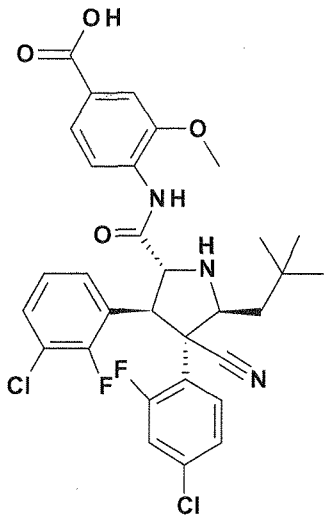
4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid ($C_{31}H_{29}Cl_2F_2N_3O_4$) (Compound A) is a potent and selective inhibitor of the p53-MDM2 interaction that activates the p53 pathway and induces cell cycle arrest and/or apoptosis in a variety of tumor types expressing wild-type p53 in vitro and in vivo. Compound A belongs to a novel class of MDM2 inhibitors having potent anti-cancer therapeutic activity, in particular in leukemia such as AML and solid tumors such as for example non-small cell lung, breast and colorectal cancers.

The above-identified international patent application and US Patent describe Compound A in crystalline form and is herein incorporated by reference in its totality. The crystalline form of the compound has an on-set melting point of approximately 277 °C. The crystalline forms have relatively low aqueous solubility (<0.05 μg/mL in water) at physiological pHs (which range from pH1.5-8.0) and consequently less than optimal bioavailability (high variability). It is thus desirable to obtain a form of the compound which has improved solubility/dissolution rate and bioavailability.

Summary

The present disclosure provides an amorphous form of Compound A which is substantially free of crystalline compound. The compound is present in a compound/polymer complex in an amount equal to or greater than 30% of the complex, by weight.

One aspect of the disclosure is a physically stable solid dispersion comprising a compound having an aqueous solubility of less than 1 μg/ml and a melting point of > 270°C together with a stabilizing polymer, wherein the compound is 4-{[(2R, 3S, 4R, 5S)-4-(4-Chloro-2-Fluoro-Phenyl)-3-(3-Chloro-2-Fluoro-Phenyl)-4-Cyano-5-(2,2-Dimethyl-Propyl)-Pyrrolidine-2-Carbonyl]-Amino}-3- Methoxy -Benzoic Acid, of the formula (A)

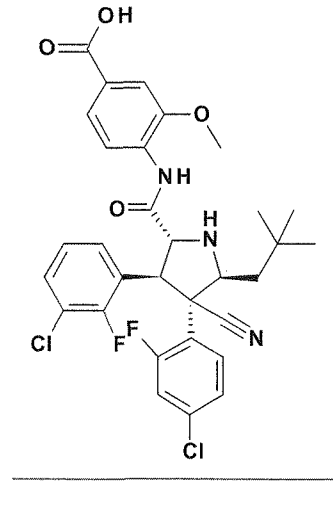


(A), and

wherein the stabilizing polymer is hypromellose acetate succinate (HPMCAS) or Copovidone (PVP VA 64).

Another aspect of the disclosure is a unit dose solid formulation comprising the solid dispersion as defined herein, together with ~~commonly used~~ pharmaceutical ingredients selected from the group consisting of disintegrants, diluents, lubricants, glidants together with a film coat.

Another aspect of the disclosure is a method for preparing a solid dispersion of a compound having an aqueous solubility of less than 1 μg/ml and an ionic polymer which comprises forming a solution of the compound and the polymer in dimethyl-acetamide, or any other suitable solvent and co-precipitating the drug with the polymer using anti-solvent, wherein the compound is 4-{[(2R, 3S, 4R, 5S)-4-(4-Chloro-2-Fluoro-Phenyl)-3-(3-Chloro-2-Fluoro-Phenyl)-4-Cyano-5-(2,2-Dimethyl-Propyl)-Pyrrolidine-2-Carbonyl]-Amino}-3- Methoxy -Benzoic Acid, of the formula (A)



(A), and

wherein the stabilizing polymer is hypromellose acetate succinate (HPMCAS) or Copovidone (PVP VA 64).

Another aspect of the disclosure is a pharmaceutical preparation containing the solid dispersion as defined herein, together with additional pharmaceutically acceptable adjuvants.

Another aspect of the disclosure is the solid dispersion as defined herein for use as a medicament for the treatment of cancer, in particular AML or prostate cancer.

An embodiment of the disclosure is a pharmaceutical composition comprising the complexes of the disclosure wherein Compound A is present in a therapeutically effective amount.

Another embodiment of the disclosure is that the complex of the amorphous drug substance with the polymer is stable at high drug load.

Another embodiment of the disclosure is a process for making the complexes of the disclosure that contains pharmaceutically active compounds in stabilized amorphous form.

The key features of the disclosure are:

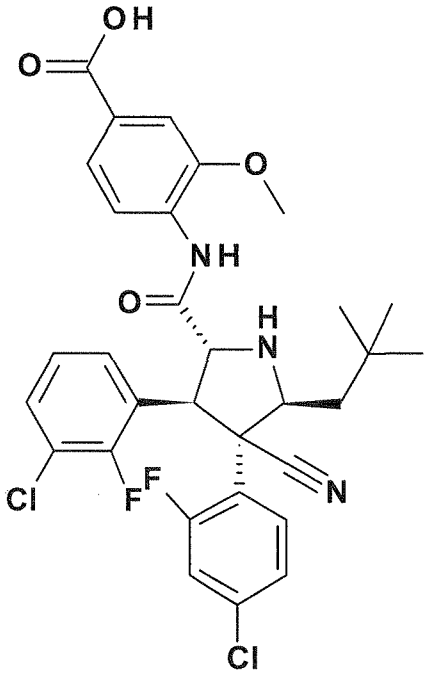
a) Preparation of stabilized solid amorphous dispersion of Compound A,

b) Drug loading of 10-70% in the final product.

