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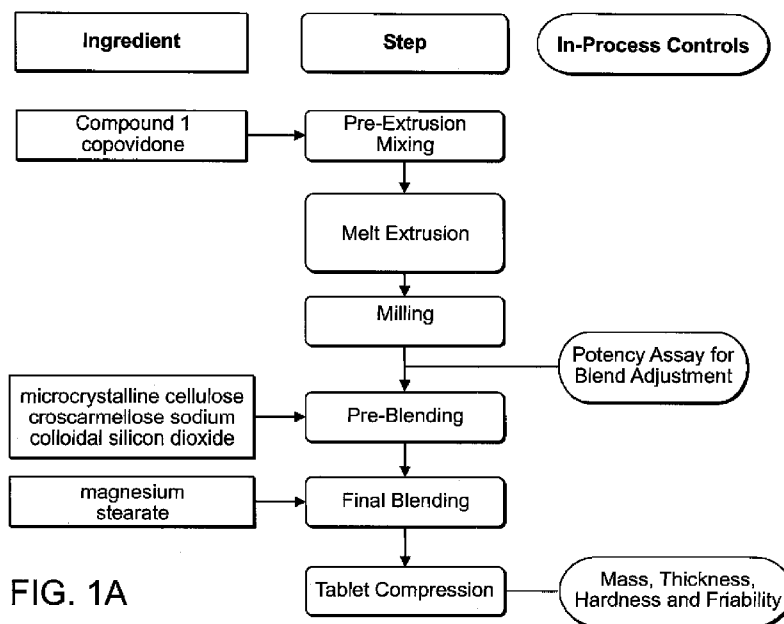


FIG. 1A

(57) Abstract: The invention relates to a pharmaceutical composition comprising Compound 1 or a pharmaceutically acceptable salt thereof for the treatment of cancer and a process for its preparation. The invention also relates to administering the pharmaceutical composition to a patient according to an intermittent dosing regimen.

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PHARMACEUTICAL FORMULATIONS OF A PAN-RAF KINASE INHIBITOR, PROCESSES FOR THEIR PREPARATION, AND METHODS OF USE

RELATED APPLICATIONS

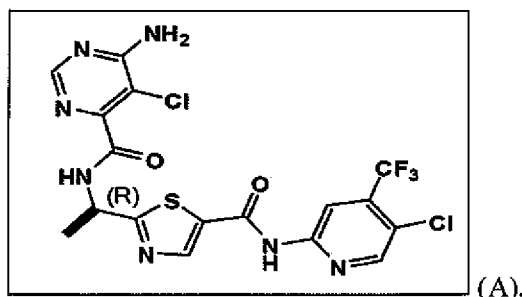
[0001] The present application claims priority from U.S. provisional patent application no. 61/970,595, filed on March 26, 2014, and U.S. provisional patent application no. 62/048,527, filed on September 10, 2014, both which are hereby incorporated by reference.

SEQUENCE LISTING

[0002] This application contains a Sequence Listing which is submitted herewith in electronically readable format. The electronic Sequence Listing file was created on March 19, 2015, is named "sequencelisting.txt" and has a size of 21 kb. The entire contents of the Sequence Listing in the electronic sequencelisting.txt file are incorporated herein by this reference.

[0003] The present invention relates to pharmaceutical compositions comprising the pan-Raf kinase inhibitor (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof and processes for their preparation. The present invention also relates to methods of treating cancer, comprising administering such compositions to a patient according to an intermittent dosing regimen, and to the use of such compositions in the manufacture of medicaments.

[0004] Compound 1 has the chemical structure (A):



[0005] Compound 1 is a potent, small molecule class II pan-Raf kinase inhibitor being developed for the treatment of solid tumors, including locally advanced, metastatic, and/or unresectable melanoma and BRAF and NRAS mutation-positive cancers. The RAF kinases (A-RAF, BRAF, and C-RAF) are key components of the mitogen-activated protein kinase (MAPK) pathway that controls cell proliferation and survival signaling. (Downward J. *Nature Reviews, Cancer* 2003;3(1):11-22; Wellbrock C, et al. *Nature Reviews Molecular Cell Biology* 2004;5(11):875-85). The MAP kinase (MAPK) pathway is a central signal transduction pathway that is dysregulated in a large number of developmental disorders. The MAPK pathway, which is composed of RAS, RAF, MAPK or extracellular signal-regulated kinase kinase (MEK), and extracellular signal-regulated kinase (ERK), integrates signals from receptors on the cell surface including cancer-related receptor tyrosine kinases such as the epidermal growth factor receptor, mesenchymal-epithelial transition factor (MET), and vascular endothelial growth factor receptor (Avruch J., *Biochim Biophys Acta* 2007;1773(8):1150-60). Genetic alterations in the MAPK pathway are among the most common in human cancers. Up to 60% of melanomas harbor BRAF mutations (Davies H., et al. *Nature* 2002;417(6892):949-54) and KRAS mutations have been estimated in roughly 60%, 30%, and 15% of pancreatic, colon, and lung tumors, respectively (Vakiani E, et al. *J Pathol* 2011;223(2):219-29). BRAF mutations are also found in 40% of papillary or anaplastic thyroid cancers (Kimura ET, et al. *Cancer Res* 2003;63(7):1454-7) and in a small percentage of several other types of tumor (Vakiani E, et al.). A majority of reported BRAF mutations are a substitution of glutamic acid for valine at the amino acid position of 600 (the V600E mutation). The BRAF V600E mutation constitutively activates BRAF and downstream signal transduction in the MAPK pathway (Davies H., et al.).

[0006] Compound 1 is an inhibitor of wild-type and mutant Raf kinases and is currently in Phase I clinical trials in patients with relapsed or refractory solid tumors followed by a dose expansion in patients with BRAF and NRAS mutation-positive cancers. Compound 1, its preparation and its use in the treatment of Raf-mediated diseases is disclosed in WO 2009/006389, filed June 30, 2008. Additionally, WO 2013/144923 discloses methods for the treatment of non-BRAFV600E mutant melanoma in patients comprising administering a Raf inhibitor and a MEK inhibitor. The above-mentioned patent applications are herein incorporated by reference.

