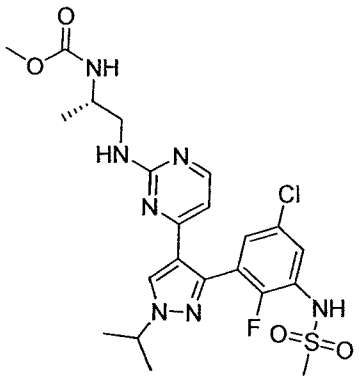
PHARMACEUTICAL FORMULATIONS

BACKGROUND

This invention relates to solid oral pharmaceutical formulations of (S)-methyl (1-((4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)propan-2-yl)carbamate (COMPOUND A) and the use of these formulations for treating proliferative diseases, such as solid tumor diseases.

The COMPOUND A has the chemical structure:



Its preparation and its use as an inhibitor of B-RAF for the treatment of proliferative diseases, such as solid tumor diseases, like melanoma and colorectal cancer, are described in WO 2011/025927, which is here incorporated by reference in its entirety.

COMPOUND A is a BCS class II compound exhibiting poor aqueous solubility at weakly acidic and neutral pH which poses a challenge for oral bioavailability and therapeutic effect. The compound exhibits typical weak base solubility characteristics and is highly soluble at low pH, starts to decline at around pH 3.0 and remains low at intrinsic solubility level over the range of neutral pH. Upon emptying from the stomach, COMPOUND A has the tendency to quickly precipitate out of solution due to an abrupt solubility drop in intestinal pH. This significantly

reduces COMPOUND A that is available for intestinal absorption. The present invention relates to orally bioavailable pharmaceutical solid dispersion formulations of COMPOUND A.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 represents the 2 stage dissolution profile of the formulation described in Example 1.
Figure 2 represents the 2-Stage (pH 2 first 60 min to 6.8 after 60 min) dissolution of the formulations described in Examples 2-7.
Figure 3 represents the dissolution profile of the tablet formulation described in Example 8.

DETAILED DESCRIPTION OF THE INVENTION

COMPOUND A is a BCS class II compound which exhibits typical weak base solubility characteristics: higher solubility at low pH, and limited solubility around neutral pH. Therapeutic compounds with such solubility characteristics typically present pharmaceutical formulation scientists with a challenge while attempting to prepare oral formulations capable of improving oral bioavailability of the therapeutic compound. Such challenges in preparing solid oral dosage forms of COMPOUND A are overcome, according to the present invention, by formulating the compound as a solid dispersion.

Solid dispersions are specialized pharmaceutical formulations. The most suitable solid dispersion formulation is the one that enhances solubility and dissolution rate and maintains the stability of the drug substance in an amorphous state. In a typical solid dispersion formulation the drug substance is uniformly dispersed in a solid matrix which promotes dissolution of the drug in the gastrointestinal tract and maintains the drug in a high energy amorphous state.

Pharmaceutical solid dispersions are produced by techniques known in the art, for example, solvent evaporation, kneading and melt extrustion.

According to the present invention, an inner phase is prepared. The inner phase is a solid dispersion comprising COMPOUND A in a suitable polymer matrix, which is composed, for example, of a hydrophilic binder, a surfactant and optional additional excipients, which are known in the art, followed by milling to reduce particle size.

Prior to tableting or encapsulation, the inner phase is preferably combined with additional excipients, which are collectively referred to herein as the external phase. One or more of an acidifier, a filler, a disintegrant, a flow enhancer and a lubricant are typically included in the external phase.

Thus, the present invention relates to a solid oral pharmaceutical formulation which comprises a solid dispersion comprising COMPOUND A.

In one embodiment, the present invention is a solid oral pharmaceutical formulation which comprises:

(a) an inner phase which is a solid dispersion comprising COMPOUND A, and
(b) an external phase which comprises additional excipients.

Preferably, the internal phase, or, more preferably, the external phase comprises an acidifier.

The present invention further relates to a solid oral pharmaceutical formulation which comprises:

(a) an inner phase which is a solid dispersion comprising COMPOUND A, a hydrophilic binder and a surfactant; and
(b) an external phase which comprises additional excipients.

In another embodiment, the present invention is a solid oral pharmaceutical formulation which comprises:

(a) an inner phase which is a solid dispersion comprising COMPOUND A, a hydrophilic binder, a surfactant and

(b) an external phase which comprises one or more of an acidifier, a filler, a disintegrant, a flow enhancer and a lubricant.

