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(54) Title: PROLONGED RELEASE PHARMACEUTICAL COMPOSITIONS OF IVABRADINE

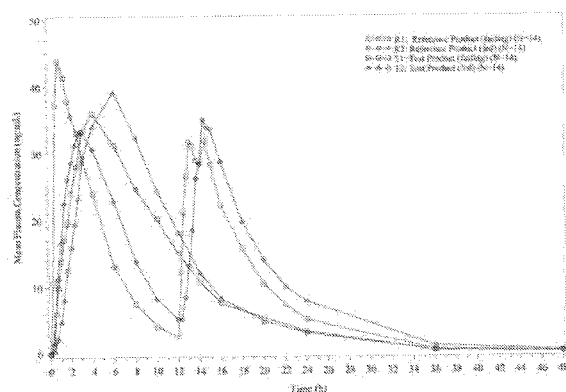


FIG. 1A

(57) Abstract: The present disclosure describes prolonged release pharmaceutical compositions of ivabradine, N-desmethyl ivabradine, or pharmaceutically acceptable salts thereof.



PROLONGED RELEASE PHARMACEUTICAL COMPOSITIONS OF IVABRADINE

TECHNICAL FIELD

[0001] The present disclosure relates to prolonged release pharmaceutical compositions
5 of ivabradine and pharmaceutically acceptable salts thereof.

BACKGROUND

[0002] Ivabradine is a medication used for the symptomatic management of stable heart-
related chest pain and heart failure not fully managed by beta blockers. There are several
marketed formulations of immediate release ivabradine or pharmaceutically acceptable salts
10 thereof. However, under physiological conditions, when administered in the form of a tablet,
ivabradine is rapidly released from tablet. Following oral administration, a peak plasma
level reached in about 1 hour under fasting conditions.

[0003] However, there are certain drawbacks of administering the immediate release
dosage

15 forms of ivabradine or pharmaceutically acceptable salts thereof. The high solubility of
ivabradine, and therefore the rapid dissolution in the gastrointestinal tract, followed by rapid
absorption into the blood stream causes an abrupt reduction of the heart rate which results in
the patient experiencing symptoms related to bradycardia such as dizziness, fatigue or
hypotension.

SUMMARY OF THE INVENTION

[0004] The effectiveness of ivabradine is limited by its high solubility, low mean
residence time, and short half-life. Accordingly, there exists a need for pharmaceutical
compositions of ivabradine which provide prolonged release of drug and maintain the blood
25 drug concentration in therapeutic window for, preferably, at least 24 hours thereby avoiding
the complications of fast dissolution.

[0005] In one aspect, disclosed are solid prolonged release compositions comprising
ivabradine, N-desmethyl ivabradine, or a pharmaceutical salt thereof. In some aspects, the
ivabradine of the disclosed compositions may have a peak plasma concentration between
30 about 3 hours to about 8 hours after administration of the composition to a subject in the

fasting state or between about 4 hours to about 10 hours after administration of the composition to a subject in the fed state.

[0006] In some aspects, the prolonged release compositions comprise about 3 to about 12% by weight of ivabradine, N-desmethyl ivabradine, or a pharmaceutical salt thereof, about 35% to about 65% by weight of polymer selected from hydroxypropyl methyl cellulose, polyvinyl acetate/polyvinylpyrrolidone, hydroxyethyl cellulose, hydroxypropyl cellulose or mixtures thereof, about 20% to about 60% by weight of dibasic calcium phosphate, and about 0.25% to about 1.25% by weight of magnesium stearate.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] FIGS. 1A-1B are graphs of the mean plasma concentration versus time for ivabradine plotted linearly (FIG. 1A) and semi logarithmically (FIG. 1B).

[0008] FIGS. 2A-2B are graphs of the mean plasma concentration versus time for N-desmethyl ivabradine plotted linearly (FIG. 2A) and semi logarithmically (FIG. 2B).

[0009] FIG. 3 is a box plot of the mean heart rate (HR) change from baseline to 3 months following treatment with ivabradine immediate release or prolonged release tablets. The boxes represent the inter quartile range (IQR). The symbols inside the boxes are the mean values and those outside the boxes are data values beyond ± 1.5 IQR. Whiskers are drawn at minimum and maximum data points between the ± 1.5 IQR.

DETAILED DESCRIPTION

[0010] Disclosed herein are prolonged release compositions of ivabradine. The compositions can be used for once-a-day administration of ivabradine.

1. Definitions

[0011] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. In case of conflict, the present document, including definitions, will control. Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can be used in practice or testing of the present disclosure. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting.

[0012] The terms “comprise(s),” “include(s),” “having,” “has,” “can,” “contain(s),” and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or

words that do not preclude the possibility of additional acts or structures. The singular forms “a,” “an” and “the” include plural references unless the context clearly dictates otherwise. The present disclosure also contemplates other embodiments “comprising,” “consisting of,” and “consisting essentially of,” the embodiments or elements presented herein, whether explicitly set forth or not.

[0013] The modifier “about” used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (for example, it includes at least the degree of error associated with the measurement of the particular quantity). The modifier “about” should also be considered as disclosing the range defined by the absolute values of the two endpoints. For example, the expression “from about 2 to about 4” also discloses the range “from 2 to 4.” The term “about” may refer to plus or minus 10% of the indicated number. For example, “about 10%” may indicate a range of 9% to 11%, and “about 1” may mean from 0.9-1.1. Other meanings of “about” will be apparent from the context, such as rounding off, so, for example “about 1” may also mean from 0.5 to 1.4.

[0014] For the recitation of numeric ranges herein, each intervening number there between with the same degree of precision is explicitly contemplated. For example, for the range of 6-9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the number 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, and 7.0 are explicitly contemplated.

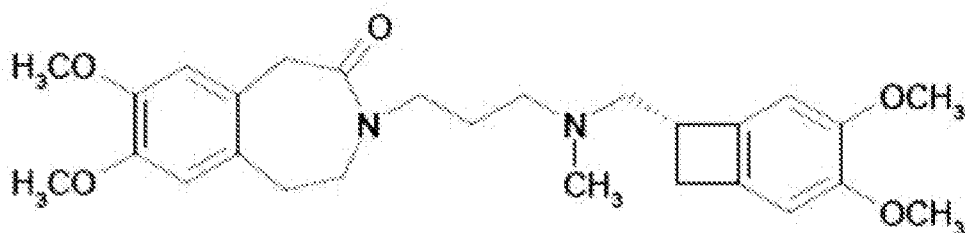
[0015] The term “prolonged release” herein refers to any formulation or composition that comprises an active drug and which is formulated to release the drug for longer duration of time and to provide a longer duration of pharmacological response after administration of the composition than is ordinarily not experienced after administration of a corresponding immediate release formulation comprising the same drug in the same amount. Prolonged release formulations include, inter alia, those formulations described elsewhere as “controlled release”, “delayed release”, “sustained release”, “extended release”, “programmed release”, “time release,” “modified release” and/or “rate controlled” formulations or compositions. Further for the purposes of this disclosure, “prolonged release” refers to release of an active pharmaceutical agent over a prolonged period of time, such as for example over a period of 8, 12, 16 or 24 hours.

[0016] By “pharmaceutically acceptable” is meant a carrier comprised of a material that is not biologically or otherwise undesirable.

[0017] The term “ivabradine” as used in the disclosure is meant to cover ivabradine in the form of free base or its pharmaceutically acceptable salt(s), hydrate(s), solvate(s) and

physiologically functional derivative(s) and precursors thereof. The term also includes all polymorphic forms, whether crystalline or amorphous. The chemical name for ivabradine is 3-(3-{[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7yl)methyl] methyl amino}propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one, hydrochloride.

- 5 The molecular formula is $C_{27}H_{36}N_2O_5$, HCl, and the molecular weight (free base + HCl) is 505.1. The chemical structure of ivabradine is as follows:



2. Compositions of the Present Disclosure

- 10 [0018] The present disclosure provides solid prolonged release compositions comprising ivabradine, N-desmethyl ivabradine, or a pharmaceutical salt thereof. The ivabradine of the disclosed compositions may have a peak plasma concentration between about 3 hours to about 8 hours after administration of the composition to a subject in the fasting state or between about 4 hours to about 10 hours after administration of the composition to a subject in the fed state.

- 15 [0019] The present disclosure also provides a solid prolonged release composition comprising:

- (a) ivabradine, N-desmethyl ivabradine, or a pharmaceutical salt thereof;
- (b) at least one polymer; and
- (c) optionally one or more pharmaceutically acceptable carriers.

- 20 [0020] In one aspect, the solid prolonged release composition comprises polymer selected from hydroxypropyl methyl cellulose, polyvinyl acetate/polyvinylpyrrolidone, hydroxyethyl cellulose, hydroxypropyl cellulose or mixtures thereof.

[0021] In one aspect, the solid prolonged release composition comprises

- 25 about 3% to about 12% by weight of ivabradine, N-desmethyl ivabradine, or a pharmaceutical salt thereof;

about 35% to about 65% by weight of polymer selected from hydroxypropyl methyl cellulose, polyvinyl acetate/polyvinylpyrrolidone, hydroxyethyl cellulose, hydroxypropyl cellulose or mixtures thereof;

- 30 optionally one or more pharmaceutically acceptable carriers. The % by weight is based on total weight of the composition.

[0022] The prolonged release composition can be coated with a film. In some embodiments, the composition is coated with about 2% to about 4% by weight of a film coating material. The film coating can be any of those known in the art. In some embodiments, the film coating material can be a mixture of titanium dioxide, polyethylene glycol, hydroxypropyl methyl cellulose, glycerin, yellow iron oxide non-irradiated, and red iron oxide non-irradiated.

[0023] The composition is a solid dosage form that includes, but is not limited to, tablets, pills, dragees, caplets, mini-tablets, pellets, granules, capsule, capsule filled with mini-tablets or pellets or combinations thereof. In some embodiments the composition is a tablet.

[0024] In an embodiment, the present disclosure provides a solid prolonged release composition comprising:

ivabradine, N-desmethyl ivabradine, or a pharmaceutical salt thereof;

polymer selected from hydroxypropyl methyl cellulose, polyvinyl acetate/polyvinylpyrrolidone, hydroxyethyl cellulose, hydroxypropyl cellulose or mixtures thereof;

dibasic calcium phosphate; and

magnesium stearate.

[0025] The prolonged release composition may include about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11% or about 12% by weight of ivabradine, N-desmethyl ivabradine, or a pharmaceutical salt thereof. In certain embodiments, the composition comprises about 8% by weight of ivabradine, N-desmethyl ivabradine, or a pharmaceutical salt thereof.

[0026] In some embodiments, the prolonged release composition comprises hydroxypropyl methyl cellulose. The composition may comprise about 35% to about 65% by weight hydroxypropyl methyl cellulose. In some embodiments, the composition comprises about 35%, about 40%, about 45%, about 50%, about 55%, about 60% or about 65% by weight hydroxypropyl methyl cellulose. In certain embodiments, the composition comprises about 50% by weight of hydroxypropyl methyl cellulose.

[0027] The prolonged release composition may include about 20% to about 60%, about 20% to about 50%, about 20% to about 40%, about 20% to about 30%, about 30% to about 60%, about 30% to about 50%, about 30% to about 40%, about 40% to about 50%, about 40% to about 60% or about 50% to about 60% by weight dibasic calcium phosphate. In some embodiments, the composition comprises about 41% by weight of dibasic calcium phosphate.

[0028] The prolonged release composition may include about 0.25%, about 0.5%, about 0.75%, about 1.00%, or about 1.25% by weight of magnesium stearate. In certain embodiments, the composition comprises about 1% by weight magnesium stearate.

[0029] In an embodiment, the present disclosure provides a composition comprising:

- 5 ivabradine is present in an amount ranging from 5.39 to 8.09% by weight;
 hydroxypropyl methyl cellulose is present in an amount ranging from 25 to 55% by weight;
 dibasic calcium phosphate is present in an amount ranging from 35.91 to 65.91% by weight; and
10 magnesium stearate is present in an amount of 1% by weight.

