ABSTRACT

ORALLY DISINTEGRATING TABLET FORMULATIONS OF IVABRADINE

The present invention relates to an orally disintegrating pharmaceutical formulation comprising ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof and one or more pharmaceutically acceptable excipients.

CLAIMS

1. An orally disintegrating pharmaceutical formulation comprising ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof and one or more pharmaceutically acceptable excipients.

2. The orally disintegrating pharmaceutical formulation according to claim 1, wherein ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof is present in an amount of between 0.50% to 15.00%, preferably between 1.50% to 15.00% by weight of total formulation.

3. The orally disintegrating pharmaceutical formulation according to claim 1, wherein one or more pharmaceutically acceptable excipient selected from the group comprising super-disintegrants, fillers, sweeteners, lubricants, binders, flavouring agents or mixtures thereof.

4. The orally disintegrating pharmaceutical formulation according to claim 3, wherein the super-disintegrant is in an amount of between 0.10% and 20.00%, preferably between 0.50% and 15.00%by weight of total formulation.

5. The orally disintegrating pharmaceutical formulation according to any preceding claim, wherein the weight ratio of ivabradine to super-disintegrant is in the range of between 0.15 and 30.00, preferably between 0.15 and 20.00.

6. The orally disintegrating pharmaceutical formulation according to claim 3, the super-disintegrant is selected from the group comprising crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose (L-HPC), povidone, alginic acid and alginates, cross-linked alginic acid, , sodium carboxymethyl starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, docusate sodium, soy polysaccharide, guar gum, gellan gum, xanthan gum, magnesium alumina silica, polyacrylin potasium, poloxamer, sodium lauryl sulphate, calcium silicate, sodium glycine carbonate or ion exchange resins or mixtures thereof.

7. The orally disintegrating pharmaceutical formulation according to claim 6, wherein the super-disintegrant is selected from crospovidone, croscarmellose sodium, sodium starch glycolate or mixtures thereof.

8. The orally disintegrating pharmaceutical formulation according to claim 3, wherein the filler is in amount of between 5.00% and 80.00%, preferably 5.00% and 50.00% by weight of total formulation.

9. The orally disintegrating pharmaceutical formulation according to any preceding claims, comprising;
    a. 0.50 – 15.00 % ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof
    b. 0.10 – 20.00 % super-disintegrant
    c. 5.00 – 80.00 % filler
    d. 0.01 – 3.00 % sweetener
    e. 0.10 – 5.00 % flavouring agent
    f. 0.10 – 10.00 % lubricant

10. The orally disintegrating pharmaceutical formulation according to any preceding claims, comprisig;
    a. 0.50 – 15.00 % ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof
    b. 0.10 – 20.00 % super-disintegrant
    c. 5.00 – 80.00 % filler
    d. 0.01 – 3.00 % sweetener
    e. 0.10 – 50.00 % binder
    f. 0.10 – 5.00 % flavouring agent
    g. 0.10 – 10.00 % lubricant

DESCRIPTION

ORALLY DISINTEGRATING TABLET FORMULATIONS OF IVABRADINE

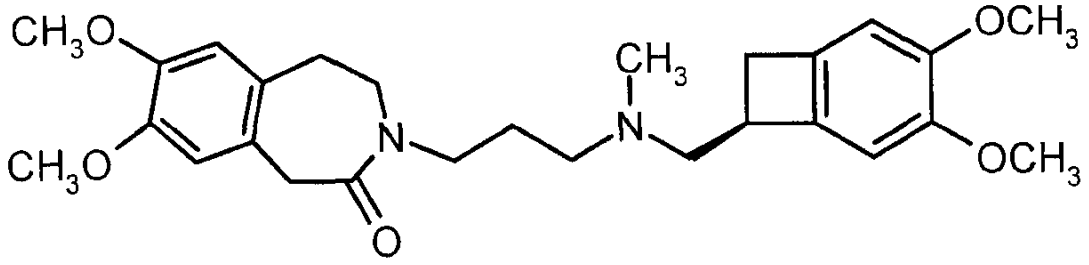
Field of Invention

The present invention relates to an orally disintegrating pharmaceutical formulation comprising ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof and one or more pharmaceutically acceptable excipients.

