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(54) Prasugrel tablet formulations

(57) A solid pharmaceutical tablet formulation, comprising prasugrel, or a pharmaceutically acceptable salt thereof and pullulan as a filling agent.

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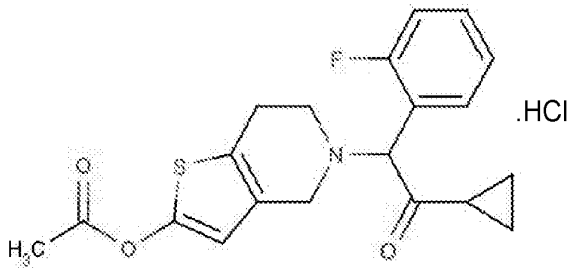
Description

Field of Invention

[0001] The present invention relates to formulations of prasugrel or a pharmaceutically acceptable salt of prasugrel. The present invention particularly relates to stable tablet formulations of prasugrel with desired levels of solubility and dissolution rate.

Background of Invention

[0002] Prasugrel hydrochloride is a member of the thienopyridine class and inhibits the activation and aggregation of platelets by means of P2Y12 and ADP receptors. Its chemical designation is 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno [3,2-c]pyridine hydrochloride, with the chemical structure illustrated below in Formula 1.



Formula 1

[0003] Prasugrel hydrochloride is a white solid. Prasugrel hydrochloride is well soluble at pH 2, weakly soluble at pH 3 to 4, and is substantially insoluble at pH 6 to 7.5.

[0004] Prasugrel hydrochloride is marketed under the trademark Effient® in 5 or 10 mg dosages. It is initially administered in a dosage amount of 60 mg, as a loading dose. It is used in preventing or treating thrombosis and cardiovascular diseases.

[0005] Searching the patent literature reveals various patents in relation to prasugrel.

[0006] Patent application EP1298132, for instance, discloses a prasugrel hydrochloride salt, a method for obtaining this salt, and its use for thrombosis and embolism.

[0007] Patent application EP1728794 discloses a prasugrel maleate salt, a method for obtaining this salt, and its use for thrombosis and embolism.

[0008] Patent application WO2006135605 discloses a formulation containing prasugrel hydrochloride, packaged in an air and moisture impervious gas-inerted blister pack.

[0009] Stability-related problems do occur in a plurality of active agents, including prasugrel, under the influence of ambient and physical conditions. Prasugrel is an active agent that is highly-susceptible to air and humidity. When prasugrel is exposed to air and humidity, it degrades structurally and develops behavioral changes. As a result of this fact, two main problems emerge. The first problem is that the stability of prasugrel products developed is not of desired level and the shelf life thereof is shortened. The second problem is that prasugrel is reactive against the excipients employed in developing formulations containing prasugrel. This fact causes impurities to occur in formulation and leads to incorporation of undesired components into the formulation.

[0010] Due to the abovementioned drawbacks, a novelty is required in the art of prasugrel hydrochloride formulations used for preventing and treating thrombosis and cardiovascular diseases.

Object and Brief Description of Invention

[0011] The present invention provides a prasugrel formulation, eliminating all aforesaid problems and brining additional advantages to the relevant prior art.

[0012] Accordingly, the main object of the present invention is to obtain a formulation of prasugrel, which is stable and has desired levels of solubility and dissolution rate.

[0013] Another object of the present invention is to develop a multi-coating, providing the stability of prasugrel-con-

taining formulation and not affecting the solubility and dissolution rates thereof.

[0014] A further object of the present invention is to obtain a stable prasugrel formulation with high bioavailability.

[0015] Another object of the present invention is to provide a high dissolution rate for such stable prasugrel formulations with high bioavailability.

[0016] A further object of the present invention is to avoid any aggregation of ingredients of the composition and to provide a desired level of flowability during production, thanks to convenient excipients used while the formulation is obtained.

[0017] A solid pharmaceutical tablet formulation has been developed to carry out all objects, referred to above and to emerge from the following detailed description.

[0018] According to a preferred embodiment of the present invention, said novelty comprises prasugrel, or a pharmaceutically acceptable salt thereof and pullulan as a filling agent.

[0019] According to a preferred embodiment of the present invention, the weight ratio of prasugrel to pullulan is between 0.20 to 50, preferably 0.25 to 10, and more preferably 0.25 to 4.

[0020] According to a preferred embodiment of the present invention, prasugrel or a pharmaceutically acceptable salt thereof is used in a granular form.

[0021] According to another preferred embodiment of the present invention, said granules of prasugrel, or of a pharmaceutically acceptable salt thereof, further comprise at least one coating layer which contains pullulan.

[0022] Another preferred embodiment according to the present invention further comprises at least one or a proper mixture of binders, lubricants, and glidants.

[0023] According to a preferred embodiment of the present invention, said binder is at least one or a mixture of polyvinylpyrrolidone (povidone), hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, and other cellulose derivatives, and gelatin, with polyvinylpyrrolidone being preferred.