[0030] In an embodiment, the present disclosure provides a composition comprising:

- about 8% by weight of ivabradine hydrochloride;
 about 50% by weight of hydroxypropyl methyl cellulose;
 about 41% by weight of dibasic calcium phosphate; and
15 about 1% by weight of magnesium stearate.

The percentage (%) by weight is based on total weight of the composition.

[0031] In one aspect, the present disclosure further provides a solid prolonged release composition comprising:

- ivabradine in an amount ranging from 7.81 to 8.09% by weight;
20 hydroxypropyl methyl cellulose in an amount ranging from 48.31 to 50% by weight;
 dibasic calcium phosphate in an amount ranging from 40.01 to 40.41% by weight;
 magnesium stearate is present in an amount of 0.97-1% by weight; and
25 colourant in an amount of 2.90% by weight.

[0032] The prolonged release composition may further include pharmaceutically acceptable carriers. The term “pharmaceutically acceptable carrier,” as used herein, means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material, or formulation auxiliary of any type. Some examples of materials which can serve as
30 pharmaceutically acceptable carriers are sugars such as, but not limited to, lactose, glucose and sucrose; starches such as, but not limited to, corn starch and potato starch; cellulose and its derivatives such as, but not limited to, sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as, but not limited to, cocoa butter and suppository waxes; oils such as, but not limited to, peanut oil,

cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols; such as propylene glycol; esters such as, but not limited to, ethyl oleate and ethyl laurate; agar; buffering agents such as, but not limited to, magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as, but not limited to, sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0033] Carriers for systemic (i.e., oral) administration typically include at least one of diluents, lubricants, binders, disintegrants, colorants, flavors, sweeteners, antioxidants, preservatives, glidants, solvents, suspending agents, wetting agents, surfactants, combinations thereof, and others.

[0034] Suitable diluents include sugars such as glucose, lactose, dextrose, and sucrose; diols such as propylene glycol; calcium carbonate; sodium carbonate; sugar alcohols, such as glycerin; mannitol; and sorbitol. The amount of diluent(s) in a systemic or topical composition is typically about 50% to about 90% by weight.

[0035] Suitable lubricants include silica, talc, stearic acid and its magnesium salts and calcium salts, calcium sulfate; and liquid lubricants such as polyethylene glycol and vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma. The amount of lubricant(s) in a systemic or topical composition is typically about 5% to about 10% by weight.

[0036] Suitable binders include polyvinyl pyrrolidone; magnesium aluminum silicate; starches such as corn starch and potato starch; gelatin; tragacanth; and cellulose and its derivatives, such as sodium carboxymethylcellulose, ethyl cellulose, methylcellulose, and microcrystalline cellulose. The amount of binder(s) in a systemic composition is typically about 5% to about 50% by weight.

[0037] Suitable disintegrants include agar, alginic acid and the sodium salt thereof, effervescent mixtures, croscarmellose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion exchange resins. The amount of disintegrant(s) in a systemic or topical composition is typically about 0.1% to about 10% by weight.

[0038] Suitable colorants include a colorant such as an FD&C dye. When used, the amount of colorant in a systemic or topical composition is typically about 0.005% to about 0.1% by weight.

[0039] Suitable flavors include menthol, peppermint, and fruit flavors. The amount of flavor(s), when used, in a systemic or topical composition is typically about 0.1% to about 1.0% by weight.

[0040] Suitable sweeteners include aspartame and saccharin. The amount of sweetener(s) in a systemic or topical composition is typically about 0.001% to about 1% by weight.

[0041] Suitable antioxidants include butylated hydroxyanisole ("BHA"), butylated hydroxytoluene ("BHT"), and vitamin E. The amount of antioxidant(s) in a systemic or topical composition is typically about 0.1% to about 5% by weight.

[0042] Suitable preservatives include benzalkonium chloride, methyl paraben and sodium benzoate. The amount of preservative(s) in a systemic or topical composition is typically about 0.01% to about 5% by weight.

[0043] Suitable glidants include silicon dioxide. The amount of glidant(s) in a systemic or topical composition is typically about 1% to about 5% by weight.

[0044] Suitable solvents include water, isotonic saline, ethyl oleate, glycerine, hydroxylated castor oils, alcohols such as ethanol, and phosphate buffer solutions. The amount of solvent(s) in a systemic or topical composition is typically from about 0 to about 100% by weight.

[0045] Suitable suspending agents include AVICEL RC-591 (from FMC Corporation of Philadelphia, Pa.) and sodium alginate. The amount of suspending agent(s) in a systemic or topical composition is typically about 1% to about 8% by weight.

[0046] Suitable surfactants include lecithin, Polysorbate 80, and sodium lauryl sulfate, and the TWEENS from Atlas Powder Company of Wilmington, Del. Suitable surfactants include those disclosed in the C.T.F.A. Cosmetic Ingredient Handbook, 1992, pp. 587-592; Remington's Pharmaceutical Sciences, 15th Ed. 1975, pp. 335-337; and McCutcheon's Volume 1, Emulsifiers & Detergents, 1994, North American Edition, pp. 236-239. The amount of surfactant(s) in the systemic or topical composition is typically about 0.1% to about 5% by weight.

[0047] The selection of ingredients in the carrier for oral compositions depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this disclosure.

[0048] Solid compositions can be coated by conventional methods, typically with pH or time-dependent coatings, such that a disclosed compound is released in the gastrointestinal tract in the vicinity of the desired application, or at various points and times to extend the desired action. The coatings typically include one or more components selected from cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, EUDRAGIT® coatings (available from Evonik Industries of Essen, Germany), waxes and shellac.

[0049] In yet another embodiment, the present disclosure provides a process for preparing the solid prolonged release composition, wherein the process comprises a direct compression method. In a further embodiment, the present disclosure provides that the process for preparing the disclosed composition comprises preparing a tablet dosage form, comprising:

- (a) blending ivabradine, N-desmethyl ivabradine, or a pharmaceutical salt thereof, the at least one polymer, and pharmaceutically acceptable carriers together to obtain a pharmaceutical tablet formulation; and
- (b) compressing the tablet formulation obtained in step (a) to form a compressed tablet dosage form.

3. Pharmacokinetics

[0050] After administration of the prolonged release composition to a subject in the fasting state, ivabradine may have a peak plasma concentration between about 3 hours to about 8 hours.

[0051] The plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fasting state at about 3 hours can be between about 22.0 and about 59.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fasting state at about 3 hours can be at least 22.0 ng/mL, at least 23.0 ng/mL, at least 24.0 ng/mL, at least 25.0 ng/mL, at least 26.0 ng/mL, at least 27.0 ng/mL, at least 28.0 ng/mL, at least 29.0 ng/mL, at least 30.0 ng/mL, at least 31.0 ng/mL, at least 32.0 ng/mL, at least 33.0 ng/mL, at least 34.0 ng/mL, at least 35.0 ng/mL, at least 36.0 ng/mL, at least 37.0 ng/mL, at least 38.0 ng/mL, at least 39.0 ng/mL, at least 40.0 ng/mL, at least 41.0 ng/mL, at least 42.0 ng/mL, at least 43.0 ng/mL, at least 44.0 ng/mL, at least 45.0 ng/mL, at least 46.0 ng/mL, at least 47.0 ng/mL, at least 48.0 ng/mL, at least 49.0 ng/mL, at least 50.0 ng/mL, at least 51.0 ng/mL, at least 52.0 ng/mL, at least 53.0 ng/mL, at least 54.0 ng/mL, at least 55.0 ng/mL, at least 56.0 ng/mL, at least 57.0 ng/mL, at least 58.0 ng/mL, or at least 59.0 ng/mL. The plasma concentration of ivabradine after administration

of the composition to a subject in the fasting state at about 3 hours can be less than 59.0 ng/mL, less than 58.0 ng/mL, less than 57.0 ng/mL, less than 56.0 ng/mL, less than 55.0 ng/mL, less than 54.0 ng/mL, less than 53.0 ng/mL, less than 52.0 ng/mL, less than 51.0 ng/mL, less than 50.0 ng/mL, less than 49.0 ng/mL, less than 48.0 ng/mL, less than 47.0 ng/mL, less than 46.0 ng/mL, less than 45.0 ng/mL, less than 44.0 ng/mL, less than 43.0 ng/mL, less than 42.0 ng/mL, less than 41.0 ng/mL, less than 40.0 ng/mL, less than 39.0 ng/mL, less than 38.0 ng/mL, less than 37.0 ng/mL, less than 36.0 ng/mL, less than 35.0 ng/mL, less than 34.0 ng/mL, less than 33.0 ng/mL, less than 32.0 ng/mL, less than 31.0 ng/mL, less than 30.0 ng/mL, less than 29.0 ng/mL, less than 28.0 ng/mL, less than 27.0 ng/mL, less than 26.0 ng/mL, less than 25.0 ng/mL, less than 24.0 ng/mL, or less than 23.0 ng/mL. In some embodiments, mean plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fasting state at about 3 hours can be about 30.0 to about 35.0 ng/mL.

[0052] The plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fasting state at about 4 hours can be between about 20.0 and about 56.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fasting state at about 4 hours can be at least 20.0 ng/mL, at least 21.0 ng/mL, at least 22.0 ng/mL, at least 23.0 ng/mL, at least 24.0 ng/mL, at least 25.0 ng/mL, at least 26.0 ng/mL, at least 27.0 ng/mL, at least 28.0 ng/mL, at least 29.0 ng/mL, at least 30.0 ng/mL, at least 31.0 ng/mL, at least 32.0 ng/mL, at least 33.0 ng/mL, at least 34.0 ng/mL, at least 35.0 ng/mL, at least 36.0 ng/mL, at least 37.0 ng/mL, at least 38.0 ng/mL, at least 39.0 ng/mL, at least 40.0 ng/mL, at least 41.0 ng/mL, at least 42.0 ng/mL, at least 43.0 ng/mL, at least 44.0 ng/mL, at least 45.0 ng/mL, at least 46.0 ng/mL, at least 47.0 ng/mL, at least 48.0 ng/mL, at least 49.0 ng/mL, at least 50.0 ng/mL, at least 51.0 ng/mL, at least 52.0 ng/mL, at least 53.0 ng/mL, at least 54.0 ng/mL, or at least 55.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fasting state at about 4 hours can be less than 56.0 ng/mL, less than 55.0 ng/mL, less than 54.0 ng/mL, less than 53.0 ng/mL, less than 52.0 ng/mL, less than 51.0 ng/mL, less than 50.0 ng/mL, less than 49.0 ng/mL, less than 48.0 ng/mL, less than 47.0 ng/mL, less than 46.0 ng/mL, less than 45.0 ng/mL, less than 44.0 ng/mL, less than 43.0 ng/mL, less than 42.0 ng/mL, less than 41.0 ng/mL, less than 40.0 ng/mL, less than 39.0 ng/mL, less than 38.0 ng/mL, less than 37.0 ng/mL, less than 36.0 ng/mL, less than 35.0 ng/mL, less than 34.0 ng/mL, less than 33.0 ng/mL, less than 32.0 ng/mL, less than 31.0 ng/mL, less than 30.0 ng/mL, less than 29.0 ng/mL, less than 28.0 ng/mL, less than 27.0 ng/mL, less

than 26.0 ng/mL, less than 25.0 ng/mL, less than 24.0 ng/mL, less than 23.0 ng/mL, less than 22.0 ng/mL, or less than 21.0 ng/mL. In some embodiments, the mean plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fasting state at about 4 hours can be about 33.0 to about 38.0 ng/mL.

