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(54) Title: A SOLID ORAL COMPOSITION COMPRISING ELTROMBOPAG CHOLINE

(57) Abstract: The present invention relates to a solid oral composition comprising eltrombopag choline and at least one pharmaceutically acceptable excipient. The present invention also relates to a simple, rapid, cost effective, time-saving and industrially convenient process.

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DESCRIPTION

A SOLID ORAL COMPOSITION COMPRISING ELTROMBOPAG CHOLINE

Field of the Invention

The present invention relates to a solid oral composition comprising eltrombopag choline and at least one pharmaceutically acceptable excipient. The present invention also relates to a simple, rapid, cost effective, time-saving and industrially convenient process.

Background of the Invention

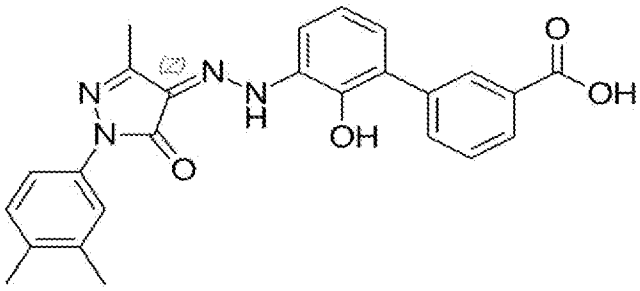
Thrombopoietin (THPO), also known as megakaryocyte growth and development factor (MGDF), is a protein that in humans is encoded by the THPO gene.

The thrombopoietin receptor agonists mimic the action of thrombopoietin on its receptor and stimulate the activation, proliferation and maturation of megakaryocytes, resulting in an increase in circulating platelet counts. Thrombopoietin itself acts in this manner, but when recombinant thrombopoietins were used clinically, they were found to cause rebound thrombocytopenia, probably due to induction of anti-thrombopoietin antibodies. For this reason, direct administration of thrombopoietin was abandoned as an approach to treating thrombocytopenia and other approaches for activating the thrombopoietin receptor were sought.

Two thrombopoietin receptor agonists were subsequently developed and are now in clinical use for chronic idiopathic thrombocytopenic purpura (ITP) and for other thrombocytopenic conditions.

Eltrombopag is an orally active thrombopoietin receptor agonist with megakaryopoiesis stimulating activity. Eltrombopag binds to and stimulates the platelet thrombopoietin receptor (TPO-R or CD110), a member of the hematopoietin receptor superfamily. Activation of TPO-R leads to the proliferation and differentiation of megakaryocytes, thereby increasing the production of blood platelets.

The chemical name of eltrombopag is 3-[3-[[2-(3,4-dimethylphenyl)-5-methyl-3-oxo-1H-pyrazol-4-yl]diazenyl]-2-hydroxyphenyl] benzoic acid and its chemical structure is shown in the Formula 1.



Formula 1: Eltrombopag

Eltrombopag is marketed under the trade name Promacta® by GlaxoSmithKline and Ligand Pharmaceuticals as eltrombopag olamine for the treatment of conditions leading to thrombocytopenia.

Eltrombopag has been disclosed in U.S. Patent Nos. 7,332,481 and 7,160,870, as well as WO 01/89457; and in EP Patent No. 1,294,378. Eltrombopag bisethanolamine salt and eltrombopag olamine salt has been disclosed in WO 03/098992 and U.S. Patent No. 8,052,994, respectively.

Some salts of eltrombopag, especially olamine, presents the formulator with unique concerns when attempting to formulate this compound into a suitable solid oral pharmaceutical dosage form with a desirable pharmacokinetic profile. Some of the concerns is that slow dissolution of the compound from solid dosage forms, the tendency of the compound to form insoluble metal complexes when contacted with excipients that contain a coordinating metal, and the tendency of the compound to under-go a Maillard reaction when contacted with excipients that contain reducing sugars.

Due to the problems of eltrombopag described above, compositions comprising the new eltrombog salt are needed.

WO 19/071111A1 discloses eltrombopag choline. The solid state form of eltrombopag choline disclosure have advantageous properties chemical or polymorphic purity, dissolution profile, bioavailability, morphology or crystal habit, stability - such as chemical stability as well as thermal and mechanical stability with respect to polymorphic conversion, stability towards dehydration and/or storage stability, a lower degree of hygroscopicity, low content of residual solvents.

