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(54) Title: A PHARMACEUTICAL COMPOSITION OF REGORAFENIB

(57) Abstract: The present invention relates to a pharmaceutical composition comprising: i) a core comprising regorafenib and at least one pharmaceutically acceptable excipient, and ii) a coating comprising poloxamer (polyoxyethylene–polyoxypropylene copolymer) and at least one pharmaceutically acceptable excipient. The invention further relates to a process for the preparation of the said pharmaceutical composition and its use for treating disorders.

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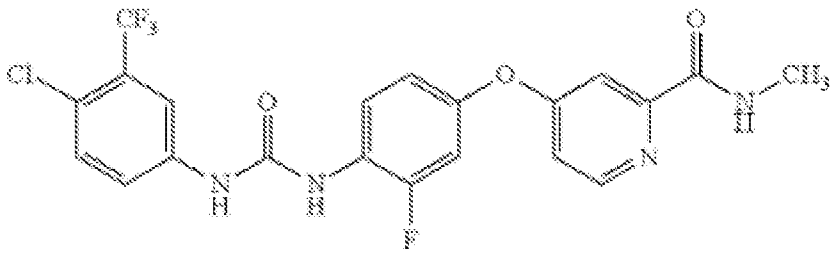
A PHARMACEUTICAL COMPOSITION OF REGORAFENIB

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising: i) a core comprising regorafenib and at least one pharmaceutically acceptable excipient, and ii) a coating comprising poloxamer (polyoxyethylene–polyoxypropylene copolymer) and at least one pharmaceutically acceptable excipient. The invention further relates to a process for the preparation of the said pharmaceutical composition and its use for treating disorders.

BACKGROUND OF THE INVENTION

Regorafenib is chemically known as 4-[4-({[4-chloro-3-(trifluoromethyl) phenyl] carbamoyl} amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide (I).



(I)

Regorafenib is a low molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment.

Regorafenib is marketed as Stivarga® by Bayer Pharma in Europe since 2013. The marketed product is approved in the form of 40 mg film coated tablet.

Stivarga® is indicated as monotherapy for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy, unresectable or

metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib and hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

According to European Public Assessment Report (EPAR), regorafenib is a white to slightly pink or slightly brownish solid substance, practically insoluble in water. Regorafenib is BCS Class II compound based on Biopharmaceutical Classification System.

BCS Class II compounds are drug substances with low solubility and high permeability. The bioavailability of these compounds is limited by their solubility (solvation rate). Hence, the absorption of a poorly water-soluble compound from orally administered solid dosage form is controlled by its dissolution rate in the gastrointestinal fluid present at the absorption site. It is known in the pharmaceutical arts that low-solubility drugs often show poor bioavailability or irregular absorption, the degree of irregularity being affected by factors such as dose level, fed state of the patient, and form of the drug.

Therefore, it is desirable to design a formulation which improves the rate of dissolution and thus improving the bioavailability of the BCS Class II compounds or drugs.

There are many techniques known in the art to improve the dissolution of the low-solubility drugs including particle size reduction, nanosuspension technology, using surfactant, and solid dispersion.

WO 2006026500 discloses a composition comprising a solid dispersion comprising regorafenib and a pharmaceutically acceptable matrix, wherein the matrix comprises at least one polymer from the group consisting of polyvinylpyrrolidone, copovidone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyethylene glycol or polyethylene oxide.

CN 111166724 A discloses a regorafenib nano dispersion, a tablet and a preparation method thereof; the dispersion can be prepared by dissolving regorafenib in solvent,

separately dissolving a carrier material in water, and performing liquid phase precipitation and crystallization reaction to obtain regorafenib nano-suspension; it is spray dried to spray-dried to obtain a regorafenib nano-dispersion.

CN 106913527 A discloses immediate-release pellet and immediate-release pellet consisting blank pellet core and a regorafenib-containing layer wrapped outside the pellet core is characterized in that the drug-containing layer contains micronized regorafenib and a binder. CN '527 discloses polyvinylpyrrolidone and hydroxypropyl methylcellulose for preparation of regorafenib containing layer solution.

WO 2014039677 discloses a pharmaceutical composition comprising regorafenib, a hydrate, solvate, metabolite or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof and at least one pharmaceutically acceptable excipient wherein the pharmaceutical composition is coated by a coating comprising a polyvinyl alcohol based polymer and optionally one or more further pharmaceutically acceptable excipients. According to WO '677, polyvinyl alcohol based polymer coating effectively controls particular impurity AFP-PMA as compared to conventional HPMC coating.

