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 ~~of the Invention~~

The present ~~invention~~ 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.

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.

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.

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

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

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

The key features of the disclosure ~~inventions~~ are:

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

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