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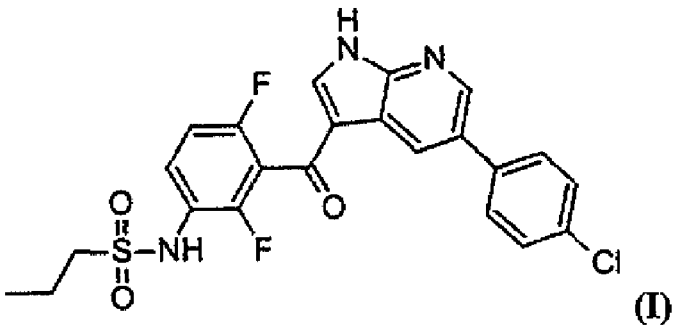

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(57) Abstract: The present invention relates to new solid forms of N-(3-{[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl}-2,4-difluorophenyl)propane-1-sulfonamide, known as vemurafenib (formula I), in the form of a stable amorphous mixture with a polymer, or amorphous salts. The invention further comprises various preparation methods of the amorphous forms of this active pharmaceutical ingredient (API) and their use for a pharmaceutical composition.

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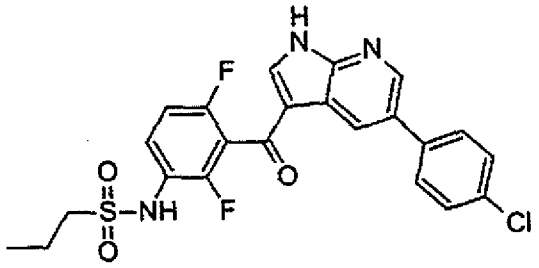
Amorphous forms of vemurafenib

Technical Field

The invention relates to new solid forms of N-(3-{[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl}-2,4-difluorophenyl)propane-1-sulfonamide, known as vemurafenib (formula 1),



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in the form of a stable amorphous mixture with a polymer, or amorphous salts. The invention further comprises various preparation methods of the amorphous forms of this active pharmaceutical ingredient (API) and their use for a pharmaceutical composition.

Background Art

Vemurafenib is used in pharmacy for the treatment of aggressive, resistant and advanced forms of melanomas and skin cancer. Its synthesis was first described in the patent application WO2007/002433. In the later application WO2010/114928, two crystalline forms of vemurafenib (Forms I and II) are described and characterized. A novel method of synthesis of the free base of vemurafenib is described in the patent application WO2012/010538. The applications WO2010/114928 and WO2012/161776 describe salts of vemurafenib with methanesulfonic, toluenesulfonic, maleic, oxalic and dichloroacetic acids and with the inorganic acids sulphuric, hydrobromic and hydrochloric acids. These applications also describe amorphous forms of vemurafenib stabilized by ionizable polymers. The application WO2010/129570 describes amorphous forms of vemurafenib with amino acids (L-lysine and L-arginine). The application WO2013/087546 describes preparation methods and pharmaceutical compositions of amorphous forms of vemurafenib with polyvinyl pyrrolidone (non-ionizable polymer).

Disclosure of Invention

The invention provides amorphous forms of vemurafenib stabilized by means of a copolymer polyvinyl caprolactam - polyvinyl acetate - polyethylene glycol (Soluplus™) and a polymer of hydroxypropyl cellulose (HPC), amorphous sodium and potassium salts of vemurafenib, processes for their preparation and their use for a pharmaceutical composition.

The present solution, wherein the amorphous form of vemurafenib is stabilized with the copolymer polyvinyl caprolactam - polyvinyl acetate - polyethylene glycol (Soluplus™) and the hydroxypropyl cellulose (HPC) polymer, is more advantageous, compared to the use of the polymers of WO2010/114928, in that the solubility of the API is not dependent on the pH value of the solution in the physiological range (pH 1.5-7.5). Thus, vemurafenib can be released during its passage through the whole alimentary tract, which contributes to its higher absorption and bioavailability. It has been found out that if the polymer Soluplus is used, for the stabilization of the amorphous state of vemurafenib just one weight equivalent of the polymer is sufficient, which can be advantageously used for the formulation of a tablet with a lower content of the polymeric excipient to prepare a smaller tablet, which provides the patients with a higher comfort of administration.

Other aspects of the invention are the sodium and potassium salts of vemurafenib in an amorphous form, which supports its higher absorption and bioavailability. The amorphous state of these salts does not need to be stabilized with any polymeric or other carrier, which means that their solubility in not further affected. Similarly to the previous case, a lower amount of excipients can be used so that a smaller tablet can be prepared.

Brief Description of Drawings

Figure 1: X-ray powder pattern of vemurafenib with Soluplus (weight ratio 1:1; API: polymer)

Figure 2: X-ray powder pattern of vemurafenib with Soluplus (weight ratio 1:2.2; API: polymer)

Figure 3: X-ray powder pattern of vemurafenib with HPC (weight ratio 1:2.2; API: polymer)

Figure 4: X-ray powder pattern of the sodium salt of vemurafenib

Figure 5: X-ray powder pattern of the potassium salt of vemurafenib

Figure 6: DSC record of vemurafenib with Soluplus (weight ratio 1:1; API: polymer)

Figure 7: DSC record of vemurafenib with Soluplus (weight ratio 1:2:2; API: polymer)

Figure 8: DSC record of vemurafenib with HPC (weight ratio 1:2.2; API: polymer)

Figure 9: DSC record of the sodium salt of vemurafenib

Figure 10: DSC record of the potassium salt of vemurafenib

Figure 11: Dissolution rate of crystalline vemurafenib, the amorphous form of vemurafenib with Soluplus (1:1), amorphous form of vemurafenib with Soluplus (1:2), amorphous sodium salt of vemurafenib, amorphous potassium salt of vemurafenib, in a phosphate buffer pH 6.8

Detailed description of the invention

The invention relates to new solid forms of N-(3-{[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]carbonyl}-2,4-difluorophenyl)propane-1-sulfonamide, known as vemurafenib, in the form of a stable amorphous mixture with a polymer, or to amorphous salts and methods of their preparation.

Bioavailability greatly depends on whether a crystalline or amorphous product is obtained. A crystalline solid is characterized by a long-distance structure arrangement. On the other hand, amorphous solids do not exhibit this arrangement. The molecular arrangement of an amorphous solid may be represented by "frozen liquid" with rheological properties of a solid.

In this invention, the term "solid dispersion" is used, which represents any solid composition consisting of at least two components. In this case, the solid dispersion contains the pharmaceutically active ingredient (vemurafenib), which is dispersed in at least one component, e.g. in a polymer.

The term "molecular dispersion", used in this invention, refers to dispersion of a component (e.g. vemurafenib) with a polymeric matrix. In some cases, the active pharmaceutical ingredient (vemurafenib) may be dispersed in a polymeric matrix in such a way that it is immobilized in this matrix in its amorphous form. In the case of a molecular dispersion the resulting solid only has one glass transition temperature (Tg) and in this invention this is referred to as a molecular dispersion.

If a component (vemurafenib) is dispersed in the polymeric matrix in the form of amorphous clusters, this solid dispersion is referred to as a vitreous suspension. The resulting vitreous suspension has two or more glass transitions that belong to the amorphous active pharmaceutical substance and to the given polymer or polymers.

As mentioned above, compared to crystalline solids, amorphous solids have a different internal structure and a larger surface area, and therefore they exhibit a higher solubility. If the solubility and bioavailability of pharmaceutically active substances needs to be increased, they should be preferably prepared in an amorphous form.

