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(54) Title: ORAL DOSAGE FORM OF SORAFENIB TOSYLATE

(57) Abstract: ORAL DOSAGE FORM OF SORAFENIB TOSYLATE The present invention relates to an oral dosage form comprising sorafenib tosylate as an active ingredient, and which has improved properties. Further, the present invention provides a method for the preparation of the said composition.

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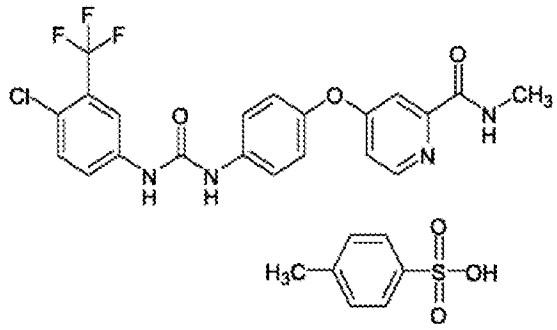
ORAL DOSAGE FORM OF SORAFENIB TOSYLATE

Field of the invention

The present invention relates to an oral dosage form comprising sorafenib tosylate as an active ingredient, and which has improved properties. Further, the present invention provides a method for the preparation of the said composition.

Background of the invention

Sorafenib tosylate, a multi-kinase inhibitor targeting several serine/threonine and receptor tyrosine kinases, is the tosylate salt of sorafenib. Sorafenib tosylate has the chemical name 4-(4-(3-(4-chloro- 3- (trifluoromethyl) phenyl) ureido) phenoxy)-N-methylpicolinamide tosylate and its chemical structure is shown in the formula I.



Formula I

Sorafenib tosylate is marketed by Bayer Pharmaceutical under the trademark NEXAVAR ® which is film-coated tablet consisting sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib and the following excipients: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide and ferric oxide red.

The known forms of sorafenib are not optimal in regard to polymorphic and chemical stability, flow properties, compressibility, dissolution rate. These properties cause disadvantages in the preparation of pharmaceutical compositions, such as tablets.

Further, it is known that sorafenib tosylate is practically insoluble in water. As such, the dissolution rate and bioavailability of conventional sorafenib tosylate formulations are likely poor.

WO 2006/034796 discloses a process for preparing sorafenib and its tosylate salt. The tosylate salt is said to be obtained in crystalline form.

WO 2006/026501 discloses pharmaceutical compositions comprising a solid dispersion of sorafenib which comprises microcrystalline cellulose. Also, the patent application is the patent of the originator.

The patent application WO2013/110644 A1 discloses a tablet form comprising a crystalline sorafenib tosylate characterized by an X-ray powder diffraction pattern showing peak maxima at 2 theta/° values of 7.7±0.2, 12.0±0.2, 19.9±0.2, and 21.6±0.2, the X-ray powder diffraction pattern being determined at a temperature of about 22° C and at least one excipient. Used excipients are microcrystalline cellulose, croscarmellose, hypromellose, magnesium stearate, sodium lauryl sulfate.

In the prior art, there are many oral dosage forms comprising sorafenib tosylate having microcrystalline cellulose as a filler. However, it is known that microcrystalline cellulose has poor to moderate flow properties. Due to these poor flow properties of both sorafenib tosylate and microcrystalline cellulose, the combination of these two substances causes some disadvantages.

Furthermore, another problem in the prior art is the use of microcrystalline cellulose and magnesium stearate at the same time. Microcrystalline cellulose and magnesium stearate are also highly hygroscopic. It may also make over lubrication and which make compressibility problems when used together. The combined use of these excipients is obviously risky to provide stability of a solid dosage form.

There still remains a need in the prior art to provide an improved oral pharmaceutical composition of sorafenib, having high solubility, dissolution rate, and accordingly a high bioavailability and a long-term stability which is also obtained by using an effective process.

Detailed description of the Invention

The main object of the present invention is to provide an oral dosage form comprising sorafenib tosylate which shows improved polymorphic and chemical stability, improved dissolution rate, excellent flow properties and the desired compressibility.

Another object of the present invention is to provide wet granulation process to obtain excellent uniformity.

Another object of the present invention is to formulate an oral dosage form which is used for the treatment of cancer, such as advanced renal carcinoma ("RCC") and metastatic renal cell carcinoma ("mRCC").

According to one embodiment of the present invention, the oral dosage form comprises sorafenib tosylate and at least one pharmaceutically acceptable excipient which is selected from the group comprising fillers, disintegrants or mixtures thereof.