In general, it is believed that solid dispersion system comes into contact with gastrointestinal media, dissolution will occur to a supersaturated state, which is more or less stabilized by the polymer. This has been shown to significantly enhance the bioavailability of poorly water-soluble BCS Class II compounds or drugs. One major challenge in administration of these compounds or drugs is the high inter-individual variability of drug performance. Another inherent issue of amorphous solid dispersions is the instability of the solid state which results in a tendency for recrystallisation of the drug and/or excipients during storage. This may be accompanied by a break-down of dissolution and bioavailability.

To avoid the variation in dissolution and bioavailability of solid dispersion of regorafenib, inventors of WO 2021156172 A1 have discovered that inclusion of stabilizing agent in the pharmaceutical composition of regorafenib provides a stable dissolution and high bioavailability with decreased variability. WO '172 discloses a pharmaceutical composition comprising a solid dispersion comprising regorafenib and at least one pharmaceutically acceptable excipient inside of the solid dispersion,

and at least one stabilizing agent, wherein the stabilizing agent is outside of the solid dispersion and the pharmaceutical composition is enteric coated. Specifically, WO '172 discloses the stabilizing agent is hydroxypropylmethylcellulose acetate succinate (HPMCAS). The pharmaceutical composition containing regorafenib and HPMCAS shows stable dissolution and high bioavailability, wherein the variability of the bioavailability is decreased.

Therefore, there still exists need to provide a stable composition of regorafenib with suitable excipient(s) that provides stable and improved dissolution rate, and thus provide desired bioavailability, which is prepared by an economically viable process and is also suitable for use on a commercial scale. To achieve this goal, it is also very important to select the excipient(s) for the preparation of solid dispersion and the excipient(s) to be used for the preparation of final formulation like coated tablet. These excipient(s) should not hinder the dissolution of compound as well as they should not have any adverse impact on stability of the composition and the excipient(s) should provide stable dissolution.

The inventors of the present invention have surprisingly found that a pharmaceutical composition comprising a core comprising regorafenib and a coating comprising poloxamer not only provides storage stable composition but also shows similar impurity profile and bioequivalance profile when compared to the reference product Stivarga® tablet.

OBJECT OF THE INVENTION

A main object of the present invention is to provide a stable pharmaceutical composition comprising: i) core comprising regorafenib and at least one pharmaceutically acceptable excipient, and ii) coating comprising poloxamer and at least one pharmaceutically acceptable excipient.

Yet another object of the present invention is to provide a pharmaceutical composition of regorafenib, which has a similar impurity profile when compared to the reference product Stivarga® tablet.

Yet another object of the present invention is to provide a pharmaceutical composition of regorafenib, which has a similar dissolution profile and bioequivalence profile when compared to the reference product Stivarga® tablet.

Yet another object of the present invention is to provide a pharmaceutical composition of regorafenib, which is devoid of above mentioned problems associated with solid dispersion of regorafenib.

Yet another object of the invention is to provide a commercially scalable, cost effective, environment friendly and robust process for the preparation of a pharmaceutical composition comprising regorafenib.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides a pharmaceutical composition comprising:

i) core comprising regorafenib and at least one pharmaceutically acceptable excipient, and

ii) coating comprising poloxamer and at least one pharmaceutically acceptable excipient.

In another aspect, the present invention provides a pharmaceutical composition comprising:

i) core comprising 1 to 20 wt.% of regorafenib and at least one pharmaceutically acceptable excipient,

ii) coating comprising 0.1 to 5 wt.% of poloxamer and at least one pharmaceutically acceptable excipient, and

wherein the weight percent is based on the total weight of the composition.

In another aspect, the present invention provides a pharmaceutical composition comprising:

i) core comprising 5 to 10 wt.% of regorafenib and at least one pharmaceutically acceptable excipient,

ii) coating comprising 0.1 to 1 wt.% of poloxamer and at least one pharmaceutically acceptable excipient, and

wherein the weight percent is based on the total weight of the composition.

In another aspect, the present invention provides a pharmaceutical composition comprising:

i) core comprising solid dispersion of regorafenib and at least one pharmaceutically acceptable excipient, and

ii) coating comprising poloxamer and at least one pharmaceutically acceptable excipient.

In another aspect, the present invention provides a pharmaceutical composition comprising:

i) core comprising solid dispersion of regorafenib and povidone, and

ii) coating comprising poloxamer and at least one pharmaceutically acceptable excipient.