- 5 [0053] The plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fasting state at about 6 hours can be between about 11.0 and about 47.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fasting state at about 6 hours can be at least 11.0 ng/mL, at least 12.0 ng/mL, at least 13.0 ng/mL, at least 14.0 ng/mL, at least 15.0 ng/mL, at least 16.0 ng/mL, at least 17.0 ng/mL, at least 18.0 ng/mL, at least 19.0 ng/mL, at least 20.0 ng/mL, at least 21.0 ng/mL, at least 22.0 ng/mL, at least 23.0 ng/mL, at least 24.0 ng/mL, at least 25.0 ng/mL, at least 26.0 ng/mL, at least 27.0 ng/mL, at least 28.0 ng/mL, at least 29.0 ng/mL, at least 30.0 ng/mL, at least 31.0 ng/mL, at least 32.0 ng/mL, at least 33.0 ng/mL, at least 34.0 ng/mL, at least 35.0 ng/mL, at least 36.0 ng/mL, at least 37.0 ng/mL, at least 38.0 ng/mL, at least 39.0 ng/mL, at least 40.0 ng/mL, at least 41.0 ng/mL, at least 42.0 ng/mL, at least 43.0 ng/mL, at least 44.0 ng/mL, at least 45.0 ng/mL, or at least 46.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fasting state at about 6 hours can be less than 47.0 ng/mL, less than 46.0 ng/mL, less than 45.0 ng/mL, less than 44.0 ng/mL, less than 43.0 ng/mL, less than 42.0 ng/mL, less than 41.0 ng/mL, less than 40.0 ng/mL, less than 39.0 ng/mL, less than 38.0 ng/mL, less than 37.0 ng/mL, less than 36.0 ng/mL, less than 35.0 ng/mL, less than 34.0 ng/mL, less than 33.0 ng/mL, less than 32.0 ng/mL, less than 31.0 ng/mL, less than 30.0 ng/mL, less than 29.0 ng/mL, less than 28.0 ng/mL, less than 27.0 ng/mL, less than 26.0 ng/mL, less than 25.0 ng/mL, less than 24.0 ng/mL, less than 23.0 ng/mL, less than 22.0 ng/mL, less than 21.0 ng/mL, less than 20.0 ng/mL, less than 19.0 ng/mL, less than 18.0 ng/mL, less than 17.0 ng/mL, less than 16.0 ng/mL, less than 15.0 ng/mL, less than 14.0 ng/mL, less than 13.0 ng/mL, or less than 12.0 ng/mL. In some embodiments, the mean plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fasting state at about 6 hours can be about 29.0 to about 34.0 ng/mL.
- 30 [0054] The plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fasting state at about 8 hours can be between about 7.0 and about 47.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fasting state at about 8 hours can be at least 7.0 ng/mL, at least 8.0 ng/mL, at least 9.0 ng/mL, at least 10.0 ng/mL, at least 11.0 ng/mL, at least 12.0

ng/mL, at least 13.0 ng/mL, at least 14.0 ng/mL, at least 15.0 ng/mL, at least 16.0 ng/mL, at least 17.0 ng/mL, at least 18.0 ng/mL, at least 19.0 ng/mL, at least 20.0 ng/mL, at least 21.0 ng/mL, at least 22.0 ng/mL, at least 23.0 ng/mL, at least 24.0 ng/mL, at least 25.0 ng/mL, at least 26.0 ng/mL, at least 27.0 ng/mL, at least 28.0 ng/mL, at least 29.0 ng/mL, at least 30.0 ng/mL, at least 31.0 ng/mL, at least 32.0 ng/mL, at least 33.0 ng/mL, at least 34.0 ng/mL, at least 35.0 ng/mL, at least 36.0 ng/mL, at least 37.0 ng/mL, at least 38.0 ng/mL, at least 39.0 ng/mL, at least 40.0 ng/mL, at least 41.0 ng/mL, at least 42.0 ng/mL, at least 43.0 ng/mL, at least 44.0 ng/mL, at least 45.0 ng/mL, or at least 46.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fasting state at about 8 hours can be less than 47.0 ng/mL, less than 46.0 ng/mL, less than 45.0 ng/mL, less than 44.0 ng/mL, less than 43.0 ng/mL, less than 42.0 ng/mL, less than 41.0 ng/mL, less than 40.0 ng/mL, less than 39.0 ng/mL, less than 38.0 ng/mL, less than 37.0 ng/mL, less than 36.0 ng/mL, less than 35.0 ng/mL, less than 34.0 ng/mL, less than 33.0 ng/mL, less than 32.0 ng/mL, less than 31.0 ng/mL, less than 30.0 ng/mL, less than 29.0 ng/mL, less than 28.0 ng/mL, less than 27.0 ng/mL, less than 26.0 ng/mL, less than 25.0 ng/mL, less than 24.0 ng/mL, less than 23.0 ng/mL, less than 22.0 ng/mL, less than 21.0 ng/mL, less than 20.0 ng/mL, less than 19.0 ng/mL, less than 18.0 ng/mL, less than 17.0 ng/mL, less than 16.0 ng/mL, less than 15.0 ng/mL, less than 14.0 ng/mL, less than 13.0 ng/mL, less than 12.0 ng/mL, less than 11.0 ng/mL, less than 10.0 ng/mL, less than 9.0 ng/mL, or less than 8.0 ng/mL. In some embodiments, the mean plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fasting state at about 8 hours can be 20.0 to about 28.0 ng/mL.

[0055] After administration of the prolonged release composition to a subject in the fed state, ivabradine may have a peak plasma concentration between about 4 hours to about 10 hours.

[0056] The plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fed state at about 4 hours can be between about 11.0 and about 53.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fed state at about 4 hours can be at least 11.0 ng/mL, at least 12.0 ng/mL, at least 13.0 ng/mL, at least 14.0 ng/mL, at least 15.0 ng/mL, at least 16.0 ng/mL, at least 17.0 ng/mL, at least 18.0 ng/mL, at least 19.0 ng/mL, at least 20.0 ng/mL, at least 21.0 ng/mL, at least 22.0 ng/mL, at least 23.0 ng/mL, at least 24.0 ng/mL, at least 25.0 ng/mL, at least 26.0 ng/mL, at least 27.0 ng/mL, at least 28.0 ng/mL, at least 29.0 ng/mL, at least 30.0 ng/mL, at least 31.0 ng/mL, at least 32.0 ng/mL, at least 33.0 ng/mL, at least 34.0

ng/mL, at least 35.0 ng/mL, at least 36.0 ng/mL, at least 37.0 ng/mL, at least 38.0 ng/mL, at least 39.0 ng/mL, at least 40.0 ng/mL, at least 41.0 ng/mL, at least 42.0 ng/mL, at least 43.0 ng/mL, at least 44.0 ng/mL, at least 45.0 ng/mL, at least 46.0 ng/mL, at least 47.0 ng/mL, at least 48.0 ng/mL, at least 49.0 ng/mL, at least 50.0 ng/mL, at least 51.0 ng/mL, or at least 52.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fed state at about 4 hours can be less than 53.0 ng/mL, less than 52.0 ng/mL, less than 51.0 ng/mL, less than 50.0 ng/mL, less than 49.0 ng/mL, less than 48.0 ng/mL, less than 47.0 ng/mL, less than 46.0 ng/mL, less than 45.0 ng/mL, less than 44.0 ng/mL, less than 43.0 ng/mL, less than 42.0 ng/mL, less than 41.0 ng/mL, less than 40.0 ng/mL, less than 39.0 ng/mL, less than 38.0 ng/mL, less than 37.0 ng/mL, less than 36.0 ng/mL, less than 35.0 ng/mL, less than 34.0 ng/mL, less than 33.0 ng/mL, less than 32.0 ng/mL, less than 31.0 ng/mL, less than 30.0 ng/mL, less than 29.0 ng/mL, less than 28.0 ng/mL, less than 27.0 ng/mL, less than 26.0 ng/mL, less than 25.0 ng/mL, less than 24.0 ng/mL, less than 23.0 ng/mL, less than 22.0 ng/mL, less than 21.0 ng/mL, less than 20.0 ng/mL, less than 19.0 ng/mL, less than 18.0 ng/mL, less than 17.0 ng/mL, less than 16.0 ng/mL, less than 15.0 ng/mL, less than 14.0 ng/mL, less than 13.0 ng/mL, or less than 12.0 ng/mL. In some embodiments, the mean plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fed state at about 4 hours can be about 32.0 to about 36.0 ng/mL.

[0057] The plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fed state at about 6 hours can be between about 24.0 and about 60.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fed state at about 6 hours can be at least 24.0 ng/mL, at least 25.0 ng/mL, at least 26.0 ng/mL, at least 27.0 ng/mL, at least 28.0 ng/mL, at least 29.0 ng/mL, at least 30.0 ng/mL, at least 31.0 ng/mL, at least 32.0 ng/mL, at least 33.0 ng/mL, at least 34.0 ng/mL, at least 35.0 ng/mL, at least 36.0 ng/mL, at least 37.0 ng/mL, at least 38.0 ng/mL, at least 39.0 ng/mL, at least 40.0 ng/mL, at least 41.0 ng/mL, at least 42.0 ng/mL, at least 43.0 ng/mL, at least 44.0 ng/mL, at least 45.0 ng/mL, at least 46.0 ng/mL, at least 47.0 ng/mL, at least 48.0 ng/mL, at least 49.0 ng/mL, at least 50.0 ng/mL, at least 51.0 ng/mL, at least 52.0 ng/mL, at least 53.0 ng/mL, at least 54.0 ng/mL, at least 55.0 ng/mL, at least 56.0 ng/mL, at least 57.0 ng/mL, at least 58.0 ng/mL, or at least 59.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fed state at about 6 hours can be less than 60.0 ng/mL, less than 59.0 ng/mL, less than 58.0 ng/mL, less than 57.0 ng/mL, less than 56.0 ng/mL, less than 55.0 ng/mL, less than 54.0

ng/mL, less than 53.0 ng/mL, less than 52.0 ng/mL, less than 51.0 ng/mL, less than 50.0 ng/mL, less than 49.0 ng/mL, less than 48.0 ng/mL, less than 47.0 ng/mL, less than 46.0 ng/mL, less than 45.0 ng/mL, less than 44.0 ng/mL, less than 43.0 ng/mL, less than 42.0 ng/mL, less than 41.0 ng/mL, less than 40.0 ng/mL, less than 39.0 ng/mL, less than 38.0 ng/mL, less than 37.0 ng/mL, less than 36.0 ng/mL, less than 35.0 ng/mL, less than 34.0 ng/mL, less than 33.0 ng/mL, less than 32.0 ng/mL, less than 31.0 ng/mL, less than 30.0 ng/mL, less than 29.0 ng/mL, less than 28.0 ng/mL, less than 27.0 ng/mL, less than 26.0 ng/mL, or less than 25.0 ng/mL. In some embodiments, the mean plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fed state at about 6 hours can be about 36.0 to about 41.0 ng/mL.

[0058] The plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fed state at about 8 hours can be between about 13.0 and about 43.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fed state at about 8 hours can be at least 14.0 ng/mL, at least 15.0 ng/mL, at least 16.0 ng/mL, at least 17.0 ng/mL, at least 18.0 ng/mL, at least 19.0 ng/mL, at least 20.0 ng/mL, at least 21.0 ng/mL, at least 22.0 ng/mL, at least 23.0 ng/mL, at least 24.0 ng/mL, at least 25.0 ng/mL, at least 26.0 ng/mL, at least 27.0 ng/mL, at least 28.0 ng/mL, at least 29.0 ng/mL, at least 30.0 ng/mL, at least 31.0 ng/mL, at least 32.0 ng/mL, at least 33.0 ng/mL, at least 34.0 ng/mL, at least 35.0 ng/mL, at least 36.0 ng/mL, at least 37.0 ng/mL, at least 38.0 ng/mL, at least 39.0 ng/mL, at least 40.0 ng/mL, at least 41.0 ng/mL, or at least 42.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fed state at about 8 hours can be less than 43.0 ng/mL, less than 42.0 ng/mL, less than 41.0 ng/mL, less than 40.0 ng/mL, less than 39.0 ng/mL, less than 38.0 ng/mL, less than 37.0 ng/mL, less than 36.0 ng/mL, less than 35.0 ng/mL, less than 34.0 ng/mL, less than 33.0 ng/mL, less than 32.0 ng/mL, less than 31.0 ng/mL, less than 30.0 ng/mL, less than 29.0 ng/mL, less than 28.0 ng/mL, less than 27.0 ng/mL, less than 26.0 ng/mL, less than 25.0 ng/mL, less than 24.0 ng/mL, less than 23.0 ng/mL, less than 22.0 ng/mL, less than 21.0 ng/mL, less than 20.0 ng/mL, less than 19.0 ng/mL, less than 18.0 ng/mL, less than 17.0 ng/mL, less than 16.0 ng/mL, less than 15.0 ng/mL, or less than 14.0 ng/mL. In some embodiments, the mean plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fed state at about 8 hours can be about 31.0 to about 34.0 ng/mL.

