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(54) Title: SOLID DOSAGE FORM CONTAINING SORAFENIB TOSYLATE

(57) Abstract: The invention relates to a solid dosage form containing Sorafenib tosylate which is used in pharmacy and medicine. An advantage of the composition according to the invention is improved bioavailability and tolerability, possibility of its applicable at lower optimal therapeutic doses that created balance between reduction of adverse drug reactions and abilility to overcome acquired resistance in the course of therapy. A solid dosage form, according to the invention, comprising Sorafenib tosylate, a precipitation inhibitor in an amount of 0.5 to 25% by weight, preferably from 0.5% to 15%, and most preferably from 1% to 10% and optionally other excipients.

Solid dosage form containing Sorafenib tosylate

Field of the invention

The invention relates to a solid dosage form containing Sorafenib tosylate which is used in pharmacy and medicine, in particular for the treatment of unresectablehepatocellular carcinoma, advanced renal cell carcinoma, and progressive, locally advanced or metastatic, differentiated thyroid carcinoma.

Background of the invention

Sorafenib, also known as BAY 43-9006, is omega carboxyaryl substituted diphenyl urea with the chemical name 4- {4 - [({[4-chloro-3- (trifluoromethyl) phenyl] amino} amino] phenoxy} -N-methylpyridine-2-carboxamide. Sorafenib has been synthesized by Bayer and has been described for the first time in patent application WO0042012. Various polymorphic modifications of the chemical substance sorafenib (WO2006034797) are also known, each of which exhibits different stability.

Sorafenib has been specified to be an inhibitor of the raf kinase enzyme and is indicated for the treatment of hyperproliferative diseases, such as cancer, especially for the treatment of unresectablehepatocellular carcinoma, advanced renal cell carcinoma and progressive, locally advanced or metastatic, differentiated (papillary / follicular (Hürthle-cell) thyroid carcinoma, radioactive iodine-refractory. Sorafenib is used as a single agent or in combination with other anticancer therapeutics.

Sorafenib is practically insoluble in water, poorly soluble in ethanol and soluble in PEG. Due to its water insolubility, there is a problem with the dissolution rate and the bioavailability of the conventional formulations containing it. It would be desirable to increase the dissolution rate and bioavailability for a faster infusion of the drug. Application of sorafenib are usually associated also with high and serious side effects such as ischemic heart disease and/or infarction, bleeding, hypertension, skin reaction at the limbs, gastrointestinal perforations,

thrombocytopenia, anemia, etc., which are directly dependent of the dose. Therefore, dose reduction would reduce the side effects associated with taking this drug.

Patent application WO2008008733 describes a tablet formulation of good pharmacokinetic properties and bioavailability that contains sorafenib nanoparticles of dimensions less than 2000 nm stabilized with at least one surface stabilizer. The dosage form containing these nanoparticles may be prepared with or without the addition of further pharmaceutically acceptable excipients such as fillers and binders.

The European Patent EP 1868579 of Bayer discloses an immediate release tablet formulation containing more than 55% of the total weight of sorafenib tosylate salt with a particle size of 0.5 to 10 µm and as auxiliaries: microcrystalline cellulose as a filler in a portion of from 3 to 20%, croscarmellose sodium as a disintegrant in a proportion of 5 to 12%, hypromellose as a binder in a proportion of 0.5 to 8%, magnesium stearate as a lubricant in a proportion of from 0.2 to 8% and sodium lauryl sulfate as a surfactant in a proportion of from 0.1 to 2% by weight of the composition. Prior to administration, the tablet dissolves in water and disintegrates for 6 minutes. This patent protects the Nexavar® market product that Bayer has marketed since 2006.

The disadvantage of this dosage form is that in order to achieve the optimal therapeutic effect it has to be taken in a specific way and the optimal therapeutic daily intake is high.

Object of the present invention is to provide a pharmaceutical composition of sorafenyl tosylate with improved bioavailability and tolerability applicable at lower optimal therapeutic doses to balance the reduction of adverse drug reactions with the need for dose adjustment to overcome the acquired resistance in the therapy process.