In another aspect, the present invention provides a pharmaceutical composition comprising:

i) core comprising solid dispersion of regorafenib and povidone, and

ii) coating comprising 0.1 to 1 wt.% of poloxamer and at least one pharmaceutically acceptable excipient.

wherein the solid dispersion containing 1 to 20 wt.% of regorafenib based on the total weight of the composition.

In another aspect, the present invention provides a tablet comprising:

i) 5 to 10 wt.% of regorafenib,

ii) about 0.1 wt.% to about 5 wt.% of poloxamer,

iii) 10 wt.% to 50 wt.% of one or more of diluents,

iv) 5 wt.% to 50 wt.% of one or more of disintegrants,

v) 0.1 wt.% to 5 wt.% of one or more lubricant,

vi) 0.1 wt.% to 5 wt.% of one or more glidant, and

vii) 10 wt.% to 50 wt.% of one or more of recrystallization inhibitor based on the total weight of the composition,

wherein the poloxamer is present in a coating.

In another aspect, the present invention provides a process for the preparation of the pharmaceutical composition comprises:

i) prepare core comprising regorafenib and a pharmaceutically acceptable excipient;
ii) coating the core obtained in step (i) with coating composition comprising poloxamer.

In another aspect, the present invention provides a process for the preparation of the pharmaceutical composition comprises:

a. dissolve regorafenib and a pharmaceutically acceptable excipient in suitable solvent to obtain solution or suspension;
b. prepare granules by mixing solution or suspension of step a) with a pharmaceutically acceptable excipient;
c. dry the granules of step b), and optionally mix with pharmaceutically acceptable excipients to obtain granule mixture;
d. optionally, compress the granule mixture obtained in step c) to obtain tablets;
e. coat the granules obtained in step c) or tablets obtained in step d) with coating composition comprising poloxamer.

In another aspect, the present invention provides a process for the preparation of the pharmaceutical composition comprises:

a. dissolve regorafenib and povidone in suitable solvent to obtain solution;
b. prepare granules by mixing solution of step a) with a pharmaceutically acceptable excipient;
c. dry the granules of step b), and optionally mix with pharmaceutically acceptable excipients to obtain granule mixture;
d. optionally, compress the granule mixture obtained in step c) to obtain tablets;
e. coat the granules obtained in step c) or tablets obtained in step d) with coating composition comprising poloxamer.

In another aspect, the present invention provides a process for the preparation of the pharmaceutical composition comprises:

a. dissolve regorafenib and povidone in a mixture of acetone and ethanol to obtain solution;
b. prepare granules by mixing solution of step a) with microcrystaline cellulose and croscarmellose sodium;
c. dry the granules of step b), and optionally mix with colloidal silicon dioxide, croscarmellose sodium and magnesium stearate to obtain granule mixture;
d. optionally, compress the granule mixture obtained in step c) to obtain tablets;
e. coat the granules obtained in step c) or tablets obtained in step d) with coating composition comprising poloxamer.

In another aspect, the present invention provides a process for the preparation of the pharmaceutical composition comprises:

a. dissolve regorafenib and povidone in a mixture of acetone and ethanol to obtain solution;
b. prepare granules by spraying the solution of step a) onto the mixture of microcrystaline cellulose and croscarmellose sodium;
c. dry the granules of step b), and optionally mix with colloidal silicon dioxide, croscarmellose sodium and magnesium stearate to obtain granule mixture;
d. optionally, compress the granule mixture obtained in step c) to obtain tablets;
e. coat the granules obtained in step c) or tablets obtained in step d) with coating composition comprising poloxamer.

In another aspect, the present invention provides a pharmaceutical composition of any of the above aspects, wherein the said composition remains stable after storage for 3 months at 40°C and 75% relative humidity (RH).

In another aspect, the present invention discloses a use of such pharmaceutical composition as medicament in the treatment of metastatic colorectal cancer (CRC) and hepatocellular carcinoma (HCC).

The details of one or more embodiments of the present invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention will now be more specifically illustrated as hereunder.

The term “%”, “wt.%” or “%w/w” used in this specification means the percentage by the total weight of the composition unless otherwise stipulated.

The term "about" can indicate a difference of 10 percent of the value specified. Numerical ranges as used herein are meant to include every number and subset of numbers enclosed within that range, whether particularly disclosed or not. Further, these numerical ranges should be construed as providing support for a claim directed to any number or subset of numbers in that range.

The term “composition” or “formulation” as used in the present invention means a coated solid pharmaceutical composition, wherein the solid pharmaceutical composition includes, without limitation, tablets, caplets, pellets, granules, capsules and beads.

