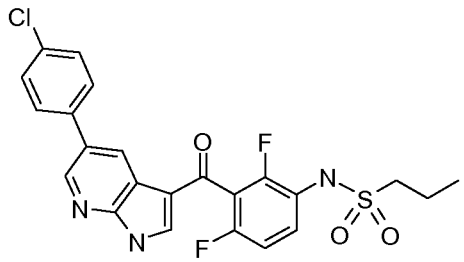
PROPANE-I-SULFONIC ACID { 3- [5- (4 -CHLORO-PHENYL) -1H-PYRROLO [2, 3-B] PYRIDINE-3-CARBONYL] -2, 4-DIFLU0R0-PHENY L)-AMIDE COMPOSITIONS AND USES THEREOF)

The present invention is related to an improved method for the manufacture of solid dispersions, in particular Micro-precipitated Bulk Powder (MBP), containing the compound Propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide (formula 1) and Hydroxypropylmethylcellulose Acetate Succinate (HPMCAS).



Formula 1

The compound of formula 1, methods of synthesizing it as well as conventional pharmaceutical formulations containing that compound have been disclosed in WO 2007002433 and WO 2007002325. The compound of formula 1 shows valuable pharmaceutical properties as potential medicament for the inhibition of cancer proliferation, in particular solid tumor growth.

Background of the Invention

Compounds that have low solubility in water (for example, certain compounds in crystalline form), have a low dissolution rate and as a result can exhibit poor bioavailability. Poorly bioavailable compounds can present problems for therapeutic administration to a patient, often due to unpredictability in dose/therapy effects caused by erratic absorption of the compound by

the patient. For example, the intake of food may affect the ability of the patient to absorb such poorly bioavailable compounds, thus potentially requiring dosing regimens to take into account the effect of food. In addition, when dosing, a large safety margin may be required for the dose as a result of the unpredictable dose effects. Further, due to poor bioavailability, a large dose of the compound may be required to achieve a desired therapeutic effect, thus potentially resulting in undesired side effects.

The amorphous form of Compound 1 has improved solubility in water as compared to the crystalline form, but is unstable as it has a tendency to crystallize. Thus it is desired to formulate Compound I so that it may exist stably primarily in amorphous form

HPMCAS is a polymer that has been used for the manufacture of solid dispersions (SD) of drugs (see for example H. Konno, L. S. Taylor, *Journal of Pharmaceutical Sciences, Vol. 95, No.12*, **2006**, 2692-2705).

EP 0 901 786 B1 discloses a composition comprising a spray-dried solid dispersion of a poorly water soluble drug and HPMCAS. Disclosed drugs are glycogen phosphorylase inhibitors and 5-lipoxygenase inhibitors as disclosed in WO 96/39385 and WO 95/05360 respectively.

EP 1 368 001 B1 discloses a pharmaceutical formulation comprising the drug bicalutamide and an enteric polymer, like HPMCAS. Disclosed methods for evaporating the solvent include rotary evaporation, spray drying, lyophilisation and thin film evaporation. It is further disclosed that other techniques may be used such as solvent controlled precipitation, pH controlled precipitation, spray congealing and supercritical fluid technology (eg, the Solution Enhanced Dispersion by Supercritical Fluid (SEDS) technique).

EP 0 344 603 B1 discloses formulating HPMCAS with a drug designated as NZ-105. The patent discloses formulations prepared by dissolving NZ-105 and HPMCAS in an organic solvent and removing the solvent by means of vacuum-drying, spray-drying, freeze-drying, or the like. More specifically, dispersions of HPMCAS and NZ-105 are formed by (1) fluidized bed granulation by coating either calcium hydrogen phosphate particles or lactose crystals or 2) vacuum drying with

lactose to form a solid cake that is then pulverized to form a powdery material. Particle sizes are described to be in the range of 100 to 400 mesh (0.037 mm to 0.149 mm).

EP 0 580 860 discloses a process for the preparation of a solid dispersion of drug dissolved in a polymer, which polymer is inter alia HPMCAS. The claimed process is characterized by the use of a twin-screw extruder being equipped with paddle means.