Claims

1. A physically stable solid dispersion comprising a compound having an aqueous solubility of less than 1 µg/ml and a melting point of > 270°C together with a stabilizing polymer, wherein the compound is ~~:~~

~~2. The solid dispersion of claim 1 wherein the compound having an aqueous solubility of less than 1 µg/ml is~~ 4-{[(2R, 3S, 4R, 5S)-4-(4-Chloro-2-Fluoro-Phenyl)-3-(3-Chloro-2-Fluoro-Phenyl)-4-Cyano-5-(2,2-Dimethyl-Propyl)-Pyrrolidine-2-Carbonyl]-Amino}-3- Methoxy - Benzoic Acid, of the formula (A)



(A)~~:~~, and

~~3. The solid dispersion of claim 1 or 2,~~ wherein the stabilizing polymer is hypromellose acetate succinate (HPMCAS) or ~~:~~

~~4. The solid dispersion of claim 1or 2, wherein the stabilizing polymer is EUDRAGIT® L-100 or Eudragit L100-55.~~

~~5. The solid dispersion of claim 1 or 2, wherein the stabilizing polymer is~~ Copovidone (PVP VA 64).

~~6~~2. The solid dispersion according to ~~any one of~~ claim ~~2 to 5~~1 wherein the ratio of the amount by weight of the Compound A ~~according to claim 2~~ within the solid dispersion to the amount by weight of the stabilizing polymer therein is between 5:95 to 70:30.

~~7~~3. The solid dispersion of claim ~~5~~ 1 wherein the ratio of the amount by weight of the Compound A within the solid dispersion to the amount by weight of the stabilizing polymer therein is ~~preferably~~ 30:70 to 50:50.

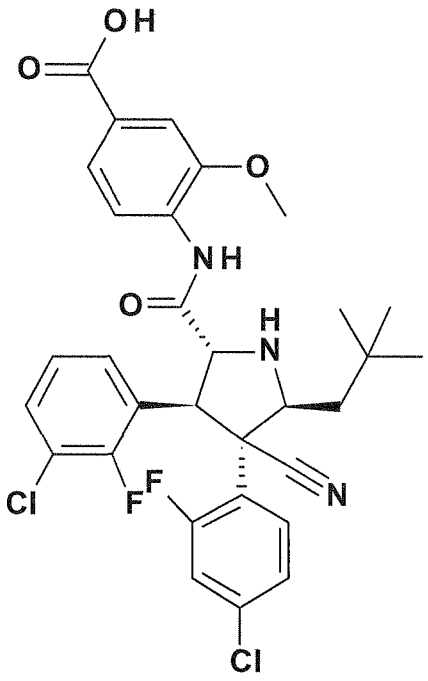
~~8~~4. The solid dispersion of claim ~~7~~3, wherein the solid dispersion is obtained by spray drying of a solution comprising the Compound A and the Copovidone (PVP VA 64).

~~9~~5. The solid dispersion of claim ~~7~~3, wherein the solid dispersion is obtained by microprecipitation of a solution comprising the Compound A and the hypromellose acetate succinate (HPMCAS).

~~10~~6. A unit dose solid formulation comprising the solid dispersion according to any one of claims ~~6~~ 1 to ~~9~~5, together with ~~commonly used~~ pharmaceutical ingredients selected from the group consisting of disintegrants, diluents, lubricants, glidants together with a film coat.

~~11~~7. The unit dose solid formulation according to claim ~~10~~6, comprising approximately 80% of the solid dispersion according to any one of claims ~~6~~ 1 to ~~9~~ 4 as an amorphous solid dispersion, together with about 7% croscarmellose sodium, about 6.8% mannitol, about 4% crospovidone, about 1.5% colloidal silicon dioxide and about 0.7% of magnesium stearate which is then encapsulated or compressed and coated as tablet.

~~12~~8. A method for preparing a solid dispersion of a compound having an aqueous solubility of less than 1 µg/ml and an ionic polymer which comprises forming a solution of the compound and the polymer in dimethyl-acetamide, or any other suitable solvent and co-precipitating the drug with the polymer using anti-solvent, wherein the compound is 4-{[(2R, 3S, 4R, 5S)-4-(4-Chloro-2-Fluoro-Phenyl)-3-(3-Chloro-2-Fluoro-Phenyl)-4-Cyano-5-(2,2-Dimethyl-Propyl)-Pyrrolidine-2-Carbonyl]-Amino}-3- Methoxy -Benzoic Acid, of the formula (A)



(A), and

wherein the stabilizing polymer is hypromellose acetate succinate (HPMCAS) or Copovidone (PVP VA 64).

~~13~~9. A pharmaceutical preparation containing the solid dispersion according to any one of claim 1 to ~~9~~5, together with additional pharmaceutically acceptable adjuvants.

~~14~~10. The solid dispersion according to any one of claim 1 to ~~8~~ 5 for use as a medicament for the treatment of cancer, in particular AML or prostate cancer.

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