Summary of the invention

The solid formulation according to the invention includes sorafenib tosylate and a precipitation inhibitor in an amount of 0.5 to 25% by weight, more preferably from 0.5% to 15%, and most preferably from 1% to 10% as well as optionally one or more other excipients.

Preferably, the precipitation inhibitor is hydroxypropyl methylcellulose (hypromellose) with a viscosity higher than 10 cps.

In one embodiment, the precipitation inhibitor is selected from the group of compounds: hydroxypropylcellulose, carboxymethylcellulose, methylcellulose, hydroxyethylcellulose, polyvinyl alcohol, polyacrylates, methylcellulose, polyvinyl pyrrolidone, copovidone and pregelatinised starch.

The precipitation inhibitor is included in the solid dosage formulation to eliminate the precipitation of sorafenib tosyl after passing into the gastrointestinal fluids of the patient by preventing growth of the active compound crystals in the solution. Thus, a greater amount of sorafenib tosylate remains in the dissolved state, which improves the extent of absorption, increases efficacy, and increases its bioavailability.

In another embodiment, the pharmaceutical composition also includes other excipients such as binders, fillers, plasticizers, surfactants and wetting agents.

The pharmaceutical composition of the solid dosage form according to the invention may be in the form of a tablet in a form of coated tablets, which is coated with film-forming agents, coating materials and colorants or in the form of a pharmaceutical capsule.

The oral solid formulation containing sorafenib tosylate is prepared by the wet granulation process, as the manufacturing process includes the following steps:

a) sorafenib tosylate with at least one pharmaceutically acceptable excipient is wet granulated with an aqueous solution of the precipitantion inhibitor ;

(b) the granulate is blended with the lubricant and optionally with one or more further pharmaceutically acceptable excipient;
c) Lubricated granules are compressed as tablets or filled into capsules or filling them into pharmaceutical capsules.

In another embodiment, the resulting tablets may be coated with one or more pharmaceutically acceptable coatings.

In another embodiment, the granulation process may be dry granulation and direct compression.

An advantage of the composition according to the invention is the creation of a pharmaceutical composition of sorafenyl tosylate with improved bioavailability and tolerability applicable at lower optimal therapeutic doses that balance between reduction of adverse drug reactions and dose adjustment in order to overcome acquired resistance in the course of therapy.

Description of the enclosed figures

The pharmaceutical composition and its properties have been investigated and the results of the investigations are presented graphically in the following figures:

Figure 1 presents graphically the results of a dissolution profile study of the composition of the film-coated tablet of Example 1 according to the invention.

Figure 2 graphically represents the comparative evaluation of the results of the in vitro dissolution of the tablet formulation obtained according to Example 1 and the market medicinal product of sorafenib tosylate Nexavar®.

Figure 3 presents a graphical representation of the comparative evaluation of an in vivo study of the tablet formulation prepared according to Example 1 and the market medicinal product of sorafenib tosylate Nexavar®.

Examples of implementation

The pharmaceutical composition of the solid formulation containing sorafenib tosylate according to the invention is illustrated by the following exemplary embodiments:

Example 1: Preparation of a film-coated tablet containing Sorafenib tosylate

To prepare the film-coated tablet containing Sorafenib tosylate according to the invention, the following components are used:

Components of the composition	% w/w
Sorafenib Tosylate	49.82
Microcrystalline cellulose	41.57
Hypromellose , viscosity 15cps	2.00
Sodium starch glycolate	5.00
Sodium lauryl sulfate	0.31
Sodium stearyl fumarate	1.30
Opadry coating	3.00

Sorafenib tosylate was co-sifted along with microcrystalline cellulose and sodium starch glycolate. The blend is loaded in to the Fluidized bed processor and granulated using solution of hypromellose and Sodium lauryl sulfate in water. Granules were lubricated with Sodium stearyl fumarate and compressed into tablet. The core tablets were then coated with Opadry film coating.

Example 2: Test to determine the dissolution profile of the film-coated tablets prepared in Example 1.

The dissolution profile of the film-coated tablets prepared in Example 1 was carried out according to the method described in USP under the following conditions: 0.01N HCl with 0.25% SLS, 900mL, 50rpm, in dissolution apparatus 2 over a time period of 60 min. The results of the dissolution test conducted are shown in Table 1 and are presented graphically in Figure 1.