[0007] The advancement of Compound 1 has been somewhat hampered by its physical characteristics, specifically its bioavailability. For example, Compound 1 has low aqueous solubility and a moderate log p. Both can adversely affect its oral bioavailability. Any improvement in the physical characteristics of Compound 1, would potentially offer a more

beneficial therapy. Accordingly, it is an object of the present invention to provide a pharmaceutical composition comprising Compound 1 that is stable and which allows for rapid dissolution and enhanced oral bioavailability. Furthermore, it is believed that the efficacy of Compound 1 correlates with drug exposure. Accordingly, it is desirable to be able to administer Compound 1 at the highest possible dose i.e., the highest possible dose at which the side-effect profile is acceptable. A dosing regimen that achieves a higher exposure thereby would provide a meaningful benefit in the treatment of patients with Compound 1. For examples, the dosing regimen of the present invention provides effective treatment of cancer, NRAS and BRAF positive-mutated cancer.

SUMMARY OF THE INVENTION

[0008] The present invention provides pharmaceutical compositions as described herein with superior properties, including rapid dissolution and increased oral bioavailability. The present invention also provides processes for the preparation of said pharmaceutical compositions. Furthermore, the present invention provides an intermittent dosing regimen for the improved treatment of cancer. Accordingly, the present invention relates to the following:

- 1) A pharmaceutical composition comprising (1) a solid dispersion extrudate comprising Compound 1 and (2) one or more pharmaceutically acceptable excipients.
- 2) A process for preparing a pharmaceutical composition, which comprises the steps of:
 - (i) extruding a mixture of Compound 1 or a pharmaceutically acceptable salt thereof and vinylpyrrolidinone-vinyl acetate copolymer to form a solid dispersion extrudate;
 - (ii) blending the resulting solid dispersion extrudate with one or more pharmaceutically acceptable excipients.
- 3) A method for the treatment of NRAS or BRAF positive-mutated cancer in a patient in need of such treatment, comprising administering an effective amount of a pharmaceutical composition comprising Compound 1 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients, to the patient according to an intermittent dosing regimen, wherein the dosing regimen comprises administering the composition once or twice a week and the total amount of the composition administered each week is from about 400 mg to about 1000 mg.

DETAILED DESCRIPTION OF THE INVENTION

[0009] Figure 1A is a flow diagram illustrating a representative process for the preparation of pharmaceutical compositions of the invention corresponding to tablets produced according to Example 1, 2, or 3.

[0010] Figure 1B is a flow diagram illustrating a representative process for the preparation of pharmaceutical compositions of the invention corresponding to tablets produced according to Examples 1, 4, 5, and 6.

[0011] Figure 2 is an X-ray powder diffraction (XRPD) of Compound 1 tablets, capsules and constituent raw materials used in the manufacture of animal trial and stability samples.

[0012] Figure 3 is a dissolution profile for compositions of the invention used in preclinical bioavailability studies (Example 6). Diamond = tablet; Square = capsule.

[0013] Figure 4 is a graph which shows the mean plasma profiles over time for formulations of Compound 1 prepared by hot melt extrusion (HME) and spray drying (SDD) in tablet (Tab) and capsule (Cap) form (Example 6).

[0014] Figure 5 is a graph which shows the potency difference as a function of the premixing process (bag blend vs. high shear mixing) (Example 7).

[0015] Figure 6 is an XRPD spectrum of a solid dispersion extrudate of Compound 1 and copovidone produced according to Example 1, procedure 2.

[0016] Figures 7A is an HPLC trace of a solid dispersion extrudate of Compound 1 and copovidone produced according to Example 1, procedure 2.

[0017] Figure 7B is an HPLC trace of Compound 1 solid dispersion extrudate produced according to Example 1, procedure 2.

[0018] Figure 8 is a representative XRPD pattern of crystalline Compound 1.

[0019] The present invention provides a process for the preparation of a pharmaceutical composition with improved absorption. Compound 1 exhibits a low solubility (< 1 mg/ml) and a moderate log p (3.63), thus the bioavailability of Compound 1 is limited by its solubility. We have found that the dissolution property of Compound 1 can be improved by making amorphous solid dispersions prepared by hot melt extrusion. According to the process of the present invention, it is possible to provide, from Compound 1, a formulation wherein the dissolution rate and oral bioavailability of the drug are high. Furthermore, the solid dispersion extrudate of the present invention has superior stability at room temperature.

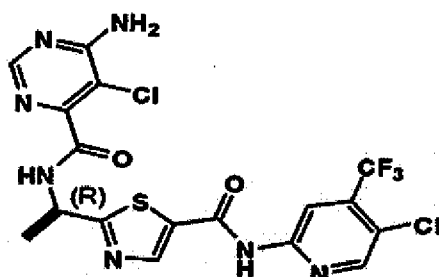
[0020] The pharmaceutical composition of the present invention has superior effects as a medicament in NRAS and/or BRAF positive-mutated cancers. The pharmaceutical composition of the present invention can be administered orally and safely to a patient.

[0021] The present invention provides a method for the treatment of cancer in a patient, wherein the cancer has an NRAS or BRAF positive-mutation, by intermittent administration of a pharmaceutical composition as described here, wherein the intermittent dosing regimen is a weekly administration and the amount administered each week is from about 400 mg to about 1000 mg. The intermittent dosing regimen provides a higher unit dose, which allows for the achievement of higher concentrations of Compound 1 and a higher degree of pathway inhibition for a window of time within the dosing interval, without compromising overall dose density.

[0022] It is believed, without being bound by theory, that the strong clinical benefits afforded by the pharmaceutical compositions disclosed herein result from improved bioavailability and higher exposures of Compound 1.