F. Tanno et. al. disclose the use of HPMCAS as a carrier in solid dispersions. The specific drug used as a model substance in the study is Nifedipine. The solid dispersions were obtained by spraying a mixture of HPMCAS and the drug in an organic solvent on a Teflon™ sheet, evaporating the solvent and removing an milling the resulting film (in *Drug Development and Industrial Pharmacy*, Vol.30, No.1, **2004**, 9-17). *Molecular Pharmaceutics, Vol. 5, No. 6,* **2008**, 1003-1019 also discloses HPMCAS spray-dried dispersions using several poorly water soluble drugs.

Bruno C. Hancock, George Zografi, *Journal of Pharmaceutical Sciences, Vol 86, No.1*, **1997**, 1-12 discloses methods for removing solvents when making solid dispersions using the so called *solvent method*, including for example spray-drying, vacuum-drying, freeze-drying or precipitation.

Summary of the Invention

In certain aspects and embodiments there are provided methods of preparing solid dispersions comprising HPMCAS and the compound of formula 1. In many embodiments the methods may use a lower amount of organic solvents as compared to other methods and as such may be more environmentally friendly; are safe when used on an industrial scale; and/or show improved properties such as stability against re-crystallization. In many aspects and embodiments the methods involve micro-precipitation of a mixture of HPMCAS and the compound of formula 1 within an aqueous phase using the conditions and process parameters as described herein.

In one embodiment there is provided a method for manufacturing a solid dispersion containing the amorphous form of the compound of formula 1 and HPMCAS, wherein the solid dispersion is obtained by introducing a solution of the compound of formula 1 and HPMCAS in the same organic solvent within an aqueous phase, and subsequent precipitation and isolation of said solid dispersion from said aqueous phase.

In certain more specific embodiments, the above method includes the following steps,

(a) dissolution of the compound of formula 1 and HPMCAS in the same organic solvent to give one single organic phase;

(b) continuously adding the organic phase obtained under (a) into an aqueous phase which is present in a mixing chamber, said mixing chamber being equipped with a high shear mixing unit and two additional openings which connect said mixing chamber to a closed loop wherein said aqueous phase is circulated and passes through the mixing chamber;

(c) precipitation of a mixture consisting of the amorphous form of the compound of formula 1 and HPMCAS out of the aqueous phase mentioned under (b), while the high shear mixer is operating and said aqueous phase is passed through the mixing chamber in a closed loop, resulting in the formation of an aqueous suspension of the precipitate;

(d) continuously circulating the aqueous suspension through the mixing chamber while the high shear mixing unit is operating and after the organic solution prepared under (a) has been completely added to the aqueous phase until a defined particle size and/or particle size distribution is obtained;

(e) isolating the solid phase from the suspension;

(f) washing of the isolated solid phase with 0.01 N HCl and/ or water; and

(g) delumping and drying of the solid phase.

In still more specific embodiments the present methods include the steps, wherein

- the organic phase in step (a) above is a 10 to 40 % solution of compound 1 and HPMCAS in DMA, the ratio of compound 1 to HPMCAS being from about 10 to 90 %(w/w) to about 60 to 40 % (w/w); and

- the continuous adding in step (b) above is achieved via an injector nozzle which is oriented in an angle between 40 and 50° to the longitudinal axis of the high shear mixer and has a distance of about 1 to about 10 mm from the rotor of said high shear mixer which is operating with a tip speed of about 15 to about 25 m/sec.

In still more specific embodiments the present methods include the step, wherein

- the continuous adding in step (b) above is achieved via an injector nozzle which is oriented in an angle of about 45° to the longitudinal axis of the high shear mixer and has a distance of about 2 to about 4 mm from the rotor of said high shear mixer which is operating with a tip speed of about 25 m/sec.

In other specific embodiments the present methods include the step, wherein

- the drying in step (g) above is achieved via fluidized bed drying.

In yet another particularly preferred embodiment, the organic phase in (a) comprises DMA, the compound of formula 1 and HPMCAS-L, and step (b) comprises adding said organic phase into aqueous (0.01 N) HCl at a mass flow ratio in the range of about 80/1 to 200/1 (aqueous phase/organic phase) while said aqueous HCl is kept at a temperature of about 2-8 °C.

In a further embodiment there are provided the solid dispersions obtained by the above-mentioned method.