Table 1

Time	Product as per example 1
min	% drug dissolved
15	77
30	92
45	98
60	100

Example 3. Comparative evaluation of in vitro dissolution of the tablet formulation prepared according to Example 1 and the market medicinal product of sorafenib tosylate Nexavar®.

The in vitro study was conducted in 900 ml of pH 6.8 buffer with 1.0% SLS using USP Apparatus II. In vitro dissolution demonstrates faster and greater dissolution compared to the formulation available on the market. The results obtained are shown in Table 2 and are shown graphically in Figure 2.

Table 2

Batch No	Nexavar® BXHRG11	Product as per example 1
Time (min)	% drug dissolved	
30	30	60
60	36	59
90	40	58
120	43	56

In vitro dissolution exhibited faster, and higher dissolution compared to marketed formulation.

Example 4 Comparative Evaluation of an In Vivo Study of the Tablet Form prepared according to Example 1 and the market medicinal product of sorafenib tosylate Nexavar®.

In-vivo pharmacokinetic study in healthy human volunteers in complete crossover manner.

Results of the in-vivo study are shown in Table 3 and graphically in Figure 3.

Table 3

Ratio, 90% C.I of Sorafenib Pilot 1 (T1) vs Reference (R)							
PK Parameter	Units	Ref Geo LSM	T1GeoLSM	Ratio (%)	90% CI		Intra Subject variability
					Lower	Upper	
Cmax	ng/ml	1596.290	3101.882	194.32	154.52	244.36	47.84
AUC72	hr*ng/ml	33653.403	67166.420	199.58	162.81	244.67	42.05

Test show higher T/R ratio for Cmax and AUC. The batch showed 194.32% T/R for Cmax and 199.58% T/R for AUC72.

Based on these observations, a bio-enhanced formulation with increased bioavailability was developed.

PATENT CLAIMS

1. A solid dosage form containing Sorafenib tosylate and excipients, characterized in that it also comprises a precipitation inhibitor in an amount of 0.5 to 25% by weight, preferably from 0.5% to 15%, and most preferably from 1% to 10%.

2. A solid dosage form containing Sorafenib tosylate according to claim 1, characterized in that the precipitation inhibitor is hydroxypropyl methylcellulose (hypromellose) with a viscosity higher than 10 cps.

3. A solid dosage form containing Sorafenib tosylate according to claim 1, characterized in that the precipitation inhibitor is selected from the group of of compounds: hydroxypropylcellulose, carboxymethylcellulose, methylcellulose, hydroxyethylcellulose, polyvinyl alcohol, polyacrylates, methylcellulose, polyvinyl pyrrolidone, copovidone and pregelatinized starch.

4. A solid dosage form containing Sorafenib tosylate according to any one of claims from 1 to 3, characterized in that it comprises and other excipients such as binders, fillers, plasticizers, surfactants and wetting agents.

5. A solid dosage form containing Sorafenib tosylate according to any one of claims from 1 to 4, characterized in that the solid dosage form may be a tablet, a film-coated tablet or a pharmaceutical capsule.