The Background of the Invention

Ivabradine, (marketed under the trade name Corlanor) is a medication used for the symptomatic management of stable heart related chest pain and heart failure not fully managed by beta blockers.

The chemical name of ivabradine is 3-{3-[{[(7S)-3,4-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl}(methyl)amino]propyl}-7,8-dimethoxy-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one and its chemical structure is shown in the Formula 1.



Formula 1

Ivabradine is a heart rate lowering agent. It acts by selective and specific inhibition of the cardiac pacemaker If current, an important ionic current that usually controls spontaneous diastolic depolarisation in the sinus node and thereby regulates heart rate.

Ivabradine molecule is disclosed in EP0534859. Ivabradine hydrochloride exhibits polymorphism. WO2006092493 discloses polymorph β of ivabradine hydrochloride, its process of preparation and compositions comprising this polymorph. Polymorph β is the most stable form and is present in the marketed product. Other polymorphic forms of ivabradine

hydrochloride are disclosed in WO2005110993, WO2006092491, WO2006092492, WO2006092494, WO2007042656, WO2007042657 and WO2013064307. It's known from the prior art, ivabradine hydrochloride crystallizes easily and polymorphic transitions of ivabradine hydrochloride take place rather easily, especially in drug products.

Amorphous ivabradine hydrochloride and methods for its preparation are disclosed in WO2008146308, CN101597261 and CN101463008.

There are also several patent applications which disclose orally administered ivabradine formulations. US Patent Application 20050106238 discloses an orodispersible solid pharmaceutical composition comprising ivabradine and this composition is characterised in that it comprises ivabradine or a pharmaceutically acceptable salt thereof and granules consisting of co-dried lactose and starch.

Conventional tablet dosage forms constitute a preferred route of administration but certain groups of patients including geriatric, bed-ridden, uncooperative, nauseated, on reduced water intake, and patients having dysphagia, difficulty in swallowing, encounter problems while taking these dosage forms. Moreover, patients while travelling may have little or no access to water, limiting the use of conventional tablet dosage forms. As ivabradine is prescribed chronically, such a problem could lead to a high level of patient non-compliance.

In view of this, orally disintegrating tablet compositions provide the best alternative over conventional tablet dosage forms. Orally disintegrating tablet compositions which rapidly disintegrate on contact with saliva or in a small amount of water, offer increased convenience and ease of administration with the potential to achieve better patient compliance.

In addition, ivabradine is an active agent which has a stability problem. Therefore, it is necessary to avoid degradation and polymorphic transition of ivabradine over the shelf life of the product. Mechanical stress associated with process and using high amount of excipients lead to polymorphic transformation of ivabradine. Therefore, it is important to choose excipients and use them in a specific amount that decrease the degradation and sustain the stability.

Ivabradine has also content uniformity problem, because of the low dose API, which is a pharmaceutical analysis parameter for the quality control of capsules or tablets. In this present invention, these problems are also solved by drug and excipient particle size values, mixing strategy and adjusting the ratio of excipients.

Over the past decades, orally disintegrating tablets (ODTs) have gained considerable attention as a preferred alternative to conventional tablets due to improved efficacy, bioavailability, rapid onset of action, better patient compliance and acceptance. ODTs are solid dosage forms containing active ingredients which disintegrate rapidly through buccal mucosa. ODTs typically have a disintegration time ranging from 30 seconds to 3 minutes. Mostly preferred within approximately 20-30 seconds. It is desirable in the treatment of a number of diseases including pediatric and geriatric treatments.

However, it is not easy to develop orally disintegrating formulations for all active agents because of several different reasons and requirements such as disintegration, stability, compressibility and taste masking. Dosage form must disintegrate in the oral cavity with the existence of saliva in a short period of time. So, those compositions should have a porous structure. Orally disintegrating tablets are usually pressed with lower compression forces than conventional tablets to obtain a higher porosity. However, these porous characteristics tend to be very sensitive to humidity and fragility and may be lead to stability problems.

To fulfill all these requirements, the orally disintegrating tablet composition of ivabradine needs to be adapted in particular by a careful excipient selection give a suitable porous structure with suitable disintegrating time and high stability.