[0059] The plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fed state at about 10 hours can be between about 8.0

and about 40.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fed state at about 10 hours can be at least 8.0 ng/mL at least 9.0 ng/mL, at least 10.0 ng/mL, at least 11.0 ng/mL, at least 12.0 ng/mL, at least 13.0 ng/mL, at least 14.0 ng/mL, at least 15.0 ng/mL, at least 16.0 ng/mL, at least 17.0 ng/mL, at least 18.0 ng/mL, at least 19.0 ng/mL, at least 20.0 ng/mL, at least 21.0 ng/mL, at least 22.0 ng/mL, at least 23.0 ng/mL, at least 24.0 ng/mL, at least 25.0 ng/mL, at least 26.0 ng/mL, at least 27.0 ng/mL, at least 28.0 ng/mL, at least 29.0 ng/mL, at least 30.0 ng/mL, at least 31.0 ng/mL, at least 32.0 ng/mL, at least 33.0 ng/mL, at least 34.0 ng/mL, at least 35.0 ng/mL, at least 36.0 ng/mL, at least 37.0 ng/mL, at least 38.0 ng/mL, or at least 39.0 ng/mL. The plasma concentration of ivabradine after administration of the composition to a subject in the fed state at about 10 hours can be less than 40.0 ng/mL, less than 39.0 ng/mL, less than 38.0 ng/mL, less than 37.0 ng/mL, less than 36.0 ng/mL, less than 35.0 ng/mL, less than 34.0 ng/mL, less than 33.0 ng/mL, less than 32.0 ng/mL, less than 31.0 ng/mL, less than 30.0 ng/mL, less than 29.0 ng/mL, less than 28.0 ng/mL, less than 27.0 ng/mL, less than 26.0 ng/mL, less than 25.0 ng/mL, less than 24.0 ng/mL, less than 23.0 ng/mL, less than 22.0 ng/mL, less than 21.0 ng/mL, less than 20.0 ng/mL, less than 19.0 ng/mL, less than 18.0 ng/mL, less than 17.0 ng/mL, less than 16.0 ng/mL, less than 15.0 ng/mL, less than 14.0 ng/mL, less than 13.0 ng/mL, less than 12.0 ng/mL, less than 11.0 ng/mL, less than 10.0 ng/mL, or less than 9.0 ng/mL. In some embodiments, the mean plasma concentration of ivabradine after administration of the prolonged release composition to a subject in the fed state at about 10 hours can be about 21.0 to about 26.0 ng/mL.

4. Methods of Use

[0060] The disclosed compositions can be used in methods of treating a disease or disorder in a subject in need thereof. The method may comprise administering the prolonged release composition to the subject in need thereof. In some embodiments, the method may comprise administering the disclosed composition for once per day.

[0061] Disorders in which a patient would benefit from treatment with the compositions disclosed herein include those which are associated with or accompanied by cardiac arrhythmia. The disease or disorder can be selected from the group consisting of chronic heart failure with systolic dysfunction, heart-related chest pain and heart failure. Use of the disclosed prolonged release composition can be suitable for the treatment of systolic dysfunction, heart-related chest pain and heart failure.

[0062] In the methods of use described herein, additional therapeutic agent(s) can be administered simultaneously or sequentially with the disclosed compositions. Sequential

administration includes administration before or after the disclosed compositions. In other embodiments, there can be an interval of time between administration of the additional therapeutic agent and the compositions.

5. Examples

Example 1 Compositions and pH Dependence of Dissolution

A. Batch 1

Ingredient	% w/w
Intra granular ingredients	
Ivabradine hydrochloride eq. to ivabradine 15 mg	8.09
Hydroxypropyl methylcellulose (HPMC)	50.00
Lactose monohydrate	40.91
Isopropyl alcohol	q.s.
Extra granular ingredients	
Magnesium stearate	1.00
Total	100.00

10 [0063] Manufacturing Process:

1. Ivabradine hydrochloride, hydroxypropyl methylcellulose (HPMC) and lactose monohydrate were sifted through No. 40 sieve and mixed in rapid mixer granulator for 15 minutes.
2. Mixture of step 1 was granulated by adding isopropyl alcohol.
3. The wet granules obtained in step 2 were dried to get LOD between 2-3%.
4. The dried granules of step 3 were passed through No. 30 sieve.
5. Magnesium stearate was passed through No. 60 sieve and mixed with step 4 granules for 2 minutes.
6. The lubricated granules of step 5 were compressed in tablets.
7. The dissolution of tablets was determined in 900mL, 0.1N HCl, USP Type I, 50 RPM.

Table 1: Dissolution of Batch 1 in 900 mL 0.1N HCl, USP Type I, 50 RPM

Time (Hours)	% Drug Released
1	23
2	35
4	47
6	59
8	68
10	77
12	85
16	95
20	101
24	104

B. Batch 2-8

Batch No	2	3	4	5	6	7	8
Ingredients	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
Ivabradine hydrochloride eq. to ivabradine 15 mg/10mg	8.09	8.09	5.39	8.09	8.09	8.09	8.09
Dibasic calcium phosphate anhydrous	35.91	40.91	43.61	38.41	65.91	60.91	50.91
Hydroxypropyl methylcellulose (HPMC)	55.00	50.00	50.00	52.50	25.00	30.00	40.00
Magnesium stearate	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Total	100	100	100	100	100	100	100

[0064] Manufacturing Process:

- 5 1. Ivabradine hydrochloride, dibasic calcium phosphate anhydrous and hydroxypropyl methylcellulose (HPMC) were sifted through No. 40 sieve and mixed.
2. Magnesium stearate was sifted through No. 60 sieve and added to step 1 mixture and mixed for 1 minute 30 seconds.
3. The lubricated blend of step 2 was compressed into tablets.
- 10 4. The dissolution of tablets was determined in 900 mL, 0.1N HCl, USP Type I, 50 RPM.

Table 2: Dissolution of Batch 2-8 in 900mL 0.1N HCl, USP Type I, 50 RPM

Batch No.	2	3	4	5	6	7	8
Time (Hours)	% Drug released						
1	21	25	23	23	33	26	26
2	33	39	36	35	48	41	41
4	50	59	55	54	69	66	64
6	64	74	70	69	84	83	81
8	74	84	81	79	92	91	91
10	80	91	88	86	95	96	98
12	84	95	93	90	96	98	102
16	90	100	98	96	96	98	105
20	92	102	99	98	96	98	107
24	93	103	100	98	96	97	105

15 **[0065]** The dissolution of Batch no.3 was tested in various types of dissolution media.

Table 3: Dissolution of Batch 3 Under Various Media Conditions (900ml, USP Type I (Basket), 50 RPM)

Media	0.1N HCl	pH4.5	pH6.8	Water	0.1N HCl (2 hours) followed by	40 % Alcohol in 0.1N HCl
Time (Hours)	Cumulative % Drug Release					
0.5	16	16	15	15	15	16
1	25	24	25	28	25	23
2	39	37	38	43	38	34
4	59	56	51	63	51	51
6	74	70	67	77	67	63
8	84	81	77	87	77	73
10	91	89	85	93	85	81
12	95	95	90	98	90	87
16	100	103	97	108	97	94
20	102	107	100	-	-	99
24	103	110	102	-	-	101

5 C. Batch 9

Ingredient	% w/w
Intra granular ingredients	
Ivabradine hydrochloride eq. to ivabradine 15mg	8.09
Lactose anhydrous	35.91
Polyvinyl acetate/polyvinylpyrrolidone	55.00
Extra granular ingredients	
Magnesium stearate	1.00
Total	100.00

[0066] Manufacturing Process:

1. Ivabradine hydrochloride, polyvinylacetate/polyvinyl pyrrolidone and lactose anhydrous were sifted through No. 40 sieve and mixed in blender for 20 minutes.
- 10 2. Magnesium stearate was sifted through No. 60 sieve and added to step 1 mixture and mixed for 1 minute 30 seconds.
3. The lubricated blend of step 2 was compressed into tablets.

Table 4: Dissolution of Batch 9 in 900mL 0.1N HCl, USP Type I, 50 RPM

Time (hours)	% Drug Released
1	37
2	50
4	71
6	88
8	97
10	101
12	103
16	105

15 D. Batch 10

Ingredients	% w/w
Ivabradine hydrochloride eq. to. Ivabradine 15mg	8.09
Lactose anhydrous	40.91
Hydroxy propyl methyl cellulose (HPMC)	50.00
Magnesium stearate	1.00
Total	100.0

[0067] Manufacturing Process:

- 5 1. Ivabradine hydrochloride, dibasic calcium phosphate anhydrous and hydroxypropyl methylcellulose (HPMC) were sifted through No. 40 sieve and mixed.
2. Magnesium stearate was sifted through No. 60 sieve and added to step 1 mixture and mixed for 1 minute 30 seconds.
3. The lubricated blend of step 2 was compressed into tablets.
- 10 4. The dissolution of tablets was determined in 900 mL, 0.1N HCl, USP Type I, 50 RPM.

Table 6: Dissolution of Batch 10 in 900mL 0.1N HCl, USP Type I, 50 RPM

Time (Hours)	% Drug released
1	23
2	35
4	53
6	67
8	77
10	84
12	88
16	94
20	99
24	98

E. Batch 11-14

Batch No.	11	12	13	14
Ingredient	% w/w	% w/w	% w/w	% w/w
Ivabradine hydrochloride eq. to. Ivabradine 15mg	7.81	8.09	8.09	8.04
Anhydrous dibasic calcium phosphate	40.01	41.41	41.41	21.31
Hydroxy propyl methyl cellulose (HPMC)	48.31	-	-	-
Hydroxy propyl methyl cellulose (HPMC)	-	50.00	-	-
Hydroxy propyl methyl cellulose (HPMC)	-	-	50.00	49.75
Hydroxy propyl methyl cellulose (HPMC)	-	-		19.90

Magnesium stearate	0.97	1.00	1.00	1.00
Total	-	100	100	100
Colorant	2.90	-	-	-
Purified water	-	-	-	-
Total weight of coated tablet	100	-	-	-

[0068] Manufacturing Process:

- 5 1. Ivabradine hydrochloride, dibasic calcium phosphate anhydrous and hydroxypropyl methylcellulose (HPMC) were sifted through No. 40 sieve and mixed.
2. Magnesium stearate was sifted through No. 60 sieve and added to step 1 mixture and mixed for 1 minute 30 seconds.
3. The lubricated blend of step 2 was compressed into tablets.
- 10 4. Compressed tablets of step 3 were coated with the aqueous dispersion of colorant.
5. The dissolution of tablets was determined in 900 ml, 0.1N HCl, USP Type I, 50 RPM.

Table 7: Dissolution of Batch 11-14 in 900ml 0.1NHCl, USP Type I, 50 RPM

Batch No.	11	12	13	14
Time (Hours)	%Drug Released			
1	23	16	15	16
2	37	27	25	26
4	58	45	41	41
6	73	60	53	48
8	84	71	63	63
10	91	81	72	72
12	95	88	79	79
16	99	95	88	88

[0069] Dissolution of batch 11 was determined in 0.1N HCl, pH 4.5 and pH6.8

Table 8: Dissolution of Batch 11 under Dissolution Media with varying pH values (Volume 900ml, apparatus basket, 50 RPM)

Dissolution Media	0.1NHCl	pH4.5	pH6.8
Time (Hours)	%Drug Released		
1	23	23	20
2	37	35	44
4	58	51	60
6	73	64	73
8	84	73	82
10	91	80	88
12	95	86	93

F. Batch 15

Ingredient	%w/w
Ivabradine hydrochloride eq. to. Ivabradine 10mg	7.81
Dibasic calcium phosphate anhydrous	40.01

Hydroxy propyl methyl cellulose (HPMC)	48.31
Magnesium stearate	0.97
Total	-
Colorant	2.90
Purified water	-
Weight of coated tablet	100.0

Manufacturing Process:

- 5 1. Ivabradine hydrochloride, dibasic calcium phosphate anhydrous and hydroxypropyl methylcellulose (HPMC) were sifted through No. 40 sieve and mixed.
2. Magnesium stearate was sifted through No. 60 sieve and added to step 1 mixture and mixed.
3. The lubricated blend of step 2 was compressed into tablets.
- 10 4. Compressed tablets of step 3 were coated with the aqueous dispersion of colorant.