Definitions:

[0023] As used herein, the term "Compound 1" means the compound (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide. Additional chemical names for Compound 1 are 6-amino-5-chloro-N-[(1R)-1-[5-[[[5-chloro-4-(trifluoromethyl)-2-pyridinyl]amino]carbonyl]-2-thiazolyl]ethyl]-4-pyrimidinecarboxamide and 6-amino-5-chloro-N-[(1R)-1-(5-{[5-chloro-4-(trifluoromethyl)pyridin-2-yl]carbamoyl}-1,3-thiazol-2-yl)ethyl]pyrimidine-4-carboxamide. The chemical structure of Compound 1 is:



[0024] As used herein, "effective amount" means an amount of a therapeutic substance (e.g., a composition of the invention) that is (1) sufficient upon appropriate administration to a patient (a) to cause a detectable decrease in the severity of the disorder or disease state being treated; (b) to ameliorate or alleviate the patient's symptoms of the disease or disorder; or (c) to slow or

prevent advancement of, or otherwise stabilize or prolong stabilization of, the disorder or disease state being treated (e.g., prevent additional tumor growth of a cancer); and (2) equal to or less than the maximum tolerated dose (MTD). In any form or composition, the clinically effective amount can be expressed as amount of therapeutic substance per patient BSA, e.g., as mg/m².

[0025] As used herein, "patient" means a human being diagnosed with, exhibiting symptoms of or otherwise believed to be afflicted with a disease, disorder or condition.

[0026] As used herein, the illustrative terms "include", "such as", "for example" and the like (and variations thereof, e.g., "includes" and "including", "examples"), unless otherwise specified, are intended to be non-limiting. That is, unless explicitly stated otherwise, such terms are intended to imply "but not limited to", e.g., "including" means including but not limited to.

[0027] The terms "about" and "approximately" as used herein, are interchangeable, and should generally be understood to refer to a range of numbers around a given number, as well as to all numbers in a recited range of numbers (e.g., "about 5 to 15" means "about 5 to about 15" unless otherwise stated). Moreover, all numerical ranges herein should be understood to include each whole integer within the range.

[0028] "Crosopovidone" is a cross-linked homopolymer of vinyl pyrrolidone (VP). One brand of crosopovidone is Polyplasdone® XL-10.

[0029] The term "vinylpyrrolidone-vinyl acetate copolymer" means a polymer comprising vinylpyrrolidone and vinyl acetate. Names and abbreviations for vinylpyrrolidone-vinyl acetate copolymer include, but are not limited to, copovidone, copovidonum, copolyvidone, copovidon, PVP-VAc-Copolymer. Copovidone is a vinylpyrrolidinone-vinyl acetate copolymer comprised of 6 parts of vinylpyrrolidone and 4 parts of vinyl acetate e.g., CAS 25086-89-9. Examples of copovidone commercial products are Kollidon® VA 64 and Kollidon® 64 Fine. Another example is "Plasdone S-630," a 60:40 random copolymer of N-vinyl pyrrolidinone and vinyl acetate.

[0030] "Eudragit®" is an anionic copolymer based on methacrylic acid and methyl methacrylate.

[0031] "HPMCAS" refers to hypromellose acetate succinate, a polymer containing acetyl and succinoyl groups. There are different types of HPMCAS, which dissolve at different pHs.

[0032] "Poloxamer" is a nonionic triblock copolymer composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene.

[0033] "w/w" means by weight. For example, 40% w/w means that the mass of the substance is 40% of the total mass of the solution or mixture. For example, 40% extrudate w/w is

3400 g (1360 g Compound 1 + 2040 g copovidone) of a composition having a total mass of 8500 g.

[0034] As used herein, the term “substantially amorphous” refers to a solid material having little or no long range order in the position of its molecules. For example, a substantially amorphous material has less than about 30% crystallinity (e.g., less than about 25% crystallinity, less than about 20% crystallinity, less than about 15% crystallinity, less than about 10% crystallinity, less than about 5% crystallinity, less than about 4% crystallinity). It is also noted that the term ‘substantially amorphous’ includes the descriptor, ‘amorphous’, which refers to a material having no (0%) crystallinity.

[0035] As used herein, the term “crystalline” and related terms used herein, when used to describe a substance, component or product is substantially crystalline as determined by X-ray diffraction and/or FT-Raman microscopy.

[0036] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A “pharmaceutically acceptable salt” means any non-toxic salt of Compound 1 that, upon administration to a recipient, is capable of providing, either directly or indirectly, Compound 1 or an active metabolite or residue thereof.

[0037] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of Compound 1 include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate,

undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of Compound 1. Water or oil-soluble or dispersible products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

Pharmaceutical Compositions

[0038] The present invention relates to pharmaceutical compositions comprising the pan-Raf kinase inhibitor Compound 1 or a pharmaceutically acceptable salt thereof. The present invention includes the following embodiments:

[0039] Embodiment [1]: A pharmaceutical composition comprising (1) a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) one or more pharmaceutically acceptable excipients.

[0040] Embodiment [2]: A pharmaceutical composition comprising (1) from about 10% to about 50% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) from about 50% to about 90% w/w of one or more pharmaceutically acceptable excipients comprising a filler, disintegrant, glidant and lubricant.

[0041] Embodiment [3]: A pharmaceutical compositions comprising (1) from about 10% to about 50% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) from about 50% to about 90% w/w of one or more pharmaceutically acceptable excipients comprising a filler, disintegrant, glidant, lubricant, film-coating agent, colorant, and plasticizer.

[0042] Embodiment [4]: A pharmaceutical composition comprising (1) from about 20% to about 40% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) from about 60% to about 80% w/w of one or more pharmaceutically acceptable excipients comprising a filler, disintegrant, glidant and lubricant.

[0043] Embodiment [5]: A pharmaceutical composition comprising (1) from about 20% to about 40% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically

acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) from about 60% to about 80% w/w of one or more pharmaceutically acceptable excipients comprising a filler, disintegrant, glidant, lubricant, film-coating agent, colorant, and plasticizer.