The term “Regorafenib” as used in the present invention includes, but is not limited to, Regorafenib *per se* or its pharmaceutically acceptable hydrates, pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable prodrugs thereof or anhydrous regorafenib, and also its various crystalline and amorphous forms. Preferably, the composition of present invention comprises anhydrous form of regorafenib or regorafenib monohydrate, which may be in the crystalline form, amorphous form or mixture thereof. More preferably, the composition of present invention comprises anhydrous regorafenib.

The term “core” means as used in the present invention means uncoated solid pharmaceutical composition includes, without limitation, tablets, caplets, pellets, granules, capsule and beads. Preferably, tablets or granules.

The term "solid dispersion" refers to a system in a solid state comprising at least two components, wherein one component is dispersed throughout the other component

or components. The term "solid dispersion" as used herein, refers to stable solid dispersions comprising amorphous drug substance and carrier. Further the term "solid dispersion" as used herein also refers to stable solid dispersions comprising amorphous drug substance and carrier with or without adsorbent/ absorbent. By "amorphous drug substance," it is meant that the amorphous solid contains drug substance in a substantially amorphous solid state form i.e. at least about 80% of the drug substance in the dispersion is in an amorphous form. More preferably at least about 90% and most preferably at least about 95% of the drug substance in the dispersion is in amorphous form.

The term "stable" or "stability" means that the pharmaceutical dosage form is physically and chemically stable, whereas "chemically stable" means that the solid pharmaceutical dosage form when stored at 40 °C and 75 % relative humidity for 3 or 6 months, each of the degradation impurity and total impurities remain within ICH limit.

The term "similarity factor" or f2 factor as used herein refers to one way of comparing dissolution profiles of two different products. (Multisource Pharmaceutical Products: Guidelines on Registration Requirements to establish Interchangeability, Quality Assurance and Safety: Medicines, Essential Drugs and Medicines Policy, World Health Organization, 1211 Geneva 27, Switzerland) This model independent mathematical approach compares the dissolution profile of the two products: test and reference (or two strengths, or pre- and post-approved products from the same manufacturer). Tests are recommended to be performed under the same test conditions. The dissolution time points for both the profiles should be the same, for example for immediate release products e.g. 10, 15, 30, 45, 60 minutes and for extended release products, e.g., 1, 2, 3, 5 and 8 hours. Only one time point should be considered after 85% dissolution of the reference product. An f2 value of 50 or greater (50-100) ensures sameness or equivalence of the two curves, and thus the performance of the two products. The similarity factor f2 should be computed using the equation: f2 =50 log {[l+(l/n) t=1 n (Rt - Tt) 2]-0-5 100} where Rt and Tt are the cumulative percentage of the drug dissolved at each of the selected n time points of the comparator (reference) and (test) product respectively.

In one aspect, the present invention provides a pharmaceutical composition comprising:

a. core comprising regorafenib and at least one pharmaceutically acceptable excipient, and
b. coating comprising poloxamer and at least one pharmaceutically acceptable excipient.

In one embodiment, a composition of the present invention comprises 1 to 20 wt.% of regorafenib, preferably 5 to 10 wt.% of regorafenib based on the total weight of the composition.

In one embodiment, a composition of the present invention comprises coating comprising poloxamer in amount from about 0.1 to 5 wt.%, preferably, about 0.1 to 1 wt.% based on the total weigh of the composition.

In embodiments, a pharmaceutical composition of the present invention further comprises one or more pharmaceutically acceptable excipients. The excipients to be used in accordance with the present invention are well known and are those excipients which are conventionally used by the person skilled in the art. Depending on the dosage form chosen for the pharmaceutical composition, the person skilled in the art will be able to select suitable pharmaceutically acceptable excipients. The pharmaceutical excipient can be selected from excipient can be selected from diluent, disintegrant, lubricant, glidant and recrystallization inhibitor.

Diluent includes, but are not limited to, lactose, mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch, dextrates, dextran, dextrin, dextrose, maltodextrin, calcium carbonate, dibasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide and mixtures thereof.

The amount of diluent is preferably from about 10 wt.% to about 50 wt.%, more preferably from about 10 wt.% to about 30 wt.% based on the total weight of the composition.

Disintegrant includes, but are not limited to, sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, Crospovidone, polyvinylpyrrolidone, methylcellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinized starch, and sodium alginate and mixtures thereof. The amount of the disintegrant is preferably from 5 wt.% to about 50 wt.%, more preferably from 20 wt.% to 40 wt.% based on the total weight of the composition.