Table 9: Dissolution of Batch 15 under Dissolution Media with varying pH values (Volume 900ml, apparatus basket, 50 RPM)

Dissolution Media	0.1NHCl	pH4.5	pH6.8
Time (Hours)	% Drug Released		
1	25	27	27
2	38	42	42
4	59	64	61
6	74	78	76
8	84	90	86
10	93	98	92
12	94	101	98

15 G. Batch 16

Ingredients	% w/w
Ivabradine hydrochloride eq. to ivabradine 15 mg	7.81
Dibasic calcium phosphate anhydrous	40.01
Hydroxy propyl methyl cellulose (HPMC)	48.31
Magnesium stearate	0.97
Weight of uncoated tablet	-
Colorant	2.90
Purified water	-
Weight of coated tablet	100

[0070] Manufacturing Process:

- 20 1. Ivabradine hydrochloride, dibasic calcium phosphate anhydrous and hydroxypropyl methylcellulose (HPMC) were sifted through No. 40 sieve and mixed in blender for 20 minutes.
2. Magnesium stearate was sifted through No. 60 sieve and added to step1 mixture and mixed for 3 minutes.
- 25 3. The lubricated blend of step 2 was compressed into tablets.
4. Compressed tablets of step 3 were coated with the aqueous dispersion of colorant.

Table 10: Dissolution of Batch 16 in 900mL 0.1N HCl, USP Type I, 50 RPM

Time (Hours)	% Drug released
1	24
2	38
4	58
6	73
8	83
10	89
12	93

5

Example 2

Bioavailability and Pharmacokinetics of the Prolonged Release Ivabradine Tablets

[0071] Ivabradine is rapidly released from immediate release tablets and is highly water soluble (>10mg/mL). Because of this, ivabradine is rapidly and almost completely absorbed after oral administration. However, ivabradine is eliminated with a half-life of about 2 hours in plasma and an effective half-life of 11 hours. The usual recommended starting dose of immediate release ivabradine is 5 mg twice daily. The maintenance dose should not exceed 7.5 mg twice daily.

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A. Treatments

[0072] **Test Product-T:** Ivabradine prolonged release tablet 15mg.

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[0073] **Reference Product-R:** Coralan[®] 7.5 mg (ivabradine hydrochloride) Tablets (Manufactured by Les Laboratoires Servier Industries, France. Imported and Marketed in India by Serdia[®] Pharmaceuticals Pvt. Ltd., Mumbai).

[0074] The treatment sequences were followed as outlined in Table 11 where: T1=Test Product under fasting condition; T2=Test Product under fed condition; R1=Reference Product under fasting condition; and R2=Reference Product under fed condition.

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Table 11. Treatment Sequence

	Period I	Period II	Period III	Period IV
Sequence 1	Treatment R1	Treatment T1	Treatment R2	Treatment T2
Sequence 2	Treatment T1	Treatment R1	Treatment T2	Treatment R2

[0075] A screening phase was carried out within 28 days prior to the scheduled dosing day of Period I. The subjects were administered the study drug in each period. The sequence of administration was determined by randomly. Based on the elimination half-life of ivabradine and N-desmethylated derivative, a washout period of 7 days was kept in

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between the dosing days of the study periods. The duration of the clinical part of the study was 30 days.

Treatments Administered for Period I & II (Fasting Condition)

[0076] For Test product: After an overnight fast of at least 10 hours, a single oral dose (15 mg) of the test product was administered with 240 mL of drinking water at ambient temperature with the subjects in sitting posture.

[0077] For Reference product:

[0078] *First dose:* After an overnight fast of at least 10 hours, a single oral dose (7.5 mg) of the reference product was administered with 240 mL of drinking water at ambient temperature with the subjects in sitting posture.

[0079] *Second dose:* After a fast of at least 2 hours at 12 hours of first dose, a single oral dose (7.5 mg) of the reference product was administered with 240 mL of drinking water at ambient temperature with the subjects in sitting posture.

Treatments Administered for Period III & IV (Fed Condition)

[0080] For Test product: After an overnight fast of at least 10 hours, the subjects were served a standardized high fat and high calorie vegetarian breakfast, which they consumed within 30 minutes. A single oral dose (15 mg) of the test product was administered to the subjects at 30 minutes after serving the breakfast. The IMP was administered in sitting posture with 240mL of drinking water at ambient temperature.

[0081] For Reference product:

[0082] *First dose:* After an overnight fast of at least 10 hours, the subjects were served a standardized high fat and high calorie vegetarian breakfast, which they consumed within 30 minutes. A single oral dose (7.5mg) of the reference product was administered to the subjects at 30 minutes after serving the breakfast. The IMP was administered in sitting posture with

240 mL of drinking water at ambient temperature.

[0083] *Second dose:* After a fast of at least 2 hours at 12 hours of first dose, the subjects were served a standardized high fat and high calorie vegetarian meal, which they consumed within 30 minutes. A single oral dose (7.5mg) of the reference product was administered to the subjects at 30 minutes after serving the meal. The IMP was administered in sitting posture with 240 mL of drinking water at ambient temperature.

B. Pharmacokinetics

[0084] Pharmacokinetic Measurements. The following pharmacokinetic parameters were calculated for ivabradine and N-desmethyated derivative (S18982), the active metabolite of ivabradine:

- 5 • Primary Parameters: AUC_{0-t} and $AUC_{0-\infty}$; and
- Secondary Parameters: C_{max} , T_{max} , λ_z , $t_{1/2}$, $AUC_{\%Extrap_obs}$ and T_{lag} .

[0085] Each of the parameters are derived individually for each subject under fasting (Period I and Period II) and fed (Period III and Period IV) conditions from the plasma concentration vs. time profiles of ivabradine and N-desmethyated derivative (S18982) using non-compartmental model of Phoenix® WinNonlin® Version 6.4 (Certara L.P.).

[0086] The maximum measured plasma concentration (C_{max}) and the time of observing the peak concentration (T_{max}) were calculated from the plasma concentration vs. time profile of the individual subjects. The units of C_{max} and T_{max} were ng/mL and hour (h) respectively.

15 **[0087]** Area under the plasma concentration vs. time curve (AUC_{0-t}) in ng.h/mL from time zero to the last measurable concentration was calculated by linear trapezoidal rule.

[0088] Area under the plasma concentration vs. time curve ($AUC_{0-\infty}$) in ng.h/mL from time zero to infinity; Where $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, C_t is the last measurable concentration and λ_z is the terminal rate constant. The $AUC_{0-\infty}$ was the sum of measurable and extrapolated parts.

20 **[0089]** First order rate constant associated with the terminal (log-linear) portion of the curve was estimated via linear regression of time vs. log concentration. The terminal rate constant (λ_z) parameter was calculated by linear least squares regression analysis using at least last three or more non- zero plasma concentration values. The unit of λ_z is hour⁻¹ (1/h).

[0090] Terminal half-life was calculated using the formula: $0.693/\lambda_z$.

[0091] $AUC_{\%Extrap_obs}(\%)$: Residual area in percentage was determined by the formula: $[(AUC_{0-\infty} - AUC_{0-t})/AUC_{0-\infty}] \times 100$

30 **[0092]** T_{lag} is the time prior to the first measurable (non-zero) plasma concentration. The unit of T_{lag} is hour(h).

[0093] Drug Concentration Measurements. Venous blood samples were withdrawn at pre-dose (0 hour) and regular intervals following. The pre-dose blood samples were collected within a period of 60 minutes before the dosing. The post-dose in-house blood

samples were collected within ± 02 minutes from the scheduled time for all the subjects. For the reference product, a total of 31 blood samples, each of 4mL were collected from each subject in respective period. For the test product, a total of 21 blood samples, each of 4mL were collected from each subject in respective period.

- 5 [0094] The plasma samples of the subject were analyzed using an LC-MS/MS method with an 8-point calibration curve for ivabradine and N-desmethyl ivabradine.

C. Results

- 10 [0095] The plasma concentrations measured throughout the treatment sequences for ivabradine are shown in Tables A-D and summarized in the graphs in FIGS. 1A-1B. With respect to Tables A-D, the plasma concentrations of ivabradine for the test product T1 (fasting conditions) is shown in Table A, test product T2 (fed conditions) in Table B, reference product R1 (fasting conditions) in Table C, and reference product R2 (fed conditions) in Table D.

[0096] Table A

Time (h)	Mean	SD	Min	Max
0.000	0.000	0.0000	0.000	0.000
0.250	1.184	0.7705	0.000	2.566
0.500	5.980	3.2475	1.127	13.151
0.750	9.914	4.9356	4.527	20.545
1.000	13.836	6.9776	5.294	28.647
1.333	17.012	7.2334	6.374	27.949
1.667	19.516	6.1746	8.937	27.350
2.000	24.055	6.0766	10.652	33.569
2.500	28.103	7.8679	14.159	44.682
3.000	33.353	9.5894	22.625	59.002
4.000	35.964	9.6875	20.357	55.785
6.000	31.291	11.1872	11.344	46.412
8.000	24.650	11.6781	7.539	46.499
10.000	20.132	10.9914	3.477	39.628
12.000	15.008	9.0331	1.780	30.636
14.000	10.707	6.3438	1.001	20.613
16.000	7.487	4.6669	0.669	13.747
20.000	5.203	3.5926	0.403	13.040
24.000	3.226	2.9826	0.253	11.724
36.000	0.352	0.4174	0.000	1.331
48.000	0.116	0.1812	0.000	0.556

[0097] Table B

Time (h)	Mean	SD	Min	Max
0.000	0.015	0.0567	0.000	0.212
0.333	0.470	0.5929	0.000	2.115
0.667	2.353	2.4374	0.299	8.847
1.000	4.868	3.9400	0.575	13.427
1.333	8.293	5.4510	0.734	18.766
1.667	12.685	8.2231	1.044	24.950
2.000	15.920	9.4364	1.718	28.436
2.333	19.501	9.8546	2.797	32.846
2.667	23.391	9.4991	5.593	34.829
3.000	28.884	9.4804	7.947	45.962
4.000	34.093	11.0259	11.914	52.676
6.000	39.247	8.4884	24.862	59.313
8.000	32.426	8.3776	13.927	42.849
10.000	24.465	8.4001	8.744	39.115
12.000	18.209	6.5107	8.936	27.335
14.000	12.107	5.0100	5.730	19.492
16.000	8.206	4.7757	3.117	18.851
20.000	4.758	3.2972	1.475	12.378
24.000	3.031	2.2357	0.827	8.813
36.000	0.411	0.4365	0.000	1.679
48.000	0.145	0.2221	0.000	0.785

[0099] Table C

Time(h)	Mean	SD	Min	Max
0.000	0.000	0.0000	0.000	0.000
0.250	10.759	12.7160	0.259	42.935
0.500	37.232	22.8967	7.468	78.701
0.750	43.871	15.9169	23.589	78.744
1.000	42.539	13.0479	22.821	70.300
1.333	41.320	13.8283	24.066	71.105
1.667	37.784	10.3793	24.829	58.776
2.000	35.573	10.8342	21.659	55.457
2.500	32.990	12.1626	18.127	64.558
3.000	29.306	8.3542	16.066	42.261
4.000	23.947	6.7408	10.732	33.178
6.000	13.114	4.0024	5.270	19.291
8.000	7.431	2.6932	2.483	11.834
10.000	4.052	1.8194	1.052	7.313
12.000	2.512	1.1860	0.612	4.646
12.250	12.145	17.4814	0.565	52.936
12.500	21.111	25.9827	0.553	71.538
12.750	26.430	22.7849	0.638	70.727
13.000	31.675	23.2300	0.677	67.829
13.333	31.070	19.7300	0.797	56.824
13.667	28.902	16.0932	1.889	50.093
14.000	28.391	14.4798	4.332	50.363
14.500	31.791	10.6851	16.179	47.963
15.000	28.324	7.8457	14.442	42.278
16.000	22.237	7.1259	10.367	36.071
18.000	15.643	6.2641	5.385	31.045
20.000	10.378	5.6439	3.375	25.532
22.000	7.190	4.2874	2.441	17.956
24.000	4.951	2.7856	1.769	11.744
36.000	0.514	0.5073	0.000	1.704
48.000	0.118	0.2075	0.000	0.625

