invention does not hint about the formulations of Ivabradine.

WO/2007/042657 this patent relates to the $\gamma(d)d$ crystalline form of ivabradine hydrochloride having general characterisitic formula which is determined by its X-ray diffraction pattern on powder. This invention hints about formulating Ivabradine in conventional dosage forms but it doesn't relate to sustained release preparations of Ivabradine.

WO/2005/110993 describes a novel method of synthesising ivabradine and the salts thereof for addition to a pharmaceutically acceptable acid in a suitable dosage form.. This invention also doesn't provide hint about sustained release formulations of Ivabradine.

- 5 WO/2002/100408 discloses the new methods of treating pain by targeting HCN pacemaker channels. This invention also does not relate to sustained release formulations of Ivabradine.

Careful review of all the cited prior arts indicates that no one has tried to formulate sustained release formulation of Ivabradine or its salts which can be administered easily and may provide the drug release upto 24 hours thereby reducing the dosing frequency and also side effects associated with multiple administration of conventional dosage forms. The conventional tablet dosage forms of the instant release tablets are highly prone to dose dumping and which can produce side effects with less duration of pharmacological action. If the sustained release dosage forms are administered then the same can produce uniform release profiles for better therapeutic effect and obviating the drug dumping. Hence the main objective of the present invention was to formulate the novel drug delivery system wherein the Ivabradine or its salts or derivatives may be compounded in such way that it can extend the drug release in the formulation up to 24 hours. The same will help for better therapeutic efficacy in relieving the anginal pain caused due to cardiovascular problems.

Summary of the Invention:

According to one aspect there is provided a sustained release composition of Ivabradine, which is capable of releasing at least 80% of active drug in 24 hours, the said composition comprising:

- a) Ivabradine as a base or salt thereof or suitable derivative thereof as active ingredient in therapeutically effective amount;
- b) Release retarding polymers selected from the group comprising cellulose ethers in amount of about 30% to 90 % by weight;
- c) pharmaceutically acceptable excipients selected from the category of binders, diluents, lubricants, glidants, solvents, co solvents, preservatives, buffering agents,

acidifiers, surfactant, channeling agents, release retardants, coating materials, colorants, and flavors.

Another aspect of the present invention comprises a method of manufacturing the sustained release dosage form of Ivabradine or its salts which comprises the steps of dispensing, sieving, sifting, lubrication, compression and optionally coating.

Brief Description of the Drawings:

Figure 1. Representative drug release profile of Example 1 to Example 32.

Figure 2. Drug release profile of sustained release tablets of Ivabradine or its salt after stability study.

Figure 3. Comparative drug release profile of sustained release tablets of Ivabradine of Example 2 versus immediate release tablets of Ivabradine.

Figure 4. Drug release profile of sustained release formulations where the weight ratio of drug to total amount of release retardant polymer was taken below 1:5 and above 1:15.

Figure 5. Drug release profile of sustained release formulation of Ivabradine where weight of release retarding polymer was below 30 % and above 90%.

Figure 6. Drug release profile of sustained release tablets of Ivabradine where stearic acid is used as in Example 31

Detailed Description of the Invention:

The invention described herein is a sustained release formulation of Ivabradine or its salt thereof. The formulation comprises of the drug or its congeners incorporated into one or more release retarding polymers of different viscosities in a specific weight ratio in the range of 1:5 to about 1:15. More preferably the present invention is in the form of sustained release matrix tablets designed to release and maintain the effective amount of Ivabradine in plasma upto 24 hours.

This formulation is capable of providing therapeutically effective concentration of Ivabradine upto 24 hours after an administration to mammals, including humans suffering from anginal pains. It may be combined with other cardiovascular drugs for the therapeutically beneficial effects and for the cure of cardiovascular diseases. Present

invention greatly reduces the risk of angina pectoris and manages the pain associated with it by releasing the drug round the clock after single administration.

5 The formulation releases not more than about 30% of the drug in first two hours, not more than, about 70% of drug in 8 hours and not less than about 80 % in 24 hours. The same formulation can be prepared by incorporation of Ivabradine with other anti anginal or other cardiovascular drugs for either immediate release of later or sustained release of both the drugs.

10 The drugs may be formulated as a tablet, granules/pellets/pills in capsules or as bilayered tablets or by filling in the sachet or by formulating as oral liquids or injections.

Present invention is directed to a novel sustained release oral pharmaceutical formulation for the treatment of cardiovascular diseases. More preferably the present invention
15 comprises the oral sustained release matrix tablets for the treatment of chronic stable angina pectoris and cardiac arrhythmias thereby minimizing dosing frequency and reducing side effects which are associated with multiple dosing of conventional dosage forms of Ivabradine.

20 The present invention comprises the oral sustained release tablets containing Ivabradine or its salts incorporated into matrix of release retarding polymers with or without addition of other pharmaceutically acceptable pharmaceutical aids.

One preferred embodiment of the present invention comprises a sustained release
25 formulation of a Ivabradine or its derivatives incorporated into one or more release retarding polymers with other suitable tableting excipients like diluent, binder, glidant, anti adhesives, lubricants, coating materials and other pharmaceutical additives in appropriate amount which provides the drug release in such a way as to maintain its therapeutically effective concentration up to 24 hours.

30

One preferred embodiment of the present invention comprises a oral sustained release matrix tablets in which Ivabradine or its salt is incorporated with suitable release retardant

preferably from cellulose ethers followed by their formation into tablets using either direct compression or dry granulation or wet granulation.

One of the preferred embodiments of the present invention comprises sustained release
5 tablets containing Ivabradine or its salt thereof incorporated with cellulose ether, preferably hydroxypropyl methylcellulose (HPMC) as release retardant polymer in such a way as to form the total weight ratio of drug to release retardant polymer is in the range of about 1:5 to about 1:15.