[0044] Embodiment [6]: A pharmaceutical composition comprising (1) from about 40% to about 50% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) from about 60% to about 50% w/w of one or more pharmaceutically acceptable excipients comprising a filler, disintegrant, glidant and lubricant.

[0045] Embodiment [7]: A pharmaceutical composition comprising (1) from about 40% to about 50% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) from about 60% to about 50% w/w of one or more pharmaceutically acceptable excipients comprising a filler, disintegrant, glidant, lubricant, film-coating agent, colorant, and plasticizer.

[0046] Embodiment [8]: A pharmaceutical composition in the form of a 5 mg tablet or capsule comprising about 10% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) about 90% w/w of one or more pharmaceutically acceptable excipients. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0047] Embodiment [9]: A pharmaceutical composition in the form of a 20 mg tablet or capsule comprising about 20% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) about 80% w/w of one or more pharmaceutically acceptable excipients. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0048] Embodiment [10]: A pharmaceutical composition in the form of a 70 mg tablet or capsule comprising about 32% w/w/ of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) about 68% of one or more pharmaceutically acceptable excipients. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0049] Embodiment [11]: A pharmaceutical composition in the form of a 100 mg tablet or capsule comprising about 40% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) about 60% w/w of one or more pharmaceutically acceptable excipients. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0050] The percentage by weight (w/w) of solid dispersion in the pharmaceutical compositions described herein is important for the disintegration rate of the composition. In one aspect, a pharmaceutical composition prepared at about 40% w/w solid dispersion exhibited rapid dissolution, achieving full release in less than 10 minutes.

[0051] Embodiment [12]: The pharmaceutical composition of any one of embodiments [1] through [11], wherein the solid dispersion extrudate comprises Compound 1.

[0052] Embodiment [13]: The pharmaceutical composition of any one of embodiments [1] through [11], wherein the solid dispersion extrudate comprises the pharmaceutically acceptable salt of Compound 1.

[0053] Embodiment [14]: The pharmaceutical composition of any one of embodiments [1] through [13], wherein the vinylpyrrolidinone-vinyl acetate copolymer is copovidone. In one aspect, the copovidone is Kollidon® VA 64. In one aspect, the copovidone is Kollidon® VA 64 Fine.

[0054] Embodiment [15]: The pharmaceutical composition of any one of embodiments [1] through [14], wherein the solid dispersion extrudate is amorphous.

[0055] The amorphous character of the solid dispersion extrudate can be detected using analytical methods, including but not limited to, microscopic methods (scanning electronic microscopy (SEM), polarized light microscopy (PLM), hot stage microscopy (HSM)), thermal methods (differential scanning calorimetry (DSC) modulated DSC (mDSC), diffraction methods such as X-ray powder diffraction (XRPD), and spectroscopic methods (FT-Infrared (IR), FT-Raman, solid state NMR (ssNMR) and confocal raman microscopy (CRM)). In one aspect, the amorphous character of the solid dispersion extrudate is detected by X-ray powder diffraction (XRPD). In one aspect, the solid dispersion extrudate exhibits no residual crystalline character. Figure 6 is an XRPD spectrum of a solid dispersion extrudate produced according to Example 1, procedure 1. The XRPD spectrum shows the amorphous character of the solid dispersion extract.

[0056] Embodiment [16]: The pharmaceutical composition of any one of embodiments [1] through [15], wherein the glass transition temperature (TG) of the solid dispersion extrudate is from about 45 °C to about 120 °C.

[0057] Embodiment [17]: The pharmaceutical composition of any one of embodiments [1] through [16], wherein the glass transition temperature (TG) of the solid dispersion extrudate is from about 60 °C to about 110 °C.

[0058] Embodiment [18]: The pharmaceutical composition of any one of embodiments [1] through [17], wherein the solid dispersion extrudate comprises < about 3% w/w of the S-

enantiomer of 2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide.

[0059] In one aspect, the total amount of impurities, including the S-enantiomer of 2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide of the solid dispersion extrudate is less than or equal to about 3.0% w/w or more than or equal to about 97.0% w/w of the desired R-enantiomer, Compound 1. In one aspect, the total amount of the S-enantiomer is \leq about 3%, \leq about 2.7%, \leq about 2.5%, \leq about 2.3%, \leq about 2.1%, \leq about 1.9%, \leq about 1.7%, \leq about 1.5%, \leq about 1.3%, \leq about 1.1%, \leq about 0.9%, \leq about 0.8%, \leq about 0.7%, \leq about 0.5%, \leq about 0.3%, \leq about 0.1%. Figures 7A and 7B are HPLC traces of a solid dispersion extrudate produced according to the method described in Example 1, procedure 2. Optimization of the conditions of the extrusion process reduces formation of the S-enantiomer.

[0060] Embodiment [19]: The pharmaceutical composition of any one of embodiments [1] through [18], wherein the amount of Compound 1 is from about 3% to about 17% w/w.

[0061] Embodiment [20]: The pharmaceutical composition of any one of embodiments [1] through [19], wherein the amount of is from about 7% to about 17% w/w.

[0062] Embodiment [21]: The pharmaceutical composition of any one of embodiments [1] through [20], wherein the amount of Compound 1 is from about 8% to about 16% w/w.

[0063] Embodiment [22]: The pharmaceutical composition of any one of embodiments [1] through [8] or [12] through [19], wherein the composition is in the form of a 5 mg tablet or capsule, wherein the amount of Compound 1 is about 4% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0064] Embodiment [23]: The pharmaceutical composition of any one of embodiments [1] through [7], [9], or [12] through [21], wherein the composition is in the form of a 20 mg tablet or capsule, wherein the amount of Compound 1 is about 8% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0065] Embodiment [24]: The pharmaceutical composition of any one of embodiments [1] through [7], [10], or [12] through [21], wherein the composition is in the form of a 70 mg tablet or capsule, wherein the amount of Compound 1 is about 13% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0066] Embodiment [25]: The pharmaceutical composition of any one of embodiments [1] through [7] or [11] through [21], wherein the composition is in the form of a 100 mg tablet or capsule, wherein the amount of Compound 1 is about 16% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0067] Embodiment [26]: The pharmaceutical composition of any one of embodiments [1] through [25], wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer is from about 5% to about 25% w/w. In one aspect, the copolymer is copovidone. In one aspect, the amount of copovidone is from about 5% to about 25% w/w.