According to another embodiment of the present invention, the weight ratio of fillers to disintegrants is 1.0-10.0, preferably 2.0-5.0. These ratios are important in order to provide stability in the form.

According to another embodiment of the present invention, the oral dosage form comprising sorafenib tosylate is present in the form of polymorph III.

As used herein, 'particle size' means the cumulative volume size distribution as tested by any conventionally accepted method such as the laser diffraction method (i.e. Malvern analysis). The term d (0.1) means, the size at which 10% by volume of the particles are finer and d (0.5) means the size at which 50% by volume of the particles are finer and d (0.9) means the size at which %90 by volume of the particles are finer.

According to another embodiment of the present invention, sorafenib tosylate is micronized and has a mean particle size less than 10 µm, preferably less than 8 µm.

According to another embodiment of the present invention, sorafenib tosylate has a d (0.1) particle size is less than 4 µm, preferably less than 3 µm, preferably less than 2 µm, d (0.5) particle size is less than 6 µm, preferably less than 5 µm, preferably less than 4 µm, d (0.9) particle size is less than 10 µm, preferably less than 9 µm, preferably less than 8 µm.

The oral dosage form comprising micronized sorafenib tosylate provides improved dissolution profiles. Rapid dissolution of an administered active agent is preferable, as faster dissolution generally leads to faster onset of action and greater bioavailability. Additionally, a faster dissolution rate would allow for a larger dose of the drug to be absorbed, which would increase drug efficacy.

According to another embodiment of the present invention, the dosage form is free of microcrystalline cellulose. It is known that microcrystalline cellulose has poor to moderate flow properties so the filler is not appropriate for the oral dosage forms comprising sorafenib tosylate.

Also, in the present invention, preferably magnesium stearate is used as a lubricant. It makes over lubrication and which make compressibility problems when used together with microcrystalline cellulose and magnesium stearate. And the combined use of these excipients is obviously risky to provide stability of a solid dosage form.

Also, microcrystalline cellulose may create an allergic reaction in some patients. Because it is not absorbed, symptoms of allergic reaction are likely to be limited to gastrointestinal symptoms such as diarrhea or gas.

Therefore, the present invention provides at least one filler which, on the one hand, fulfills the requirements which are demanded of such a material but, on the other hand, is more cost favourable than the expensive microcrystalline cellulose.

In comparison to the prior art, in the present invention, the selection of using filler has also importance to obtain the desired dissolution rate.

Suitable fillers are selected from the group comprising lactose, dicalcium phosphate, lactose monohydrate, starch, pregelatinized starch, dextrose, sucrose, fructose, maltose, sorbitol, polysaccharides, dextrates, lactitol, maltodextrin, trehalose or mixtures thereof.

According to another embodiment of the present invention, the filler is lactose or dicalcium phosphate or mixtures thereof.

The selected filler, lactose or dicalcium phosphate or mixtures thereof, according to the present invention is very well suited. Using the excipients in the form provides excellent flow properties so overcome compressibility problems. It also provides long-term stability.

According to another embodiment of the present invention, the amount of fillers in the dosage form is 20.0% to 45.0%, preferably 30.0% to 40.0%, more preferably 30.0% to 35.0% and most preferably 32.0% to 35.0% by weight.

Suitable disintegrants are selected from the group comprising crospovidone, low-substituted hydroxypropyl cellulose, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose, docusate sodium, guar gum, polyacryline potassium, sodium alginate, sodium starch glycolate, alginic acid, alginates, ion-exchange resins, magnesium aluminum silica or mixtures thereof.

According to another embodiment of the present invention, the disintegrant is crospovidone or low-substituted hydroxypropyl cellulose or mixtures thereof.

According to another embodiment of the present invention, the amount of disintegrants in the dosage form is 3.0% to 20.0%, preferably 5.0% to 15.0%, more preferably 7.0% to 13.0% and most preferably 9.0% to 12.0%by weight.

According to another embodiment of the present invention, the dosage form further comprising binders, surfactants, lubricants or mixtures thereof.

Suitable binders are selected from group comprising hydroxypropyl methyl cellulose, methyl cellulose, carboxymethyl cellulose, polyethylene glycol, polyvinyl alcohol, polyvinyl acetate, polyvinylpyrrolidone, sugars, glucose syrups, natural gums, pregelatinized starch, gelatins, pullulan, agar, alginate, sodium alginate, glycyrrhizin, polymethacrylates, collagen, hyaluronic acid, poloxamer, polyacrylamide, aluminum hydroxide, bentonite, cetostearyl alcohol, polyoxyethylene-alkyl ethers, polydextrose, polyethylene oxide, xylitol, sucrose stearate or mixtures thereof.