10 One of the preferred embodiments of the present invention comprises an oral sustained release matrix tablets in which Ivabradine or its salt is incorporated with methacrylic acids and its derivatives to formulate sustained release tablets using either direct compression or dry granulation or wet granulation.

15 One of the embodiments of the present invention includes preparation of sustained release tablets of Ivabradine with stearic acid. The technique involves various combinations of stearic acid with other fatty acid esters that includes glyceryl monostearate, palmitic, behenic acid, glyceryl behenate, glyceryl palmitostearate, hydrogenated castor oil or other natural waxes.

20

Ivabradine or its salts also may be formulated using nanotechnology platform to make a composition, using GRAS approved excipients to use as transdermal delivery or as parenteral forms or as solid dosage forms either singularly or with suitable anti hypertensives.

25

The present invention is in the form of tablet, capsule, granules, sachet, typically a tablet with or without coating, bi-layered tablet, functional coated tablets or caplets, time-release tablets or caplets, floating tablets, matrices containing wax or polymer, controlled release beads, granules, spheroids that are contained within a capsule or administered
30 from a sachet or other unit dose powder device in combination with other beneficial drugs or as a combination kit of sustained release dosage forms for the administration in mammals.

The present invention is preferably a tablet formulation in which Ivabradine is incorporated in a matrix that comprises cellulose ethers preferably hydroxypropyl methyl cellulose herein after referred as HPMC and other excipients as discussed herein.

- 5 The tablet is prepared selectively by dry granulation, wet granulation, direct compression or melt extrusion.

Ivabradine hydrochloride may also be formulated into sustained release tablets with combination of other drugs selected from the categories of antihypertensives, antianginals and antihyperlipidemic drugs used for treating the cardiovascular diseases and which are biocompatible and are not contraindicated with Ivabradine or its derivatives for the potential therapeutic benefits. Non limiting examples of such categories of drugs which can be combined with Ivabradine to formulate the sustained release formulation are: α -adrenoceptor antagonists, β -adrenoceptor antagonists, antiarrhythmic agents, calcium channel blockers, angiotensin receptor antagonists (like losartan; valsartan; candasartan), diuretics, antiplatelet agents, and antihyperlipidemics including fibric acid derivatives and HMG CoA reductase inhibitors, anticoagulants, ACE inhibitors.

Present invention may also be formulated in the form of sustained release compositions of Ivabradine or its salts in combination with drugs from other categories which provides synergistic effects with Ivabradine for the treatment of angina pectoris. Examples of these categories of drugs are but not limited to antihyperlipidemics, beta-blockers, diuretics, ACE inhibitors, antagonists, direct acting vasodilators, short and long acting nitrates, adrenergic blocking agents, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, aspirin, and other anti-platelet agents like Ticlopidine, clopidogrel, prasugrel or the combinations of the any of the foregoing.

Present composition of Ivabradine may also be formulated in combination with other drugs in the form of bilayer tablets. Such bilayer tablets may contain one layer providing immediate release of one drug and another layer providing sustained release of another drug. Sustained release layer of Ivabradine may be combined with immediate release layer of another class of drug or vice versa. Examples of drugs which can be formulated

in the combination with Ivabradine or its salts as normal tablets or bilayer tablets include but are not limited to ramipril, alfentanil, alprazolam, amlodipine, terazosin hydrochloride, dexamethasone, diazepam, digoxin, digitoxin, ethynil estradiol, fluoxetine, sartans like losartan, lovastatin, midazolam, nifedipine, paracetamol, simvastatin, 5 clopidogrel, aspirin, heparin, warfarin, erythrityl tetranitrate, dipyridamole, gallopamil, ranolazine or salt there of and others in their therapeutic amounts.

Instead of bilayer tablets, combination of sustained release and immediate release granules may also be prepared with or without other excipients which can be filled in 10 capsule or sachets. The same may also be formulated as sustained release liquid preparations using suitable vehicle, or can be compressed as a chewable tablet or sublingual tablet with suitable base. Such compressed tablets may be coated optionally with suitable coating materials or colorants either dissolved or dispersed in a suitable solvent.

15

Hydroxypropyl methylcellulose (HPMC) is a cellulose derivative belonging to group of cellulose ethers, having etherified anhydrous glucose rings. The present invention was formulated using only one type of HPMC as well as more than one type of HPMC.

20 Hydroxypropyl methylcellulose (HPMC) is commercially available in various grades, under so many trade names. The grades mentioned under the particular trade names represents the differences in methoxy and hydropropoxy content as well as viscosity and molecular weight of HPMC.

25 The present invention makes use of various types of grades of HPMC differing in the viscosity ranging from 40 cps to 22000 cps. Cellulose ethers such as HPMC K100 LV, HPMC K4M, HPMC K15M and HPMC K100M were used to formulate the present invention which bears the preferable viscosity values of about 80-120cps, about 300-5600 cps, about 11000 -22000 cps and about 80000-120000 respectively.

30

Release retardant polymers in the present sustained release formulation of Ivabradine may also be selected from natural or partly or totally synthetic cellulose ethers, hydrophobic polymers, hydrophilic polymers, natural gums and water insoluble polymers.

- 5 The release retarding polymer is present in about 30% to 90% amount by weight of the composition, preferably about 50% to about 90% of the composition, more preferably about 70% to about 90% of the composition.

10 The release retarding polymer is present as a single or in combination of two different viscosity grade polymers where the viscosity of such polymers is in the range of about 60 to 1,20,000 cps.