[0024] According to a preferred embodiment of the present invention, said glidants comprise at least one or a mixture of colloidal silicone dioxide, talk, aluminum silicate, magnesium silicate, with colloidal silicone dioxide being preferred.

[0025] According to a preferred embodiment of the present invention, suitable disintegrants include at least one or a mixture of sodium starch glycolate, croscarmellose sodium, crospovidone, sodium alginate, gums, starch, and magnesium aluminum silicate, with croscarmellose sodium being preferred.

[0026] According to a preferred embodiment of the present invention, suitable lubricants include at least one or a mixture of sodium stearyl fumarate, magnesium stearate, polyethylene glycol, stearic acid, metal stearates, boric acid, sodium chloride benzoate and acetate, sodium or magnesium lauryl sulfate, with magnesium stearate being preferred.

[0027] A preferred embodiment according to the present invention comprises at least one coating layer. The coating layer comprises at least one or a mixture of polyvinyl alcohol, methacrylic acid derivatives, hydroxypropyl methylcellulose, and carboxymethyl cellulose.

[0028] A further preferred embodiment according to the present invention provides a method for preparing a solid pharmaceutical formulation, this method comprising the steps of

a. coating the particles of the active agent with pullulan in a fluidized bed system,
b. mixing the pullulan-coated active agent particles with a filler, binder, disintegrant, and lubricant-glidants,
c. compressing the mixture into tablets, and
d. film-coating the tablets compressed.

[0029] In a further preferred embodiment according to the present invention, said pharmaceutical formulation comprises the following ingredients:

a. core

a. prasugrel or a pharmaceutically acceptable salt or polymorph thereof at 1 to 20% by weight,
b. pullulan at 0.1 to 4% by weight,
c. microcrystalline cellulose at 5.0 to 90% by weight,
d. polyvinylpyrrolidone at 0.25 to 5% by weight,
e. croscarmellose sodium at 0.2 to 10% by weight,
f. colloidal silicone dioxide at 0.1 to 5% by weight,
g. magnesium stearate at 0.1 to 10% by weight;

b. coating

a. polyvinyl alcohol at 0.5 to 5% by weight, or
b. hydroxypropyl methylcellulose at 0.5 to 5% by weight, or a properly-proportioned mixture thereof.

Detailed Description of Invention

Example

[0030]

Unit Formula	Amount in tablet (%)- Example 1	Amount in tablet (%)- Example 2	Amount in tablet (%)- Example 3
Core tablet			
prasugrel	5	5	5
pullulan	-	1.25	3.5
microcrystalline cellulose	80.5	79.25	77
polyvinylpyrrolidone	4	4	4
croscarmellose sodium	4	4	4
colloidal silicone dioxide	0.5	0.5	0.5
magnesium stearate	1	1	1
Film coating			
Opadry AMB -OY- B 28920 white	5	5	5
Prasugrel/pullulan	-	4	1.42

[0031] The formulation according to the present invention is prepared as follows. The active agent particles are coated with pullulan in a fluidized bed system. Then, pullulan-coated active agent particles are mixed with pullulan, microcrystalline cellulose, polyvinylpyrrolidone, croscarmellose sodium, colloidal silicone dioxide, and magnesium stearate. The mixture is compressed into tablets. Finally, the tablets compressed are coated with a film comprising Opadry AMB -OY- B 28920 white or Opadry II 85 F28751 white, or a properly-proportioned mixture thereof. Opadry AMB -OY- B 28920 white comprises polyvinyl alcohol, whereas Opadry II 85 F28751 white comprises hydroxypropyl methylcellulose. Said tablets are packaged into alu-alu blister.

[0032] The term granule, as used herein, means a powder, particle, or a pellet form of prasugrel or of a pharmaceutically acceptable salt of prasugrel.

Stability Test Results

[0033]

Samples	Remaining 4 weeks at 55 C° and % 85 relative humidity
Amount of active ingredient of Example 1	% 89
Amount of active ingredient of Example 2	% 92
Amount of active ingredient of Example 3	% 96

[0034] With the invention, it has been surprisingly found that stable prasugrel formulations can be obtained which show good solubility and dissolution rates, and thus high bioavailability.

[0035] The formulation obtained is used in preventing or treating thrombosis, embolism and cardiovascular diseases.

[0036] It is further possible to use the following additional excipients in the formulation.

[0037] Suitable coating agents include, but are not restricted to, hydroxypropyl methylcellulose, polyethylene glycol, polyvinylpyrrolidone, polyvinylpyrrolidone-vinyl acetate copolymer (PVP-VA), pullulan like polymers, and all kinds of Opadry, as well as pigments, dyes, titanium dioxide and iron oxide, talk.

[0038] Suitable colorants include, but are not restricted to, at least one or a mixture of food, drug, and cosmetic (FD&C) dyes (FD&C blue, FD&C green, FD&C red, FD&C yellow, FD&C lake), ponceau, indigo drug & cosmetic (D&C) blue, indigotine FD&C blue, carmoisine indigotine (indigo Carmine); iron oxides (e.g. iron oxide red, yellow, black), quinoline

yellow, flame red, brilliant red (carmine), carmoisine, sunset yellow.