[0068] Embodiment [27]: The pharmaceutical composition of any one of embodiments [1] through [26], wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer is from about 12% to about 24% w/w. In one aspect, the copolymer is copovidone. In one aspect, the amount of copovidone is from about 12% to about 24% w/w.

[0069] Embodiment [28]: The pharmaceutical composition of any one of embodiments [1] through [27], wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer is from about 11% to about 24% w/w. In one aspect, the copolymer is copovidone. In one aspect, the amount of copovidone is from about 11% to about 24% w/w.

[0070] Embodiment [29]: The pharmaceutical composition of any one of embodiments [1] through [8], [12] through [19], [22], or [26], wherein the composition is in the form of a 5 mg tablet or capsule, wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer is about 6% w/w. In one aspect, the copolymer is copovidone. In one aspect, the amount of copovidone is about 6% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0071] Embodiment [30]: The pharmaceutical composition of any one of embodiments [1] through [7], [9], [12] through [21], [23], or [26] through [28], wherein the composition is in the form of a 20 mg tablet or capsule, wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer about 12% w/w. In one aspect, the copolymer is copovidone. In one aspect, the amount of copovidone is about 12% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0072] Embodiment [31]: The pharmaceutical composition of any one of embodiments [1] through [7], [10], [12] through [21], [24], or [26] through [28], wherein the composition is in the form of a 70 mg tablet or capsule, wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer about 19% w/w. In one aspect, the copolymer is copovidone. In one aspect, the amount of copovidone is about 19% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0073] Embodiment [32]: The pharmaceutical composition of any one of embodiments [1] through [7], [11] through [21], or [25] through [28], wherein the composition is in the form of a 100 mg tablet or capsule, wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer is about 24% w/w. In one aspect, the copolymer is copovidone. In one aspect, the amount of

copovidone is about 24% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0074] Embodiment [33]: The pharmaceutical composition of any one of embodiments [1] through [32], wherein one or more pharmaceutically acceptable excipients comprises a disintegrant, wherein the disintegrant comprises croscarmellose sodium. Croscarmellose sodium serves as a disintegrant for immediate release. Disintegration is a function of the type of superdisintegrant and solid dispersion loading within the formulation.

[0075] Embodiment [34]: The pharmaceutical composition of any one of embodiments [1] through [33], wherein one or more pharmaceutically acceptable excipients comprises a disintegrant, wherein the disintegrant comprises croscarmellose sodium and wherein the amount of croscarmellose sodium is from about 4% to about 9% w/w.

[0076] Embodiment [35]: The pharmaceutical composition of any one of embodiments [1] through [34], wherein one or more pharmaceutically acceptable excipients comprises a disintegrant, wherein the disintegrant comprises croscarmellose sodium and wherein the amount of croscarmellose sodium is from about 5% to about 8% w/w.

[0077] Embodiment [36]: The pharmaceutical composition of any one of embodiments [1] through [9], [12] through [23], [26] through [30], or [33] through [35], wherein the composition is in the form of a 5 mg or 20 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a disintegrant, wherein the disintegrant comprises croscarmellose sodium and wherein the amount of croscarmellose sodium is about 5% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0078] Embodiment [37]: The pharmaceutical composition of any one of embodiments [1] through [8], [12] through [19], [22], [26] through [29], or [33] through [35], wherein the composition is in the form of a 5 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a disintegrant, wherein the disintegrant comprises croscarmellose sodium and wherein the amount of croscarmellose sodium is about 5% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0079] Embodiment [38]: The pharmaceutical composition of any one of embodiments [1] through [7], [9], [12] through [21], [23], [26] through [28], [30], or [33] through [36], wherein the composition is in the form of a 20 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a disintegrant, wherein the disintegrant comprises croscarmellose sodium and wherein the amount of croscarmellose sodium is about 5% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0080] Embodiment [39]: The pharmaceutical composition of any one of embodiments [1] through [7], [10] through [21], [24] through [28], or [31] through [35], wherein the composition is in the form of a 70 or 100 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a disintegrant, wherein the disintegrant is croscarmellose sodium and wherein the amount of croscarmellose sodium is about 8% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0081] Embodiment [40]: The pharmaceutical composition of any one of embodiments [1] through [7], [11] through [21], [25] through [28], [32] through [35], or [39], wherein the composition is in the form of a 100 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a disintegrant, wherein the disintegrant is croscarmellose sodium and wherein the amount of croscarmellose sodium is about 8% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0082] Embodiment [41]: The pharmaceutical composition of any one of embodiments [1] through [7], [10], [12] through [21], [24], [26] through [28], [31], [33] through [35], or [39], wherein the composition is in the form of a 70 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a disintegrant, wherein the disintegrant is croscarmellose sodium and wherein the amount of croscarmellose sodium is about 8% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0083] Embodiment [42]: The pharmaceutical composition of any one of embodiments [1] through [41], wherein one or more pharmaceutically acceptable excipients comprises a glidant, wherein the glidant comprises colloidal silicon dioxide. In one aspect, colloidal silicon dioxide aids the flow property of the formulation blend (blended powder).

[0084] Embodiment [43]: The pharmaceutical composition of any one of embodiments [1] through [42], wherein one or more pharmaceutically acceptable excipients comprises a glidant, wherein the glidant comprises colloidal silicon dioxide and wherein the amount of colloidal silicon dioxide is about 0.5% to about 6% w/w.

[0085] Embodiment [44]: The pharmaceutical composition of any one of embodiments [1] through [43], wherein one or more pharmaceutically acceptable excipients comprises a glidant, wherein the glidant comprises colloidal silicon dioxide and wherein the amount of colloidal silicon dioxide is about 3% to about 6% w/w.