Hydrophilic polymers includes protein, a polysaccharide, a polyacrylate, a hydrogel, polyvinyl alcohol or polyvinyl pyrrolidone, carbopols, polyethylene oxides, magnesium
15 aluminum silicate, modified starch derivatives or a derivative of such hydrophilic polymers. Hydrophobic polymers includes ethyl cellulose, a copolymer of acrylic acid and methacrylic acid esters, polyethylene, polyamide, polyvinylchloride, polyvinyl acetate. Examples of water insoluble polymers includes acrylic acid polymers and copolymer such as polyacrylic acids, acrylic resins, acrylic latex dispersions, cellulose
20 acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate acrylates, polymethacrylates, polyethylene oxide and its salt such as sodium, potassium, calcium salt, ammonium, high molecular weight polyethylene glycol or their mixtures, psyllium husk. Natural gums such as xanthan gum, guar gum, locust bean gum, gums derived from Tamarindus indica, acacia gum, tragacanth, karaya gum, modified cellulosic,
25 agar, pectin, carrageen, alginate, carboxypoly methylene, gelatin, casein, zein, bentonite . The most preferred cellulose ethers which may be selected includes materials from the group of alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose such as methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and carboxymethylcellulose and its suitable pharmaceutically acceptable salts such as sodium,
30 potassium and calcium salt.

The other excipients apart from release retarding polymers used were compression aids such as diluents, binders, lubricants, glidants and coating materials.

Selection of Fillers is critical point in present invention as it have important role on drug
5 release from the matrix formulation. Suitable filler may be selected from glucose, mannitol, sorbitol, xylitol, compressible sugar, sucrose, sugar alcohol, monobasic sodium phosphate, dibasic sodium phosphate, tribasic sodium phosphate, calcium phosphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, crosslinked carboxymethylcellulose and its salts such as sodium, potassium and calcium salt, starch
10 and its derivatives, crospovidone, cyclodextrins and its derivatives.

Binders may be selected from the materials like povidone (polyvinylpyrrolidone); acacia, tragacanth, carrageen, alginates, and others such as carboxypolymethylene, gelatin, and starch and modified starch derivatives which is present in concentration of about 1 to 5 %
15 of the total weight of the composition.

Lubricants and flow aids may be selected from magnesium stearate, sodium stearyl fumarate, stearic acid and its derivatives, silicon dioxide or talc to prepare the sustained release formulation of Ivabradine or its salt.
20

Solvent for wet granulation in the present invention may be selected from water, alcohol, methylene chloride, acetone or their suitable mixture. From the alcohol class, the most preferred are methanol, ethanol and isopropanol.

25 The matrix tablet of the present invention was prepared by either wet granulation method or dry granulation method or direct compression method or melt extrusion but preferably wet granulation.

The dry granulation can also be applied as it involves few steps and great economical
30 advantages over wet granulation method. In this method the granules are formulated by press granulation technique. The pre-compression of the blend i.e. slugging can also be done followed by crushing and sieving for obtaining the granules.

Further in a preferred embodiment of the present invention, a sustained release formulation comprises not more than 90% of total concentration of release retardant polymers. The drug to excipients ratio was maintained in range of about 1:8 to 1: 20, more preferably about 1:15. Sustained drug release profile of Ivabradine was observed from the different prepared formulations of Ivabradine using above mentioned release retarding excipients and other excipients.

Various concentrations of release retardant polymer were employed to formulate sustained release tablets of Ivabradine or its salt with desired drug release was achieved only when the weight ratio of drug to total concentration of release retardant polymers was employed in the range of about 1: 5 to 1:15.

Following are non limiting examples of the present invention.

15 **Examples 1**

Sustained release tablets of Ivabradine were prepared by dry granulation. The drug Ivabradine hydrochloride (6.5%), microcrystalline cellulose (16.49%) and HPMC K-15M (54.5%) were weighed, sieved and mixed. To this mixture talc (0.3%) and magnesium stearate (0.3%) were added. This powder blend was processed for slugging at the pressure of about 3- 4 kg/cm². To this blend, HPMC-K100M (19.39%), talc (0.6%) and magnesium stearate (1.81%) were added followed by passing it through the sieve. This final blend was compressed in to the tablets using tablet punching machine.

Examples 2

25 8.085 % Ivabradine hydrochloride was mixed with 89.41 % amount of HPMC K-15M, 0.25 % talc and 0.25 talc. This powder blend was processed for slugging at the pressure of about 3- 4 kg/cm². To this blend, talc (0.5 %) and magnesium stearate (1.5 %) were added followed by passing it through the sieve. This final blend was compressed in to the tablets using tablet punching machine. The tablets were optionally coated with suitable coating materials.

Example 3

6.53% Ivabradine or its salt was mixed with 13.46% microcrystalline cellulose, 54.54% amount of HPMC K15M and 18.18% amount of HPMC K 100M. The mixture was processed for granulation using 2.42% solution of PVP K 30 in isopropyl alcohol.

5 Granules were dried and to this mixture 1.84% talc, 1.81% magnesium stearate and 1.21 % aerosil was added. This blend was finally compressed into tablets at suitable pressure using tablet punching machine.

Example 4

10 9.8 % Ivabradine or its salt was mixed with 12.01 % microcrystalline cellulose, 52.72 % amount of HPMC K15M and 18.18 % amount of HPMC K 100M. The mixture was processed for granulation using 2.42 % solution of PVP K 30 in isopropyl alcohol. Granules were dried and to this mixture 1.84 % talc, 1.81 % magnesium stearate and 1.21 % aerosil was added. This blend was finally compressed into tablets at suitable

15 pressure using tablet punching machine.

Examples 5

The Ivabradine hydrochloride (5.39%), lactose (52.6%) and HPMC K-15M (40%) were weighed, sieved and mixed, the talc (1%) and magnesium stearate (1%) were also

20 weighed, sieved and mixed. Both of the above powder blends were mixed properly. The dry granulation method was used to formulate the granules. The blend was pre-compressed, which was further crushed and sieved to get the granules. The blend was then compressed at suitable pressure to prepare tablets of optimum hardness. The tablets were evaluated for drug release pattern and assay content. The tablets were further coated

25 optionally with suitable coating materials.