Suitable lubricants and/or glidants are selected from magnesium stearate, hydrogenated vegetable oil, glyceryl behenate, glyceryl monostearate, stearic acid, sodium stearyl fumarate, sodium starch fumarate, calcium stearate, zinc stearate, aluminum silicate, talc, colloidal silicon dioxide, sucrose esters of fatty acid, waxes, silica gel, or mixtures thereof. The present invention comprises a lubricant in an amount of from about 0.1 wt.% to about 10 wt.%, preferably, 0.1 wt.% to about 2 wt.% based on the total weight of the composition.

The recrystallization inhibitor includes, but are not limited to, polyvinylpyrrolidone (povidone), tyloxapol, fatty acid glycerol polyethylene glycol esters, fatty acid polyethylene glycol esters, polyethylene glycols, glycerol ethers, a cyclodextrin (for example alpha-, beta- or gamma-cyclodextrin, e.g. alkylated, hydroxyalkylated, carboxyalkylated or alkyloxycarbonyl-alkylated derivatives, or mono- or diglycosyl-alpha-, beta- or gamma-cyclodextrin, mono- or dimaltosyl-alpha-, beta- or gamma-cyclodextrin or panosyl-cyclodextrin), polysorbate 20, polysorbate 80 or mixtures of thereof. Preferably, the recrystallization inhibitor is polyvinylpyrrolidone. The present invention comprises a recrystallization inhibitor in an amount of from about 10 wt.% to about 50 wt.%, preferably, 10 wt.% to about 40 wt.% based on the total weight of the composition

In another aspect, the present invention provides a tablet comprising:

i) 5 to 10 wt.% of regorafenib,
ii) about 0.1 wt.% to about 5 wt.% of poloxamer,
iii) 10 wt.% to 50 wt.% of one or more of diluents,
iv) 5 wt.% to 50 wt.% of one or more of disintegrants,
v) 0.1 wt.% to 5 wt.% of one or more lubricant,

vi) 0.1 wt.% to 5 wt.% of one or more glidant, and

vii) 10 wt.% to 50 wt.% of one or more of recrystallization inhibitor based on the total weight of the composition, wherein the poloxamer is present in a coating.

The core of the present invention is further be coated with poloxamer, a film- forming polymer and one or more pharmaceutically acceptable excipients, using techniques well known in the art e.g., spray coating in a conventional coating pan, or a fluidized bed processor, or dip coating. Alternatively, coating can also be performed using a hot melt technique.

The coating comprises poloxamer and a pharmaceutically acceptable excipient. The pharmaceutically acceptable excipient includes film-forming polymers, opacifiers, plasticizer, flow aids/glidant or pigment. The suitable film-forming polymer is selected from the group comprising hydroxypropyl methyl cellulose, ethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, cellulose acetate, hydroxypropyl methyl cellulose phthalate, cellulose acetate trimellitate, methacrylic acid copolymers e.g., Eudragit®, polyvinylpyrrolidone, polyvinyl alcohol, polyethylene glycol, or mixtures thereof. A preferred film- forming polymer is hydroxypropyl methyl cellulose. Other suitable film-forming polymers which are known in the art may also be used. The film coating may also contain opacifiers like titanium dioxide, plasticizer like polyethylene glycol, flow aids like talc and pigment like iron oxide yellow or red iron oxide.

The process for the preparation of the coating composition comprises mixing poloxamer with suitable coating excipients such as a film- forming polymer, opacifiers, plasticizer and pigment in a suitable solvent. The coating can also be prepared by mixing poloxamer and marketed coating material like Aquarius prime™ in suitable solvent.

In another aspect, the present invention provides a pharmaceutical composition comprising:

i) core comprising solid dispersion of regorafenib and at least one pharmaceutically acceptable excipient, and

ii) coating comprising poloxamer and at least one pharmaceutically acceptable excipient.

The process to obtain solid dispersion of the present invention includes, but is not limited to, solvent evaporation method, fusion method, kneading method, melting method, spray drying method, co-grinding method, lyophilization technique, hot melt extrusion, melt agglomeration, supercritical fluid (SCF) technology and the like.

In one embodiment, the solid dispersion of the present invention is prepared by dissolving regorafenib in a suitable solvent with or without additional excipient and spray it onto pharmaceutically acceptable excipients using suitable technology like fluid bed technology.

Suitable solvents in the present invention includes, but are not limited to, ethanol, methanol, isopropanol, acetone, N,N-dimethylformamide, water or mixture thereof.

The pharmaceutical composition of the present invention can be obtained by using known conventional methods. The process to obtain granulates includes, but is not limited to, wet granulation, fluid bed granulation, spray drying, dry granulation, slugging, and roller compaction.