[00100] Table D

Time (h)	Mean	SD	Min	Max
0.000	0.000	0.0000	0.000	0.000
0.333	1.615	2.3529	0.000	7.407
0.667	11.193	18.1400	0.399	53.728
1.000	16.579	21.7819	0.933	65.244
1.333	22.438	23.6984	1.509	67.264
1.667	26.101	20.4174	1.353	63.278
2.000	28.668	17.0291	1.351	57.375
2.333	31.207	15.8512	1.283	57.137
2.667	32.818	14.4764	1.213	50.783
3.000	33.258	13.4321	1.403	46.871
4.000	30.585	7.0456	15.747	39.009
6.000	22.806	7.3331	8.877	38.354
8.000	13.772	5.0404	4.973	24.424
10.000	8.112	3.1977	2.517	13.829
12.000	5.126	2.4624	1.234	9.543
12.333	5.091	2.3872	1.210	9.758
12.667	8.481	6.7698	1.436	24.517
13.000	13.138	10.8332	1.487	36.179
13.333	18.502	15.0738	1.607	41.067
13.667	26.219	19.4147	2.182	53.583
14.000	28.412	18.3346	6.113	57.109
14.333	35.094	16.8763	9.667	59.165
14.667	33.783	13.0423	12.128	53.748
15.000	33.594	10.7406	15.058	48.700
16.000	28.655	7.2713	13.079	39.792
18.000	19.668	6.3442	9.605	29.238
20.000	13.993	6.4196	6.384	31.634
22.000	9.913	4.9327	5.673	24.520
24.000	7.757	4.6054	3.628	21.894
36.000	1.043	0.8138	0.265	3.380
48.000	0.321	0.2929	0.000	1.082

[00102] The plasma concentrations measured throughout the treatment sequences for N-desmethyl ivabradine are shown in Tables E-H and summarized in the graphs in FIGS. 2A-2B. With respect to the tables, the plasma concentrations of N-desmethyl ivabradine for the test product T1 (fasting conditions) is shown in Table E, test product T2 (fed conditions) is shown in Table F, reference product R1 (fasting conditions) is shown in Table G, and reference product R2 (fed conditions) is shown in Table H.

[00103] Table E

Time (h)	Mean	SD	Min	Max
0.000	0.000	0.0000	0.000	0.000
0.250	0.000	0.0000	0.000	0.000
0.500	0.473	0.2335	0.000	1.019
0.750	0.949	0.4683	0.387	1.966
1.000	1.300	0.6646	0.420	2.712
1.333	1.693	0.7673	0.459	2.740
1.667	1.935	0.6537	0.451	2.665
2.000	2.542	0.8525	0.591	3.516
2.500	3.031	1.0186	0.936	4.604
3.000	3.835	1.0629	2.408	6.706
4.000	4.421	1.2981	2.681	7.473
6.000	4.561	1.0824	2.723	6.609
8.000	3.832	0.9315	1.971	5.338
10.000	3.726	1.0427	1.324	5.993
12.000	3.193	0.9163	1.218	5.289
14.000	2.708	1.1882	0.785	6.275
16.000	2.073	0.5420	0.660	2.663
20.000	1.857	0.5349	0.544	2.663
24.000	1.638	0.5170	0.566	2.468
36.000	0.635	0.2525	0.214	1.087
48.000	0.322	0.1936	0.000	0.604

[00105] Table F

Time (h)	Mean	SD	Min	Max
0.000	0.000	0.0000	0.000	0.000
0.333	0.000	0.0000	0.000	0.000
0.667	0.063	0.1642	0.000	0.530
1.000	0.307	0.2916	0.000	0.873
1.333	0.554	0.4510	0.000	1.567
1.667	0.821	0.5596	0.000	1.868
2.000	1.149	0.6932	0.000	2.338
2.333	1.459	0.7625	0.282	2.636
2.667	1.839	0.7206	0.570	2.802
3.000	2.294	0.6747	0.779	3.219
4.000	3.064	0.8676	1.479	4.276
6.000	4.523	1.1361	2.538	6.622
8.000	4.287	1.3075	3.138	7.717
10.000	4.004	1.1469	2.900	7.315
12.000	3.570	0.7624	2.681	5.350
14.000	2.830	0.6623	2.022	3.859
16.000	2.312	0.5723	1.525	3.083
20.000	1.857	0.5315	1.242	2.693
24.000	1.694	0.5022	1.004	2.514
36.000	0.677	0.2994	0.387	1.361
48.000	0.328	0.2377	0.000	0.832

[00107] Table G

Time (h)	Mean	SD	Min	Max
0.000	0.000	0.0000	0.000	0.000
0.250	0.827	0.9846	0.000	2.816
0.500	3.916	2.1220	0.446	6.641
0.750	5.104	1.8481	2.367	8.275
1.000	5.019	1.7586	2.284	8.035
1.333	4.674	1.6784	2.450	8.636
1.667	4.467	1.4077	2.671	7.059
2.000	4.337	1.3439	2.425	7.438
2.500	4.016	1.2465	1.966	6.972
3.000	4.022	1.2987	2.339	7.571
4.000	3.755	1.0832	2.305	6.728
6.000	3.450	0.8644	2.375	5.806
8.000	2.642	0.5728	1.753	4.115
10.000	2.108	0.4792	1.455	3.227
12.000	1.675	0.3211	1.065	2.361
12.250	2.396	1.7049	0.977	6.824
12.500	3.557	2.8936	1.135	9.776
12.750	4.028	2.3244	1.224	7.591
13.000	4.790	2.7312	1.136	10.834
13.333	4.643	2.3575	1.158	9.468
13.667	4.319	1.9035	1.212	8.133
14.000	4.353	1.7036	1.557	7.822
14.500	4.665	1.2665	2.650	7.704
15.000	4.725	1.0905	3.375	7.688
16.000	4.129	0.8831	3.040	6.526
18.000	3.643	0.8572	2.293	5.675
20.000	3.137	0.6984	1.923	4.465
22.000	2.797	0.6958	1.765	4.056
24.000	2.562	0.5479	1.735	3.506
36.000	0.942	0.2814	0.494	1.522
48.000	0.495	0.1735	0.271	0.831

[00109] Table H

Time (h)	Mean	SD	Min	Max
0.000	0.000	0.0000	0.000	0.000
0.333	0.023	0.0871	0.000	0.326
0.667	0.482	0.8143	0.000	2.592
1.000	0.960	1.2274	0.000	3.470
1.333	1.413	1.3520	0.000	3.662
1.667	1.848	1.3106	0.000	4.082
2.000	2.241	1.4053	0.000	4.354
2.333	2.512	1.3559	0.000	4.701
2.667	2.638	1.0903	0.000	4.441
3.000	2.834	0.9642	0.000	4.220
4.000	3.004	0.7824	2.191	5.403
6.000	2.998	0.8026	1.970	4.727
8.000	2.377	0.5108	1.491	3.353
10.000	1.993	0.4248	1.230	2.835
12.000	1.636	0.3515	1.001	2.332
12.333	1.565	0.3252	1.138	2.275
12.667	1.693	0.4008	1.186	2.352
13.000	2.050	0.7696	1.187	3.305
13.333	2.444	1.2011	1.109	4.898
13.667	3.009	1.4787	1.103	6.064
14.000	3.398	1.5516	1.301	6.541
14.333	3.828	1.3267	1.726	6.702
14.667	3.878	1.1323	1.817	6.010
15.000	3.891	0.9989	2.321	6.061
16.000	3.753	0.7387	2.567	5.458
18.000	3.278	0.6769	2.272	4.514
20.000	2.850	0.6319	1.905	4.139
22.000	2.466	0.4609	1.776	3.304
24.000	2.447	0.5592	1.761	3.586
36.000	1.045	0.3301	0.666	1.737
48.000	0.548	0.2249	0.249	1.017

[00110] A summary of the pharmacokinetic parameters of ivabradine for Test Product-T1 and Reference Product-R1 under fasting conditions are shown in Table 12 and the

5 pharmacokinetic parameters of ivabradine for Test Product-T2 and Reference Product-R2 under fed conditions are summarized in Table 13.

Table 12. Descriptive Statistics of Formulation Means for Ivabradine under Fasting Conditions (Period I and Period II)

Parameters (Units)	Mean±SD (untransformed data)	
	Test Product-T1 (N=14)	Reference Product-R1 (N=14)
T _{max} (h)*	4.000(3.000-8.000)	1.000(0.500-14.500)
C _{max} (ng/mL)	38.740±9.4497	50.196±14.7521
AUC _{0-t} (ng.h/mL)	397.740±160.0233	432.219±129.1801
AUC _{0-∞} (ng.h/mL)	402.540±159.2814	437.345±127.4905
Λ _z (1/h)	0.151±0.0413	0.184±0.0369
t _{1/2} (h)	4.844±1.0661	3.902±0.7866
AUC_%Extrap_obs (%)	1.440±1.4878	1.485±1.7027
T _{lag} (h)*	0.000(0.000-0.250)	0.0 (0.000-0.000)

*T_{max} and T_{lag} are represented as median (min-max) value.

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Table 13. Descriptive Statistics of Formulation Means for Ivabradine under Fed Conditions (Period III and Period IV)

Parameters (Units)	Mean±SD (untransformed data)	
	TestProduct-T2 (N=14)	ReferenceProduct-R2 (N=14)
T _{max} (h)*	6.000(4.000-10.000)	3.000(1.333-14.333)
C _{max} (ng/mL)	41.451±8.5845	45.759±12.5515
AUC _{0-t} (ng.h/mL)	423.776±125.3288	497.036±145.0155
AUC _{0-∞} (ng.h/mL)	427.452±124.9312	499.975±146.3887
Λ _z (1/h)	0.144±0.0283	0.158±0.0331
t _{1/2} (h)	4.959±0.8996	4.556±0.8391
AUC_%Extrap_obs (%)	0.985±0.7954	0.566±0.2168
T _{lag} (h)*	0.000(0.000-0.366)	0.000(0.000-0.350)

*T_{max} and T_{lag} are represented as median (min-max) value.

- 10 [00111] The pharmacokinetic parameters of N-desmethyl ivabradine for Test Product-T1 and Reference Product-R1 under fasting conditions are summarized in Table 14 and the pharmacokinetic parameters of N-desmethyl ivabradine for Test Product-T2 and Reference Product-R2 under fed conditions are summarized in Table 15.

Table 14. Descriptive Statistics of Formulation Means for N-Desmethyl Ivabradine under Fasting Conditions (Period I and Period II)

Parameters (Units)	Mean±SD (untransformed data)	
	Test Product-T1 (N=14)	Reference Product-R1 (N=14)
T _{max} (h)*	6.000(3.000-10.017)	12.500(0.750-15.000)
C _{max} (ng/mL)	4.934±1.1539	6.785±2.0501
AUC _{0-t} (ng.h/mL)	86.099±20.5061	109.841±21.1940
AUC _{0-∞} (ng.h/mL)	92.334±21.5424	117.323±21.7097
Λ _z (1/h)	0.065±0.0144	0.071±0.0120
t _{1/2} (h)	11.110±2.3729	10.039±1.6555
AUC_%Extrap_obs (%)	6.793±3.2603	6.426±2.9767
T _{lag} (h)*	0.250(0.250-0.500)	0.000(0.000-0.250)

*T_{max} and T_{lag} are represented as median (min-max) value.