Example 6

The formulation prepared with HPMC K4M was also able to sustained the release of drug upto 24 hours. Ivabradine hydrochloride (5.39%) was mixed with HPMC K4M (40%) and

30 dicalcium phosphate (52.6%). The tablets were formulated by dry granulation i.e. slugging. The granules were lubricated with talc (1%) magnesium stearate (1%) and

finally compressed into tablets. The tablets were evaluated for drug release and assay content.

Example 7

5 Ivabradine hydrochloride (5.39%) was mixed with the tablets prepared with HPMC K15M (60%) and microcrystalline cellulose (32.61%). The powder blend was processed for dry granulation method. The granules were lubricated with talc (1%) and magnesium stearate (1%) and followed by its compression into tablets using tablet punching machine.suitable hardness. The tablets were evaluated for in vitro drug release pattern and
10 assay content.

Example 8

The tablets were prepared by replacing release retarding polymer with HPMC K100M (60%) in the formulae of example 7. Tablets formulated by this composition also
15 provided satisfactory drug release profile.

Example 9

The sustained release tablets were also formulated with non aqueous wet granulation method using isopropyl alcohol as a solvent. Ivabradine or its salts (5.39%), HPMC K4M
20 (40%) and diluent MCC (52.6%) were mixed and granulated with IPA. The granules were dried and further lubricated with talc (1%) and magnesium stearate (1%). The granules were compressed into tablets and evaluated for drug release and assay content. The tablets were coated further with suitable colour optionally.

Example 10

25 The formula of Example 6 was repeated by employing wet granulation process. The tablets by wet granulation were also formulated using combination of binder solution i.e. IPA and water in the ratio of 8:2. Tablets prepared by this method also provided the desired drug release up to 24 hours.

Example 11

The tablets were formulated using higher amount of release retardant polymer and granulation was carried out using combination of solvents IPA and water in the at a ratio of 8:2. The active pharmaceutical ingredient Ivabradine or its salt drug (10.78%), MCC (27.22) and release retarding polymer HPMC K4M (60%) were sieved and mixed. The powder blend was granulated using binder solution of isopropyl alcohol and water in 8:2 ratio.. Granules were dried, followed by its lubrication with talc (1%) and magnesium stearate (1%) and were finally compressed into tablets. The compressed tablets were further evaluated for drug release profile and assay content.

Example 12

The sustained release tablets were formulated by replacing release retardant polymer with HPMC K100M in same amount as that was used in example 11. The blend was granulated with. isopropyl alcohol and water in the ratio of 8:2. The granules were then dried & compressed. The formulated tablets showed satisfactory dissolution profile when tested in vitro.

Example 13

Here two different release retardant polymers were used in the combination. The combination of two different viscosity polymers were also found to produce sustained drug release when one release retarding polymer i.e. HPMC K4M (29.7%) and drug (5.33%) were granulated by binder solution containing IPA: water in ratio of 8:2 and dried. The another release retarding polymer i.e. HPMC K100M (44.1%) and diluent MCC (19.8%) were added extra-granularly. The blend was lubricated with talc (0.4%) and magnesium stearate (0.4%) and compressed to get tablets which were further evaluated for drug release and assay content.

Example 14

The addition of extra amount of release retarding polymer extra-granularly also showed desired in vitro drug release pattern. Drug (5.33%) and HPMC K 100M (44.16%) were granulated by binder solution containing IPA: water in ratio of 8:2. The resulting granules were dried. To this granulated mixture polymer HPMC K 100M (29.7%) along with

diluent MCC (19.8%) were mixed extragranularly. The blend was lubricated with talc (0.4%) and magnesium stearate (0.4%). The blend was processed for compression under suitable pressure to formulate tablets. The resulting tablets were evaluated for drug release and assay content. Tablet showed good in vitro drug release profile with desired characteristics.

Example 15

The drug Ivabradine hydrochloride (5.39%), diluent MCC (13.6%) and one release retarding polymer HPMC K 4M (30%) were granulated by solvent (IPA: water in ratio of 8:2). The granules were dried at suitable temperature and mixed with another release retardant polymer HPMC K100M (30%) along with remaining quantity of diluent MCC (20%). The blend was lubricated with talc (0.5%) and magnesium stearate (0.5%). The lubricated granules were compressed into tablets. The tablets were evaluated for drug release and assay content. The tablets were coated with suitable colouring material optionally.

Example 16

Ivabradine hydrochloride (6.73 %), release retarding polymer HPMC K4M (37.5%) and MCC (17.01%) were mixed and granulated with IPA: water (8:2) solvent mixture. After drying the granules were lubricated with talc (0.6%) and magnesium stearate (0.6%). Remaining amount of release retarding polymers HPMC K-4M (15%) and HPMCK-100M (22.5%) were added extra-granularly. The granules were compressed and resulting tablets were evaluated for drug release profile and assay content.

Example 17

The composition of previous example 16 also produced the sustained release effect of drug when tablets were formulated with non aqueous wet granulation technique. The solvent used was iso-propyl alcohol which contained PVP K30 (3.21%). The amount of MCC was reduced to (13.8%).

Example 18

Here, the sustained release formulation of Ivabradine was also prepared with higher amount of PVP K30. The procedure applied was same as that of used in previous example 17. i.e. non aqueous wet granulation method. The solvent used was IPA which contained
5 PVP K 30 (4.6%). The drug Ivabradine hydrochloride was weighed (6.73%) and was mixed with one release retarding polymer HPMC K-4M (42.18%) and diluent MCC (6.38%). The powder blend was granulated by 4.68 % PVP K 30 solution in isopropyl alcohol. The granules were dried and mixed with remaining amount of first release retarding polymer HPMC K-4M (13.1%) and another grade of release retarding polymer
10 i.e. Hydroxy-propyl-methyl-cellulose HPMC K-100M (24.3%). The granules were compressed to tablets which were further evaluated for drug release profile and assay content.