In this present invention, a solid oral composition comprising eltrombopag choline is improved for the treatment of conditions leading to thrombocytopenia. It is used to overcome the disadvantages and side effects of the active agent's other salts meanwhile increasing the dissolution rate and stability in the desired manner.

Detailed Description of the Invention

The main object of the present invention is to eliminate problems and bringing additional advantages to the relevant prior art.

The more clearly main object of the present invention is to provides a solid oral composition comprising eltrombopag choline having desired dissolution profile, stability (chemical stability or towards dehydration and/or storage stability) for the treatment of conditions leading to thrombocytopenia.

Another object of the present invention is to provides a process for a solid oral composition comprising eltrombopag choline. The process is a simple, rapid, cost effective, time-saving and industrially convenient method.

According to one embodiment of the present invention, a solid oral composition comprising eltrombopag choline and at least one pharmaceutically acceptable excipient. The solid state form of eltrombopag choline has advantageous properties chemical or polymorphic purity, dissolution profile, bioavailability, stability. While creating the formulation for the treatment of conditions leading to thrombocytopenia, using eltrombopag choline was achieved effective treatment by making a low cost and easy production.

According to one embodiment of the present invention, the amount of eltrombopag choline is between 3.0% and 40.0% by weight in the total formulation. This amount provides an effective treatment for the treatment of conditions leading to thrombocytopenia.

According to one embodiment of the present invention, the amount of eltrombopag choline is between 5.0% and 35.0%, between 6.0% and 30.0%, between 7.0% and 27.0%, by weight in the total formulation.

According to one embodiment of the present invention, at least one pharmaceutically acceptable excipient is selected from the group comprising diluents, binders, disintegrants, lubricants, glidants or mixtures thereof.

In general terms, excipients provided in a formulation may positively or negatively influence the physicochemical and pharmacokinetic properties, e.g. the solubility, absorption, bioavailability of an active agent. For this reason, the excipients which accompany an active agent have to be selected in a careful and conscious manner while a formulation is developed. The formulations should have no physicochemical incompatibility between the active agents and the excipients. In the present invention, all excipients selected are compatible with eltrombopag choline.

Suitable diluents are selected from the group comprising microcrystalline cellulose, starch, pregelatinize starch, powdered cellulose, mannitol, spray-dried mannitol, dextrose, sucrose, sorbitol, xylitol, inorganic salts, polysaccharides, dicalcium phosphate, sodium chloride, dextrates, lactitol, maltodextrin, sucrose-maltodextrin mixture, trehalose, sodium carbonate, sodium bicarbonate or mixtures thereof.

According to one embodiment of the present invention, the amount of diluents is between 45.0% and 90.0% by weight in the total formulation.

According to one embodiment of the present invention, the amount of diluents is between 50.0% and 85.0% by weight in the total formulation.

According to one embodiment of the present invention, the diluent is microcrystalline cellulose or mannitol or mixtures thereof.

It has now surprisingly been found that using binders help to provide the desired dissolution profile.

Suitable binders are selected from the group comprising polyvinylpyrrolidone, sodium carboxymethyl cellulose, polyethylene glycol, polyvinyl alcohol, pregelatinized starch, natural gums, sucrose, sodium alginate, gelatin, carrageenan, guar gum, carbomer, polymethacrylates, methacrylate polymers, gelatin, alginate, alginic acid, xanthan gum, hyaluronic acid, pectin, polysaccharides, carbomer, poloxamer, polyacrylamide, polyoxyethylene-alkyl ether, polydextrose, polyethylene oxide or mixtures thereof.

According to one embodiment of the present invention, the amount of binders is between 0.05% and 10.0% by weight in the total formulation. Preferably, it is between 0.1% and 5.0% by weight in the total formulation. In the present invention, used binder's rate is very important in the solid oral composition. Thanks to the rate, dissolution problems are solved and surprisingly better dissolution profile is gained.

According to one embodiment of the present invention, the binder is polyvinylpyrrolidone. The active ingredient did not interact at polyvinylpyrrolidone, and polyvinylpyrrolidone also ensured that the composition had the desired dissolution profile.