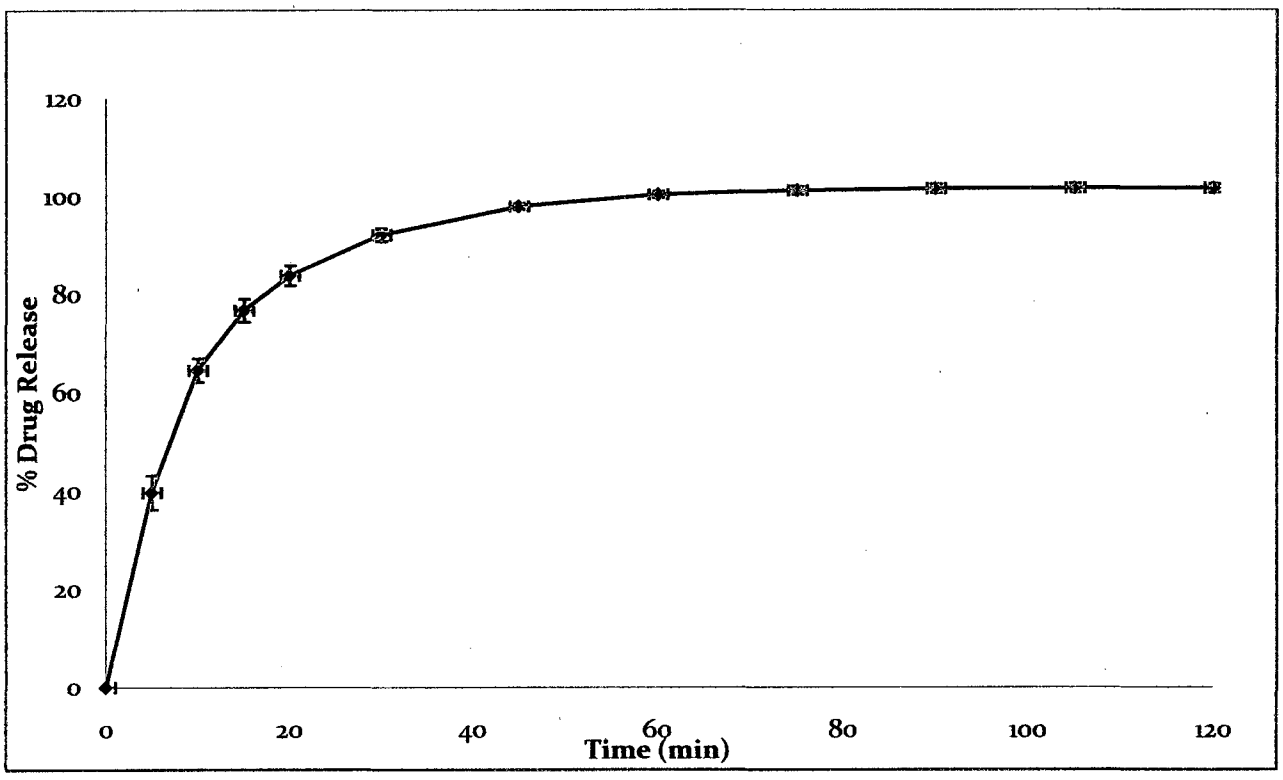

Fig.1

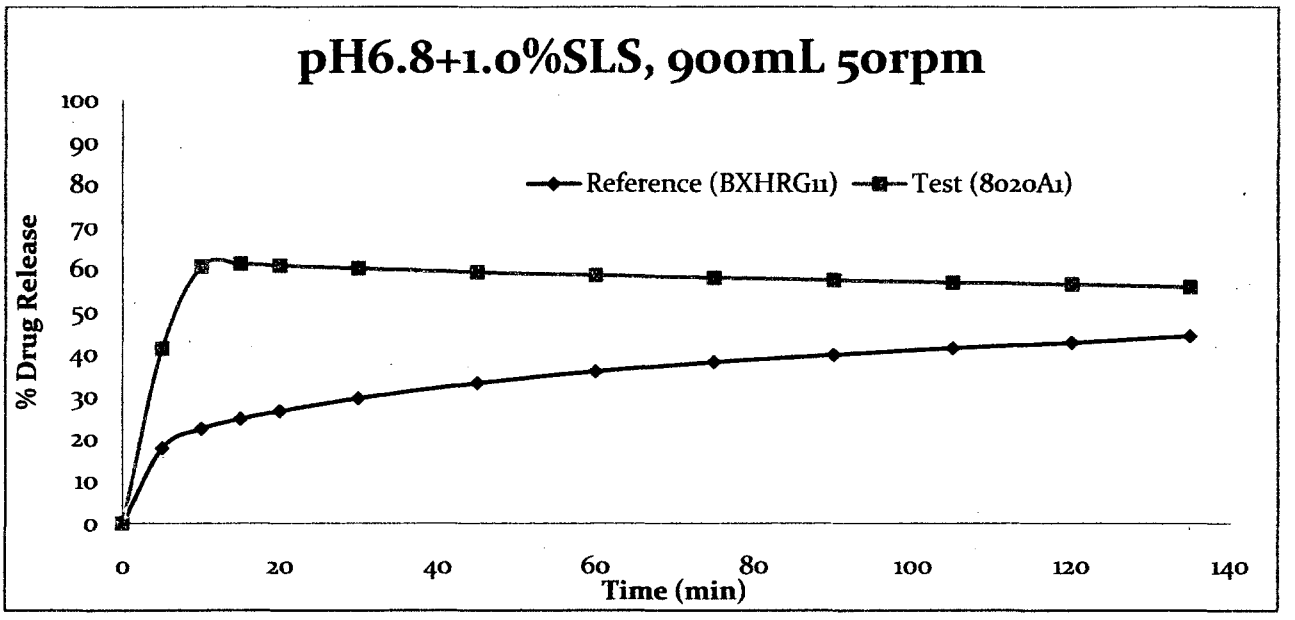
pH6.8+1.0%SLS, 900mL 50rpm
% Drug Release
100
90
80
70
60
50
40
30
20
10
0
Reference (BXHRG11)
Test (8020A1)
0
20
40
60
80
100
120
140
Time (min)