Example 19

15 The drug (6.73%), MCC (6.38%) and release retarding polymer HPMC K4M (42.18%) were sieved and granulated using IPA as solvent containing PVP K30 (4.68%) as binder. The granules were dried and lubricated with talc (0.62%) and magnesium stearate (1.87%). The another release retarding polymer HPMC K100M (37.5%) was added extra-granularly to above blend. The granules were then compressed into tablets. Tablets were
20 coated optionally further with suitable coating materials comprising approved colorants.

Example 20

The sustained release tablets were also formulated by replacing the diluent MCC with dicalcium phosphate (DCP). 6.73 % Ivabradine was mixed with 17.01 % DCP, 37.5 %
25 HPMC K4M, 0.62 % talc and 0.62 % magnesium stearate. Blend was triturated with 8:2 solution of isopropyl alcohol and water. This mixture was processed for pre-compression. After that remaining 15% HPMC K4M and 22.5 % HPMC K100M was added to the slugged mixture. Finally the blend was compressed into the tablets

Example 21

30 Ivabradine hydrochloride (6.34%) was weighed accurately, sieved and mixed with DCP (16.01%) and HPMC K4M (35.29%) properly. The blend was granulated with solvent

mixture of isopropyl alcohol and water (8:2). The granules were dried and mixed with additional quantity of HPMC K4M (14.11%) along with HPMC K100M (27.05%) extragranularly and the final blend was lubricated with talc (0.58%) and magnesium stearate (0.58%). The free flowing granules were compressed into tablets at suitable pressure and evaluated for parameters like release profile and assay content.

Example 22

The tablets were also formulated by introducing ethyl cellulose into the formulae. The drug Ivabradine hydrochloride (6.73%), DCP (54.51%) HPMC K4M (35.5%) were mixed appropriately. The powder blend was granulated with ethyl cellulose (1.25%) in IPA. The granules were lubricated to improve the flow property with talc (1%) and magnesium stearate (1%) after drying. The lubricated granules were compressed into tablets, which were evaluated for release profile and assay content. The tablets were coated further optionally with suitable approved colouring material.

Example 23

The Ivabradine HCl (6.73%), DCP (54.51%) were mixed and granulated with ethylcellulose (1.25%) in IPA. The granules were mixed with release retarding polymer HPMC K4M (13.62%) and HPMC K100M (21.87%). The blend was lubricated with talc (1%) and magnesium stearate (1%). The lubricated granules were compressed to tablets, which were evaluated for release profile and assay content. The tablets were coated further optionally with suitable approved colour to improve the elegance of the finished formulation.

Example 24

The drug, MCC, and release retarding polymer HPMC K4M were taken at 6.73%, 17.01% and 50% concentration respectively. They were sieved and mixed. The blend was granulated by binder solution of IPA and water (8:2). The granules were dried, and mixed with another grade of release retarding polymer HPMC K100M (24.25%). The powder blend was lubricated with talc (1%) and magnesium stearate (1%) and compressed. The tablets evaluated for drug release and assay content.

Example 25

The drug, MCC, and release retarding polymer HPMC K4M were taken at 5.39%, 13.61% and 40% concentration respectively. They were sieved and mixed. The blend was granulated by binder solution of IPA and water (8:2). The granules were dried, and mixed
5 with additional amount of release retarding polymer HPMC K4M (11.5%) along with another release retarding polymer HPMC K100M (27.5%). The powder blend was lubricated with talc (1%) and magnesium stearate (1%) and compressed. The tablets evaluated for drug release and assay content.

10 Example 26

Active substance Ivabradine hydrochloride (6.53%), MCC (16.49%) and release retarding polymer HPMC K15M (54.54%) were weighed, sieved and mixed properly. This powder mixture was granulated using solvent mixture of IPA and water (8:2). The obtained granules were dried at suitable temperature and were mixed with another grade of release
15 retarding polymer HPMC K100M (20%). The above blend was lubricated to improve the flow property with talc (0.6%) and magnesium stearate (1.81%). The granules were compressed at suitable hardness. The tablets were evaluated for release profile and assay content.

20 Example 27 to Example 30

Examples 27 to 30 were formulated by applying dry granulation technique. The common procedure for the preparation of sustained release tablets of these examples was to mix active medicament Ivabradine or its salt with diluent microcrystalline cellulose and HPMC K15 M (HPMC K100 M in case of example 30) in the specified amount as
25 mentioned in the table below. This step was followed by addition of lubricant and glidant into the previous blend. The next step involved pre-compression (slugging) of this blend. In the next step the formed slug was broken and HPMC K100 M was added along with lubricant and glidant in the remaining quantity. The amount of the materials to be added after pre-compression is shown as asterisk mark. The final blend was then compressed
30 into tablets using suitable tablet compression machine. The tablets were evaluated for drug content and invitro drug release profile.

Example	27	28	29	30
Drug	6.53	6.53	6.53	9.8
MCC	40.73	28.61	16.49	16.26
HPMC K-15M	30.30	42.42	54.54	-----
HPMC K-100M	19.39*	19.39*	19.39*	51.51+19.39*
Talc	0.3+0.6*	0.3+0.6*	0.3+0.6*	0.3+0.6*
Mg. Stearate	0.3+1.81*	0.3+1.81*	0.3+1.81*	0.3+1.81*

Example 31

Sustained release tablets of Ivabradine or its salt were prepared by using stearic acid by melt granulation technique. The stearic acid was used in 58.07 % amount and drug was also added in 10.8 % proportions. The granules were prepared by melt granulation technique. This was mixed with 29.15 % amount of lactose followed by its lubrication with talc (1.09%) and magnesium stearate (1%). The granules were compressed into tablets. The blend was punched using direct compression and the tablets prepared by this method showed the drug release up to 24 hours when tested in vitro for drug dissolution profile as depicted in Figure 6.