5 **Table 15. Descriptive Statistics of Formulation Means for N-Desmethyl Ivabradine under Fed Conditions (Period III and Period IV)**

Parameters (Units)	Mean±SD (untransformed data)	
	Test Product-T2 (N=14)	Reference Product-R2 (N=14)
T _{max} (h)*	6.000(4.017-10.000)	14.333(2.333-20.000)
C _{max} (ng/mL)	4.885±1.1884	4.538±0.9687
AUC _{0-t} (ng.h/mL)	84.033±18.9702	92.725±14.9871
AUC _{0-∞} (ng.h/mL)	90.950±21.3056	102.153±18.2247
Λ _z (1/h)	0.066±0.0135	0.064±0.0135
t _{1/2} (h)	10.908±2.0601	11.262±2.1692
AUC_%Extrap_obs (%)	7.446±2.8951	8.963±3.9776
T _{lag} (h)*	0.676(0.333-2.000)	0.667(0.000-3.000)

*T_{max} and T_{lag} are represented as median (min-max) value.

10 **[00112]** In summary, the plasma levels of ivabradine rose, after administration of the prolonged release formulations of this disclosure, for between about three to ten hours and then began to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty-four-hour period while maintaining at least a threshold therapeutic level of the drug during the entire twenty-four hour period. In contrast, the conventional immediate release tablets give peak blood plasma levels in 0.5 to 2.5 hours.

[00113] The maximum inhibition effect of heart rate reduction with respect to plasma concentration of ivabradine is comparable for all the formulations (T1, T2, R1 and R2) which is ~10 beats/min. The maximum inhibition effect of heart rate reduction with respect to plasma concentration of N-desmethylated derivative (S18982) is comparable for all the formulations (T1, T2, R1 and R2) which is ~13 beats/min. Based on above PK-PD analysis it can be inferred that the plasma levels of ivabradine and N-desmethylated derivative can be potentially related to reduction in heart rate.

[00114] The prolonged release composition of the present disclosure when administered to healthy human volunteers provided a relatively flattened and steady plasma profile over 24 hours in comparison to conventional immediate release preparation of ivabradine products. Further, the prolonged release composition of the present disclosure when administered as single tablet per day maintained the comparable area under the plasma concentration vs time curve with that of two tablets (given 12 hours apart, 1 tablet morning and 1 tablet evening) of the conventional immediate release preparations.

[00115] Administration of test product of this disclosure provided a method for obtaining flattened drug plasma concentration vs time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. Therefore, the administration of the prolonged release tablet eliminated the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release tablets.

Example 3

Efficacy of Prolonged Release Ivabradine Tablets in Patients with Stable Chronic Heart Failure

[00116] In the general population and in patients with coronary heart disease or HF, increased heart rate (HR) is directly correlated with all-cause or CV mortality. Cardiovascular (CV) risk with increased HR was first reported by the Framingham study. Thereafter, the risk of increased HR for mortality has been extensively studied, suggesting the higher risk in clinical outcomes with increased HR in the general population and in patients with HF. In a long-term follow-up study of Framingham, the general population presented an increase in all-cause mortality by 14% at every 10 beats per minute (bpm) increase in HR. Whereas, in patients with HF, resting HR of more than 80 bpm caused myocardial dysfunction which further deteriorated HF. Ivabradine prolonged release (PR)

were compared to immediate release (IR) tablets in stable chronic heart failure patients with systolic dysfunction.

[00117] Patients who are already stabilized for greater than one month on stable doses of ivabradine 5 mg or 7.5 mg received either a 10 or 15 mg dose of the prolonged release ivabradine once daily (test product in Example 2) or a 5 or 7.5 mg dose of the immediate release ivabradine (reference product in Example 2) twice daily. The resting HR was assessed before starting the treatment regimen and after 16, 46, and 91 days by taking 3 consecutive ECGs within 30 minutes by automated standard 12-lead ECG, and the mean HR derived from readings was determined.

[00118] At baseline visit the mean $\pm$ SD of resting HR (bpm) of patients under PR arm, IR arm and overall was reported as 62.8 ± 9.47 , 63.6 ± 8.85 and 63.2 ± 9.15 respectively. After 3 months treatment period, the mean $\pm$ SD of resting HR (bpm) for patients under PR arm, IR arm and overall was reported as 63.9 ± 9.35 , 63.7 ± 9.59 and 63.8 ± 9.44 with a mean change from baseline of 1.1 ± 8.42 , 0.0 ± 7.99 and 0.6 ± 8.20 respectively, indicating no undue effect of study treatments on resting HR (bpm) of patients. FIG. 3 shows no difference in summary statistics (mean, median, Q1, Q3) between PR and IR group for mean change from baseline to 3 Months in HR. Change in HR post ivabradine PR and IR treatments were also assessed with respect to gender and age-group which did not result to any significant finding.

[00119] The prolonged release composition of the present disclosure when administered as one tablet per day consecutively for 3 months was effective in stabilizing the heart rate when administered to patients suffering from congestive heart failure with systolic dysfunction, in contrast to conventional preparations which has to be administered as two tablets (one tablet morning and one tablet evening) for achieving the similar efficacy.

[00120] It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the disclosure, which is defined solely by the appended claims and their equivalents.

[00121] Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including without limitation those relating to the chemical structures, substituents, derivatives, intermediates, syntheses, compositions, formulations, or methods of use of the disclosure, can be made without departing from the spirit and scope thereof.

Claims:

1. A solid prolonged release composition comprising ivabradine, N-desmethyl ivabradine, or a pharmaceutical salt thereof, wherein ivabradine has a peak plasma concentration
5 between about 3 hours to about 8 hours after administration of the composition to a subject in the fasting state or between about 4 hours to about 10 hours after administration of the composition to a subject in the fed state.
2. The composition as claimed in claim 1 comprising:
about 3 to about 12% by weight of ivabradine, N-desmethyl ivabradine, or a
10 pharmaceutical salt thereof;
about 35 to about 65% by weight of polymer selected from hydroxypropyl methyl cellulose, polyvinyl acetate/polyvinylpyrrolidone, hydroxyethyl cellulose, hydroxypropyl cellulose and mixtures thereof;
about 20 to about 60% by weight of dibasic calcium phosphate; and
15 about 0.25 to about 1.25% by weight of magnesium stearate.
3. The composition as claimed in claims 1 or 2, wherein the composition is a tablet.
4. The composition as claimed in any of claims 1-3, wherein the composition is coated with about 2 to about 4% by weight of a film coating material.
5. The composition as claimed in claim 4, wherein the film coating material is a mixture of
20 titanium dioxide, polyethylene glycol, hydroxypropyl methyl cellulose, glycerin, yellow iron oxide non-irradiated, and red iron oxide non-irradiated.
6. The composition as claimed in any of claims 1-5, wherein the composition comprises:
about 8% by weight of ivabradine hydrochloride;
about 50% by weight of hydroxypropyl methyl cellulose;
25 about 41% by weight of dibasic calcium phosphate; and
about 1% by weight of magnesium stearate.
7. The composition as claimed in any of claims 1-6, wherein the plasma concentration of ivabradine at about 3 hours after administration of the composition to a subject in a fasting state is about 22.0 to about 59.0 ng/mL.
- 30 8. The composition as claimed in any of claims 1-7, wherein the plasma concentration of ivabradine at about 4 hours after administration of the composition to a subject in a fasting state is about 20.0 to about 56.0 ng/mL.

9. The composition as claimed in any of claims 1-8, wherein the plasma concentration of ivabradine at about 6 hours after administration of the composition to a subject in a fasting state is about 11.0 to about 47.0 ng/mL.
10. The composition as claimed in any of claims 1-9, wherein the plasma concentration of ivabradine at about 8 hours after administration of the composition to a subject in a fasting state is about 7.0 to about 47.0 ng/mL.
11. The composition as claimed in any of claims 1-9, wherein the plasma concentration of ivabradine at about 4 hours after administration of the composition to a subject in a fed state is about 11.0 to about 53.0 ng/mL.
12. The composition as claimed in any of claims 1-6 and 11, wherein the plasma concentration of ivabradine at about 6 hours after administration of the composition to a subject in a fed state is about 24.0 to about 60.0 ng/mL.
13. The composition as claimed in any of claims 1-6 and 11-12, wherein the plasma concentration of ivabradine at about 8 hours after administration of the composition to a subject in a fed state is about 13.0 to about 43.0 ng/mL.
14. The composition as claimed in any of claims 1-6 and 11-13, wherein the plasma concentration of ivabradine at about 10 hours after administration of the composition to a subject in a fed state is about 8.0 to about 40.0 ng/mL.
15. A method of treating a disease or disorder comprising administering the prolonged release composition of any of claims 1-14.
16. The method of claim 15, wherein the composition is administered once per day.
17. The composition as claimed in any of claims 1-14, wherein the composition is used in a treatment of a disease or a disorder selected from the group consisting of chronic heart failure with systolic dysfunction, heart-related chest pain and heart failure.
18. A solid prolonged release composition comprising:
- a) ivabradine, N-desmethyl ivabradine, or a pharmaceutical salt thereof;
 - b) at least one polymer selected from hydroxypropyl methyl cellulose, polyvinyl acetate/polyvinylpyrrolidone, hydroxyethyl cellulose, hydroxypropyl cellulose and mixtures thereof;
 - c) dibasic calcium phosphate; and
 - d) magnesium stearate.
19. The composition as claimed in claim 18, wherein:
- a) the ivabradine, N-desmethyl ivabradine, or a pharmaceutical salt thereof is present in an amount of about 3 to about 12% by weight;

- b) the polymer is hydroxypropyl methyl cellulose, polyvinyl acetate/polyvinylpyrrolidone, hydroxyethyl cellulose, hydroxypropyl cellulose or mixtures thereof is present in an amount of about 35 to about 65% by weight;
- 5 c) the dibasic calcium phosphate is present in an amount of about 20 to about 60% by weight; and
- d) the magnesium stearate is present in an amount of about 0.25 to about 1.25% by weight.
- 10 20. Use of the prolonged release composition of any of claims 1-14 or 18-19 for the treatment of systolic dysfunction, heart-related chest pain and heart failure.