In another aspect, the present invention provides a process for the preparation of the pharmaceutical composition comprises:

i) prepare core comprising regorafenib and a pharmaceutically acceptable excipient;
ii) coating the core obtained in step (i) with coating composition comprising poloxamer.

In another aspect, the present invention provides a process for the preparation of the pharmaceutical composition comprises:

a. dissolve regorafenib and a pharmaceutically acceptable excipient in suitable solvent to obtain solution or suspension;
b. prepare granules by mixing solution or suspension of step a) with a pharmaceutically acceptable excipient;

c. dry the granules of step b), and optionally mix with pharmaceutically acceptable excipients to obtain granule mixture;
d. optionally, compress the granule mixture obtained in step c) to obtain tablets;
e. coat the granules obtained in step c) or tablets obtained in step d) with coating composition comprising poloxamer.

In another aspect, the present invention provides a process for the preparation of the pharmaceutical composition comprises:

a. dissolve regorafenib and povidone in a mixture of acetone and ethanol to obtain solution;
b. prepare granules by mixing solution of step a) with microcrystaline cellulose and croscarmellose sodium;
c. dry the granules of step b), and optionally mix with colloidal silicon dioxide, croscarmellose sodium and magnesium stearate to obtain granule mixture;
d. optionally, compress the granule mixture obtained in step c) to obtain tablets;
e. coat the granules obtained in step c) or tablets obtained in step d) with coating composition comprising poloxamer.

In another aspect, the present invention provides a process for the preparation of the pharmaceutical composition comprises:

a. dissolve regorafenib and povidone in a mixture of acetone and ethanol to obtain solution;
b. prepare granules by spraying the solution of step a) onto the mixture of microcrystaline cellulose and croscarmellose sodium;
c. dry the granules of step b), and optionally mix with colloidal silicon dioxide, croscarmellose sodium and magnesium stearate to obtain granule mixture;
d. optionally, compress the granule mixture obtained in step c) to obtain tablets;
e. coat the granules obtained in step c) or tablets obtained in step d) with coating composition comprising poloxamer.

Moreover, the pharmaceutical composition of the present invention is very suitable for production on commercial scale making use of equipment and techniques commonly used in industry.

The following examples are intended to illustrate the scope of the present invention but not to limit it thereto.

Examples

Example 1: A tablet composition comprising Regorafenib & coating comprising poloxamer

Table-1

Strength		40 mg
No	**Ingredient**	**mg / tb**
Core tablet		
1.	**Microcrystalline Cellulose**	100.00
2.	**Croscarmellose Sodium**	163.00
3.	**Regorafenib**	40.00
4.	**Povidone K25**	160.00
5.	**Acetone**	480.00
6.	**Ethanol**	120.00
7.	**Colloidal Silicon Dioxide**	2.40
8.	**Magnesium Stearate**	3.60
Coating		
9.	**Aquarius Prime Pink***	10.00
10.	**Poloxamer 188**	2.40
11.	**Purified Water**	88.00
Weight		481.40

*Aquarius Prime Pink contains hypromellose, titanium dioxide, polyethylene glycol, talc, red iron oxide, yellow iron oxide

Process for the preparation:

1. Regorafenib (40 mg) and povidone (160 mg) were dissolved in a mixture of acetone (480 mg) and ethanol (120 mg) to obtain solution;
2. The granules were obtained by spraying the solution of step 1 onto the mixture of microcrystalline cellulose (100 mg) and croscarmellose sodium (150 mg);

3. The granules of step 2 were dried and mixed with colloidal silicon dioxide (2.4 mg), croscarmellose sodium (13 mg) and magnesium stearate (3,6 mg) to obtain granule mixture;
4. The granule mixture obtained in step 3 was compressed to obtain tablets; and
5. the tablets were coated with mixture of poloxamer (2.4 mg) and Aquarius Prime Pink (10 mg).

Example 2: A tablet composition comprising Regorafenib & coating comprising Eudragit E PO

Table-2

Strength		**40 mg**
No	**Ingredient**	
Core tablet		
1.	**Microcrystalline Cellulose**	100,00
2.	**Croscarmellose Sodium**	154,00
3.	**Regorafenib**	40,00
4.	**Povidone K25**	160,00
5.	**Acetone**	480,00
6.	**Ethanol**	120,00
7.	**Colloidal Silicon Dioxide**	2,40
8.	**Magnesium Stearate**	3,60
Coating		
9.	**Eudragit E PO***	12,00
10.	**Purified Water**	60,00
Weight		472 ,00

*Eudragit E PO contains basic butylated methacrylate copolymer, sodium laurylsulpate, stearic acid, talc, titanium dioxide

Process for the preparation: The tablets were prepared using same process of example 1 by replacing coating of poloxamer and Aquarius Prime Pink with Eudragit E PO.