The dried precipitate can be further processed into any type of solid pharmaceutical preparations or dosage forms, which are known to the person of skill in the art. Particularly preferred are oral dosage forms such as tablets, capsules, pills, powders, suspensions, pasts and the like. Detailed

descriptions of suitable excipients as well as methods for making such pharmaceutical preparations can for example be found in: Raymond C. Rowe et al, *Handbook of Pharmaceutical Excipients, 6th edition*, **2009**, Pharmaceutical Press (Publ.); ISBN-10: 0853697922.

Consequently, so obtained pharmaceutical preparations form further embodiments provided herein.

Detailed Description of the Invention

The compound of formula 1, which is an active pharmaceutical ingredient (API), and the excipient Hydroxypropylmethylcellulose Acetate Succinate (HPMCAS) is dissolved in an organic, water miscible solvent in a feed hopper. In a second vessel an aqueous phase of defined temperature is pumped in a loop outside of the vessel, while passing through a high shear mixer (HSM, rotor / stator unit). A schematic drawing of the process can be seen in Fig. 1. The temperature of both solutions was controlled during the complete manufacturing process. The solution with the API and excipient (organic phase) is dosed with a defined flow rate into the mixing chamber, containing the rotor / stator tools, while the high shear unit (dispersing unit) is operating. During the mixing of the two liquids (aqueous- and organic phase) an almost water insoluble precipitate, which is a mixture of amorphous API and HPMCAS with a defined ratio, is formed, leading to a suspension of micro precipitated bulk powder (MBP) in the outer phase (mixture of water and organic solvent). After complete addition of the organic phase the suspension was forced a number of passes through the dispersing unit in order to adjust the particle size. Subsequently the suspension was centrifuged and washed with a water phase several times in order to remove the organic solvent and finally was washed additionally with pure water. The obtained wet MBP was delumped and dried to a water content below 2 % by weight (w/w). The MBP was obtained as a white, free flowing powder.

The compound of formula 1 can be synthesized according to methods disclosed in WO 2007002433 or WO 2007002325.

The term "HPMCAS" means Hydroxypropylmethylcellulose Acetate Succinate (trade name: AQOAT, available from Shin-Etsu Chemical Industry Co., Ltd., Japan or appointed distributors), which is available in the following grades: AS-LF, AS-MF, AS- HF, AS-LG, AS-MG and AS-HG. The solubility of the different HPMCAS grades as well as their drug release behaviour depends on the pH-value of the environment. Accordingly, the release behaviour of a drug can be tailored in the range of about pH5.2 to about pH6.5 by the choice of the appropriate HPMCAS grade (see product information brochure for AQOAT). Therefore, in one embodiment, the compound of formula 1 is in a solid dispersion with at least one polymer selected from HPMCAS grades AS-L, AS-M, AS-H. It is, however, contemplated that a mixture of two or more of the various HPMCAS grades can also be used in accordance with the present invention.

The term "solid dispersion" as used herein means a solid state material formed by a high molecular weight compound, such as a polymer, preferably HPMCAS, wherein a low molecular weight compound, such as the compound of formula 1, is molecularly dispersed. Preferably the solid dispersion exists as a one phase system. An especially preferred solid dispersion according to the present invention is a microprecipitated bulk powder (MBP) essentially consisting of HPMCAS and the compound of formula 1 which is predominantly in its amorphous form.

The "organic solvent" mentioned under step (a) means any organic solvent wherein both the compound of formula 1 and HPMCAS are miscible. Preferred organic solvents are N-Methylpyrrolidone, Dimethylformamide, Dimethylsulfoxide, Dimethylacetamide (DMA), with DMA being the most preferred. The combined amount of the compound of formula 1 and HPMCAS together in the organic phase can be within the range of about 10 to 40 weight%, preferably about 15 to 40 weight%, more preferably about 25 to 40, most preferably about 35 weight% . The weight ratio of the compound of formula 1 / HPMCAS within the organic solvent is from about 10/90 to about 60/40 weight%, more preferably from about 30/70 to about 60/40 weight%, and most preferably about 30/70 weight%, respectively. Preferably, the temperature of the organic solvent is adjusted between 50 and 110 °C, preferably 60 and 90 °C, most preferred at about 70 °C prior to its addition to the mixing chamber as mentioned under step (b). The

mixture of the compound of formula 1 and HPMCAS in the organic solvent is also designated herein as the "organic phase" or "DMA phase".