Suitable disintegrants are selected from the group comprising croscarmellose sodium, sodium starch glycolate, starch, crospovidone, low-substituted hydroxypropyl cellulose, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose, docusate sodium, guar gum, low substituted hydroxypropyl cellulose, polyacryline potassium,

sodium alginate, corn starch, alginic acid, alginates, ion-exchange resins, sodium dodesyl sulphate, poloxamer, sodium glycine carbonate or mixtures thereof.

According to one embodiment of the present invention, the amount of disintegrants is between 1.0% and 25.0% by weight in the total formulation. Preferably, it is between 1.0% and 20.0%, between 1.0% and 15.0% by weight in the total formulation.

According to one embodiment of the present invention, the disintegrant is croscarmellose sodium or sodium starch glycolate or mixtures thereof.

Suitable lubricants are selected from the group comprising sodium stearyl fumarate, magnesium stearate, calcium stearate, zinc stearate, boric acid, hydrogenated vegetable oil, sodium chlorate, magnesium lauryl sulfate, sodium oleate, sodium acetate, sodium benzoate, polyethylene glycol or mixtures thereof.

According to one embodiment of the invention, the amount of the lubricants is 0.1% to 5.0% or 0.1% to 4.0% by weight of the total composition.

According to one embodiment of the invention, the lubricant is sodium stearyl fumarate.

Suitable glidants are selected from the group comprising colloidal silicon dioxide, corn starch, talc or mixtures thereof.

According to one embodiment of the invention, the amount of the glidants is 0.05% to 5.0% or 0.05% to 3.0% by weight of the total composition.

According to one embodiment of the invention, the glidant is colloidal silicon dioxide.

As used here in, 'particle size distribution' means the cumulative volume size distrubition as tested by any conventionally accepted method such as the laser diffraction method (i.e. malvern analysis) .The term d(0.9) means, the size at which 90% by volume of the particles are finer.

According to one embodiment of the invention, eltrombopag choline has a particle size of d(0.9) less than 150 µm or less than 140 µm or less than 130 µm or less than 120 µm or less than 110 µm or less than 100 µm or less than 90 µm or less than 80 µm or less than 70 µm or less than 60 µm or less than 50 µm or less than 40 µm or less than 30 µm or less than 20 µm. This property provides improved flow properties, also it helps to provide the desired dissolution profile.

According to one embodiment of the invention, eltrombopag choline has a particle size of d(0.9) less than 10 µm.

According to one embodiment of the present invention, the solid oral composition is in the form of tablets, capsules, strips, powders, pastilles, sachets, effervescent compositions, pills, coated bead systems, granules, microspheres, dragees, films. Preferably, the solid oral composition is in the form of tablets or capsules.

According to an embodiment of this present invention, the solid oral composition is formulated as tablet comprising film-coated tablets, bilayer tablets, inlay tablets, orally disintegrating tablets, compressed tablets, coated or uncoated tablets, multilayer tablets, mini tablets, buccal tablets, sublingual tablets, effervescent tablets, immediate release tablets, modified release tablets, gastric disintegrating tablets, chewable tablets, dispersing tablets or lozenges.

According to one embodiment of the invention, preferably the solid oral composition is in the form of tablet and the tablet are coated film-coating comprising coating agents.

Suitable coating agents are selected from the group comprising copovidone, polymethacrylates, polydextrose, polyethoxylated sorbitan, oleic acid, polyalkylacrylates copolymers, triacetin, hydroxyl propyl methyl cellulose, colloidal silicon dioxide, lactose monohydrate, medium chain triglycerides, hydroxypropyl cellulose, white wax, polyvinyl alcohol, polyethylene glycol, talc, polyvinyl alcohol-polyethylene glycol copolymers (Kollicoat® IR), ethylcellulose dispersions (Surelease®), polyvinylprolidone, polyvinylprolidone-vinyl acetate copolymer (PVP-VA), all kinds of Opadry®, pigments, dyes, titanium dioxide, iron oxide or mixtures thereof.

According to one embodiment of the present invention, the amount of coating comprising coating agents is between 0.1% and 5.0% by weight in the total formulation. Preferably, it is between 1.5% and 3.5% by weight in the total formulation.

In this present invention, the solid oral composition can be prepared as tablet form. Tablet comprises at least one type of particle, for example; mini-tablets, pellets, core, agglomerates, granules, powders, liposomes, sphericals or mixtures thereof.