Fig.2

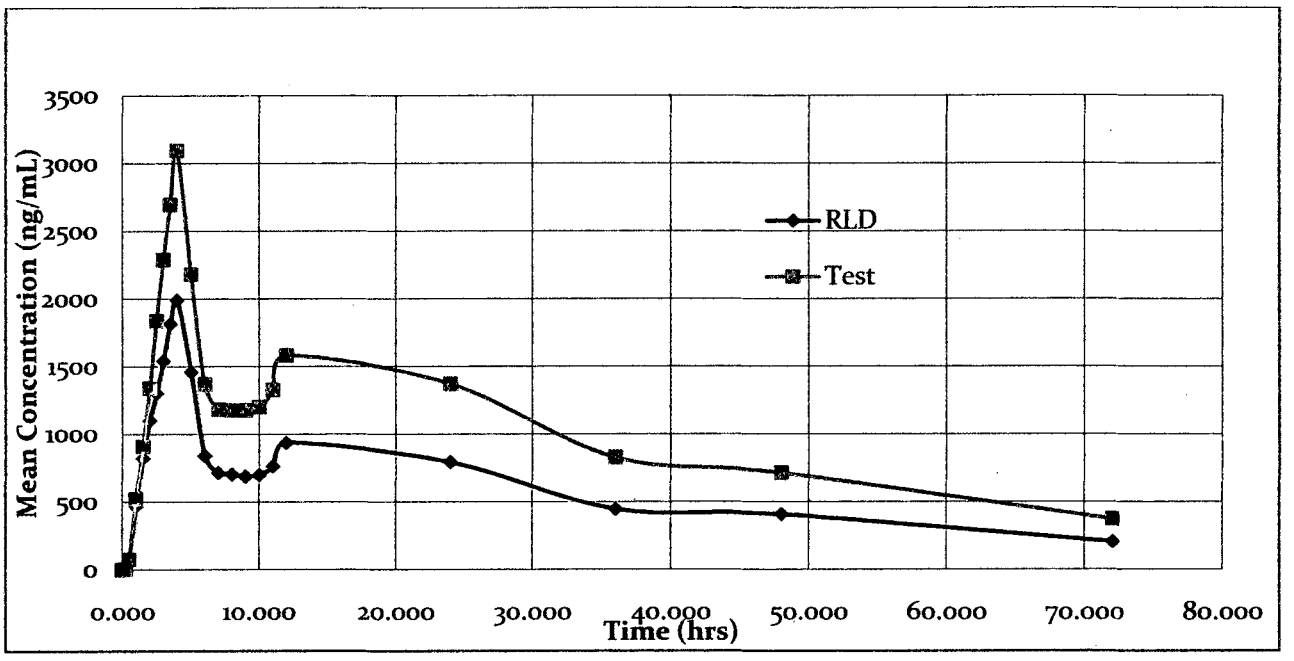
3500
3000
2500
2000
1500
1000
500
0
Mean Concentration (ng/mL)
RLD
Test
0.000
10.000
20.000
30.000
40.000
50.000
60.000
70.000
80.000
Time (hrs)

Fig.3