The "aqueous phase" mentioned under step (b) preferably consists of acidic water (pH<7), most preferably of 0.01 N hydrochloric acid (HCl). The aqueous phase is kept at a temperature between about 2 and about 60 °C, preferably between about 5 and about 20 °C, most preferably about 5 °C . The aqueous phase circulates out of the bottom valve of its reservoir ((**1**) of Fig. 1) due to the stream created by the high shear mixer or with an auxiliary pump, preferably a rotary lobe pump, then passes through the high shear mixer, back into the reservoir. Preferably, the outlet of the loop is placed under the fluid level maintained in the reservoir, in order to prevent foaming.

The addition of the organic phase to the mixing chamber as mentioned in step (b) above is achieved via an injector nozzle which directly points into the aqueous phase. Any conventional nozzle known to the person of skill in the art can be used. Preferred injector nozzles show central or acentric geometry are isolated and have a diameter of about 1 to 10 mm. The acentric (not centered) geometry and a diameter of 5 mm are especially preferred. The injector nozzle may point to the rotor of the high shear mixing unit in an angle between 0 and 90°, preferably between 40 and 50°, most preferably at 45° (α, Fig. 2). During the process according to the present invention, the distance between the point of the injector nozzle and the tip of the rotor of the high shear mixing unit is about 1 to 10 mm, preferably about 2 to 4 mm and most preferably about 2.6 mm. The addition of the organic phase is preferably carried out at dosing rates of about 60/1 to about 300/1 (i.e. mass flow ratio of aqueous phase/organic phase during precipitation), preferably about 70/1 to about 120/1 and most preferably at about 100/1. Final ratio of aqueous phase/organic phase after precipitation is in the range of about 5/1 - 12/1 preferably 7/1 - 10/1 and most preferably at 8.5/1.

While the organic phase is added (injected) into the aqueous phase of the mixing chamber, the high shear mixing unit is operating. Any conventional high shear mixing unit (rotor/stator unit) known to the person of skill in the art can be applied. Especially preferred are toothed disk

dispersing units. The preferred rotor geometry according to the present invention uses a rotor/stator unit with a radial single teeth row or double teeth row or combination thereof. Rotors with conical teeth rows can also be applied. The tip speed of the rotor is from about 15 to about 25 m/sec., preferably 25 m/sec.

Subsequent to the complete addition of the organic phase into the aqueous phase, the obtained suspension, thus the precipitate consisting of the amorphous compound of formula 1 and HPMCAS in the aqueous phase, is further circulated in the closed loop containing the high shear mixing unit. Outside of the high shear mixing unit the circulation must be carried out with the aid of an auxiliary pump, preferred a rotary lobe pump. The suspension passes the high shear mixing unit several times, up to the moment where a desired particle size and/or particle size distribution is obtained. Usually the suspension passes the high shear mixing unit about 1 to 60 times, most preferably 6 times. The particle size and/or particle size distribution can be controlled by standard techniques, well known to the person of skill in the art, such as for example dynamic light scattering. The preferred particle size according to the present invention is with in the range of D50 = 80 – 230 μm preferably D50 = 80 – 160 μm.

Isolation of the solid dispersion (MBP) according to step (e) above can be carried out by using conventional filter techniques or centrifuges. Prior to isolation, the suspension is preferably adjusted to about 5 to 10 °C. Subsequently, the isolated solid dispersion is washed with acidic water; preferably 0.01 N HCl followed by further washing with pure water in order to substantially remove the organic solvent (step (f)). The isolated (wet) solid dispersion (MBP) usually shows a water content between 60 and 70 % (w/w), which requires drying before any further processing. The drying can be carried out using any standard techniques known to the person of skill in the art, for example using a cabinet dryer at temperatures between 30 and 50 °C, preferably at about 40 °C and at reduced pressure, preferably below 20 mbar. Several drying procedures can be combined or used sequentially, whereby the use of fluidized bed drying is especially preferred as the final drying step according to the present invention.