According to another embodiment of the present invention, the binder is hydroxypropyl methyl cellulose and the amount of hydroxypropyl methyl cellulose in the dosage form is 1.0% to 10.0%, preferably 1.0% to 5.0%, preferably 2.0% to 5.0% by weight.

Suitable surfactants are selected from the group comprising sodium lauryl sulfate, benzalkonium chloride, docusate sodium, glyceryl esters, poloxamer, polyethylene alkyl ethers, polyglyceryl esters, polysorbates, sorbitan esters, polyoxyethylene esters, polyoxyethylene stearates, sodium stearate, calcium oleate, hexadecyl pyridinium chloride or mixtures thereof.

According to another embodiment of the present invention, the surfactant is sodium lauryl sulfate and the amount of sodium lauryl sulfate in the dosage form is 0.01% to 3.0%, preferably 0.01% to 2.0%, preferably 0.1% to 1.0% by weight.

Suitable lubricants are selected from the group comprising magnesium stearate, silica, silicon dioxide, talc, calcium stearate, stearic acid, polyethylene glycol, sodium stearyl fumarate, magnesium lauryl sulfate, fumaric acid, glyceryl palmito sulphate, hydrogenated vegetable oil, zinc stearate or mixtures thereof.

According to another embodiment of the present invention, the lubricant is magnesium stearate and the amount of magnesium stearate in the dosage form is 0.01% to 3.0%, preferably 0.01% to 2.0%, preferably 0.1% to 1.0% by weight.

According to another embodiment of the present invention, the dosage form is a tablet or a capsule or a granule. Preferably the dosage form is a tablet, more preferably coated tablet.

According to one embodiment, the oral dosage form further comprises at least one coating to protect the composition against the moisture and maintain the stability. Preferably the coating is film coating.

Suitable film coating ingredients are selected from the group comprising hydroxypropylmethyl cellulose (hypromellose), hydroxypropyl cellulose, polyvinyl alcohol (PVA), polyethylene glycol (PEG), talc, polyvinyl alcohol-polyethylene glycol copolymers (Kollicoat IR), ethylcellulose dispersions (Surelease), polyvinylpyrrolidone, polyvinylpyrrolidone-vinyl acetate copolymer (PVP-VA) and all kinds of Opadry®, pigments, dyes, titanium dioxide, iron oxides or polymethylmetacrylate copolymers (Eudragit) or mixtures thereof.

According to another embodiment of the present invention is to provide a stable dosage form by the manufacturing process. The oral dosage form of the present invention is 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 or solvent evaporation.

It has surprisingly been found that the oral dosage form of excellent uniformity and showing improved dissolution can be obtained when it is prepared by wet granulation process. Wet granulation process provides efficiently compressibility, so it can achieve good dissolution and disintegration properties.

According to one embodiment of the invention, the oral dosage form is prepared by using wet granulation.

During wet granulation process, a liquid solvent is used. Suitable liquid solvents are selected from the group comprising pure water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, glycol or mixtures thereof. Preferably, the solvent is pure water.

Example 1:

Ingredients	Weight %
Sorafenib tosylate	45.0-55.0
Fillers	30.0-36.0
Disintegrants	7.0-13.0
Hydroxypropyl methylcellulose	2.0-5.0
Sodium lauryl sulfate	0.01-2.0
Magnesium stearate	0.01-2.0
Film coating	1.0-5.0

Example 2:

Ingredients	Weight %
Sorafenib tosylate	40.0-70.0
Lactose or dicalcium phosphate or mixtures thereof as filler	20.0-45.0
Crospovidone or low-substituted hydroxypropyl cellulose or mixtures thereof as disintegrant	3.0-20.0
Hydroxypropyl methylcellulose	1.0-10.0
Sodium lauryl sulfate	0.01-3.0
Magnesium stearate	0.01-3.0
Film coating	1.0-5.0

Example 3:

Ingredients	Weight %
Sorafenib tosylate	51.0-53.0
Lactose or dicalcium phosphate or mixtures thereof as filler	32.0-35.0
Crospovidone or low-substituted hydroxypropyl cellulose or mixtures thereof as disintegrant	9.0-12.0
Hydroxypropyl methylcellulose	1.0-5.0
Sodium lauryl sulfate	0.1-1.0
Magnesium stearate	0.1-1.0
Film coating	2.0-4.0

Process for example 1 or 2 or 3;

The process for the preparation of the tablet comprises the following steps:

a) Mixing sorafenib tosylate, hydroxypropyl methylcellulose, sodium lauryl sulfate and at least one filler,
b) Granulating step (a) with pure water,
c) Drying the obtained mixture, then sieving it,
d) Adding at least one disintegrant and then mixing,
e) Adding magnesium stearate and then mixing,
f) Then, pressing to form tablets,
g) Coating the tablets with a film coating.