According to another embodiment of the present invention, the solid oral composition is formulated as capsule form. Capsule comprises at least one type of particle, for example; mini-capsules, mini-tablets, pellets, core, agglomerates, granules, powders, liposomes, sphericals or mixtures thereof.

The solid form composition of the present invention may be prepared, using standard techniques and manufacturing processes well known in the art, such as direct compression, wet or dry granulation, hot melt granulation, hot melt extrusion, fluidized bed granulation, extrusion/spheronization, slugging, spray drying and solvent evaporation.

Furthermore, the solid oral composition is obtained by using a wet granulation method therefore, a simple and low-cost production method was employed.

According to another embodiment of the present invention, the solid oral composition comprises;

- 5.0 – 30.0 % by weight of eltrombopag choline
- 45.0 – 85.0 % by weight of diluents
- 0.05 – 10.0 % by weight of binders
- 1.0 – 25.0 % by weight of disintegrants of the total composition.

According to another embodiment of the present invention, the solid oral composition comprises;

- 5.0 – 35.0 % by weight of eltrombopag choline
- 45.0 – 90.0 % by weight of diluents
- 0.05 – 10.0 % by weight of binders
- 1.0 – 25.0 % by weight of disintegrants
- 0.1 – 5.0 % by weight of lubricants
- 0.05 – 5.0 % by weight of glidants of the total composition.

Example 1: The solid oral composition comprising eltrombopag choline

Ingredients	% by weight
Eltrombopag choline	5.0 - 35.0
Diluents	45.0 - 90.0
Binders	0.05 - 10.0
Disintegrants	1.0 - 25.0
Lubricants	0.1 - 5.0
Glidants	0.05 - 5.0
TOTAL	**100**

Example 2: The tablet formulation comprising eltrombopag

Ingredients	% by weight
Eltrombopag choline	5.0 – 30.0
Microcrystalline cellulose	25.0 – 75.0
Mannitol	5.0 – 27.0
Polyvinylpyrrolidone	0.1 – 5.0
Croscarmellose sodium	3.0 – 15.0
Colloidal silicon dioxide	0.05 - 3.0
Sodium stearyl fumarate	0.1 – 5.0
Coating	0.1 – 5.0
TOTAL	**100**

Example 3: The tablet formulation comprising eltrombopag

Ingredients	% by weight
Eltrombopag choline	5.0 – 30.0
Microcrystalline cellulose	25.0 – 75.0
Mannitol	5.0 – 27.0
Polyvinylpyrrolidone	0.1 – 5.0
Sodium starch glycolate	1.0 – 10.0
Colloidal silicon dioxide	0.05 - 3.0
Sodium stearyl fumarate	0.1 – 5.0
Coating	0.1 – 5.0
TOTAL	**100**

Process for example 2 or 3;

a) Mixing eltrombopag choline, microcrystalline cellulose, mannitol, polyvinylpyrrolidone,
b) Granulating the mixture with water in a high-shear wet granulator,
c) Wet milling the granule and drying in fluid bed dryer,
d) Sieving the mixture and obtained homogeneous powder,
e) Adding microcrystalline cellulose, disintegrant (croscarmellose sodium or sodium starch glycolate), colloidal silicon dioxide and mixing,
f) Adding sodium stearyl fumarate and mixing,
g) Compressing the mixture to form of a tablet,
h) Coating tablets.

CLAIMS

1. A solid oral composition comprising eltrombopag choline and at least one pharmaceutically excipient.

2. The solid oral composition according to claim 1, wherein amount of eltrombopag choline is between 3.0% and 40.0% by weight in the total formulation.

3. The solid oral composition according to claim 1, wherein at least one pharmaceutically acceptable excipient is selected from the group comprising diluents, binders, disintegrants, lubricants, glidants or mixtures thereof.

4. The solid oral composition according to claim 3, wherein diluents are selected from the group comprising microcrystalline cellulose, starch, pregelatinize starch, powdered cellulose, mannitol, spray-dried mannitol, dextrose, sucrose, sorbitol, xylitol, inorganic salts, polysaccharides, dicalcium phosphate, sodium chloride, dextrates, lactitol, maltodextrin, sucrose-maltodextrin mixture, trehalose, sodium carbonate, sodium bicarbonate or mixtures thereof.