The hydrophilic binder should be suitable for complete miscibility with COMPOUND A and upon formulation dissolution, serve as a precipitation inhibitor of COMPOUND A. Suitable hydrophilic binders for inclusion in the inner phase include copovidone, hydroxypropylmethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, and methacrylate copolymer, polyethylene oxide, HPMC acetate succinate, HPMC phthalate. Copovidone is especially useful as the hydrophilic binder. KOLLIDON VA64, which is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a ratio of 6:4 by mass and is available from BASF, is highly suitable for use as a hydrophilic binder in the inner phase.

The surfactant should be suitable for use in melt extrusion to enhance dissolution and solubilization of COMPOUND A. In some cases, the surfactant may help reduce the process temperature through its plasticizing effect. Suitable surfactants for inclusion in the inner phase include poloxamers, such as Poloxamer 188, sodium lauryl sulphate, Tween 80, sorbitol, polysorbate 20, polysorbate 80, Vitamin E TPGS, and polyethylene glycol.

Additional excipients that may optionally be included in the inner phase include acidifiers, and plasticizers.

In the preferred embodiments, the internal phase, or preferably the external phase comprises an acidifier to control the microenvironmental pH in the acidic range. Suitable acidifiers include organic acids such as citric acid, succinic acid, maleic acid, tartaric acid, malic acid and adipic acid.

Suitable fillers, disintegrants, flow enhancers and lubricants are known to those of skill in the art.

Especially useful fillers include lactose, maltodextrin, mannitol, microcrystalline cellulose, pregelatinized starch, and sucrose esters.

Useful disintegrants include crospovidone, croscarmellose sodium, sodium starch glycolate, microcrystalline cellulose, and pregelatinized starch.

Useful flow enhancers include colloidal silicon dioxide, talc, magnesium stearate, and mannitol.

Useful lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, hydrogenated castor oil, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, zinc stearate, talc, microcrystalline cellulose, and sucrose esters.

In different embodiments of the present invention, the inner phase comprises various ranges of %w/w of active agent, hydrophilic binder and surfactant. For instance, the present inner phase can comprise 5-70% Compound A, 10-90% of hydrophilic binder, and 5-30% surfactant, preferably 5-50% Compound A, 30-80% of hydrophilic binder, and 5-30% surfactant, more preferably 5-40% Compound A, 50-80% of hydrophilic binder, and 5-20% surfactant.

In different embodiments of the present invention, the external phase comprises various ranges of %w/w of acidifier, filler, disintegrant, flow enhancer and lubricant. For instance, the present external phase can comprise 1-70% acidifier, 20-70% filler, 0-30% disintegrant, 0-10% flow enhancer and 0-10% lubricant, preferably 2-60% acidifier, 30-70% filler, 5-20% disintegrant, 0.5-5% flow

enhancer and 0.5-5% lubricant, more preferably 10-40% acidifier, 20-40% filler, 1-15% disintegrant, 1-5% flow enhancer and 1-5% lubricant.

In different embodiments of the present invention, the solid oral dosage form, for example, capsules or tablets, are a blend of the internal and external phases in a ratio of from 100:0 to 30:70, preferably 80:20 to 40:60, most preferably 75:25 to 50:50.

Stabilization of an amorphous form of COMPOUND A in a solid dispersion formulation enhances bioavailability, attributable to a higher dissolution rate and kinetic solubility of the amorphous form in comparison to its crystalline form.

When COMPOUND A stays in amorphous form, an increase in kinetic solubility and dissolution rate as well as in oral bioavailability is achieved using the solid dispersion formulation.

In one embodiment, the present invention is formulated as a capsule, such as hard gelatin capsule or a soft elastic capsule. Alternatively, the present invention is in the form of a tablet or a pill. In these solid oral formulations the amount of COMPOUND A can be present in the ranges of 1-1500 mg, 2.5-800 mg, or 5-400 mg, with preferred examples including 10 mg, 20 mg, 25 mg, 50 mg , 100 mg, 200 mg, 400 mg and 500 mg.

The solid oral formulations of the present invention can be administered to treat diseases which respond to inhibition of B-RAF, particularly diseases that are characterzed by a mutation in B-RAF, particularly melanoma and colorectal cancer.

Thus, the present invention further relates to the use of a solid oral pharmaceutical formulation described above for the preparation of a medicament for the treatment of a proliferative disease, especially wherein the proliferative disease is a solid tumor disease characterized by a mutation in B-RAF, such as melanoma or colorectal cancer.