[0086] Embodiment [45]: The pharmaceutical composition of any one of embodiments [1] through [44], wherein one or more pharmaceutically acceptable excipients comprises a glidant, wherein the glidant comprises colloidal silicon dioxide and wherein the amount of colloidal silicon dioxide is from about 3.5% to about 4.5% w/w.

[0087] Embodiment [46]: The pharmaceutical composition of any one of embodiments [1] through [45], wherein one or more pharmaceutically acceptable excipients comprises a glidant, wherein the glidant comprises colloidal silicon dioxide and wherein the amount of colloidal silicon dioxide is about 4.5% w/w.

[0088] Embodiment [47]: The pharmaceutical composition of any one of embodiments [1] through [43], wherein one or more pharmaceutically acceptable excipients comprises a glidant, wherein the glidant comprises colloidal silicon dioxide and wherein the amount of colloidal silicon dioxide is from about 0.5% to about 5% w/w.

[0089] Embodiment [48]: The pharmaceutical composition of any one of embodiments [1] through [43] or [47], wherein one or more pharmaceutically acceptable excipients comprises a glidant, wherein the glidant comprises colloidal silicon dioxide and wherein the amount of colloidal silicon dioxide is from about 0.5% to about 2% w/w.

[0090] Embodiment [49]: The pharmaceutical composition of any one of embodiments [1] through [43] or [47] through [48], wherein one or more pharmaceutically acceptable excipients comprises a glidant, wherein the glidant comprises colloidal silicon dioxide and wherein the amount of colloidal silicon dioxide is about 0.5% w/w. In one aspect, the amount of colloidal silicon dioxide provides increased stability. In one aspect, the amount of colloidal silicon dioxide provides increased hardness of the tablet.

[0091] Embodiment [50]: The pharmaceutical composition of any one of embodiments [1] through [9], [11] through [23], [25] through [30], [32] through [40], or [42] through [47], wherein the composition is in the form of a 5, 20, or 100 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a glidant, wherein the glidant comprises colloidal silicon dioxide and wherein the amount of colloidal silicon dioxide is about 4.5% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0092] Embodiment [51]: The pharmaceutical composition of any one of embodiments [1] through [8], [10] through [22], [24] through [29], [31] through [37], or [39] through [49], wherein the composition is in the form of a 5, 70, or 100 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a glidant, wherein the glidant comprises colloidal silicon dioxide and wherein the amount of colloidal silicon dioxide is about 0.5% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[0093] Embodiment [52]: The pharmaceutical composition of any one of embodiments [1] through [51], wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose.

[0094] Embodiment [53]: The pharmaceutical composition of any one of embodiments [1] through [52], wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose and wherein the amount of microcrystalline cellulose is from about 40% to about 81% w/w.

[0095] Embodiment [54]: The pharmaceutical composition of any one of embodiments [1] through [53], wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose and wherein the amount of microcrystalline cellulose is from about 46% to about 81% w/w.

[0096] Embodiment [55]: The pharmaceutical composition of any one of embodiments [1] through [53], wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose and wherein the amount of microcrystalline cellulose is from about 40% to about 80% w/w.

[0097] Embodiment [56]: The pharmaceutical composition of any one of embodiments [1] through [55], wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose and wherein the amount of microcrystalline cellulose is from about 51% to about 74% w/w.

[0098] Embodiment [57]: The pharmaceutical composition of any one of embodiments [1] through [55], wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose and wherein the amount of microcrystalline cellulose is from about 47% to about 70% w/w.

[0099] Embodiment [58]: The pharmaceutical composition of any one of embodiments [1] through [8], [12] through [19], [22], [26], [29], [33] through [37], [42] through [47], or [50] through [55], wherein the composition is in the form of a 5 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose and wherein the amount of microcrystalline cellulose is about 80% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00100] Embodiment [59]: The pharmaceutical composition of any one of embodiments [1] through [7], [9], [12] through [21], [23], [26] through [28], [30], [33] through [36], [38], [42] through [47], or [50] through [56], wherein the composition is in the form of a 20 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose and wherein the amount of microcrystalline cellulose is from about 70% to about 74% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00101] Embodiment [60]: The pharmaceutical composition of any one of embodiments [1] through [7], [9], [12] through [21], [23], [26] through [28], [30], [33] through [36], [38], [42] through [47], or [50] through [57], wherein the composition is in the form of a 20 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose and wherein the amount of microcrystalline cellulose is about 70% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00102] Embodiment [61]: The pharmaceutical composition of any one of embodiments [1] through [7], [9], [12] through [21], [23], [26] through [28], [30], [33] through [36], [38], [42] through [47], or [50] through [56], wherein the composition is in the form of a 20 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose and wherein the amount of microcrystalline cellulose is about 74% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00103] Embodiment [62]: The pharmaceutical composition of any one of embodiments [1] through [7], [10], [12] through [21], [24], [26] through [28], [31], [33] through [35], [39], [42] through [49], or [51] through [57], wherein the composition is in the form of a 70 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose and wherein the amount of microcrystalline cellulose is about 59% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00104] Embodiment [63]: The pharmaceutical composition of any one of embodiments [1] through [7], [11] through [21], [25] through [28], [32] through [35], [39] through [40], or [42] through [57], wherein the composition is in the form of a 100 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose and wherein the amount of microcrystalline cellulose is from about 47% to about 51%w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00105] Embodiment [64]: The pharmaceutical composition of any one of embodiments [1] through [7], [11] through [21], [25] through [28], [32] through [35], [39] through [40], [42] through [49], [52] through [55], or [57], wherein the composition is in the form of a 100 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose and wherein the amount of microcrystalline cellulose is about 47% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00106] Embodiment [65]: The pharmaceutical composition of any one of embodiments [1] through [7], [11] through [21], [25] through [28], [32] through [35], [39] through [40], [42] through [49], or [52] through [57], wherein the composition is in the form of a 100 mg tablet or

capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler, wherein the filler comprises microcrystalline cellulose and wherein the amount of microcrystalline cellulose is about 51%w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00107] Embodiment [66]: The pharmaceutical composition of any one of embodiments [1] through [65], wherein one or more pharmaceutically acceptable excipients comprises a lubricant, wherein the lubricant comprises magnesium stearate. In one aspect, magnesium stearate provides lubrication of the formulation during compression.