If the temperature of a crystalline material reaches the melting point, its phase changes from the solid phase to the liquid phase. When this melt is cooled again, the crystalline structure is restored. However, if the melt is cooled at a sufficiently high rate, crystallization may be prevented by formation of a subcooled solution. The subcooled solution is cooled to achieve the glass transition (Tg), the molecules are kinetically frozen and the subcooled liquid solidifies into glass. The molecules in a subcooled liquid have a much higher mobility than in the vitreous state, as described by Remington in the publication: *The Science and Practice of Pharmacy, Pharmaceutical Press*, 21st edition.

Since molecules in the vitreous state also exhibit certain mobility, it is advantageous for the glass transition temperature to be at least 20°C, preferably 30°C, and most preferably at least 40°C above the temperature of the actual storage conditions.

The amorphous form of vemurafenib in the basic form can be stabilized with the use of a suitable polymer. The patent applications WO2010/114928 and WO2012/161776 describe examples of amorphous forms of vemurafenib stabilized with ionizable polymers. The ionizable polymers for stabilization of vemurafenib used are hydroxypropyl methylcellulose (HPMC), hypromellose acetate succinate (HPMCAS), hydroxypropyl methylcellulose phthalate (HPMCP), polymethacrylate and their derivatives. The solubility of these polymers is dependent on the pH value of the solution and their use makes it possible to influence releasing of the pharmaceutically active ingredient depending on pH of the alimentary tract.

The patent application WO2013/087546 describes preparation methods and pharmaceutical compositions of the amorphous forms of vemurafenib with polyvinyl pyrrolidone or copovidone as non-ionizable polymers.

If the polymer Soluplus is used according to the invention, just one weight equivalent of this polymer is sufficient for stabilization of the amorphous form of vemurafenib. This represents a lower amount of the polymer required for stabilization of the amorphous form of vemurafenib, than would be necessary according to the above mentioned patent publications.

There are a number of preparation methods of amorphous forms of vemurafenib stabilized by a polymer.

One of the preparation methods of stabilized amorphous forms of vemurafenib is a dissolution process. In a common dissolution process the active substance is dissolved in a solvent or in any mixture of solvents. The solvent may be water or any organic solvent. Methanol, ethanol, ethyl acetate, isopropyl alcohol, acetone, dichloromethane, tetrahydrofuran etc. may be mentioned as examples of suitable organic solvents. In the next step, a substance stabilizing the active pharmaceutical ingredient is added to this solution or suspension. The solvent is quickly removed and amorphous solid matter is produced. The solvent can be removed by means of a rotary vacuum evaporator, fluid granulation, spray drying, electrospinning, solvent freeze-drying etc.

Other options of preparation of polymer stabilized amorphous substances are methods without the use of a solvent. In these processes the active pharmaceutical ingredient (vemurafenib) is mixed with a stabilizing agent (a polymer). This mixture is heated up and melted, producing a melt. Common temperatures for the formation of a melt vary in the range of 20°C – 40°C above the Tg temperature, wherein the mixture is melted and has a suitable viscosity for its processing. The melt is subsequently cooled down, which produces an amorphous solid. Hot melt extrusion, hot melt granulation, high shear mixer, solvent-free fluid bed granulation etc. may be mentioned as some examples of such processes.

This invention is focused on the preparation of amorphous forms of vemurafenib that can be used for pharmaceutical formulation. The following polymers can be used for the preparation of polymer stabilized amorphous solid forms of vemurafenib: the copolymer polyvinyl caprolactam - polyvinyl acetate - polyethylene glycol (Soluplus™) and the hydroxypropyl cellulose (HPC) polymer.

The most frequently used polymers according to this invention are polyvinyl pyrrolidone (the copolymer polyvinyl caprolactam - polyvinyl acetate - polyethylene glycol (Soluplus™)) with the molecular weight of approximately 120,000 Da (g/mol) and the hydroxypropyl cellulose (HPC) polymer with the molecular weight of approximately 80,000 Da (g/mol).

A number of methods can be used for the preparation of the amorphous sodium and potassium salts of vemurafenib. The preparation is carried out by a reaction of vemurafenib with a respective base. The reaction is conducted in a suitable solvent, which can be ketones, esters, ethers, amides, nitriles or organic acids, alcohols, aliphatic and aromatic hydrocarbons, chlorinated hydrocarbons, water or their mixtures. Aliphatic C1-C4 alcohols, esters or their mixtures are preferred. The most commonly used solvents are acetone, ethanol, isopropanol, acetonitrile, tetrahydrofuran or their mixtures.

The final product can be obtained by precipitation, typically at temperatures in the range of –30°C to the boiling point of the solvent.

Other preparation options comprise evaporation of the solvent, wherein an amorphous solid is produced. The solvent can be removed by means of a rotary vacuum evaporator, fluid granulation, spray drying, electrospinning, solvent freeze-drying etc.

For the preparation of the amorphous solid forms of vemurafenib, the method of removing the solvent by means of a rotary vacuum evaporator has been used. The products prepared this way are summarized in Table 1, along with the results of the DSC and X-ray powder analyses.

Table 1: X-ray powder analysis and DSC analysis of the prepared samples

Sample	**X-ray powder analysis**	**DSC Tg (°C)**
vemurafenib sodium salt	amorphous sample	221
vemurafenib potassium salt	amorphous sample	190
vemurafenib Soluplus (1:1)	amorphous sample	77
vemurafenib Soluplus (1:2.2)	amorphous sample	125
vemurafenib HPC (1:2.2)	amorphous sample	43

In the case of stabilization of the amorphous form of vemurafenib with the use of polymers the results of the X-ray powder analysis have shown that vemurafenib produces amorphous solid forms (see Table 1) with the polymer Soluplus in the weight ratio (vemurafenib/Soluplus) of 1:1 and 1:2.2. In the case of the HPC polymer, the amorphous product was prepared in the weight ratio (vemurafenib/HPC) of 1:2.2.

The differential scanning calorimetry (DSC) measurement makes it possible to distinguish a solid dispersion and a molecular dispersion, wherein the amorphous solid only exhibits one glass transition value in the record. The prepared amorphous solid substances in the weight ratio formed stable molecular dispersions whose stability increases with the increasing Tg value (Hancock and Zografi, 1997).

Comparison of the Tg values from the DSC measurement showed that vemurafenib formed the most stable molecular dispersion in the weight ratio of 1:2.2 (vemurafenib/polymer) (Tg = 125°C). For the preparation of amorphous salts, the highest glass transition temperature measured was that of the prepared sodium salt of vemurafenib (Tg = 221°C).

The glass transition temperature of the potassium amorphous salt of vemurafenib was 190°C (see Table 1) and, similarly to the case of the amorphous forms of vemurafenib with the amino acids L-lysine and L-arginine (WO2010/129570), no crystalline transition of the free base of vemurafenib at 271°C was observed in the DSC record, which further supports the fact that these salts are amorphous.

The prepared samples of polymer stabilized vemurafenib were tested for stability at an elevated temperature and variable relative humidity (RH). The results of the X-ray powder diffraction show that the tested samples containing Soluplus in various weight ratios are stable under all the conditions tested (see Table 2). When HPC was used, partial recrystallization of the API was detected at the elevated relative humidity value.

Table 2: Stability of the prepared amorphous solid form of polymer stabilized vemurafenib

Sample	**Result after loading of the sample at 50°C/0% RH**	**Result after loading of the sample at 50°C/75% RH**
vemurafenib Soluplus (1:1)	stable during at least 3 days' exposure	stable during at least 3 days' exposure
vemurafenib Soluplus (1:2.2)	stable during at least 3 days' exposure	stable during at least 3 days' exposure
vemurafenib HPC (1:2.2)	a trace of recrystallization after 3 days' exposure	a trace of recrystallization after 3 days' exposure

The prepared amorphous forms of vemurafenib were further tested in terms of solubility.