The stability of the solid dispersion (MBP) according to the present invention was compared with the stability of an MBP obtained via conventional spray precipitation. "Conventional spray precipitation" means that the organic phase was sprayed onto the aqueous phase via a nozzle

which is placed outside the aqueous phase, above its surface like it is the case for many conventional spray-precipitation techniques. All further process parameters are the same for both methods. The stability, thus the inhibition of re-crystallization of the compound of formula 1, is determined by x-ray diffraction measurements, using a conventional wide angle X-ray scattering setup as it is well known to the skilled artisan. Sample preparation was identical for both MBP's. The samples were treated in a climate chamber (50 °C and 90 % humidity (RH)) for several hours respective days (0 h, 14 h, 41 h, 4 d, 6 d, 13 d) prior to X-ray measurements. The results are shown in Figure 3 (a) for the MBP obtained according to the present invention, and (b) for the MBP obtained by the conventional method. The earliest X-ray curves of both MBP's show a broad halo in the wide angle region with the absence of sharp signals, thereby clearly evidencing that both materials are in an amorphous state. Within several days, sharp signals occur in the X-ray curves obtained from the MBP manufactured by the conventional method ((**b**)in Fig. 3), but not in the X-ray curves obtained from the MBP prepared using the method as disclosed herein ((**a**)in Fig. 3).

The novel processes as provided herein can preferably be carried out using a setup as shown in the accompanying Figure 1.

The solid dispersion, in particular the MBP obtainable according to the methods provided can be used in a wide variety of forms for administration of drugs such as the compound of formula 1, including drugs that are poorly water soluble, and in particular for oral dosage forms. Exemplary dosage forms include powders or granules that can be taken orally either dry or reconstituted by addition of water to form a paste, slurry, suspension or solution; tablets, capsules, or pills. Various additives can be mixed, ground or granulated with the solid dispersion as described herein to form a material suitable for the above dosage forms. Potentially beneficial additives may fall generally into the following classes: other matrix materials or diluents, surface active agents, drug complexing agents or solubilizers, fillers, disintegrants, binders, lubricants, and pH modifiers (e.g., acids, bases, or buffers). Examples of other matrix materials, fillers, or diluents include lactose, mannitol, xylitol, microcrystalline cellulose, calcium diphosphate, and

starch. Examples of surface active agents include sodium lauryl sulfate and polysorbate 80. Examples of drug complexing agents or solubilizers include the polyethylene glycols, caffeine, xanthene, gentisic acid and cylodextrins. Examples of disintegrants include sodium starch gycolate, sodium alginate, carboxymethyl cellulose sodium, methyl cellulose, and croscarmellose sodium. Examples of binders include methyl cellulose, microcrystalline cellulose, starch, and gums such as guar gum, and tragacanth. Examples of lubricants include magnesium stearate and calcium stearate. Examples of pH modifiers include acids such as citric acid, acetic acid, ascorbic acid, lactic acid, aspartic acid, succinic acid, phosphoric acid, and the like; bases such as sodium acetate, potassium acetate, calcium oxide, magnesium oxide, trisodium phosphate, sodium hydroxide, calcium hydroxide, aluminum hydroxide, and the like, and buffers generally comprising mixtures of acids and the salts of said acids. At least one function of inclusion of such pH modifiers is to control the dissolution rate of the drug, matrix polymer, or both, thereby controlling the local drug concentration during dissolution.

As was stated earlier, additives may be incorporated into the solid amorphous dispersion during or after its formation. In addition to the above additives or excipients, use of any conventional materials and procedures for formulation and preparation of oral dosage forms using the compositions disclosed herein known by those skilled in the art are potentially useful.

Consequently, a further embodiment includes a pharmaceutical preparation containing the solid dispersion as obtained by a method as described herein.

In one embodiment, the solid dispersion may be processed into a film-coated tablet containing up to 92% of the MBP obtainable according to the process disclosed herein, and wherein the MBP consists of about 30% compound of formula (1) and about 70% HPMCAS. The remaining part of the tablet consists of a mixture of conventional disintegrants such as for example croscarmellose sodium; glidant such as for example colloidal anhydrous silica; binders such as for example hydroxypropylcellulose; lubricants such as for example Magnesium stearate; and a film coat. Any conventional film coating mixture known to the skilled person can be applied, e.g. *Opadry II pink 85F14411*. A representative mixture for a film-coated tablet is given in Example 6.

In still another embodiment, there is provided a solid dispersion as obtained according to the present process for use as a medicament.

In yet another embodiment there is provided the use of the solid dispersion obtainable by the present process in the manufacture of medicaments for the treatment of cancer, in particular solid tumors, and more particularly malignant melanomas.

In still another embodiment, there is provided the solid dispersion as obtained according to the present process for use as a medicament for the treatment of cancer, in particular solid tumors, and more particularly malignant (metastatic) melanoma.