Example 3: A tablet composition comprising Regorafenib & coating comprising poloxamer

Table-3

Strength		40 mg
No	**Ingredient**	**mg / tb**
Core tablet		
1.	**Silicified microcrystalline cellulose**	157.80
2.	**Croscarmellose Sodium**	154.20
3.	**Regorafenib**	40.00
4.	**Povidone K25**	160.00
5.	**Acetone**	480.00
6.	**Ethanol**	120.00
7.	**Colloidal Silicon Dioxide**	2.40
8.	**Magnesium Stearate**	8.6
Coating		
9.	**Aquarius Prime Pink***	12.00
10.	**Poloxamer 188**	2.70
11.	**Purified Water**	85.00
Weight		537.70

*Aquarius Prime Pink contains hypromellose, titanium dioxide, polyethylene glycol, talc, red iron oxide, yellow iron oxide

Process for the preparation:

1. Regorafenib (40 mg) and povidone (160 mg) were dissolved in a mixture of acetone (480 mg) and ethanol (120 mg) to obtain solution;
2. The granules were obtained by spraying the solution of step 1 onto the mixture of milled mixture of silicified microcrystalline cellulose (157.80 mg) and croscarmellose sodium (150 mg);
3. The granules of step 2 were dried, milled, and mixed with magnesium stearate (5 mg) and the mixture was dry granulated by roller compactor;
4. The granules of step 3 were milled and mixed with colloidal silicon dioxide (2.4 mg), croscarmellose sodium (4.20 mg) and magnesium stearate (5 mg) respectively;

5. The granules obtained in step 4 were compressed to obtain tablets; and
6. The tablets were coated with mixture of poloxamer (2.7 mg) and Aquarius Prime Pink (12 mg).

Example 4: Dissolution Data of Example 1 and Example 2 at pH: 4,5 Acetate + 0,1 %SLS 50 rpm with USP, Method II - Pedal at 37°C

Table-4

Time	Reference Product	Example 1	Example 2
5 min	17.3	17.4	5.7
10 min	38.7	38.0	25.5
15 min	55.4	55.2	43.6
20 min	70.3	69.6	64.8
30 min	90.0	88.5	80.4
45 min	96.7	97.2	89.9
60 min	97,3	98.0	89.2
***f*$_2$ value**		94.8	49.4

Dissolution of Example-1, Example-2 and reference product Stivarga® tablet were performed using standard USP apparatus II, paddles, at 50 rpm in 900 ml at pH: 4.5 Acetate + 0.1% SLS. The drug release was determined by using an HPLC method.

From the above dissolution data, it is evident that dissolution of example-1 (poloxamer in coating) is better than example-2. When f_2 value is more than 50 indicates the sameness or equivalence of Example-1 with reference product in terms of its dissolution and performance.

Example 5: Stability Result of Example 1

The tablets prepared in Example 1 were packed in HDPE bottles together with silica gel and stored for 30 days under conditions of 25°C/60% RH and 30 °C, 75% RH. The results of performed stability testing is given herein below table- 5.

Table-5

Example-1	Initial	25 °C, 60% RH, 1 Month	30 °C, 75% RH, 1 Month
AFP-PMA	0.00333	0.00347	0.00538

It can be seen from the above tables that the produced amount of the AFP-PMA is less than 0.050% in above mentioned stability conditions for Examples 1.

The monthly increase rate of AFP-PMA impurity of Example 1 of the present invention and examples given in EP 2892507 B1 patent are compared herein below Table 6.

Table-6

Storage condition	Monthly increase rate [% / Month]			
	HDPE bottles containing tablets according to Example-1 (with silica) of the present invention	**HDPE bottles containing PVA coated tablets according to Example 1 (with silica) of EP 2892507 B1**	**HDPE bottles containing PVA coated tablets according to Example-1 (with molecular sieve) of EP 2892507 B1**	**Tablets according to Example A (HPMC coated) of EP 2892507 B1**
at 25 °C, 60% RH	0.00014	0.0019	0.0008	0.0054%
at 30 °C, 75% RH	0.00205	0.0034	0.0020	-

It can be seen from the stability results given in table-6, pertain to increase rate of specific impurity AFP-PMA, it is evident that coating material of the present invention i.e. containing Poloxamer is equally capable to control the said impurity as controlled by the PVA coating employed in EP 2892507 B1.