The dissolution was done in 150 ml of a phosphate buffer pH 6.8 with addition of 0.2 % (w/v) of sodium lauryl sulphate as a wetting agent, at a constant stirring rate of 125 rpm. Samples were extracted at defined time intervals and the concentration of dissolved vemurafenib was measured with a Jena Analytik UV/Vis spectrophotometer at the wavelength of 335 nm.

Fig. 11 compares the release rate for the free acid crystalline form, the amorphous sodium and potassium salts and molecular dispersions of vemurafenib in a mixed polymer (Soluplus) in the ratios of 1:1 and 1:2. It has been demonstrated that the release rate and the kinetic solubility of the prepared molecular dispersions and salts is significantly higher (i.e. 2 to 5 times higher) than those of the crystalline free base. This result indicates that the amorphous form of vemurafenib stabilized by Soluplus, or the amorphous sodium or potassium salts will exhibit higher bioavailability as compared to the crystalline free base.

The prepared amorphous solid forms of vemurafenib according to this invention can be used for the preparation of pharmaceutical compositions, especially solid dosage forms, e.g. tablets. Such pharmaceutical compositions can contain at least one excipient from the group of fillers (e.g. lactose), binders (e.g. microcrystalline cellulose), disintegrants (e.g. sodium salt of croscarmellose), lubricants (e.g. magnesium stearate), surfactants etc. The tablets can be coated with common coating agents, e.g. polyvinyl alcohol or polyethylene glycol.

The invention is clarified in a more detailed way using the working examples below. The examples, which illustrate the preparation of the novel amorphous solid forms of vemurafenib in accordance with the invention, only have an illustrative character and do not restrict the scope of the invention in any respect.

Experimental part

X-ray powder analysis

The diffraction patterns were obtained using an X'PERT PRO MPD PANalytical powder diffractometer, used radiation CuKα (λ=1.542 Å), excitation voltage: 45 kV, anode current: 40 mA, measured range: 2 - 40° 2θ, increment: 0.01° 2θ at the dwell time at a reflection of 0.5 s; the measurement was carried out with a flat sample with the area/thickness of 10/0.5 mm. For the correction of the primary array 0.02 rad Soller slits, a 10mm mask and a 1/4° fixed anti-dispersion slit were used. The irradiated area of the sample is 10 mm, programmable divergence slits were

used. For the correction of the secondary array 0.02 rad Soller slits and a 5.0 anti-dispersion slit were used.

Differential Scanning Calorimetry (DSC)

The DSC records were measured using a Discovery DSC device made by TA Instruments. The sample charge in a standard Al pot (40 µL) was 4-5 mg and the heating rate was 5°C/min. The temperature program that was used consists of 5 min of stabilization at the temperature of -10°C and then of heating up to 225°C at the heating rate of 5°C/min (Amplitude = 0.8°C and Period = 60 s). As the carrier gas 5.0 N_2 was used at the flow rate of 50 ml/min.

Determining the dissolution rate using the method of dissolution from powder

The dissolution rate was measured using a Sotax dissolution device. The dissolution was done in 150 ml of a phosphate buffer with pH 6.8 with addition of 0.2 % (w/v) of sodium lauryl sulphate as a wetting agent, at a constant stirring rate of 125 rpm. Samples were extracted at defined time intervals and the concentration of dissolved vemurafenib was measured with a Jena Analytik UV/Vis spectrophotometer at the wavelength of 335 nm.

Examples

The starting substance for the preparation of the amorphous forms of vemurafenib was the crystalline free base of vemurafenib.

Example 1

Preparation of the amorphous solid form of vemurafenib free base stabilized by the polymer Soluplus in the weight ratio of 1:1

In a round bottomed flask with the volume of 100 ml, 100 mg of the crystalline free base of vemurafenib was dissolved in 44 ml of acetone at 40°C and 100 mg of Soluplus was added to this solution and the solution was left under stirring until complete dissolution of all the components. The solvent was evaporated with the use of a rotary vacuum evaporator at the pressure of 1 kPa. The resulting product was left to dry in a vacuum drier at the temperature of 40°C and the

pressure of 20 kPa for 12 hours. X-ray powder pattern in Fig. 1. The glass transition temperature of the molecular dispersion according to DSC was 77°C.

Example 2

Preparation of the amorphous solid form of vemurafenib free base stabilized by the polymer Soluplus in the weight ratio of 1:2.2

In a round bottomed flask with the volume of 100 ml, 100 mg of the crystalline free base of vemurafenib was dissolved in 44 ml of acetone at 40°C and 220 mg of Soluplus was added to this solution and the solution was left to be stirred until complete dissolution of all the components. The solvent was evaporated with the use of a rotary vacuum evaporator at the pressure of 1 kPa. The resulting product was left to dry in a vacuum drier at the temperature of 40°C and the pressure of 20 kPa for 12 hours. X-ray powder pattern in Fig. 2. The glass transition temperature of the molecular dispersion according to DSC was 125°C.

Example 3

Preparation of the amorphous solid form of vemurafenib free base stabilized by the polymer HPC in the weight ratio of 1:2.2

In a round bottomed flask with the volume of 100 ml, 100 mg of the crystalline free base of vemurafenib was dissolved in 44 ml of acetone at 40°C and 4 ml of a solution of HPC that was obtained by dissolution of 220 mg of HPC in ethanol at 40°C was added. The solvent was evaporated with the use of a rotary vacuum evaporator at the pressure of 1 kPa. The resulting product was left to dry in a vacuum drier at the temperature of 40°C and the pressure of 20 kPa for 12 hours. X-ray powder pattern in Fig. 3. The glass transition temperature of the molecular dispersion according to DSC was 43°C.

Example 4

Preparation of the amorphous sodium salt of vemurafenib (1:1)

In a round bottomed flask with the volume of 25 ml, 46.3 mg of the crystalline free base of vemurafenib ($9.45 \cdot 10^{-5}$ mol) was dissolved in 10 ml of acetone at 40°C. After the dissolution, the solution was left to cool down to the room temperature. 28.4 µl of a solution of NaOH ($9.46 \cdot 10^{-5}$ mol) that was produced by dissolution of 133.3 mg of NaOH in 1 ml of water was added to this

solution. The resulting solution was left to be stirred in a magnetic stirrer for 5 minutes and then the solvent was evaporated on a vacuum evaporator at the temperature of 30°C and pressure of 2 kPa. The resulting product was left to dry in a vacuum drier at the temperature of 40°C and the pressure of 20 kPa for 12 hours. X-ray powder pattern in Fig. 4. The glass transition temperature of the amorphous sodium salt of vemurafenib (1:1) according to DSC was 221°C.

Example 5

Preparation of the amorphous potassium salt of vemurafenib (1:1)

In a round bottomed flask with the volume of 25 ml, 53.5 mg of the crystalline free base of vemurafenib ($1.09 \cdot 10^{-4}$ mol) was dissolved in 12 ml of acetone at 40°C. After the dissolution, the solution was left to cool down to the room temperature. 59.7 µl of a solution of KOH ($1.09 \cdot 10^{-4}$ mol) that was produced by dissolution of 102.7 mg of KOH in 1 ml of water was added to this solution. The resulting solution was left to be stirred in a magnetic stirrer for 5 minutes and then the solvent was evaporated on a vacuum evaporator at the temperature of 30°C and pressure of 2 kPa. The resulting product was left to dry in a vacuum drier at the temperature of 40°C and the pressure of 20 kPa for 12 hours. X-ray powder pattern in Fig. 5. The glass transition temperature of the amorphous sodium salt of vemurafenib (1:1) according to DSC was 190°C.