Example 32

Sustained release tablets of Ivabradine hydrochloride were prepared using methacrylic acid polymers. 5.39 % amount of active drug Ivabradine was mixed with 40 % amount of Eudragit RS 100 and 20% amount of Eudragit RS 30D. To this mixture 32.61 % amount of microcrystalline cellulose was added. The blend was lubricated with magnesium stearate (1%) and aerosil (1%). The lubricated blend then compressed into tablets using direct compression technique with tablet press machine. The tablets were further evaluated for drug dissolution profile and assay content. The tablets prepared using these polymers sustained the drug release up to 24 hours when they were tested in vitro for drug dissolution profile

Figure 1 provides the drug release profile of the composition according to examples 1 to 32 which shows the sustained release of the drugs.

Figure 3 shows that comparison of the release profile of the sustained release composition according to present invention (Example 2) compared with known immediate drug.

5 The immediate release marketed tablets of Ivabradine used to compare with the formulation of present invention typically contains number of excipients in the core viz. lactose monohydrate, magnesium stearate, maize starch, maltodextrin, silica colloidal anhydrous, and the film-coating of hypromellose, titanium dioxide, macrogol 6000, glycerol, magnesium stearate, yellow iron oxide, red iron oxide.

10

Where as the composition disclosed in the invention contain minimum number of excipients which imparts economical benefit to the formulation and reduces the finished formulation cost.

15 The marketed formulation involves the critical processes like coating, but the inventive formulation involves the simple process of manufacturing which can be easily implemented into industry with minimum machinery requirements and is also less time consuming which ultimately increases the productivity.

20 Under mimicked physiological conditions, the active drug Ivabradine is rapidly released within 1 hour from the immediate release marketed tablets. The tablet needs to be taken at least twice a day to maintain the physiological concentration inside the body and to achieve therapeutic effect.

25 Where as the drug release profile of inventive formulation is capable of retarding the release of active drug upto 24 hours to maintain physiological concentration of drug for the complete day; thereby it minimizes the dosing frequency and also side effects which contributes in increasing the patient compliance.

30 The figure 3 clearly shows that the sustained nature of drug release of the present composition

Comparative Example A

Here, the weight ratio of drug to total concentration of release retardant polymer ratio was kept below 1:5 (drug: polymer). 10.78 % amount of active pharmaceutical ingredient Ivabradine or its salt was incorporated with 47.22 % microcrystalline cellulose and 40 %
5 HPMC K4M. The powder blend was granulated using solvent mixture of isopropyl alcohol and water in 8:2 ratio. Granules were dried, followed by lubrication with talc (1%) and magnesium stearate (1%). This final blend was compressed into tablets. The compressed tablets were further evaluated for drug release profile and assay content. The tablets prepared by this composition were not able to provide the sustained release of drug
10 with desired pattern for specified time period. The release profile is depicted in Figure 4.

Comparative Example B

Here, the weight ratio of drug to total concentration of release retardant polymer was kept above 1:15 (drug: polymer). 5.33 % amount of active pharmaceutical ingredient
15 Ivabradine or its salt was incorporated with 6.67 % amount of microcrystalline cellulose and 86 % amount of HPMC K4M. The powder blend was granulated using solvent mixture of isopropyl alcohol and water in 8:2 ratio. Granules were dried, followed by lubrication with talc (1%) and magnesium stearate (1%). This final blend was compressed into tablets. The compressed tablets were further evaluated for drug release profile and
20 assay content. The tablets prepared by this composition also were not able to provide the sustained release of drug with desired pattern for specified time period. The release profile is depicted in Figure 4.

Fig 4 shows the criticality of the ratio of the drug to the release retardant which is
25 important to impart the appropriate sustained release.

Comparative Example C

Here, the weight of release retardant polymer is kept below the concentration of the present invention i.e. 30%. 10.78 % amount of active pharmaceutical ingredient
30 Ivabradine or its salt was incorporated with diluent microcrystalline cellulose 70.22 % and release retarding polymer HPMC K4M in 17%. The powder blend was granulated using solvent mixture of isopropyl alcohol and water in 8:2 ratio. Granules were dried,

followed by lubrication with talc (1%) and magnesium stearate (1%). This final blend was compressed into tablets. The compressed tablets were further evaluated for drug release profile and assay content. The tablets prepared with this composition were failed to provide the sustained release of drug with desired release pattern. The release profile is depicted in Figure 5.

Comparative Example D

The composition containing the weight of release retardant polymer above 90% was tested for desired sustained release of drug for the time-points assigned. The composition included the active drug Ivabradine as base or in suitable salt form or suitable derivative thereof in 5.36%, the diluent MCC in 2% concentration. The above powders were mixed with the quantity of first release retardant i.e. HPMC K15 M (50%). The blend was granulated by binder solution of IPA and water (8:2) to form a wet mass which was sieved to form granules. The wet granules were dried at suitable temperature and mixed with second release retarding polymer i.e. HPMC K100M (42%), the blend was lubricated with magnesium stearate (0.5%) to modify the flow property of the granules. The granules were compressed to obtain tablets which were further evaluated for drug release and assay content. The release profile was not found as desired, the release of drug through matrix was too slow. The results were represented in graphical format in figure 5.

This clearly shows the criticality of the amount of the release retardant in achieving the required sustained release profile.

Stability Testing:

Stability study of sustained release formulations of Ivabradine and its salt was conducted as per ICH guidelines. Sustained release tablets of Ivabradine were tested periodically for appearance, thickness, diameter, weight variation, assay, product, hardness and in vitro drug release profile. Results of stability study revealed that tablets were stable in terms of above parameters. The stability profile is depicted in Figure 2.

