ABSTRACT

The present invention relates to pharmaceutical compositions comprising Sorafenib and one or more pharmaceutically acceptable excipients. More particularly, the present invention relates to tablet compositions comprising Sorafenib tosylate.

We Claim:

1. Pharmaceutical composition comprising Sorafenib tosylate and one or more pharmaceutically acceptable excipients, wherein the amount of Sorafenib tosylate is less than 39% by weight of the total composition.

2. The pharmaceutical composition of claim 1 comprising 30% to 38% of Sorafenib tosylate by weight of the total composition.

3. The pharmaceutical composition of claim 1, one or more pharmaceutically acceptable excipients is selected from one or more of diluents, disintegrants, binders, glidants, lubricants, solubilizing agents and combinations thereof.

4. The pharmaceutical composition of claim 3, wherein the diluent is selected from one or more of microcrystalline cellulose, microfine cellulose, powdered cellulose, lactose, dibasic calcium phosphate, tribasic calcium phosphate, starch, pregelatinized starch, calcium carbonate, calcium sulfate, magnesium carbonate and magnesium oxide.

5. The pharmaceutical composition of claim 3, wherein the disintegrant is selected from one or more of croscarmellose sodium, sodium starch glycolate, polacrilin potassium, crospovidone, carboxymethylcellulose calcium, carboxymethylcellulose sodium and sodium alginate.

6. Immediate release tablet composition comprising less than 39% of Sorafenib tosylate, atleast 40% of diluent, 1% to 4% of disintegrant by weight of the total composition and one or more other pharmaceutically acceptable excipients.

7. The composition according to claim 6 comprising 44% to 69% of diluent by weight of the total composition.

8. Immediate release tablet composition according to claim 6, comprising 400 mg of Sorafenib equivalent to 548 mg of Sorafenib tosylate.

9. A process for preparing composition according to claim 6 comprising the steps of: (a) sifting sorafenib tosylate and one or more excipients followed by blending into a dry mix, (b) granulating the dry mix of step (a) using binder solution followed by drying and milling to get the desired size granules, (c) blending the dried and milled granules of step (b) with extragranular excipients, followed by lubrication, and finally (d) compressing the lubricated materials of step (c) into tablets.

10. The method of treating unresectable hepatocellular carcinoma (HCC), advanced renal cell carcinoma (RCC), differentiated thyroid carcinoma (DTC) in a patient in need thereof using composition according to any of the preceding claims.

Dated this *Twenty fifth (25th)* day of February, 2015

(Signed)----------

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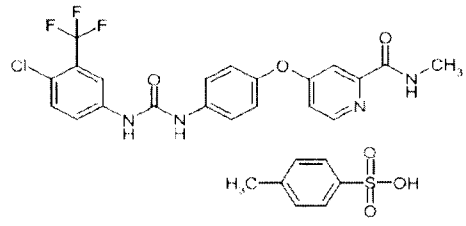
FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions comprising sorafenib and one or more pharmaceutically acceptable excipients.

BACKGROUND

Sorafenib tosylate is a kinase inhibitor described chemically as 4-(4-{3-[4-Chloro-3-(tri fluoromethyl)phenyl]ureido}phenoxy)N2methylpyridine-2-carboxamide 4-methylbenzenesulfonate and has the following structural formula,



In the United States, sorafenib tosylate is available as oral film coated tablets containing 200 mg of sorafenib with trade name Nexavar® by Bayer HealthCare.

U.S. Patent Nos. 7,235,576, 7,351,834, 7,897,623 disclose sorafenib and its salts.

WO 2006/094626 A1 assigned to Bayer Healthcare claims tablet compositions comprising sorafenib tosylate in a portion of atleast 40% by weight of the composition.

Inventors of the present invention are developing compositions of sorafenib having comparable dissolution profile as that of the marketed Nexavar® composition.

SUMMARY

The present invention relates to solid oral compositions of sorafenib with one or more pharmaceutically acceptable excipients. More particularly, the present invention relates to solid oral compositions of sorafenib tosylate.

In an embodiment, the present invention provides compositions comprising less than 39% of sorafenib tosylate based on total weight of the composition and one or more pharmaceutically acceptable excipients.

In a specific embodiment, the present invention provides an immediate release tablet composition comprising less than 39% of sorafenib tosylate based on total weight of the composition and one or more pharmaceutically acceptable excipients.

In an another embodiment, the present invention also provides an immediate release tablet composition comprising 400 mg of sorafenib equivalent to 548 mg of sorafenib tosylate.

In a further embodiment, the present invention provides process for preparation of sorafenib composition by wet granulation technique comprising the steps of: (a) sifting sorafenib and one or more excipients followed by blending into a dry mix, (b) granulating the dry mix of step (a) using binder solution followed by drying and milling to get the desired size granules, (c) blending the dried and milled granules of step (b) with extragranular excipients, followed by lubrication, and finally (d) compressing the lubricated materials of step (c) into tablets or alternatively filling into capsules.