As orally disintegrating tablet compositions are designed to rapidly disintegrate as the drug comes in direct contact with the tongue, it remains a challenge to the formulators to effectively mask the taste of drugs to increase the acceptability for these compositions.

Hence, there exists a need in the art for an improved composition of ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof to achieve desired dissolution profile and release kinetic while overcoming stability and content uniformity problems. The present invention teaches orally disintegrating tablet compositions of ivabradine with an acceptable taste.

Detailed Description of the Invention

The present invention relates to an orally disintegrating pharmaceutical composition comprising ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof and one or more pharmaceutically acceptable excipients.

According to one embodiment, ivabradine or a pharmaceutically acceptable salt used in this present invention is ivabradine hydrochloride.

According to this embodiment, ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof is present in an amount of between 0.50% to 15.00%, preferably between 1.50% to 15.00% % by weight of total formulation.

In one embodiment, the orally disintegrating tablet composition of this present invention comprises one or more pharmaceutically acceptable excipient selected from the group comprising super-disintegrants, fillers, sweeteners, lubricants, binders, flavouring agents or mixtures thereof.

As used herein, the term "super-disintegrant" is defined as the pharmaceutical ingredient that provides improved compressibility, stability as well as achieves disintegration substantially faster than the conventional disintegrants. According to this embodiment, the term "super-disintegrant" is selected from the group comprising crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose (L-HPC), povidone, alginic acid and alginates, cross-linked alginic acid, sodium carboxymethyl starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, docusate sodium, soy polysaccharide, guar gum, gellan gum, xanthan gum, magnesium alumina silica, polyacrylin potasium, poloxamer, sodium lauryl sulphate, calcium silicate, sodium glycine carbonate and ion exchange resins.

In one embodiment, the super-disintegrant is selected from crospovidone, croscarmellose sodium, sodium starch glycolate or mixtures thereof.

In this invention, the orally disintegrating tablet composition of ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof is disintegrated in less than 1 min, preferably less than 30 sec.

To develop an orally disintegrating tablet, it is very crucial to achieve superior disintegration time in oral cavity of patients. Formulation must disintegrate in the oral cavity with the existence of saliva in a short period of time. In this invention, for the orally disintegrating tablet composition comprising ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof, desired disintegration time is achieved.

It is difficult to develop orally disintegrating formulations because of several different reasons mentioned above. Those formulations should have a porous structure to achieve rapid disintegration. However, these porous characteristics may be lead to instability problems. A high degree of porosity and a very low overall density are not easily reconciled with strength and durability.

Using super-disintegrant in a specific amount is very important, because it affects density and amount of porous in the structure. Porous structure should both provide rapid disintegration in oral cavity and not to cause stability problems.

In one embodiment, the super-disintegrant is in an amount of between 0.10% and 20.00%, preferably between 0.50% and 15.00% by weight of total formulation.

In another embodiment, the weight ratio of ivabradine to super-disintegrant also affects the compressibility. In the orally disintegrating tablet composition of this present invention, the certain ratio of ivabradine to super-disintegrants is in the range of between 0.15 and 30.00, preferably between 0.15 and 20.00.

Particle size distribution of the super-disintegrant are also important to provide sufficiently good content uniformity results for the composition.

As used herein, 'particle size distribution' means the cumulative volume size distribution as tested by any conventionally accepted method such as the laser diffraction method (Malvern analysis).

Laser diffraction measures particle size distributions by measuring the angular variation in intensity of light scattered as a laser beam passes through a dispersed particulate sample. Large particles scatter light at small angles relative to the laser beam and small particles scatter light at large angles, as illustrated below. The angular scattering intensity data is then analyzed to calculate the size of the particles responsible for creating the scattering. The particle size is reported as a volume equivalent sphere diameter.

According to this measuring method, the term D10 means, the size at which 10% by volume of the particles are finer and D50 means the size at which 50% by volume of the particles are finer and D90 means the size at which 90% by volume of the particles are finer.

In the preferred embodiment of the invention, the D90 particle size value of super-disintegrant is ranging between 15 µm to 150 µm.

According to this preferred embodiment, the D50 particle size value of super-disintegrant is ranging between 7 µm to 70 µm.