CLAIMS

1. A sustained release composition of Ivabradine, which is capable of releasing at least 80% of active drug in 24 hours, the said composition comprising:

5

- a) Ivabradine as a base or salt thereof or suitable derivative thereof as active ingredient in therapeutically effective amount;
- b) Release retarding polymers selected from the group comprising cellulose ethers in amount of about 30% to 90 % by weight;
- 10 c) Pharmaceutically acceptable excipients selected from the category of binders, diluents, lubricants, glidants, solvents, co solvents, preservatives, buffering agents, acidifiers, surfactant, channeling agents, release retardants, coating materials, colorants, and flavors.

15

2. The composition according to claim 1, wherein the weight ratio of drug to release retarding polymer is about 1:5 to 1:15.

20

3. The composition as claimed in claim 1, wherein the release retarding polymer is cellulose ether which is present in about 50% to about 90% of the composition, more preferably about 70% to about 90% of the composition.

25

4. The composition according to claim 1, wherein release retarding polymer is present as a single or in combination of two different viscosity grade polymers where the viscosity of such polymers is in the range of about 60 to 1,20,000 cps.

30

5. The composition according to claim 1, wherein the binder used is selected from povidone (polyvinylpyrrolidone), acacia, tragacanth, carrageen, alginates, and others such as carboxypolymethylene, gelatin, starch and modified starch derivatives more specifically povidone (polyvinylpyrrolidone) in concentration of about 1 to 5% of the total weight of composition.

6. The composition according to claim 1, wherein the release retarding polymer are selected from the group comprising of hydrophilic and hydrophobic polymers, cellulose derivatives, natural gums and water insoluble polymers.
- 5 7. The composition according to claim 6, wherein the cellulose derivatives are selected from the group comprising methylcellulose, ethyl cellulose, hydroxomethyl cellulose, different viscosity grades of hydroxypropyl methylcellulose, hydroxy propyl cellulose, hydroxyethylcellulose, carboxymethyl cellulose.
- 10 8. The composition according to claim 6, wherein hydrophilic polymers are selected from the group comprising a protein, a polysaccharide, a polyacrylate, a hydrogel, polyvinyl alcohol or polyvinyl pyrrolidone, carbopols, polyethylene oxides, magnesium aluminum silicate, modified starch derivatives or a derivative of such
- 15 hydrophilic polymers and a combination thereof.
9. The composition according to claim 6, wherein hydrophobic polymers are selected from the group comprising of ethylcellulose, a copolymer of acrylic acid and methacrylic acid esters, polyethylene, polyamide, polyvinylchloride,
- 20 polyvinyl acetate or mixtures thereof.
10. The composition according to claim 6, wherein natural gums are selected from the group comprising of acacia, gum tragacanth, locust bean gum, guar gum, karaya gum, modified cellulosic, agar, pectin, carrageen, alginate, carboxypoly methylene,
- 25 gelatin, casein, zein, bentonite as single or in combination thereof.
11. The composition according to claim 6, water insoluble polymers are selected from the group comprising of polyacrylic acids, acrylic resins, acrylic latex dispersions, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl
- 30 methylcellulose phthalate and a combination thereof.

12. The composition according to claim 1, wherein the release retarding polymers are selected from Stearic acid with other fatty acid esters of which are but not limiting to glyceryl monostearate, palmitic, behenic acid, glyceryl behenate, glyceryl palmitostearate, hydrogenated castor oil or other natural waxes etc.

5

13. The composition according to claim 1, wherein formulation comprises of diluents/compression aids and disintegrants selected from lactose, microcrystalline cellulose, dicalcium phosphate, sucrose, mannitol, xylitol, starch; Lubricants selected from magnesium stearate, sodium stearyl fumarate and stearic acid and its derivatives, talc and colloidal silica; Flow aids selected from silicon dioxide, magnesium stearate, talc.

10

14. The composition according to claim 1, which is formulated in the form of tablet, capsule, granules, sachet, typically a tablet with or without coating, bi-layered tablet, functional coated tablets or caplets, time- release tablets or caplets, floating tablets, matrices containing wax or polymer, controlled release beads, granules, spheroids that are contained within a capsule or administered from a sachet or other unit dose powder device in combination with other beneficial drugs or as a combination kit of sustained release dosage forms for the administration in mammals.

15

20

15. The composition according to claim 1, is in the form of sustained release matrix tablets.

25

16. A process for preparation of sustained release dosage form comprising Ivabradine or its salts, release retardant in amount of about 30 to 90% and pharmaceutically acceptable excipients, said process comprising the steps of dispensing, sieving, sifting, lubrication, compression and optionally coating.

30

17. The process for preparing a sustained release formulation according to claim 16, wherein tablets, capsules, granules, beads, spheroids are formed which are optionally coated using suitable coating system comprising suitable coating

materials and colorants dissolved or dispersed in suitable aqueous or non-aqueous solvents.

- 5 18. The process as claimed in claim 17 wherein the tablet is prepared selectively by dry granulation, wet granulation, direct compression or melt extrusion.