CLAIMS

1. An oral dosage form comprising sorafenib tosylate and at least one pharmaceutically acceptable excipient which is selected from the group comprising fillers, disintegrants or mixtures thereof wherein the weight ratio of fillers to disintegrants is 1.0 - 10.0.

2. The oral dosage form according to claim 1, wherein the weight ratio of fillers to disintegrants is 2.0 - 5.0.

3. The oral dosage form according to claim 1, wherein sorafenib tosylate is present in the form of polymorph III.

4. The oral dosage form according to claim 3, wherein sorafenib tosylate is micronized and has a mean particle size less than 10 µm.

5. The oral dosage form according to claim 4, wherein sorafenib tosylate has a d (0.1) particle size is less than 4 µm, preferably less than 3 µm, preferably less than 2 µm, d (0.5) particle size is less than 6 µm, preferably less than 5 µm, preferably less than 4 µm, d (0.9) particle size is less than 10 µm, preferably less than 9 µm, preferably less than 8 µm.

6. The oral dosage form according to claim 1, wherein the dosage form is free of microcrystalline cellulose.

7. The oral dosage form according to claim 1, wherein the fillers are selected from the group comprising lactose, dicalcium phosphate, lactose monohydrate, starch, pregelatinized starch, dextrose, sucrose, fructose, maltose, sorbitol, polysaccharides, dextrates, lactitol, maltodextrin, trehalose or mixtures thereof.

8. The oral dosage form according to claim 7, wherein the filler is lactose or dicalcium phosphate or mixtures thereof.

9. The oral dosage form according to claim 1, wherein the disintegrants are selected from the group comprising crospovidone, low-substituted hydroxypropyl cellulose, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose, docusate sodium, guar gum, polyacryline potassium, sodium alginate, sodium starch glycolate, alginic acid, alginates, ion-exchange resins, magnesium aluminum silica or mixtures thereof.

10. The oral dosage form according to claim 9, wherein the disintegrant is crospovidone or low-substituted hydroxypropyl cellulose or mixtures thereof.

11. The oral dosage form according to claim 1, wherein the dosage form further comprising binders, surfactants, lubricants or mixtures thereof.

12. The oral dosage form according to claim 1, wherein the dosage form is a tablet or a capsule or a granule.

13. The oral dosage form according to claim 12, wherein the dosage form is a tablet, preferably coated tablet.

14. The oral dosage form according to claim 1, wherein the dosage form comprising;

45.0%-55.0% by weight of sorafenib tosylate
30.0%-40.0% by weight of fillers
7.0%-13.0% by weight of disintegrants
2.0%-5.0% by weight of hydroxypropyl methylcellulose
0.01%-2.0% by weight of sodium lauryl sulfate
0.01%-2.0% by weight of magnesium stearate by weight of the dosage form.

15. The oral dosage form according to claim 1, wherein the dosage form comprising;

40.0%-70.0% by weight of sorafenib tosylate
20.0%-45.0% by weight of lactose or dicalcium phosphate or mixtures thereof
3.0%-20.0% by weight of crospovidone or low-substituted hydroxypropyl cellulose or mixtures thereof
1.0%-10.0% by weight of hydroxypropyl methylcellulose
0.01%-3.0% by weight of sodium lauryl sulfate
0.01%-3.0% by weight of magnesium stearate by weight of the dosage form.

16. The oral dosage form according to claim 14 or 15, wherein the dosage form is prepared by wet granulation process.

17. The process for the preparation the oral dosage form according to claim 16, wherein the process comprising the following steps:

a) Mixing sorafenib tosylate, hydroxypropyl methylcellulose, sodium lauryl sulfate and at least one filler,
b) Granulating step (a) with pure water,

c) Drying the obtained granule, then sieving it,

d) Adding at least one disintegrant to the mixture in step (c) and then mixing,

e) Adding magnesium stearate to the mixture in step (d) and then mixing,

f) Then, pressing the final mixture into form tablets,

g) Coating the tablets with a film coating.