The pharmaceutical composition comprising intragranular component comprising a core comprising regorafenib and a coating comprising poloxamer not only provides storage stable composition but also shows similar impurity profile and bio-equivalence profile when compared to the reference product Stivarga® tablet.

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Claims

1. A pharmaceutical composition comprising:
   a. a core comprising regorafenib and at least one pharmaceutically acceptable excipient, and
   b. a coating comprising poloxamer and at least one pharmaceutically acceptable excipient.

2. The pharmaceutical composition as claimed in claim 1, wherein the core comprising a solid dispersion of regorafenib & at least one pharmaceutically acceptable excipient.

3. The pharmaceutical composition as claimed in claim 1, wherein regorafenib is present in an amount from 1 to 20 wt.%.

4. The pharmaceutical composition as claimed in claim 1, wherein poloxamer is present in an amount from about 0.1 % to about 5 wt.%.

5. The pharmaceutical composition as claimed in claim 1, wherein the pharmaceutically acceptable excipient is selected from diluent, disintegrant, lubricant, glidant, recrystallization inhibitor, film- forming polymers, opacifiers, plasticizer and pigment.

6. The pharmaceutical composition as claimed in claim 5, wherein diluent is selected from lactose, mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch, dextrates, dextran, dextrin, dextrose, maltodextrin, calcium carbonate, dibasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide and mixtures thereof.

7. The pharmaceutical composition as claimed in claim 5, wherein disintegrant is selected from sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, Crospovidone, polyvinylpyrrolidone, methylcellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinized starch, and sodium alginate and mixtures thereof.

8. The pharmaceutical composition as claimed in claim 5, wherein the lubricants and/or glidants are selected from magnesium stearate, hydrogenated vegetable oil, glyceryl behenate, glyceryl monostearate, stearic acid, sodium stearyl fumarate, sodium starch fumarate, calcium stearate, zinc stearate, aluminum silicate, talc, colloidal silicon dioxide, sucrose esters of fatty acid, waxes, silica gel and mixtures thereof.

9. The pharmaceutical composition as claimed in claim 5, wherein the recrystallization inhibitor is selected from polyvinylpyrrolidone (povidone), tyloxapol, fatty acid glycerol polyethylene glycol esters, fatty acid polyethylene glycol esters, polyethylene glycols, glycerol ethers, cyclodextrin, polysorbate 20, polysorbate 80 and mixtures of thereof.

10. A process for the preparation of the pharmaceutical composition as claimed in any of the claims above comprises:

a. dissolve regorafenib and a pharmaceutically acceptable excipient in suitable solvent to obtain solution or suspension;

b. prepare granules by mixing solution or suspension of step a) with a pharmaceutically acceptable excipient;

c. dry the granules of step b), and optionally mix with pharmaceutically acceptable excipients to obtain granule mixture;

d. optionally, compress the granule mixture obtained in step c) to obtain tablets;

e. coat the granules obtained in step c) or tablets obtained in step d) with coating composition comprising poloxamer.

11. The process for the preparation of the pharmaceutical composition as claimed in claim 10, wherein the solvent is selected from ethanol, methanol, isopropanol, acetone, N,N-dimethylformamide, water or mixture thereof.

12. The pharmaceutical composition as claimed in claim 1 is tablet comprising:

a. 5 to 10 wt.% of regorafenib,

b. about 0.1 wt.% to about 5 wt.% of poloxamer,

c. 10 wt.% to 50 wt.% of one or more of diluents,

d. 5 wt.% to 50 wt.% of one or more of disintegrants,

e. 0.1 wt.% to 5 wt.% of one or more lubricant,

f. 0.1 wt.% to 5 wt.% of one or more glidant, and

g. 10 wt.% to 50 wt.% of one or more of recrystallization inhibitor,

wherein the poloxamer is present in coating.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TR2024/050230

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/44(2006.01)i; **A61K 9/10**(2006.01)i; ***A61K 47/10***(2017.01)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

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, Medline, Google Scholar, TÜRKPATENT Databases, Google Patents, TCM

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	CN 112842998 A (SHENZHEN JIANYI BIOTECHNOLOGY CO LTD) 28 May 2021 (2021-05-28) Machine Translation - Abstract, "Background technique"	1-12
A	WO 2019241504 A1 (HANDA PHARMACEUTICALS LLC [US]) 19 December 2019 (2019-12-19) Abstract, claims 1, 4, 10	1-12
A	WO 2005065653 A1 (DU PONT [US]) 21 July 2005 (2005-07-21) Abstract	1-12

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

* Special categories of cited documents:
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 July 2024	**11 July 2024**

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Information on patent family members

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