[00108] Embodiment [67]: The pharmaceutical composition of any one of embodiments [1] through [66], wherein one or more pharmaceutically acceptable excipients comprises a lubricant, wherein the lubricant comprises magnesium stearate and wherein the amount of magnesium stearate is from about 0.3% to about 0.7% w/w.

[00109] Embodiment [68]: The pharmaceutical composition of any one of embodiment [1] through [67], wherein one or more pharmaceutically acceptable excipients comprises a lubricant, wherein the lubricant comprises magnesium stearate and wherein the amount of magnesium stearate is from about 0.4% to about 0.5% w/w.

[00110] Embodiment [69]: The pharmaceutical composition of any one of embodiments [1] through [68], wherein one or more pharmaceutically acceptable excipients comprises a lubricant, wherein the lubricant comprises magnesium stearate and wherein the amount of magnesium stearate is about 0.5% w/w.

[00111] Embodiment [70]: The pharmaceutical composition of any one of embodiments [1] through [69], wherein one or more pharmaceutically acceptable excipients comprises a lubricant, wherein the lubricant comprises magnesium stearate and wherein the composition is in the form of a 5, 20, 70, or 100 mg tablet or capsule, wherein the amount of magnesium stearate is about 0.5% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00112] Embodiment [71]: The pharmaceutical composition of any one of embodiments [1] through [9], [11] through [23], [25] through [30], [32] through [40], [42] through [47], or [48] through [70], wherein one or more pharmaceutically acceptable excipients comprises a lubricant, wherein the lubricant comprises magnesium stearate and wherein the composition is in the form of a 5, 20, or 100 mg tablet or capsule, wherein the amount of magnesium stearate is about 0.5% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00113] Embodiment [72]: The pharmaceutical composition of any one of embodiments [1] through [7], [9] through [21], [23] through [28], [30] through [36], [38] through [57], or [59] through [70], wherein one or more pharmaceutically acceptable excipients comprises a lubricant, wherein the lubricant comprises magnesium stearate and wherein the composition is in the form

of a 20, 70, or 100 mg tablet or capsule, wherein the amount of magnesium stearate is about 0.5% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00114] Embodiment [73]: The pharmaceutical composition of any one of embodiments [1] through [72] may further be film coated.

[00115] Embodiment [74]: The pharmaceutical composition of any one of embodiments [1] through [73], wherein the amount of film-coating agent by weight based on a core tablet is from about 1% to about 10% w/w.

[00116] Embodiment [75]: The pharmaceutical composition of any one of embodiments [1] through [74], wherein the amount of film-coating agent by weight based on a core tablet is from about 1.5% to about 7% w/w.

[00117] Embodiment [76]: The pharmaceutical composition of any one of embodiments [1] through [75], wherein the amount of film-coating agent by weight based on a core tablet from about 2% to about 5% w/w.

[00118] Embodiment [77]: The pharmaceutical composition of any one of embodiments [1] through [76], wherein the film coating enveloping the core tablet of the film-coated tablet contains at least one or more pharmaceutically acceptable film-forming agents.

[00119] Embodiment [78]: The pharmaceutical composition of any one of embodiments [1] through [77], wherein the film coating enveloping the core tablet of the film-coated tablet contains at least one or more pharmaceutically acceptable film-forming agents, wherein the film-forming agent comprises hypromellose.

[00120] Embodiment [79]: The pharmaceutical composition of any one of embodiments [1] through [78], wherein the film coating of the film-coated tablet may contain one or more plasticisers and/or one or more colored pigments.

[00121] Embodiment [80]: The pharmaceutical composition of any one of embodiments [1] through [79], wherein film coating of the film-coated tablet may contain one or more plasticisers and/or one or more colored pigments, wherein the plasticiser comprises polyethylene glycol.

[00122] Embodiment [81]: The pharmaceutical composition of any one of embodiments [1] through [80], wherein film coating of the film-coated tablet may contain one or more plasticisers and/or one or more colored pigments, and wherein the colored pigments comprise titanium dioxide and ferric oxide.

[00123] Embodiment [82]: The pharmaceutical composition of any one of any one of embodiments [1] through [81], wherein the film coating of the film-coated tablets comprises from about 20% to about 95% w/w of film forming agent.

[00124] Embodiment [83]: The pharmaceutical composition of any one of embodiments [1] through [82], wherein the film coating of the film-coated tablets comprises from about 50% to about 90 %w/w of film forming agent.

[00125] Embodiment [84]: The pharmaceutical composition of any one of embodiments [1] through [83], wherein the film coating of the film-coated tablets comprises from about 5% to about 40% w/w of plasticizer.

[00126] Embodiment [85]: The pharmaceutical composition of any one of embodiments [1] through [84], wherein the film coating of the film-coated tablets comprises from about 8% to about 30 % w/w of plasticizer.

[00127] Embodiment [86]: The pharmaceutical composition of any one of embodiments [1] through [85], wherein the film coating of the film-coated tablets comprises from about 0.1% to about 10 % w/w of colored pigment.

[00128] Embodiment [87]: The pharmaceutical composition of any one of embodiments [1] through [86], wherein the film coating of the film-coated tablets comprises from about 0.3% to about 5 % w/w of colored pigment.

[00129] Film coats may be prepared from a premix film coating agent, wherein the premix film coating agent comprises the trade name OPADRY®. Examples of film coating agents include OPADRY® Red 03F45081 (1008 g) (manufactured by COLORCON® JAPAN; containing hypromellose 2910, macrogol 6000, titanium oxide and red ferric oxide) and OPADRY® Yellow 03F42240 (2016 g) (manufactured by COLORCON® JAPAN; containing hypromellose 2910, macrogol 6000, titanium oxide and yellow ferric oxide).