Claims

1. An amorphous mixture of vemurafenib with a non-ionizable polymer, characterized in that the copolymer is polyvinyl caprolactam - polyvinyl acetate - polyethylene glycol - Soluplus™ or the hydroxypropyl cellulose polymer - HPC.

2. The amorphous mixture of vemurafenib with a polymer according to claim 1, characterized in that it exhibits a glass transition temperature Tg > 40°C.

3. The amorphous mixture of vemurafenib with a polymer according to claims 1 to 2, which exhibits a characteristic amorphous halo with the use of the CuKα X-ray radiation.

4. The amorphous mixture of vemurafenib with a polymer according to claims 1 to 3, characterized in that the amount of the active pharmaceutical ingredient - API relative to the polymer is in a weight ratio in the range of 1:1 to 1:3.

5. The amorphous mixture of vemurafenib with a polymer according to claim 4, characterized in that the amount of the API relative to the polymer is in the weight ratio of 1:1.

6. The amorphous mixture of vemurafenib with a polymer according to claim 4, characterized in that the amount of the API relative to the polymer is in the weight ratio of 1:2.2.

7. A process of preparing the amorphous mixture of vemurafenib with a polymer according to claims 1 to 6, characterized in that it comprises dissolution of vemurafenib in the base form with the copolymer polyvinyl caprolactam - polyvinyl acetate - polyethylene glycol - Soluplus™ or the hydroxypropyl cellulose polymer in a suitable organic solvent selected from the group consisiting of water, methanol, ethanol, isopropyl alcohol, ethyl acetate, acetone, dichloromethane, tetrahydrofuran or their mixtures, and subsequent removal of the solvent to produce an amorphous mixture.

8. The process of preparing the amorphous mixture of vemurafenib with a polymer according to claim 7, characterized in that the solvent is a mixture of acetone, dichloromethane, and ethanol.

9. The process of preparing the amorphous mixture of vemurafenib with a polymer according to claim 7, characterized in that the solvent is a mixture of acetone and water.

10. The process of preparing the amorphous mixture of vemurafenib with a polymer according to claims 1 to 6, characterized in that vemurafenib in the base form is mixed with the copolymer polyvinyl caprolactam - polyvinyl acetate - polyethylene glycol - Soluplus™ or the hydroxypropyl cellulose polymer and subsequently the mixture is heated up to produce a melt and to provide an amorphous mixture.

11. The amorphous sodium or potassium salt of vemurafenib.

12. The amorphous salt of vemurafenib according to claim 11, characterized in that it exhibits a glass transition temperature $Tg > 40°C$.

13. The amorphous salt of vemurafenib according to claims 11 to 12, which exhibits a characteristic amorphous halo with the use of the CuKα X-ray radiation.

14. The amorphous sodium or potassium salt of vemurafenib according to claims 11 to 13, characterized in that it is prepared in the molar ratio of 1:1.

15. A process of preparing the sodium or potassium salts of vemurafenib according to claims 11 to 14, characterized in that it comprises dissolution of vemurafenib with addition of a sodium or potassium base in a suitable organic solvent selected from the group consisting of water, methanol, ethanol, isopropyl alcohol, ethyl acetate, acetone, dichloromethane, tetrahydrofuran or their mixtures, and subsequent removal of the solvent, producing an amorphous mixture.

16. Use of the amorphous mixture with a polymer or of the amorphous sodium or potassium salts of vemurafenib according to any one of the preceding claims for the preparation of a pharmaceutical composition.

Figure 1:

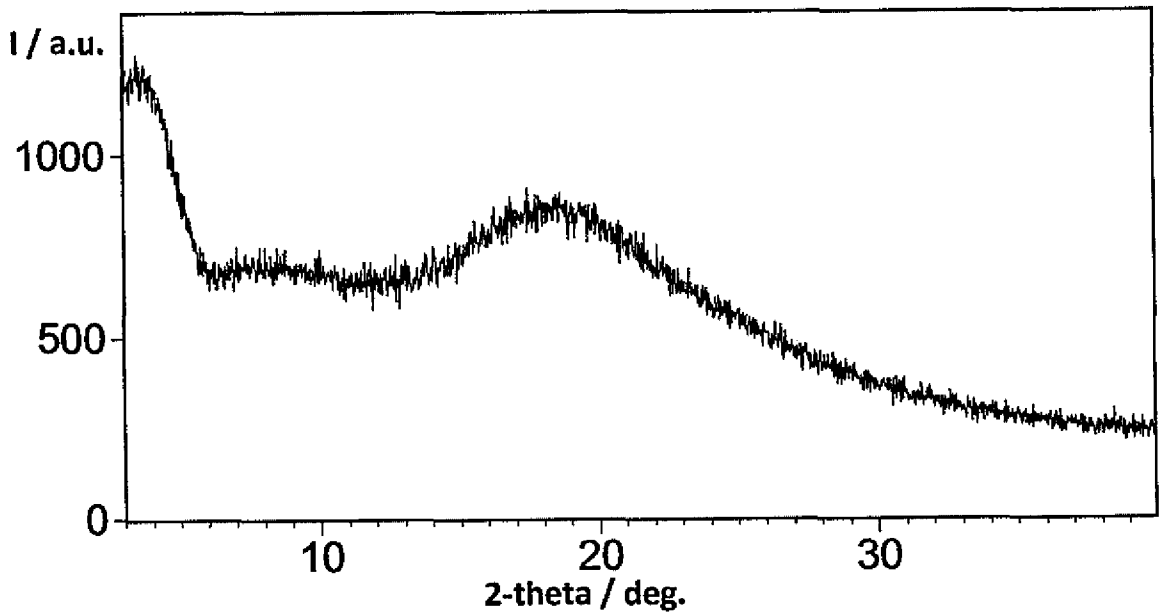


Figure 2:

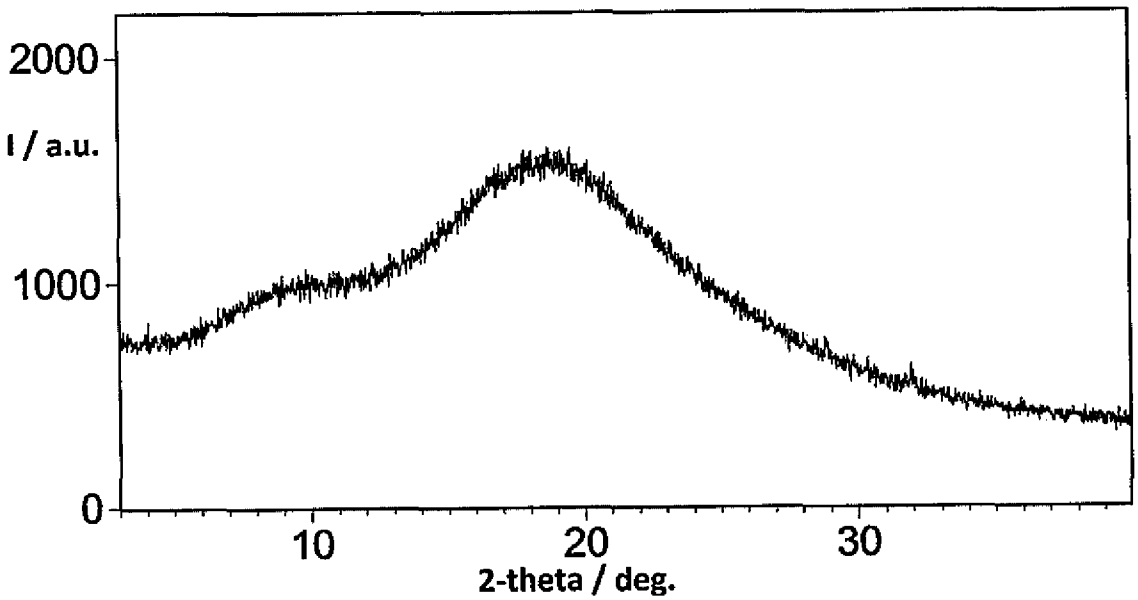


Figure 3:

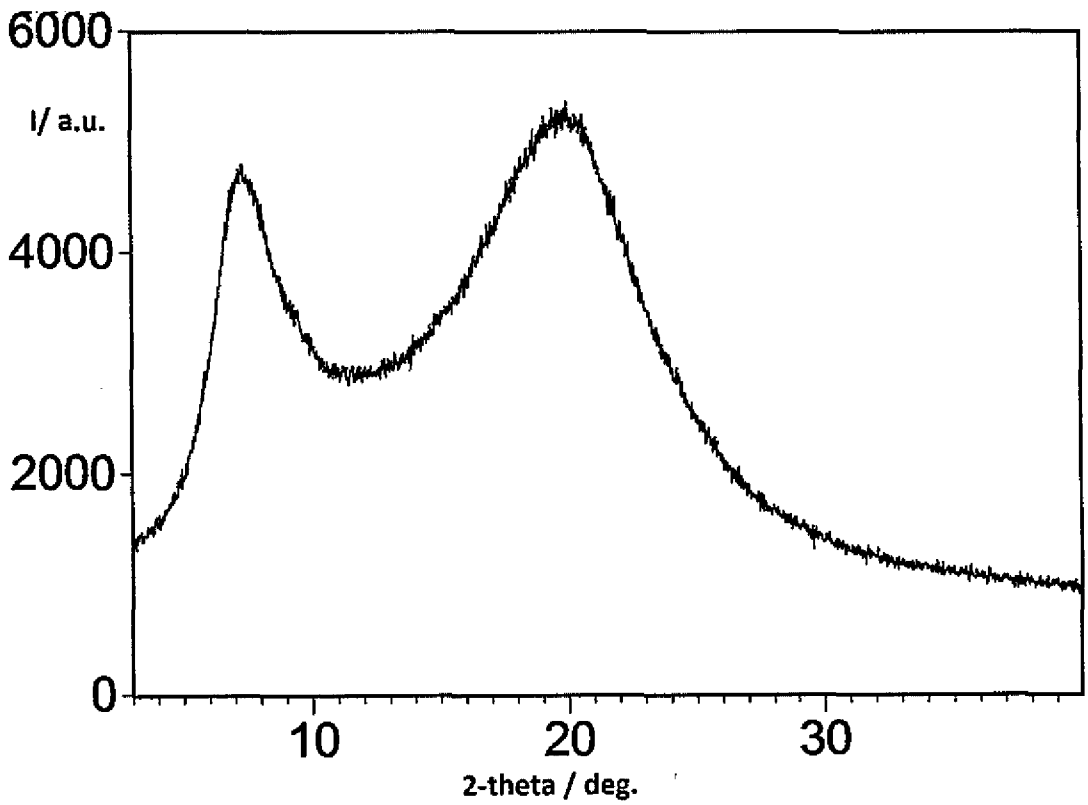


Figure 4: X-ray powder pattern of the sodium salt of vemurafenib

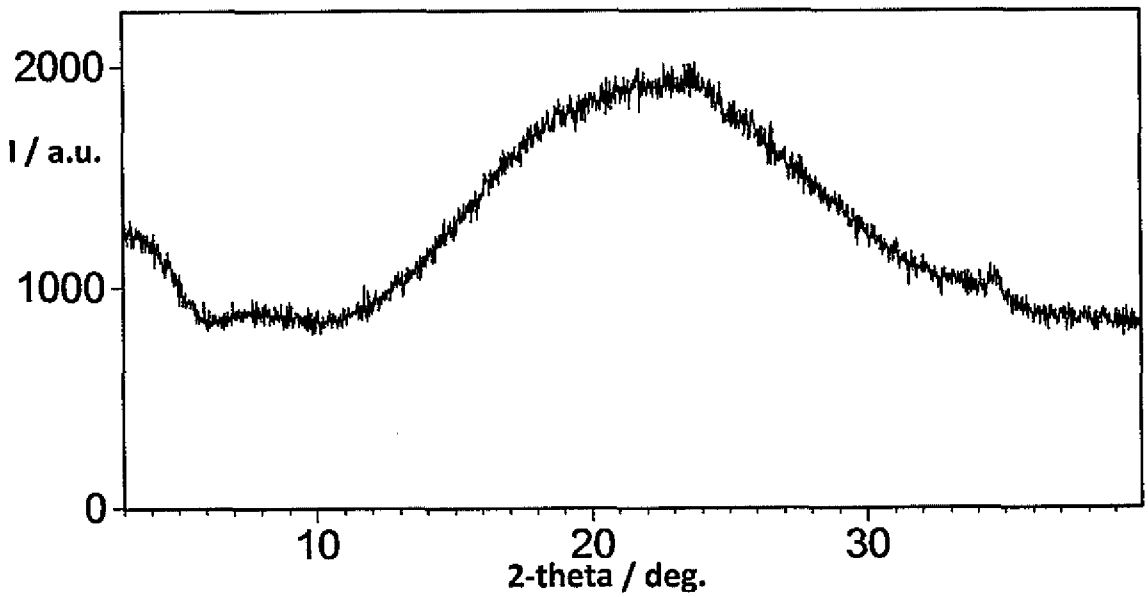


Figure 5:

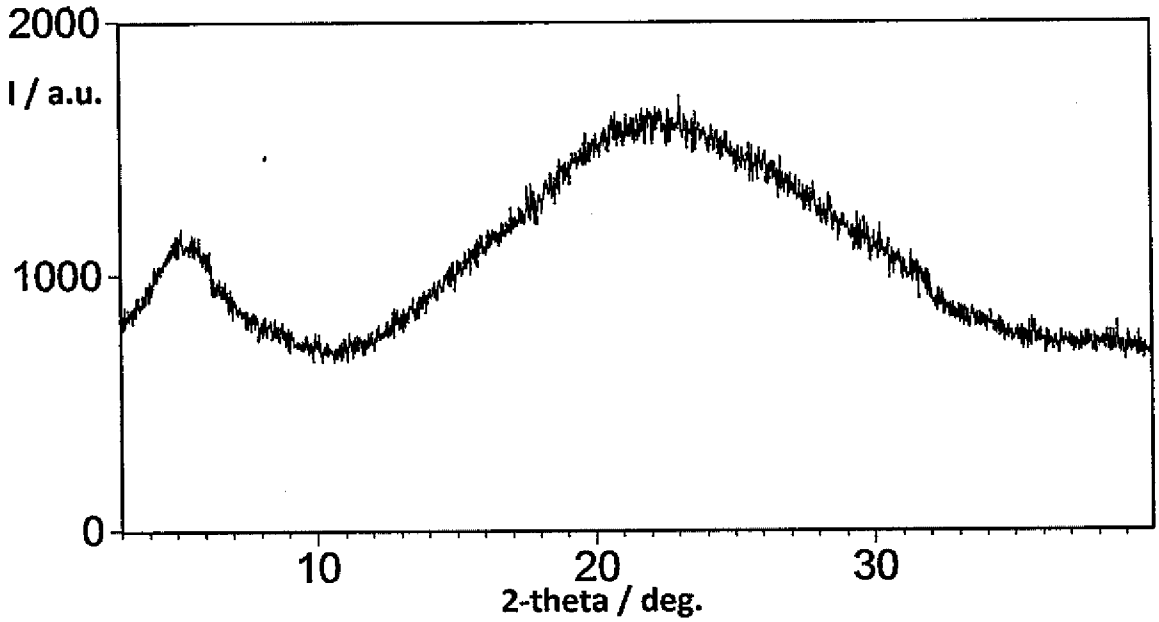


Figure 6:

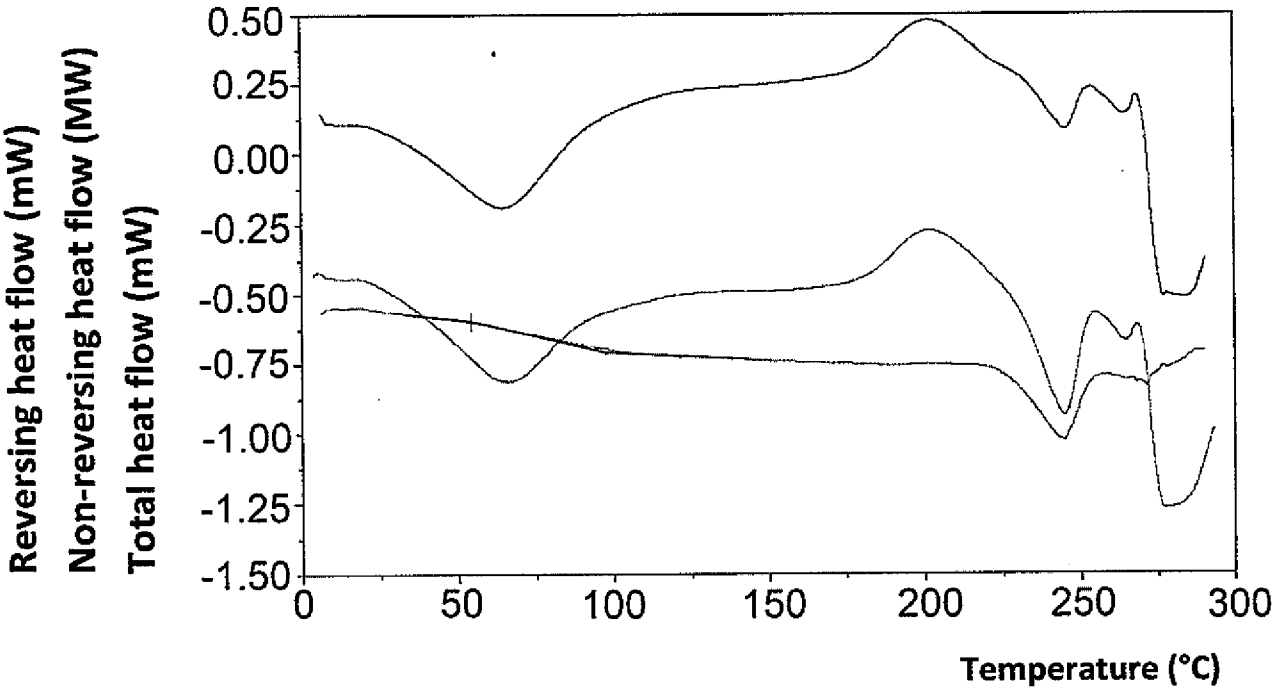


Figure 7:

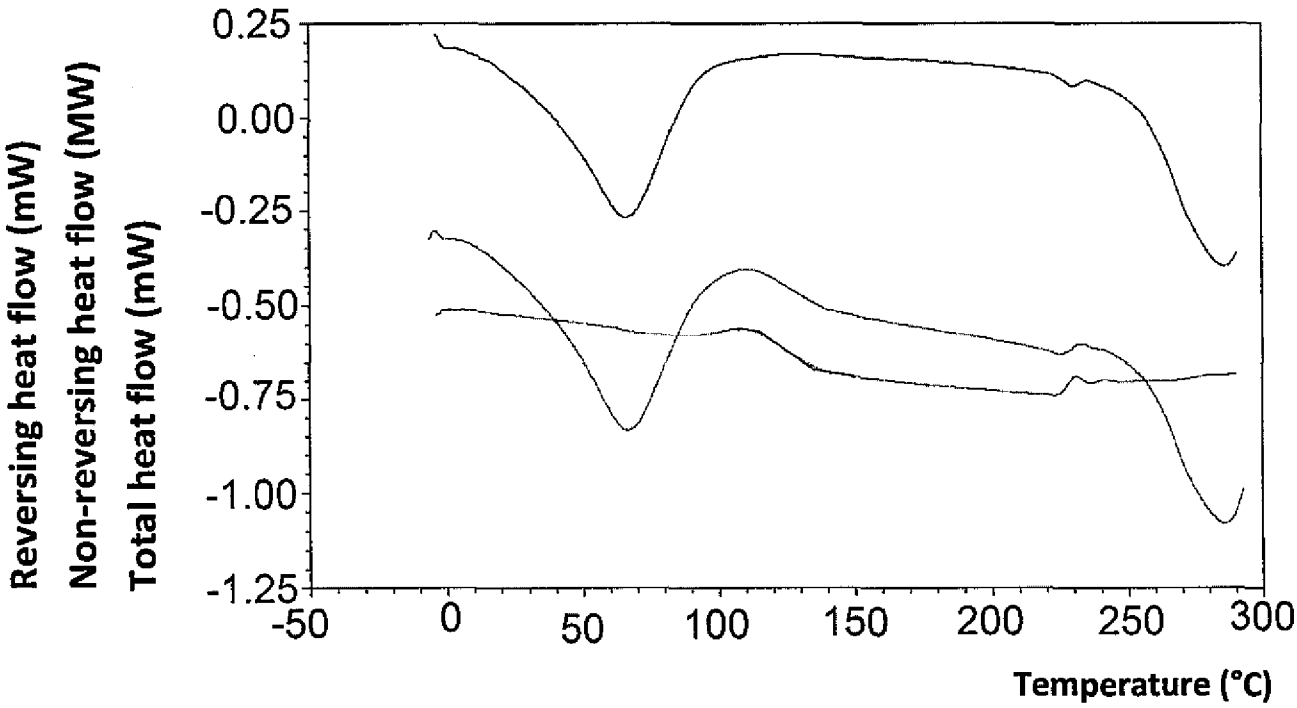


Figure 8:

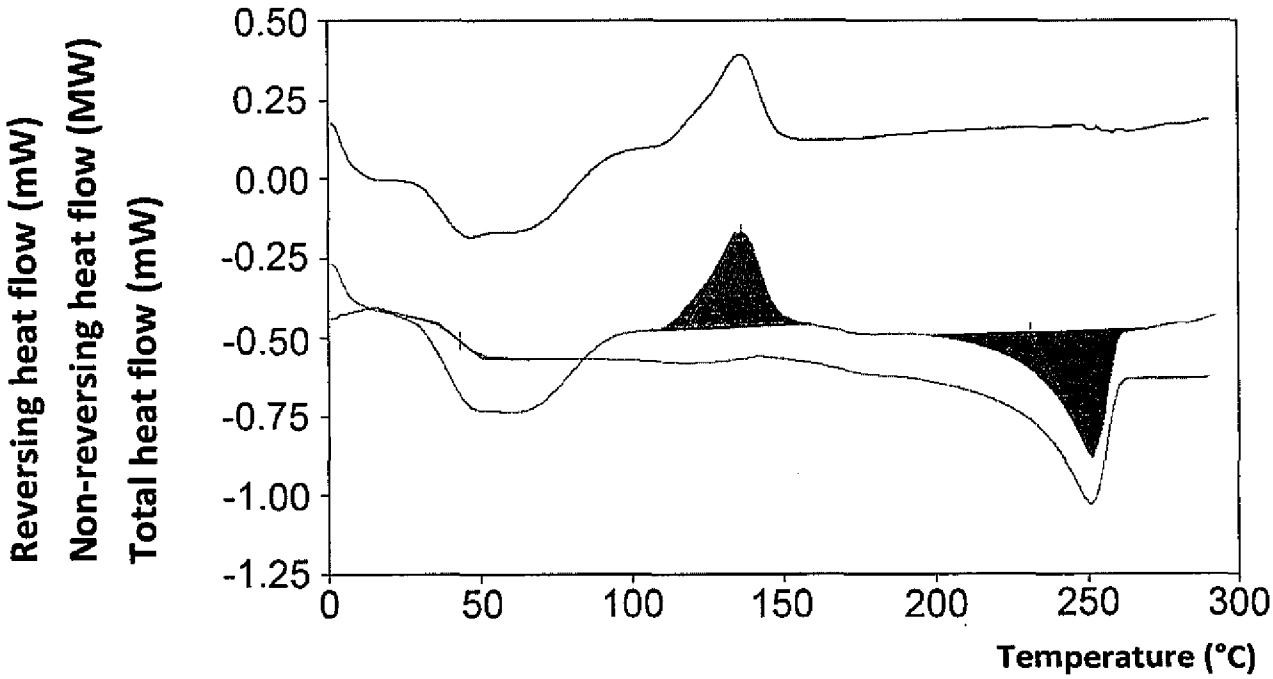


Figure 9:

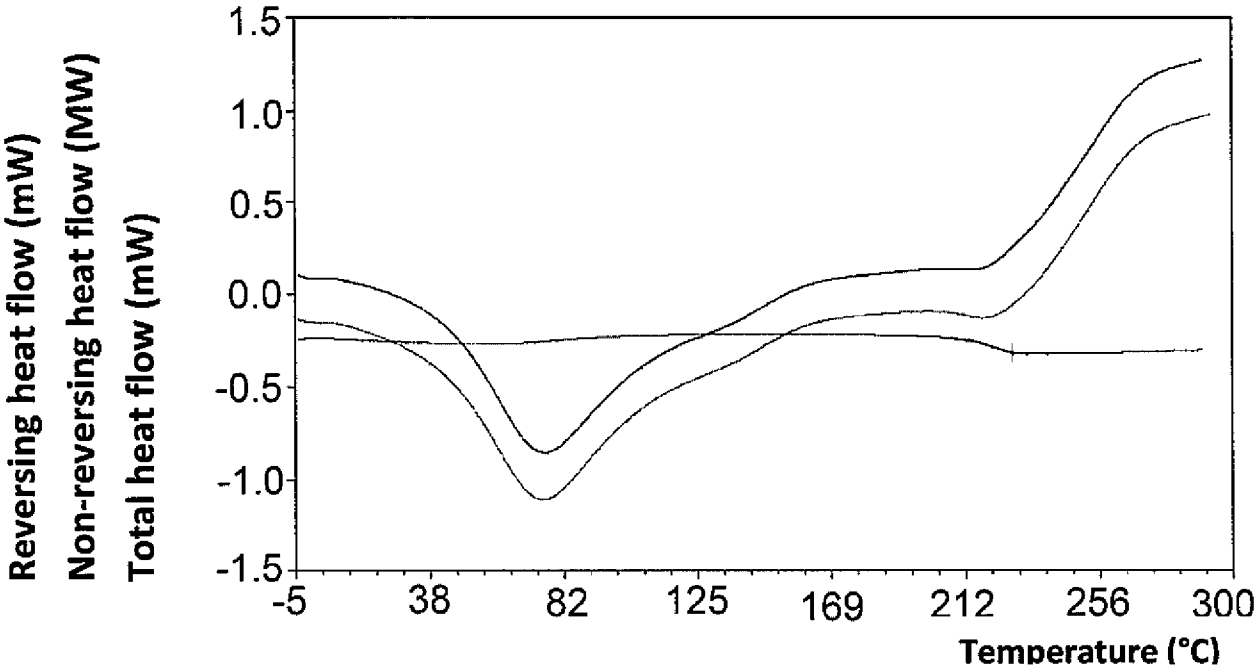


Figure 10:

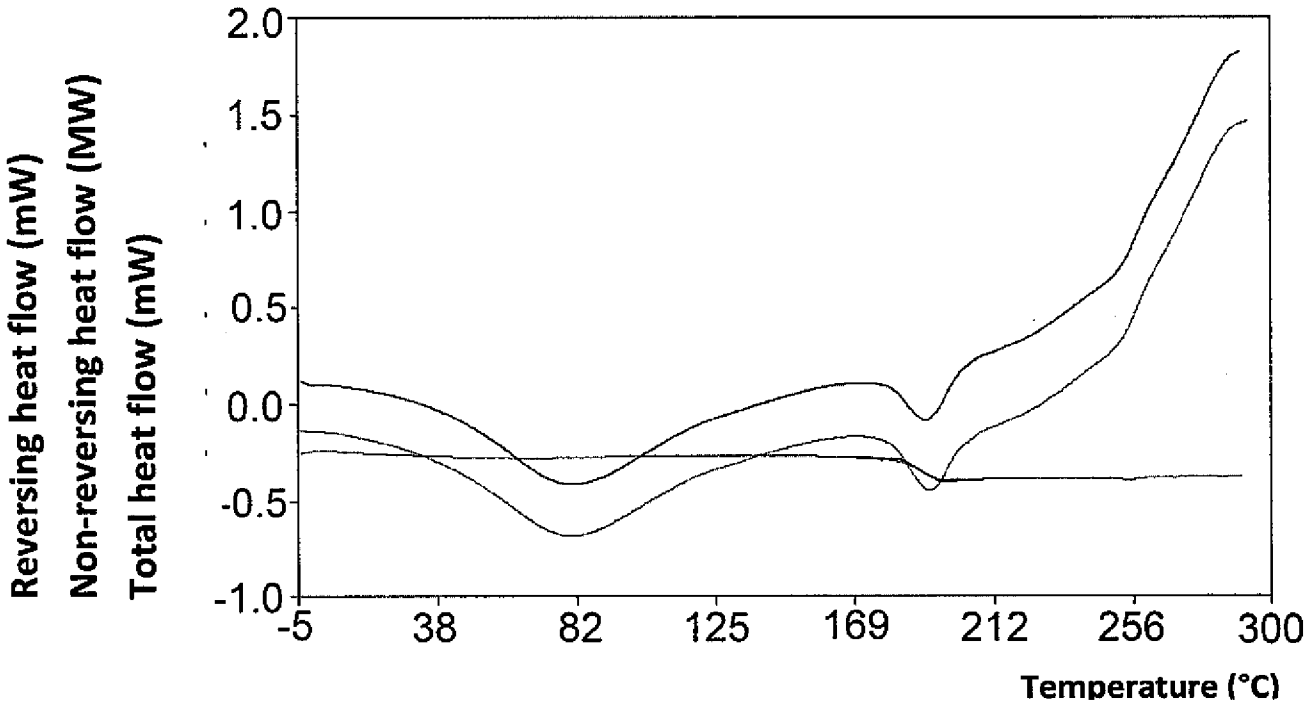
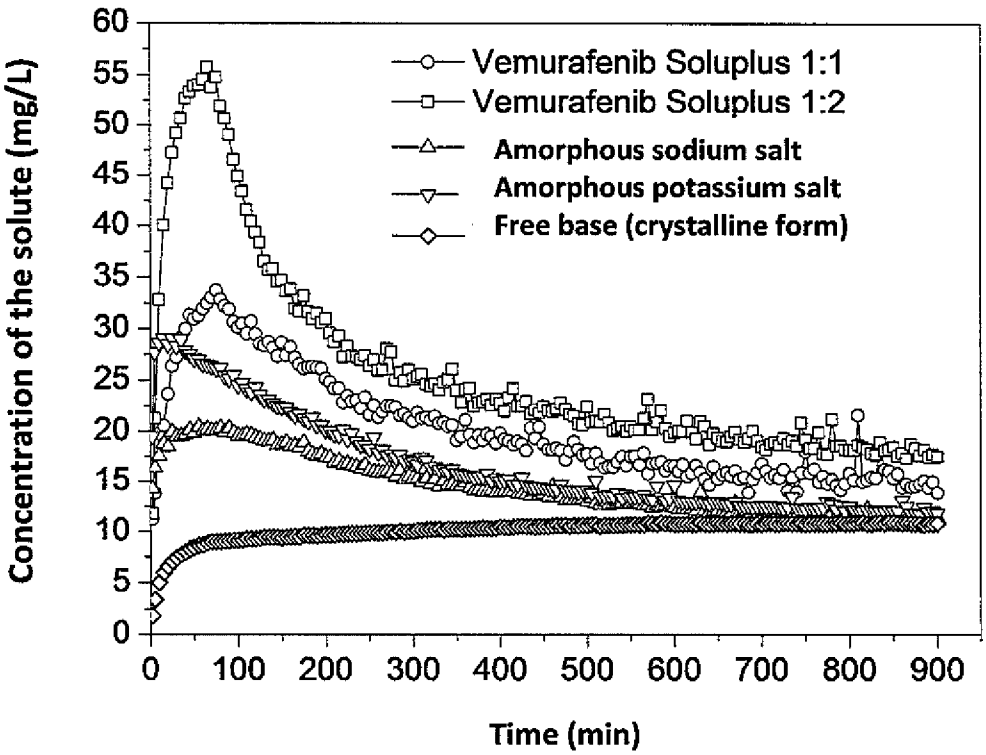


Figure 11:


Concentration of the solute (mg/L)
Time (min)
Vemurafenib Soluplus 1:1
Vemurafenib Soluplus 1:2
Amorphous sodium salt
Amorphous potassium salt
Free base (crystalline form)
0
5
10
15
20
25
30
35
40
45
50
55
60
0
100
200
300
400
500
600
700
800
900

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000039

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K47/30 A61K47/38 A61K9/14 A61K9/20
A61K31/437 A61P35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/105895 A1 (XSPRAY MICROPARTICLES AB) 18 July 2013 (2013-07-18)	1-4,16
Y	claims 1,18,19,21,22,44 page 9, lines 7-20; figure 11; example 12; tables 34,35	5-10

X	WO 2013/105894 A1 (XSPRAY MICROPARTICLES AB) 18 July 2013 (2013-07-18)	1-4,16
Y	claims 1,9,10,26,30,31; example 12; tables 34,35	5-10

Y	WO 2013/087546 A1 (F. HOFFMANN-LA ROCHE AG) 20 June 2013 (2013-06-20) cited in the application claims 1,8; examples 1,4; table 1	1-10,16

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 2016	29/09/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kiernan, Andrea

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BASF: "Soluplus -Technical information", INTERNET CITATION, July 2010 (2010-07), pages 1-8, XP002666808, Retrieved from the Internet: URL:http://www.pharma-ingredients.basf.com /Statements/Technical%20Inf ormations/EN/Pharma%20Solutions/03_090801e _Soluplus.pdf [retrieved on 2012-01-10] the whole document	1-10,16
Y	NAGY, Z.K. ET AL.: "Comparison of Electrospun and Extruded Soluplus -Based Solid Dosage Forms of Improved Dissolution", JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 101, no. 1, 23 August 2011 (2011-08-23), pages 322-332, XP55289962, ISSN: 0022-3549, DOI: 10.1002/jps.22731 abstract pages 322-323; figure 2	1-10,16
Y	LINN, M. ET AL: "Soluplus as an effective absorption enhancer of poorly soluble drugs in vitro and in vivo", EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 45, no. 3, 8 December 2011 (2011-12-08), pages 336-343, XP028440388, ISSN: 0928-0987, DOI: 10.1016/J.EJPS.2011.11.025 [retrieved on 2011-12-08] abstract page 336, paragraph 1. page 340, column 2, paragraph 4.	1-10,16
Y	SHAMMA, R.N. ET AL.: "Soluplus TM : A novel polymeric solubilizer for optimization of Carvedilol solid dispersions: Formulation design and effect of method of preparation", POWDER TECHNOLOGY, vol. 237, 29 December 2012 (2012-12-29), pages 406-414, XP028991212, ISSN: 0032-5910, DOI: 10.1016/J.POWTEC.2012.12.038 abstract pages 406-407, paragraph 1. page 408, column 2, paragraph 3.1. page 413, column 2, paragraph 4.	1-10,16

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INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2016/000039

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2016/073421 A1 (DISPERSOL TECHNOLOGIES, LLC) 12 May 2016 (2016-05-12) abstract; claims 1,6-8,15,25,30-34,39,57,61	1-3,16
X	WO 2014/027056 A1 (F. HOFFMANN-LA ROCHE AG; GENENTECH, INC.) 20 February 2014 (2014-02-20)	1-3,16
Y	page 29, paragraph [00154] pages 37-38, paragraph [00184] page 60, paragraph [00252]	1-10,16
X	WO 2010/114928 A2 (F. HOFFMANN-LA ROCHE AG; PLEXXIKON, INC.) 7 October 2010 (2010-10-07) cited in the application	1-3,16
Y	abstract; claims 1, 10, 18	1-10,16
Y	YAMADA, T. ET AL.: "Effects of grinding with hydroxypropyl cellulose on the dissolution and paricle size of a poorly water-soluble drug", CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 47, no. 9, 1999, pages 1311-1313, XP008109649, ISSN: 0009-2363 the whole document	1-10,16

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CZ2016/000039

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

1-10, 16

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-10, 16(all partially)

   An amorphous mixture of vemurafenib with polyvinyl caprolactam - polyvinyl acetate - polyethylene glycol graft copolymer (Soluplus), processes for preparing said amorphous mixture, and its use for the preparation of a pharmaceutical composition.

   ---

2. claims: 1-10, 16(all partially)

   An amorphous mixture of vemurafenib with hydroxypropyl cellulose (HPC), processes for preparing said amorphous mixture, and its use for the preparation of a pharmaceutical composition.

   ---

3. claims: 11-15(completely); 16(partially)

   An amorphous sodium or potassium salt of vemurafenib, a process for preparing said salt, and its use for the preparation of a pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2016/000039

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2016/000039

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