5. The solid oral composition according to claim 4, wherein the amount of diluents is between 45.0% and 90.0% by weight in the total formulation.

6. The solid oral composition according to claim 3, wherein binders are selected from the group comprising polyvinylpyrrolidone, sodium carboxymethyl cellulose, polyethylene glycol, polyvinyl alcohol, pregelatinized starch, natural gums, sucrose, sodium alginate, gelatin, carrageenan, guar gum, carbomer, polymethacrylates, methacrylate polymers, gelatin, alginate, alginic acid, xanthan gum, hyaluronic acid, pectin, polysaccharides, carbomer, poloxamer, polyacrylamide, polyoxyethylene-alkyl ether, polydextrose, polyethylene oxide or mixtures thereof.

7. The solid oral composition according to claim 6, wherein the amount of binders is between 0.05% and 10.0% by weight in the total formulation.

8. The solid oral composition according to claim 3, wherein disintegrants are selected from the group comprising croscarmellose sodium, sodium starch glycolate, starch, crospovidone, low-substituted hydroxypropyl cellulose, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose, docusate sodium, guar gum, low substituted hydroxypropyl cellulose, polyacryline potassium, sodium alginate, corn starch, alginic acid, alginates, ion-exchange resins, sodium dodesyl sulphate, poloxamer, sodium glycine carbonate or mixtures thereof.

9. The solid oral composition according to claim 8, wherein the amount of disintegrants is between 1.0% and 25.0% by weight in the total formulation.

10. The solid oral composition according to claim 1, wherein eltrombopag choline has a particle size of d(0.9) less than 150 µm or less than 140 µm or less than 130 µm or less than 120 µm or less than 110 µm or less than 100 µm or less than 90 µm or less than 80 µm or less than 70 µm or less than 60 µm or less than 50 µm or less than 40 µm or less than 30 µm or less than 20 µm.

11. The solid oral composition according to claim 1, wherein the solid oral composition is in the form of tablets, capsules, strips, powders, pastilles, sachets, effervescent compositions, pills, coated bead systems, granules, microspheres, dragees, films.

12. The solid oral composition according to claim 11, wherein the solid oral composition is in the form of tablets or capsules.

13. The solid oral composition according to claim 3, wherein the solid oral composition comprises;

- 5.0 – 35.0 % by weight of eltrombopag choline
- 45.0 – 90.0 % by weight of diluents
- 0.05 – 10.0 % by weight of binders
- 1.0 – 25.0 % by weight of disintegrants
- 0.1 – 5.0 % by weight of lubricants
- 0.05 – 5.0 % by weight of glidants of the total composition.

14. The solid oral composition according to any preceding claims, wherein the solid oral composition is obtained by using a wet granulation method.

15. The solid oral composition according to any preceding claims, for use in preventing or treating conditions leading to thrombocytopenia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TR2021/050799

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/4152 (2006.01)i; A61P 7/00 (2006.01)i; A61K 9/00 (2006.01)i

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; A61P

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)

EPODOC, Google Scholar, TURKPATENT Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	WO 2019071111 A1 (TEVA PHARMA [US]; ASSIA CHEM IND LTD [IL]) 11 April 2019 (2019-04-11)	
X,D	Abstract	1, 3-4, 6, 8, 11-12, 14-15
Y,D		2, 5, 7, 9-10, 13
	EP 3409272 A1 (TIEFENBACHER ALFRED E GMBH & CO KG [DE]) 05 December 2018 (2018-12-05)	
Y	Abstract, description paragraph [0064], claims 1-5	2, 5, 7, 9-10, 13
	WO 2017042839 A1 (ACTAVIS GROUP PTC EHF [IS]) 16 March 2017 (2017-03-16)	
A	Abstract, claims 1-2	1-15

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
16 December 2021	**16 December 2021**

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/TR2021/050799

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2019071111 A1	11 April 2019	EP 3692021 A1	12 August 2020
		US 2020331862 A1	22 October 2020
		US 11072586 B2	27 July 2021
EP 3409272 A1	05 December 2018	WO 2019086725 A2	09 May 2019
		AU 2019203327 A1	01 October 2020
		EP 3761966 A2	13 January 2021
WO 2017042839 A1	16 March 2017	NONE	