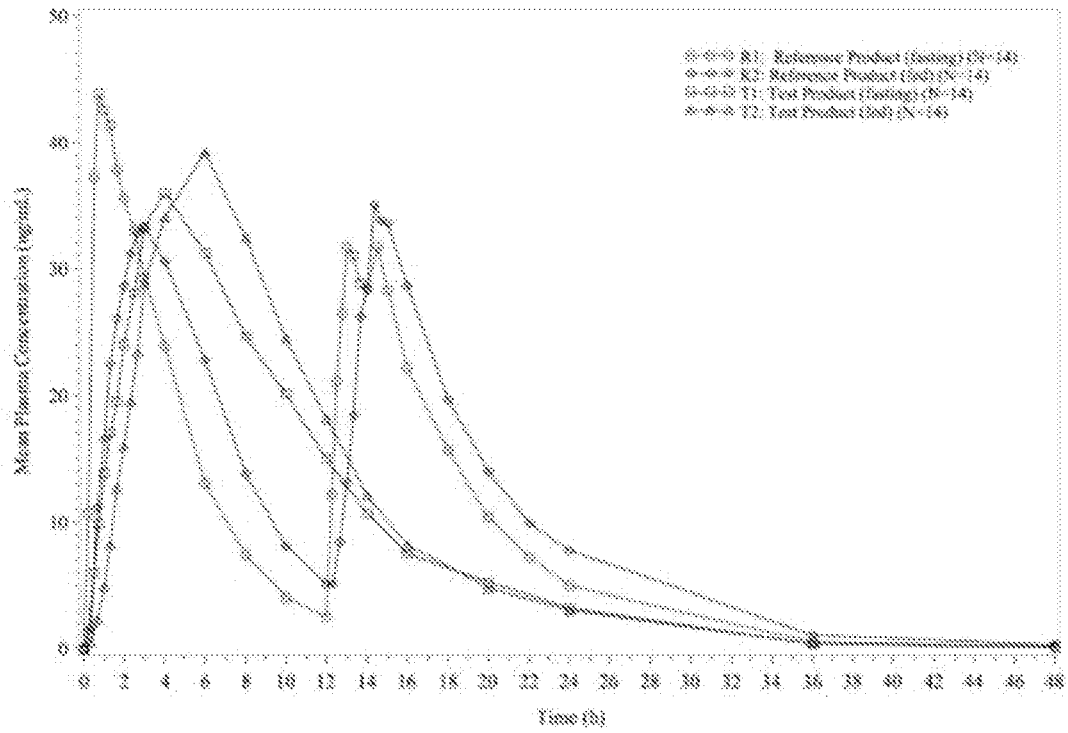


FIG. 1A

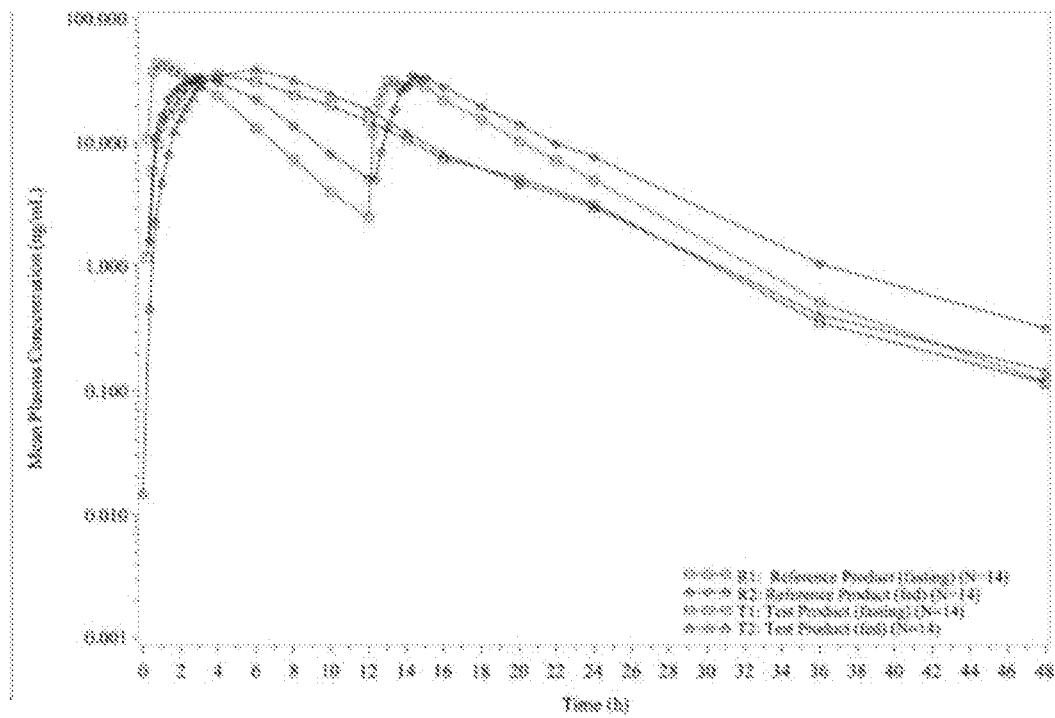


FIG. 1B

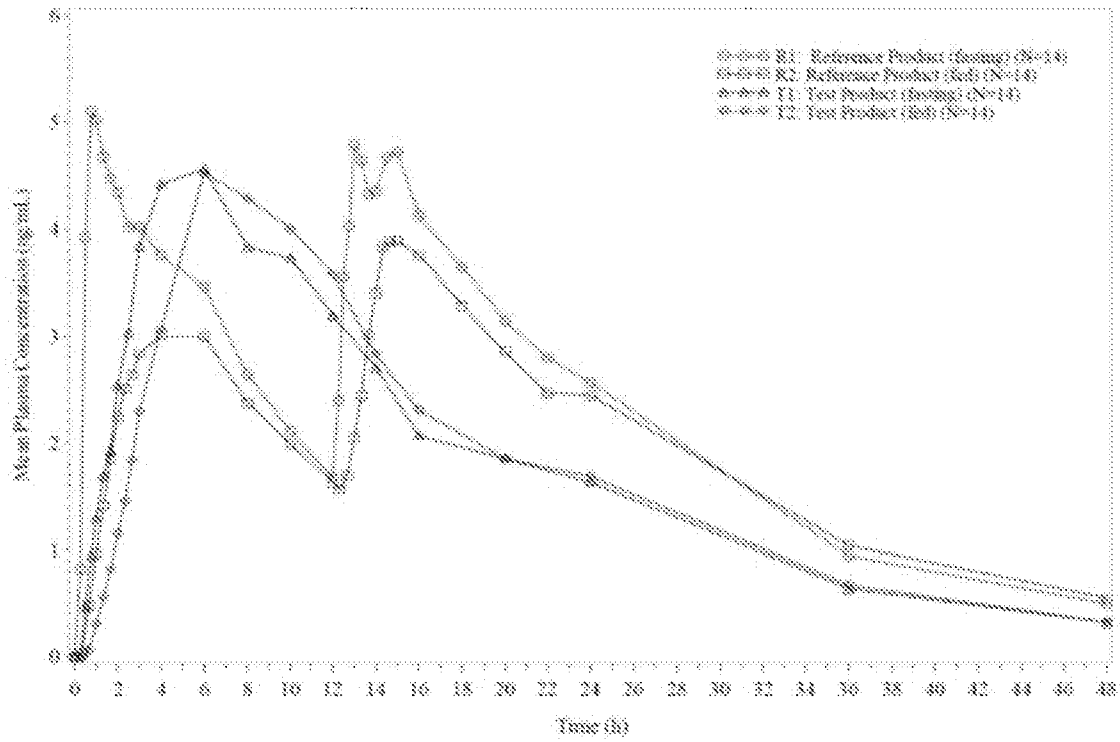


FIG. 2A

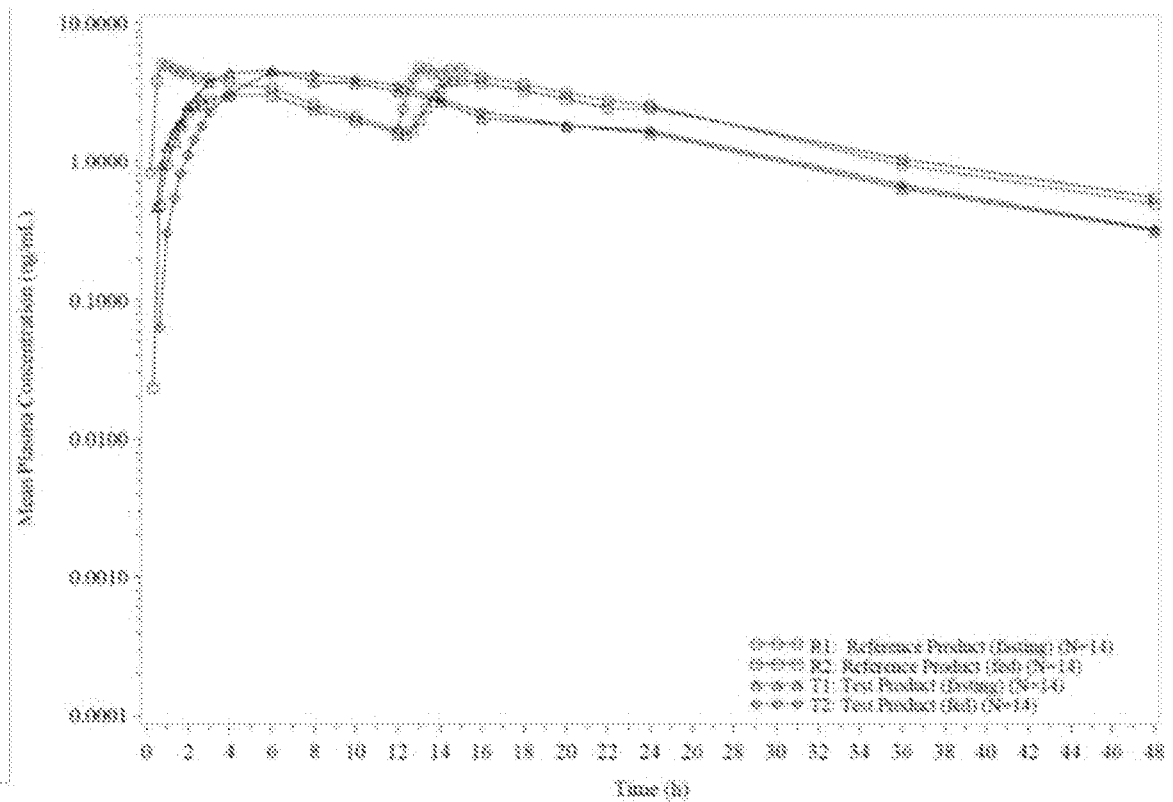


FIG. 2B

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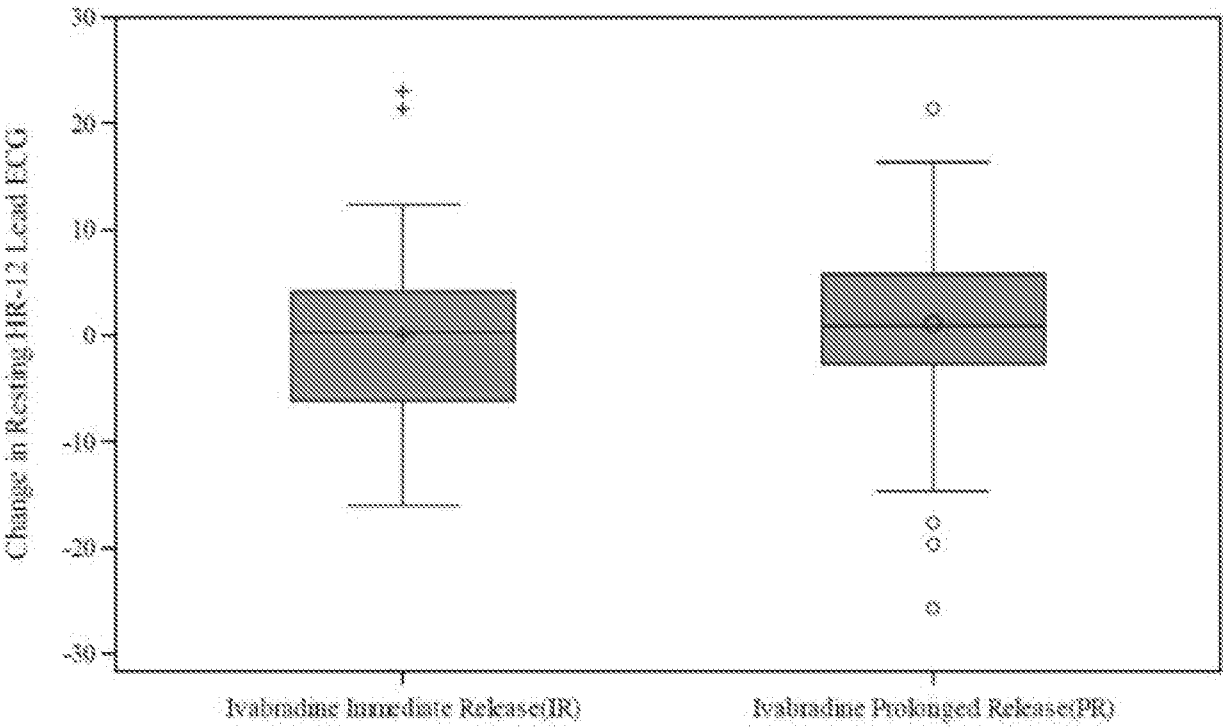


FIG. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2020/050753

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/55
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/128525 A2 (PATEL DINESH SHANTILAL [IN]; PATEL SACHIN DINESH [IN] ET AL.) 11 November 2010 (2010-11-11) page 1, line 3 - line 13 page 5, line 24 - page 6, line 7 page 7, line 4 - line 29 page 14 - page 15; example 6 claims -----	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search

4 December 2020

Date of mailing of the international search report

14/12/2020

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2020/050753

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010128525	A2	11-11-2010	NONE