The present invention further relates to a method of treating a proliferative disease which comprises administering to a patient in need of treatment a therapeutically effective amount of a formulation described herein, especially wherein the proliferative disease is a solid tumor disease characterized by a mutation in B-RAF, such as melanoma or colorectal cancer.

The following Examples are intended to illustrate, but not to limit, the invention.

Example 1

The following composition is prepared at constant drug loading of 15% and formulated into 10, 25, 50 mg and 100 mg capsules.

Ingredient	%w/w
Internal	
Compound A	15
Kollidon VA64	45
Pluronic F 68	5
External	
Succinic acid	13
Cellulose MKGR	16
Crosspovidone	5
Mg Stearate	0.5
Aerosil	0.5
Total	**100**

Ingredient	10 mg capsule	25 mg capsule	50 mg capsule	100 mg capsule
Internal Phase (mg)				
Compound A	10.0	25.0	50.0	100.0
Kollidon VA64	29.9	74.8	150.0	300.0
Poloxamer 188 (Pluronic F68)	3.3	8.4	16.7	33.3
External Phase (mg)				
Succinic acid	8.7	21.7	43.3	86.7
Cellulose microcrystalline	10.7	26.7	53.3	106.7
Crospovidone	3.3	8.4	16.7	33.3
Aerosil	0.3	0.9	1.7	3.3
Magnesium Stearate	0.3	0.9	1.7	3.3
Total (mg)	66.6	166.5	333.4	666.6

Manufacturing process:

The processing is performed by hot-melt extrusion using a 18 mm twin-screw Leistriez extruder, followed by milling the extrudates, blending with the external phase and screening. Following blending, the blend is encapsulated into pink hard gelatin capsules of size 0 and 00 for drug doses of 50 and 100 mg respectively. A step-by step approach is shown below:

Weigh the required amount of Compound A, Kollidon VA64 and Poloxamer 188

Blend the mixture

Extrude the blend on a 18 mm Leistreiz twin-screw extruder at a feed rate of 1kg/hour maintaining temperatures of 50 to 160 °C in the extruder.

Mill the extrudate

Add screened succinic acid and cellulose microcrystalline

Add and blend the milled extrudates, succinic acid and cellulose microcrystalline

Add crospovidone and aerosil
Blend the mixture
Add prescreen magnesium stearate
Blend the mixture
Encapsulation using H&K encapsulator

In-vivo monkey PK data with the resulting capsules show bioavailability suitable for oral administration with a mean Cmax of 11833 ng/ml, Tmax at 4 hours and an AUC of 32686 ng*hr/ml.

XRPD data indicate physical stability of the amorphous solid dispersion formulation (no indication of conversion to the crystalline drug substance) upon storage at accelerated stability conditions of 40 °C/ 75 % RH for 4 weeks.

In-vitro 2-stage dissolution studies indicate no change in dissolution kinetics of the solid dispersion between initial (0 week) and 4-week time point at accelerated stability storage conditions indicating no change in physical stability of the solid dispersion.

The present formulation exhibits a glass transition temperature (Tg) of 97 °C which is above the recommended drug product storage temperature of no greater than 30°C, demonstrating physical stability without conversion of the amorphous drug substance into the poorly water soluble crystalline drug substance.

The present formulation shows excellent chemical stability upon storage at accelerated stability conditions at 40 ° C/75 % RH with no evidence of any degradation products and 100% assay content results for COMPOUND A.

Example 2
The following formulation is prepared in a manner similar to that described in Example 1.

Ingredient	%w/w
Internal	
LGX818	17
PVP-K30	51
Sorbitol	5
External	
Succinic Acid	9
Cellulose MKGR	12
Crosspovidone	5
Mg Stearate	0.5
Aerosil	0.5
Total	**100**

This formulation exhibits a glass transition temperature (Tg) of 109°C demonstrating physical stability without conversion of the amorphous drug substance into the poorly water soluble crystalline drug substance.

Example 3

The following table described the results of a pharmacokinetic study in monkeys of Compound A formulated as a microemulsion dosed at 50 mg/kg and the formulations of Example 1 (Solid Dispersion 1) and Example 2 (Solid Dispersion 2) at a dose of 200 mg of Compound A.