Brief Description of the Drawings

Figure 1 shows a schematic drawing of the setup for the manufacturing of solid dispersion (MBP) according to the present invention. The setup provides two reservoirs (vessels) with temperature control means, one for providing the aqueous phase at a controlled temperature (**1**), the other for providing the organic phase at a controlled temperature (**2**). Both vessels are further equipped with automatic stirrers (3). The aqueous phase is circulated in a closed loop (**4**) using a pump (**5**), while passing a high shear mixing unit (**6**). The organic phase is added into the aqueous phase within the high shear mixing unit with the aid of a dosing pump (7) and via an injector nozzle which is shown in more detail in Fig. 2.

Figure 2 shows are more detailed schematic drawing of the high shear mixing unit ((**6**) of Fig. 1). The nozzle (**8**) is placed within the aqueous phase inside the high shear mixing unit. The nozzle can be oriented within different angles (α) with respect to the rotor (**9**) of the high shear mixing unit, and within defined distances (d) of the rotor tip.

Figure 3 shows the comparison of X-ray diffractograms obtained from two lots of solid dispersions (MBP's), manufactured via high shear mixer precipitation according to the present invention (3a) and via conventional spray precipitation (3b). The results presented in this figure

demonstrate that the spray precipitated MBP is less stable against re-crystallization than the high shear precipitated MBP as evidenced by the early occurrence of sharp signals in the diffractograms of (b), which can be allocated to the crystalline form of the compound of formula (1). Bottom line in each picture represents the initial sample, the following lines bottom up after 14 h, 41 h, 96 h, 6 d respective 13 d storage in a clime chamber (50 °C 90% RH).

Examples

The invention will become apparent by the following examples which are given for illustration of the invention rather than limiting its intended scope.

Example 1: Preparation of the DMA phase:

The concentration of the compound of formula 1 and HPMCAS in the organic solvent was 35 % (w/w), while the ratio of the compound of formula 1 and HPMCAS is 30 to 70: The temperature of the solution was adjusted to 70 °C.

In a 250 ml double jacked glass flask reactor 21 g of the compound of formula 1 were dissolved in 130 g Dimethylacetamide (DMA) at 20 – 25 °C. Under stirring. 48.9 g of HPMC-AS were added to the solution. The mixture was heated up to 70 °C. A clear solution was obtained.

Example 2: Preparation of the aqueous phase

In a double jacketed 2.0 liter reactor 1210 g of 0.01 N HCl was tempered to 5 °C. Out of the bottom valve of the reactor the water phase was circulated by the high shear mixer or with an auxiliary pump, preferred a rotary lobe pump, and then followed by the high shear mixer, back to the top of the reactor. The inlet of the recirculation into the reactor was under the fluid level in order to prevent foaming (see Fig. 1).

Example 3: Precipitation

High Shear Mixer

The tip speed of the rotor in the high shear mixer was set 25 m/sec. A rotor/stator combination with one teeth row, each for rotor and stator was used.

Dosing of the DMA solution

The DMA solution tempered at 70 °C was dosed with a gear pump via an injector nozzle, which was pointing into the mixing chamber of the high shear mixer, into the circulating aqueous phase.

Dosing rate of the DMA solution

The DMA solution was dosed into the aqueous phase resulting in a ratio of HCl/DMA, in the mixing chamber of the high shear mixer of 100/1.

Example 4: Additional dispersing in the HSM (after precipitation), isolation and washing

After addition of the DMA solution the obtained MBP suspension was dispersed for an additional time, corresponding to equivalents of the batch passing the high shear mixer. The time was corresponding to a turnover in calculated recirculation times of the batch of 6 times.

The obtained suspension, hold at 5 – 10 °C was separated from the solid MBP. This was be done by using a suction filter. The isolated MBP was washed with 0.01 N HCl (15 kg 0.01 N HCl/kg MBP) followed by a washing with water (5 kg water/kg MBP) in order to remove the DMA. The isolated (wet) MBP had a water content between 60 and 70 %.

Example 5: Delumping and Drying

Prior to drying the (wet) MBP was delumped by using a sieve mill. The (wet) MBP was dried in a cabinet dryer. During the drying process of the MBP the temperature of the product was below 40 °C in order to avoid recrystallization of the API. The pressure inside the cabinet dryer was below 20 mbar. The water content of the MBP after drying was below 2.0 % and was signed amorphous in the XRPD pattern.