In yet another embodiment, the compositions of the present invention are useful for the treatment of unresectable hepatocellular carcinoma (HCC), advanced renal cell carcinoma (RCC), differentiated thyroid carcinoma (DTC) in a patient in need thereof.

DETAILED DESCRIPTION

Described herein are solid oral compositions of sorafenib with one or more pharmaceutically acceptable excipients, more particularly of sorafenib tosylate.

The term "active ingredient" or "active agent" or "drug" used interchangeably, is defined to mean active drug (e.g. sorafenib tosylate), that induce a desired pharmacological or physiological effect.

The term "pharmaceutically acceptable" as used herein means that which is useful in preparing a pharmaceutical composition that is generally safe and non-toxic.

The term "excipient" means a pharmacologically inactive component such as a diluent, a disintegrant, a binder, a glidant, a lubricant, a surfactant of a pharmaceutical product. The excipients that are useful in preparing a pharmaceutical composition are generally safe, non-toxic and are acceptable for human use. Reference to an excipient includes both one and more than one such excipients.

The term "composition" or "pharmaceutical composition" as used herein synonymously include solid dosage forms such as capsules, tablets, granules, mini-tablets and the like meant for oral administration. Preferably, tablets.

As used in this specification, the singular forms "a", "an", and "the" include plural references unless the context clearly dictates otherwise. Thus for example, a reference to "a method" or "a process" includes one or more methods, one or more processes and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

In an embodiment, the present invention provides compositions comprising less than 39% of sorafenib tosylate based on total weight of the composition and one or more pharmaceutically acceptable excipients.

Excipients of the present invention comprise diluents, disintegrants, binders, glidants, lubricants, solubilizing agents/ surfactants and combinations thereof.

Diluents increase the bulk of a solid pharmaceutical composition. Exemplary diluents for solid compositions include, but are not limited to microcrystalline cellulose, microfine cellulose, powdered cellulose, lactose, dibasic calcium phosphate, tribasic calcium phosphate, starch, pregelatinized starch, calcium carbonate, calcium sulfate, magnesium carbonate, magnesium oxide, dextrates, dextrin, dextrose, kaolin, maltodextrin, mannitol, and sorbitol. Preferably, the diluent in the present invention is used in an amount of atleast 40% based on the total weight of the composition.

Disintegrants increase the dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach. Exemplary disintegrants include, but are not limited to carboxymethylcellulose calcium, carboxymethylcellulose sodium, croscarmellose sodium,

crospovidone, polacrilin potassium, sodium alginate and sodium starch glycolate. Preferably, the disintegrant in the present invention is used in an amount of 1% to 4% based on the total weight of the composition.

Binders according to the present invention include but are not limited to maize starch, pregelatinized starch, hydroxypropyl cellulose, hydroxypropyl methylcellulose, povidone, powdered acacia, gelatin, guar gum, carbomers and the like, and combinations thereof.

Glidants according to the present invention may include but are not limited to colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, talc, and other forms of silicon dioxide, such as aggregated silicates and hydrated silica and the like, and combinations thereof.

Lubricants according to the present invention include but are not limited to magnesium stearate, aluminium stearate, sucrose stearate, zinc stearate, stearic acid, talc, fumaric acid, palmitic acid, sodium stearyl fumarate, glyceryl monostearate, carnauba wax, mineral oils, hydrogenated vegetable oils, mineral oil, polyethylene glycols and the like and combinations thereof.

Solubilizing agents/ surfactants according to the present invention include but are not limited to sorbitan mono laurate, sodium lauryl sulphate, polyoxyethylene-polyoxypropylene block copolymers (also known as poloxamers), polyethylene glycols, sodium stearyl sulfate, sodium oleyl sulfate, sodium cetyl sulfate, sodium dodecylbenzene sulfonate, dialkyl sodium sulfosuccinates, polysorbates and the like, and combinations thereof.

In a specific embodiment, the present invention provides an immediate release tablet composition comprising less than 39% of sorafenib tosylate based on total weight of the composition and one or more pharmaceutically acceptable excipients.

Preferably, the sorafenib tosylate as used in the present invention is present in an amount of 30% to 38% based on total weight of the composition.

In an another embodiment. the present invention also provides an immediate release tablet composition comprising 400 mg of sorafenib equivalent to 548 mg of sorafenib tosylate.

Compositions of the present invention may be prepared by dry blending. For example, the blended composition of the actives and excipients may be compacted into a slug or a sheet and then

comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

Compositions for tableting of the present invention may be prepared by wet granulation. In wet granulation, active ingredient and some or all of the excipients are blended were then further mixed in the presence of a binder solution, that causes the powders to clump into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate may then be tableted, or other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

As an alternative to granulation, a blended composition may be compressed directly into tablets using direct compression techniques.

Tablets of the present invention may optionally be coated with a film coating composition.

A film coat on the tablet provides an elegant appearance, protects from moisture and further contributes to the ease with which it can be swallowed.

In yet another embodiment, the compositions of the present invention are useful for the treatment of unresectable hepatocellular carcinoma (HCC), advanced renal cell carcinoma (RCC), differentiated thyroid carcinoma (DTC) in a patient in need thereof.