According to these preferred embodiments, the D10 particle size value of super-disintegrant is ranging between 1 µm to 35 µm.

Suitable taste-masking agents may include but not limited to PVA (polyvinyl alcohol) based coating, polyvinyl alcohol-polyethylene glycol copolymers (Kollicoat IR), butyl methacrylate and methyl methacrylate (Eudragit E 100) (Poly(butyl methacrylate-co-(2-demethylaminoeethyl)methacrylate-co-methyl methacrylate)) , ethylcellulose dispersions (Surelease), Kerry-HPC, polyethylene glycol, polyvinylprolidone, polyvinylprolidone-vinyl acetate copolymer (PVP-VA) and all kinds of OpadryTM, as well as pigments, dyes, titanium dioxide, iron oxide, talc, polymethylmetacrylate copolymers (Eudragit), erythritol, glyceryl palmitostearateor acetyltributyl citrate or mixtures thereof.

Suitable fillers are selected from mannitol, xylitol, sorbitol, isomalt,(MCC), lactose, corn starch dibasic calcium phosphate, spray-dried lactose, sucrose, trehalose, LudiFlash® (mannitol, crospovidon and polivinyl acetate), starch, calcium phosphate anhydrate, calcium phosphate dihydrate, calcium phosphate trihydrate, tribasic calcium phosphate, calcium carbonate, calcium sulfate, dicalcium sulfate, sodium chloride, carboxymethyl cellulose calcium, powdered cellulose, cellulose acetate, pregelatinized starch, lactose monohydrate, sodium carbonate, sodium bicarbonate, heavy magnesium carbonate, maltodextrine, mixture of sucrose – maltodextrine, dextrose, lactitol, calcium carbonate, sugars, magnesium carbonate, polysaccharides, trehalose, inorganic salts, Pharmaburst® (mannitol, sorbitol,crospovidone and silica; aspartame; and magnesium stearate), Panexcea® (microcrystalline cellulose, HPMC ve crospovidone), F-Melt® (D-mannitol, xylitol, crospovidone, magnesium aluminometasilicate) or mixtures thereof.

Content uniformity problem of the active agent is solved by using filler. It's important to choose filler and use the filler in a specific amount for providing a good uniformity of content and avoiding stability problems. Since the composition has porous characteristics, it's sensitive to humidity and fragility which may be lead to stability problems. Furthermore, this stability problem becomes a big challenge due to polymorphic transition problem of ivabradine hydrochloride.

In one embodiment, the filler is present in an amount of between 5.00% and 80.00%, preferably between 5.00% and 50.00% by weight of total formulation.

In prior art, microcrystalline cellulose is often used as filler. In this invention, sugar-based fillers are preferably used.

In one preferred embodiment, the filler is selected from mannitol, xylitol, sorbitol, isomalt or mixtures thereof. Taste is one of the most important parameters governing patient compliance. This parameter becomes more evident since the pharmaceutical composition is in the form of orally disintegrating tablets. When the fillers are used according to this preferred embodiment, taste of formulation improves and patient compliance increases.

Suitable lubricants are selected from the group comprising sodium stearyl fumarate, sodium lauryl sulphate, zinc stearate, calcium stearate, mineral oil, talc, polyethylene glycol, glyceryl monostearate, glyceryl palmitostearate, glyceryl behenate, sodium benzoate, magnesium lauryl sulphate, fumaric acid, zinc stearate, stearic acid, hydrogenated natural oils, silica, paraffin and mixtures thereof.

In one embodiment, the lubricant is present in an amount of between 0.10% and 10.00% by weight of total formulation.

Magnesium stearate is a hydrophobic material, prolonged mixing, it forms a hydrophobic film around the active agent and retards the dissolution by retarding wetting of active agent.

In one preferred embodiment, the lubricant is sodium stearyl fumarate. Due to hydrophilic property of sodium stearyl fumarate, the formulation does not have the disadvantages of magnesium stearate in respect of tablet strength, disintegration and dissolution.