1/3

Fig. 1. Representative Drug Release profile of Example 1 to Example 32

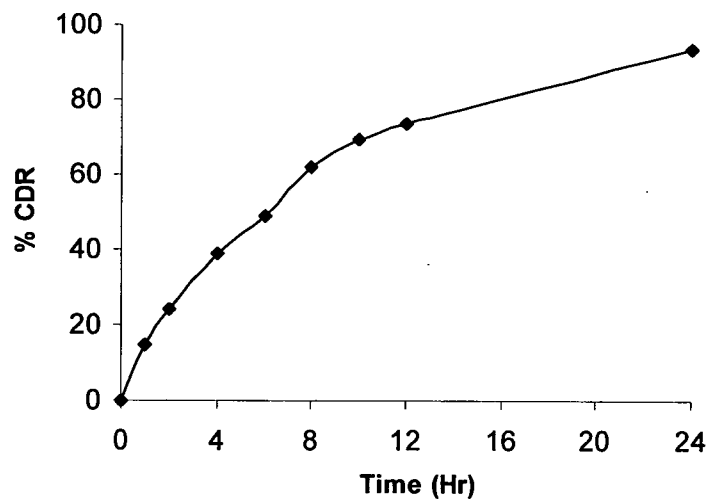
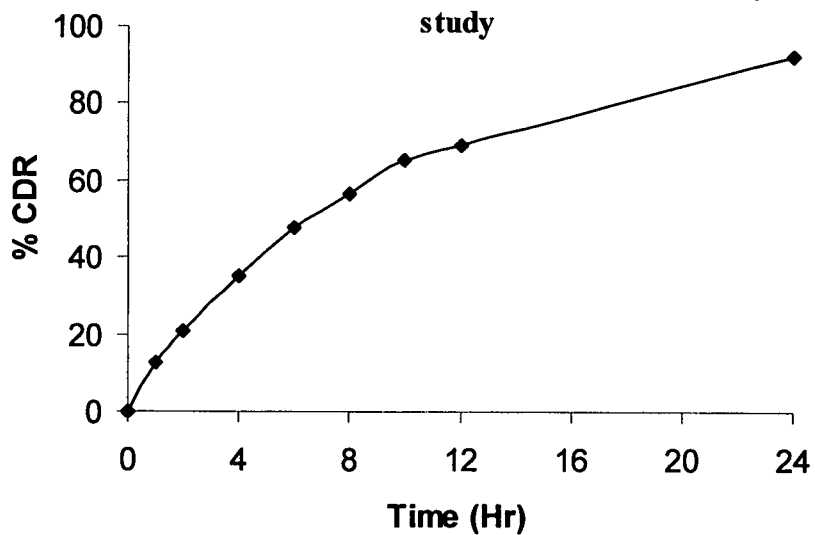
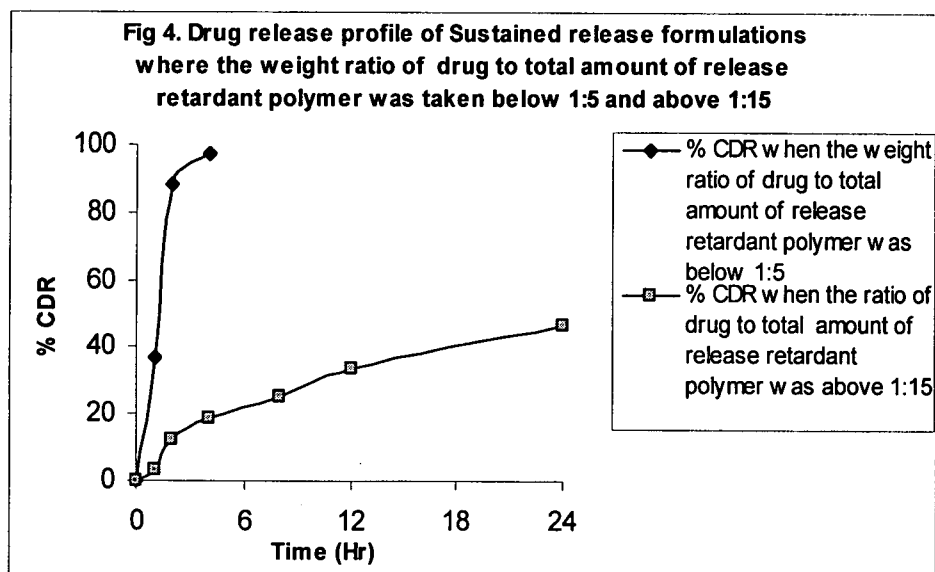
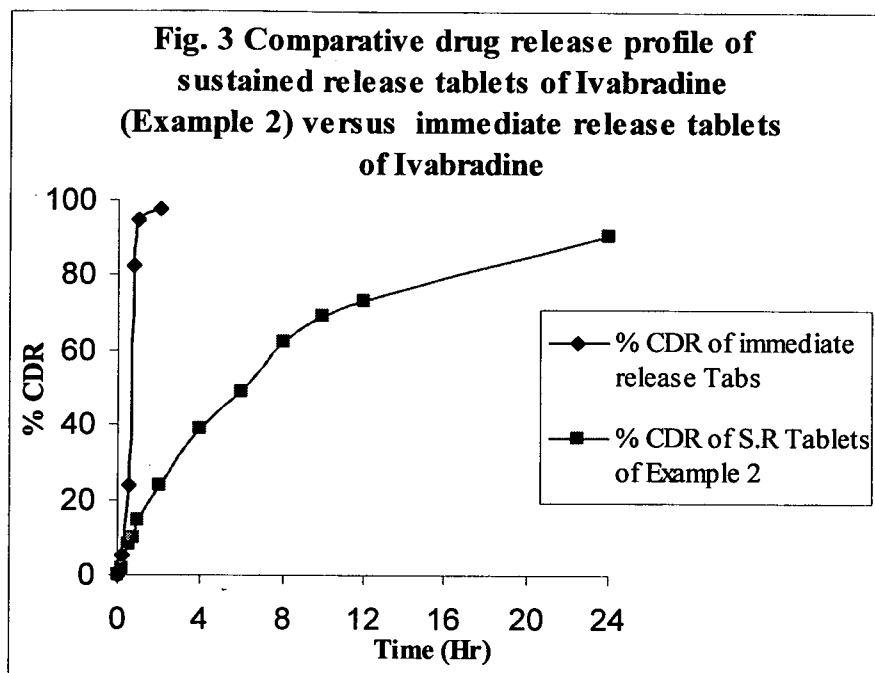


Fig. 2. Drug release profile of Sustained release tablets of Ivabradine or its salt after stability study



2/3



3/3