[0039] Suitable preservatives include, but are not restricted to, at least one or a mixture of methylparaben and propylparaben and salts thereof (e.g. sodium or potassium salts), sodium benzoate, citric acid, benzoic acid, butylated hydroxytoluene and butylated hydroxyanisole, etc..

[0040] The protection scope of the present invention is set forth in the annexed claims and cannot be restricted to the illustrative disclosures given above, under the detailed description. Any alternative embodiments to be produced by persons skilled in the art according to the basic principles, which are under the protection scope as set forth in the claims, shall be an infringement of the present invention.

Claims

1. A solid pharmaceutical tablet formulation, comprising prasugrel, or a pharmaceutically acceptable salt thereof and pullulan as a filling agent.

2. The solid pharmaceutical tablet formulation according to Claim 1, wherein the weight ratio of prasugrel to pullulan is between 0.20 to 50, preferably 0.25 to 10, and more preferably 0.25 to 4.

3. The solid pharmaceutical tablet formulation according to any of the preceding claims, wherein prasugrel, or a pharmaceutically acceptable salt thereof, is in a granular form.

4. The solid pharmaceutical tablet formulation according to any of the preceding claims, wherein the granules of prasugrel, or of a pharmaceutically acceptable salt thereof, further comprise at least one coating layer which contains pullulan.

5. The solid pharmaceutical tablet formulation according to any of the preceding claims, further comprising at least one or a mixture of binders, lubricants, and glidants.

6. The solid pharmaceutical tablet formulation according to any of the preceding claims, wherein said binder contains at least one or a mixture of polyvinylpyrrolidone (povidone), hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, and gelatin, with polyvinylpyrrolidone being preferred.

7. The solid pharmaceutical tablet formulation according to any of the preceding claims, wherein said glidant comprises at least one or a mixture of colloidal silicone dioxide, talk, aluminum silicate, and magnesium silicate, with colloidal silicone dioxide being preferred.

8. The solid pharmaceutical tablet formulation according to any of the preceding claims, wherein suitable disintegrants include at least one or a mixture of sodium starch glycolate, croscarmellose sodium, crospovidone, sodium alginate, gums, starch, and magnesium aluminum silicate, with croscarmellose sodium being preferred.

9. The solid pharmaceutical tablet formulation according to any of the preceding claims, wherein said lubricant comprises at least one or a mixture of sodium stearyl fumarate, magnesium stearate, polyethylene glycol, stearic acid, metal stearates, boric acid, sodium or magnesium lauryl sulfate, with magnesium stearate being preferred.

10. The solid pharmaceutical tablet formulation according to any of the preceding claims, comprising at least one coating layer.

11. The solid pharmaceutical tablet formulation according to any of the preceding claims, wherein said coating layer comprises at least one or a mixture of polyvinyl alcohol, methacrylic acid, hydroxypropyl methylcellulose, and carboxymethyl cellulose.

12. The solid pharmaceutical tablet formulation according to any of the preceding claims wherein said tablets are into the alu-alu blister.

13. The solid pharmaceutical tablet formulation according to any of the preceding claims, consisting of the following ingredients only:

    a. core

a. prasugrel, or a pharmaceutically acceptable salt or polymorph thereof, at 1 to 20% by weight,
b. pullulan at 0.2 to 4% by weight,
c. microcrystalline cellulose at 5.0 to 90% by weight,
d. polyvinylpyrrolidone at 0.25 to 5% by weight,
e. croscarmellose sodium at 0.2 to 10% by weight,
f. colloidal silicone dioxide at 0.1 to 5% by weight,
g. magnesium stearate at 0.1 to 10% by weight;

b. coating

a. polyvinyl alcohol at 0.5 to 5% by weight, or
b. hydroxypropyl methylcellulose at 0.5 to 5% by weight, or a properly-proportioned mixture thereof.

14. A method for preparing a solid pharmaceutical tablet formulation according to any of the preceding claims, comprising the steps of

a. coating the particles of the active agent with pullulan in a fluidized bed system,
b. mixing the pullulan-coated active agent particles with a filler, binder, disintegrant, and lubricant-glidants,
c. compressing the mixture into tablets, and
d. film-coating the tablets compressed.

15. The solid pharmaceutical tablet formulation according to any of the preceding claims for preventing or treating thrombosis, embolism, and cardiovascular diseases in mammalians, but particularly in humans.

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EUROPEAN SEARCH REPORT

Application Number
EP 11 17 4408

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	3 November 2011	van de Wetering, P

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X : particularly relevant if taken alone
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EPO FORM 1503 03.82 (P04C01)

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EUROPEAN SEARCH REPORT

Application Number
EP 11 17 4408

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The Hague	3 November 2011	van de Wetering, P

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D : document cited in the application
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

REFERENCES CITED IN THE DESCRIPTION

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- EP 1728794 A **[0007]**
- WO 2006135605 A **[0008]**