Suitable binders are selected from the group comprising erythritol, pullulan, polyvinylpyrrolidone (PVP) (povidone K30), carnauba wax, hydroxypropyl methyl cellulose

(HPMC), polymethacrylate, glyceryl behenate, hydroxypropyl cellulose (HPC), carboxymethyl cellulose (CMC), methyl cellulose (MC), hydroxyethyl cellulose, sodium carboxymethyl cellulose (Na CMC), carboxymethyl cellulose calcium, ethyl cellulose and other cellulose derivatives, polymetacrylates, polyethylene oxide, polyvinyl alcohol, polycarbophil, polyvinyl acetate and their copolymers, gelatin, starch, xanthan gum, guar gum, alginate, carrageen, kollagen, agar, pectin, hyaluronic acid, carbomer, chitosan, cellulose acetate phthalate, hydroxypropyl starch, hydroxyethyl methyl cellulose, polaxomer, polyethylene glycol (PEG), sugars, glycose syrups, natural gums, tragacanth gum, polyacrylamide, aluminum hydroxide, benthonite, laponite, setostearyl alcohol, polyoxyethylene-alkyl ethers, acacia mucilage, polydextrose and mixtures thereof.

In one preferred embodiment, the binder is selected from erythritol, pullulan, polyvinylpyrrolidone (PVP) (povidone K30) or mixtures thereof.

In one embodiment, the binder is present in an amount of between 0.10% and 50.00% by weight of formulation.

Suitable sweeteners may include but not limited to sucralose, erythritol, thaumatin, mogroside, inuline, acesulfame-K, aspartame, saccharin or its sodium and calcium salts, sodium cyclamate, sucrose, fructose, glucose, sorbitol, menthol, peppermint, cinnamon, chocolate, vanillin and fruit essences such as cherry, orange, strawberry, grape or mixtures thereof.

In one embodiment, the sweetener is sucralose.

In one embodiment, the sweetener is present in an amount of between 0.01% and 3.00% by weight of total formulation.

In orally disintegrating formulations, using a sweetener improves patient compliance. According to prior art, it is known that aspartame is used mostly as sweetener but contradictory to the prior art we have found that the effect of sucralose as a sweetener in these formulations, not only helped to improve its taste but also increased the efficacy and the conveniency of the formulation because of its positive effects over the glycemic index. There are lots of disadvantages about aspartame and it has a limited usage if you have to use it every day and also there are several incompatibilities reported in literature and safety problems (Handbook of Pharmaceutical Excipients, Reymond C Rowe, Paul J Sheskey, Marian E Quinn, sixth edition, pages 48-50). Thus, sucralose has an important role in this

aspect and even if it is used in low amounts it has a synergistic taste improvement with mannitol which is also very important issue in orally disintegrating tablet formulations.

Suitable flavouring agents may include but not limited to menthol, peppermint, cinnamon, chocolate, vanillin and fruit essences such as cherry, orange, strawberry, grape, tutti frutti etc. and mixtures thereof.

In one embodiment, the flavouring agent is present in an amount of between 0.1% and 5.00% by weight of total formulation.

Suitable coloring agents are selected from the group comprising Food, Drug & Cosmetic (FD&C) dyes (such as; FD&C blue, FD&C green, FD&C red, FD&C yellow, FD&C lakes), poncau, indigo Drug & Cosmetic (D&C) blue, indigotine FD&C blue, carmoisine indigotine (indigo Carmine); iron oxides (such as; iron oxide red, yellow, black), quinoline yellow, flaming red, carmine, carmoisine, sunset yellow and the like and mixtures thereof, preferably the coloring agent is iron oxide yellow.

In one embodiment, the coloring agent is present in an amount of between 0.001% and 3.00% by weight of total formulation.

Suitable salts of ivabradine are selected from a group comprising hydrochloride, the hydrobromide, the oxalate, the sulfate, the phosphate, the acetate, the propionate, however also salts of the ivabradine with propionic acid, maleic acid, fumaric acid, tartaric acid, nitric acid, benzoic acid, methanesulfonic acid, isethionic acid, benzenesulfonic acid, citric acid, toluenesulfonic acid, trifluoroacetic acid, and camphoric acid and also the lactate, pyruvate, malonate, succinate, glutarate, and ascorbate of the ivabradine. Further, the following salts can be employed: Laspartate, glutamate, sorbate, acinotate, gluconate, hippurate, and salts of the ivabradine with ethanesulfonic acid, mandelic acid, adipic acid, or sulfamic acid.