Treatment_ID	Subject_	Tmax (h)	Cmax ng/mL	AUClast ng*h/mL	Tlast (h)
Microemulsion (early) 1	monkey 1	2	2510	21000	30
	monkey 2	4	3410	25400	30
	monkey 3	4	727	8820	30
	Mean	3.3	2216	18407	
	SD	1.2	1366	8589	
Solid Dispersion_1 (Kollidon) Showed emesis	monkey 1	4	9830	42377	30
	monkey 2	2	13500	35816	30
	monkey 3	2	10600	24626	30
	monkey 4	2	271	1037	8
	monkey 5	8	13400	27924	24
	Mean		11833	32686	
	SD		1894	7986	
Solid Dispersion_2 (PVP-K30)	monkey 1	2	18100	43327	30
	monkey 2	2	13000	29756	30
	monkey 3	2	2220	5804	30
	monkey 4	1	14500	33177	30
	monkey 5	1	12900	21390	30
	Mean		12144	26691	
	SD		5933	14076	

Examples 2-7

The following formulations are prepared by tehniques similar to those described in Example 1, but with a single phase. The dissolution profiles of the formulations are reported in Figure 2.

Formulation 2:

Ingredients	%W/W
Compound A	25.00
Vitamin E TPGS	41.67
Polyethylene glycol 4000	26.33
Hydroxypropylmethyl cellulose	5.00
Talc	2.00

Formulation 3:

Ingredients	%W/W
Compound A	25.00
Vitamin E TPGS	41.67
Polyethylene glycol 4000	16.33
Hydroxypropylmethyl cellulose	15.00
Talc	2.00

Formulation 4:

Ingredients	%W/W
Compound A	25.00
Vitamin E TPGS	41.67
Polyethylene glycol 4000	5.92
Hydroxypropylmethyl cellulose	15.00
Maleic acid	5.41
Eudragit L100-55	5.00
Talc	2.00

Formulation 5:

Ingredients	%W/W
Compound A	25.00
Vitamin E TPGS	41.67
Polyethylene glycol 4000	5.92
Hydroxypropylmethyl cellulose	5.00
Maleic acid	5.41
Eudragit L100-55	15.00
Talc	2.00

Formulation 6:

Ingredients	%W/W
Compound A	24.00
Vitamin E TPGS	40.00
Hydroxypropylmethyl cellulose	14.40
Maleic acid	5.20
Eudragit L100-55	14.40
Talc	2.00

Formulation 7:

Ingredients	%W/W
Compound A	24.00
Vitamin E TPGS	40.00
Polyethylene glycol 4000	1.20
Hydroxypropylmethyl cellulose	14.40
Lactic acid	4.00
Eudragit L100-55	14.40
Talc	2.00

Example 8

The following formulation is prepared by tehniques similar to those described in Example 1, but in a tablet dosage form. The dissolution profile of the formulation in 0.1N HCl medium is reported in Figure 3.

Formulation 8:

Ingredient	**%w/w**
Internal	
Compound A	10.0
Kollidon VA64	30.1
Pluronic F 68	3.4
External	
Kollidon VA64	3.0
Cellulose MKGR	37.5
Crosspovidone	15.0
Mg Stearate	1.0
Total	**100**

CLAIMS

We claim:

1. A solid oral pharmaceutical formulation which comprises a solid dispersion comprising COMPOUND A.

2. A solid oral pharmaceutical formulation of claim 1, which comprises:
an inner phase which is a solid dispersion comprising COMPOUND A, and
an external phase which comprises additional excipients.

3. A solid oral pharmaceutical formulation of claim 2 wherein the internal phase or the external phase comprises an acidifier.

4. The present invention further relates to a solid oral pharmaceutical formulation of claim 2, which comprises:
an inner phase which is a solid dispersion comprising COMPOUND A, a hydrophilic binder and a surfactant; and
an external phase which comprises additional excipients.

5. A solid oral pharmaceutical formulation of claim 1, which comprises:
an inner phase which is a solid dispersion comprising COMPOUND A, a hydrophilic binder, a surfactant and
an external phase which comprises one or more of an acidifier, a filler, a disintegrant, a flow enhancer and a lubricant.

6. Use of a solid oral pharmaceutical formulation of claim 1 for the preparation of a medicament for the treatment of a proliferative disease.

7. A method of treating a proliferative disease which comprises administering to a patient in need of treatment a therapeutically effective amount of a formulation according to claim 1.

8. Use of the solid oral formulations according to claim 1 for the treatment of a disease which responds to inhibition of B-RAF.

9. Use according to claim 8 wherein the disease is characterzed by a mutation in B-RAF.

10. Use according to claim 9 wherein the disease is melanoma or colorectal cancer.