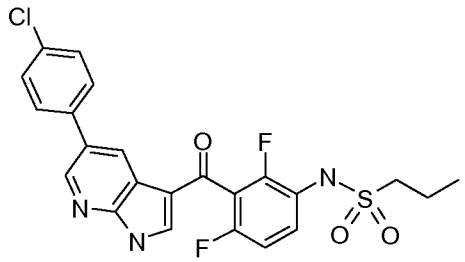
Example 6: Film coated Tablet

Component	Quantity (mg/tablet)
MBP (30% compound (1), 70% HPMCAS)	800.00
Croscarmellose sodium	29.40
Colloidal anhydrous silica	10.40
Hydroxypropylcellulose	4.25
Magnesium stearate	5.95

The above mentioned ingredients were mixed and pressed into tablets by conventional means. The film coat consists of Polyvinyl alcohol (8.00 mg), Titanium dioxide (4.98 mg), Macrogol 3350 (4.04 mg), Talc (2.96 mg) and Iron oxide red (0.02 mg). Any other conventional film coat mixture, like e.g. Opadry II pink 85F14411, may also be used.

Claims

1. A method for manufacturing a solid dispersion containing the amorphous form of the compound of formula 1



(1)

and HPMCAS, comprising the following steps:

(a) dissolution of the compound of formula 1 and HPMCAS in the same organic solvent to give one single organic phase;

(b) continuously adding the organic phase obtained under (a) into an aqueous phase which is present in a mixing chamber, said mixing chamber being equipped with a high shear mixing unit and two additional openings which connect said mixing chamber to a closed loop wherein said aqueous phase is circulated and passes through the mixing chamber;

(c) precipitation of a mixture consisting of the amorphous form of the compound of formula 1 and HPMCAS out of the aqueous phase mentioned under (b), while the high shear mixer is operating and said aqueous phase is passed through the mixing chamber in a closed loop, resulting in the formation of an aqueous suspension of the precipitate;

(d) continuously circulating the aqueous suspension through the mixing chamber while the high shear mixing unit is operating and after the organic solution prepared under (a) has been completely added to the aqueous phase until a defined particle size and/or particle size distribution is obtained;

(e) isolating the solid phase from the suspension;

(f) washing of the isolated solid phase with 0.01 N HCl and/or water; and

(g) delumping and drying of the solid phase.

2. The method according to claim 1, wherein

- the organic phase in (a) is a 10 to 40 % solution of compound 1 and HPMCAS in DMA, the ratio of compound 1 to HPMCAS being from about 10 to 90 %(w/w) to about 60 to 40 % (w/w); and

- the continuous adding in step (b) is achieved via an injector nozzle which is oriented in an angle between 40 and 50° to the longitudinal axis of the high shear mixer and has a distance of about 1 to about 10 mm from the rotor of said high shear mixer which is operating with a tip speed of about 15 to about 25 m/sec.

3. The method according to claim 2, wherein the organic phase in (a) is a 35 % solution of compound 1 and HPMCAS in DMA, the ratio of compound 1 to HPMCAS being 30 % to 70 % (w/w).

4. The method according to any one of claims 1 to 3, wherein the organic phase in (a) comprises DMA, the compound of formula 1 and HPMCAS-L, and step (b) comprises adding said organic phase into aqueous (0.01 N) HCl at a mass flow ratio in the range of about 80/1 to 200/1 (aqueous phase/organic phase) while said aqueous HCl is kept at a temperature of about 2-8 °C.

5. The solid dispersion obtainable by the method according to any one of claims 1 to 4.

6. The solid dispersion according to claim 5, characterized in that it is a microprecipitated bulk powder (MBP) wherein the compound of formula 1 is predominantly present in its amorphous form.

7. A pharmaceutical preparation containing the solid dispersion as obtainable according to the method of claims 1 to 4, optionally together with additional pharmaceutically acceptable adjuvants.

8. The solid dispersion as obtainable according to the method of claims 1 to 4 for the use as medicament.

9. The solid dispersion as obtainable according to the method of claims 1 to 4 for the use as medicament for the treatment of cancer, in particular solid tumors, more particularly malignant melanoma.

10. The novel compositions, methods and uses substantially as described herein.

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