In one preferred embodiment, the pharmaceutically acceptable salt of ivabradine is ivabradine hydrochloride.

In one embodiment of the present invention, orally disintegrating formulations comprises;

a. 0.50 – 15.00 % ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof
b. 0.10 – 20.00 % super-disintegrant
c. 5.00 – 80.00 % filler
d. 0.01 – 3.00 % sweetener
e. 0.10 – 5.00 % flavouring agent
f. 0.10 – 10.00 % lubricant
g. 0.001 – 3.00 % coloring agent

In one embodiment of the present invention, orally disintegrating formulations comprises;

a. 0.50 – 15.00 % ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof
b. 0.10 – 20.00 % super-disintegrant
c. 5.00 – 80.00 % filler
d. 0.01 – 3.00 % sweetener
e. 0.10 – 50.00 % binder
f. 0.10 – 5.00 % flavouring agent
g. 0.10 – 10.00 % lubricant
h. 0.001 – 3.00 % coloring agent

Example 1:

ingredients	**amount (%)**
ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof	0.50-15.00
mannitol	5.00-50.00
erythritol	30.00-50.00
croscarmellose sodium	0.50-15.00
sucralose	0.01-3.00
tutti frutti essence	0.1-5.00
coloring agent	0.001-3.00
sodium stearyl fumarate	0.10-10.00
Total	**100.00**

The pharmaceutical compositions mentioned above are prepared by following these steps:

a. mixing ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof, half of mannitol and half of croscarmellose sodium
b. granulating with the granulation solution which is prepared by solving a part of eryhritol and the coloring agent in the water
c. after drying the granules, adding sucralose, tutti frutti essence and the other parts of mannitol, croscarmellose sodium and erythritol to the granules and mixing until a homogeneous mixture
d. adding sodium stearyl fumarate to the mixture and mixing
e. compressing the mixture into tablets

Example 2:

ingredients	**amount (%)**
ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof	0.50-15.00
sorbitol	5.00-50.00
xylitol	0.50-30.00
sodium starch glycolate	0.10-15.00
sucralose	0.01-3.00
tutti frutti essence	0.10-5.00
sodium stearyl fumarate	0.10-10.00
coloring agent	0.001-3.00
Total	**100.00**

The pharmaceutical compositions mentioned above are prepared by following these steps:

a. mixing ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof, sorbitol, xylitol, sodium starch glycolate, sucralose, coloring agent and tutti frutti essence
b. adding sodium stearyl fumarate to this mixture and mixing
c. compressing the mixture into tablets

Example 3:

ingredients	**amount (%)**
ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof	0.50-15.00
mannitol	5.00-50.00
crospovidone	5.00-20.00
polyvinylpyrrolidone	0.10-10.00
sucralose	0.01-3.00
tutti frutti essence	0.10-5.00
sodium stearyl fumarate	0.10-10.00
coloring agent	0.001-3.00
Total	**100.00**

The pharmaceutical compositions mentioned above are prepared by following these steps:

a. mixing ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof, mannitol, polyvinylpyrrolidone, coloring agent and half of crospovidone
b. compressing the mixture into slug tablet
c. grinding the slug tablet and forming a mixture
d. adding the other half of crospovidone, sucralose and tutti frutti essence to the mixture
e. adding sodium stearyl fumarate and mixing
f. compressing the mixture into tablets

Example 4:

ingredients	**amount (%)**
ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof	0.50-15.00
isomalt	5.00-50.00
pullulan	0.10-10.00
croscarmellose sodium	0.50-15.00
sucralose	0.01-3.00
tutti frutti essence	0.10-5.00
sodium stearyl fumarate	0.10-10.00
coloring agent	0.001-3.00
Total	100.00

The pharmaceutical compositions mentioned above are prepared by following these steps:

a. mixing ivabradine or a pharmaceutically acceptable salt, solvate or polymorph thereof, isomalt, pullulan, croscarmellose sodium, sucralose, coloring agent and tutti frutti essence
b. adding a part of sodium stearyl fumarate to the mixture
c. passing the powder mixture from the roller compactor and sieving to form granules
d. adding the other part of sodium stearyl fumarate to the mixture and mixing
e. compressing the mixture into tablets