EXAMPLES

The following examples further describe and demonstrate particular embodiments within the scope of the present invention. The examples are given solely for illustration and are not to be construed as limitations as many variations are possible without departing from spirit and scope of the invention.

Example 1

Tablet compositions of sorafenib

Ingredients	mg/unit	(%w/w)
Sorafenib tosylate[#]	274.00	34.00
Lactose monohydrate	240.00	29.78

Croscarmellose sodium	15.00	1.86
Povidone	20.00	2.48
Purified water	q.s.	q.s.
Sodium lauryl sulphate	4.00	0.50
Lactose monohydrate	220.00	27.30
Croscarmellose sodium	10.00	1.24
Magnesium stearate	7.00	0.87
Core tablet weight	**790.00**	**98.04**
Opadry® red	15.80	1.96
Purified water	q.s.	q.s.
Coated tablet weight	**805.80**	**100**

274 mg of sorafenib tosylate contains 200 mg of sorafenib

Brief manufacturing process:

1. Sifting sorafenib tosylate, lactose monohydrate, croscarmellose sodium through mesh # 40 sieve,
2. blending the sifted materials of step 1,
3. preparing binder solution by dissolving povidone in purified water,
4. granulating the blend of step 2 with binder solution of step 3 and drying the granules,
5. sifting and blending lactose monohydrate, croscarmellose sodium, sodium lauryl sulphate through mesh # 40 sieve,
6. blending dried granules of step 4 with blend of step 5,
7. sifting magnesium stearate through mesh # 60 sieve,
8. lubricating blended granules of step 6 with magnesium stearate of step 7,
9. compressing lubricated blend of step 8 into tablets,
10. film coating the tablets of step 9 using Opadry® dispersion.

Example 2

Tablet compositions of sorafenib

Ingredients	mg/unit	(%w/w)
Sorafenib tosylate[#]	274.00	37.79
Mannitol	215.00	29.65
Sodium starch glycolate	15.00	2.07
Hydroxypropyl methyl cellulose	15.00	2.07
Purified water	q.s.	q.s.
Sodium lauryl sulphate	4.00	0.55
Mannitol	170.00	23.45
Sodium starch glycolate	10.00	1.38
Magnesium stearate	8.00	1.10
Core tablet weight	**711.00**	**98.06**
Opadry®	14.10	1.94
Purified water	q.s.	q.s.
Coated tablet weight	**725.10**	**100**

[#] 274 mg of sorafenib tosylate contains 200 mg of sorafenib

Brief manufacturing process:

1. Sifting sorafenib tosylate, mannitol, sodium starch glycolate, through mesh # 40 sieve,
2. blending the sifted materials of step 1,
3. preparing binder solution by dissolving povidone in purified water,
4. granulating the blend of step 2 with binder solution of step 3 and drying the granules,
5. sifting and blending mannitol, sodium starch glycolate, sodium lauryl sulphate through mesh # 40 sieve,
6. blending dried granules of step 4 with blend of step 5,
7. sifting magnesium stearate through mesh # 60 sieve,
8. lubricating blended granules of step 6 with magnesium stearate of step 7,
9. compressing lubricated blend of step 8 into tablets,

10. film coating the tablets of step 9 using Opadry® dispersion.

Example 3

Tablet compositions of sorafenib

Ingredients	mg/unit
Sorafenib tosylate#	548.00
Microcrystalline cellulose	225.00
Croscarmellose sodium	30.00
Hydroxypropyl methyl cellulose	18.00
Purified water	q.s.
Sodium lauryl sulphate	8.22
Microcrystalline cellulose	225.00
Croscarmellose sodium	14.00
Magnesium stearate	14.00
Core tablet weight	**1082.22**
Opadry®	15.22
Purified water	q.s.
Coated tablet weight	**1097.44**

548 mg of sorafenib tosylate contains 400 mg of sorafenib

Brief manufacturing process:

1. Sifting sorafenib tosylate, microcrystalline cellulose, croscarmellose sodium through mesh # 40 sieve,
2. blending the sifted materials of step 1,
3. preparing binder solution by dissolving hydroxypropyl methyl cellulose in purified water,
4. granulating the blend of step 2 with binder solution of step 3 and drying the granules,
5. sifting and blending microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate through mesh # 40 sieve,

6. blending dried granules of step 4 with blend of step 5,

7. sifting magnesium stearate through mesh # 60 sieve,

8. lubricating blended granules of step 6 with magnesium stearate of step 7,

9. compressing lubricated blend of step 8 into tablets,

10. film coating the tablets of step 9 using Opadry® dispersion.

Dated this *Seventh (7th)* day of March, 2014

(Signed)----------

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HETERO LABS LIMITED

SOLID ORAL COMPOSITIONS OF SORAFENIB

ABSTRACT

The present invention relates to pharmaceutical compositions comprising sorafenib and one or more pharmaceutically acceptable excipients. More particularly, the present invention relates to tablet compositions comprising sorafenib tosylate.