[00130] Embodiment [88]: A pharmaceutical composition which is:

Pharmaceutical Composition Formulation	(% w/w)
solid dispersion extrudate	10.0
microcrystalline cellulose	80.0
croscarmellose sodium	5.0
colloidal silicon dioxide	4.5
magnesium stearate	0.5

Pharmaceutical Composition Formulation	(% w/w)
solid dispersion extrudate	20.0
microcrystalline cellulose	70.0
croscarmellose sodium	5.0
colloidal silicon dioxide	4.5
magnesium stearate	0.5

Pharmaceutical Composition Formulation	(% w/w)
solid dispersion extrudate	40
microcrystalline cellulose	47.0
croscarmellose sodium	8.0
colloidal silicon dioxide	4.5
Magnesium stearate	0.5

Pharmaceutical Composition Formulation	(% w/w)
Solid Dispersion Extrudate	20.0
microcrystalline cellulose	74.0
croscarmellose sodium	5.0
colloidal silicon dioxide	0.5
magnesium stearate	0.5
total core tablet	100.0
OPADRY® Red (% of core tablet weight)	4.2

Pharmaceutical Composition Formulation	(% w/w)
Solid Dispersion Extrudate	32.4

microcrystalline cellulose	58.6
croscarmellose sodium	8.0
colloidal silicon dioxide	0.5
magnesium stearate	0.5
total core tablet	100.0
OPADRY® Yellow (% of core tablet weight)	3.3

Pharmaceutical Composition Formulation	(% w/w)
Solid Dispersion Extrudate	40.0
microcrystalline cellulose	51.0
croscarmellose sodium	8.0
colloidal silicon dioxide	0.5
magnesium stearate	0.5
total core tablet	100.0
OPADRY® Red (% of core tablet weight)	1.12
OPADRY® Yellow (% of core tablet weight)	2.24

[00131] Embodiment [89]: The pharmaceutical composition of any one of embodiments [1] through [88], wherein the pharmaceutical composition is substantially amorphous. In one aspect, the substantially amorphous pharmaceutical composition comprises an amount of crystalline Compound 1 or a pharmaceutically acceptable salt thereof. In one aspect, the amount of crystalline Compound 1 is less than about 30%, less than about 29%, less than about 28%, less than about 27%, less than about 26%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 4%. In one aspect, the substantially amorphous pharmaceutical composition is produced upon re-crystallization of Compound 1 or a pharmaceutically acceptable salt thereof in a pharmaceutical composition originally comprising amorphous solid dispersion extrudate.

[00132] The amorphous character of a pharmaceutical composition can be detected using analytical methods, including but not limited to, microscopic methods (scanning electronic microscopy (SEM), polarized light microscopy (PLM), hot stage microscopy (HSM)), thermal methods (differential scanning calorimetry (DSC) modulated DSC (mDSC), diffraction methods (XRPD), and spectroscopic methods (FT-Infrared (IR), FT-Raman, solid state NMR (ssNMR) and confocal raman microscopy (CRM)). In one aspect, the amorphous character of a pharmaceutical composition is detected by X-ray powder diffraction (XRPD).

[00133] In one aspect, the amount of crystalline substance in a substantially amorphous pharmaceutical composition can be determined using a calibration curve based on samples of variable crystalline content (high and low regions). In one aspect, the amount of crystalline Compound 1 or a pharmaceutically acceptable salt thereof in a substantially amorphous pharmaceutical composition of the invention may affect the solubility of the composition. In one aspect, the amount of crystalline Compound 1 or a pharmaceutically acceptable salt thereof in a substantially amorphous pharmaceutical composition of the invention may affect the bioavailability of the composition. In one aspect, less than about 30% of crystalline Compound 1 or a pharmaceutically acceptable salt thereof in a substantially amorphous pharmaceutical composition does not reduce the solubility and/or bioavailability of the composition. In another aspect, less than about 29%, less than about 28%, less than about 27%, less than about 26%, less than about 24%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 4% of crystalline Compound 1 or a pharmaceutically acceptable salt thereof in a substantially amorphous pharmaceutical composition does not significantly reduce the solubility and/or bioavailability of the composition.

[00134] Embodiment [90]: A solid dispersion extrudate comprising comprising (1) Compound 1 or a pharmaceutically acceptable salt thereof and (2) a vinylpyrrolidinone-vinyl acetate copolymer.

[00135] Embodiment [91]: The solid dispersion extrudate of embodiment [90], comprising (1) from about 30% to about 50% w/w of Compound 1 or a pharmaceutically acceptable salt thereof and (2) from about 70% to about 50% w/w of a vinylpyrrolidinone-vinyl acetate copolymer.

[00136] Embodiment [92]: The solid dispersion extrudate of any one of embodiments [90] through [91], comprising (1) from about 35% to about 45% w/w of Compound 1 or a pharmaceutically acceptable salt thereof and (2) from about 65% to about 55% w/w of a vinylpyrrolidinone-vinyl acetate copolymer.

[00137] Embodiment [93]: The solid dispersion extrudate of any one of embodiments [90] through [92], comprising (1) about 40% w/w of Compound 1 or a pharmaceutically acceptable salt thereof and (2) about 60% w/w of a vinylpyrrolidinone-vinyl acetate copolymer.

[00138] Embodiment [94]: The solid dispersion of any one of embodiments [90] through [93], wherein the solid dispersion extrudate comprises Compound 1. In one aspect, Compound 1 is present as substantially pure. "Substantially pure" means greater than ninety-five percent pure.

[00139] Embodiment [95]: The solid dispersion of any one of embodiments [90] through [93], wherein the solid dispersion extrudate comprises a pharmaceutically acceptable salt of Compound 1.

[00140] Embodiment [95A]: The solid dispersion of any one of embodiments [90] through [95], wherein the vinylpyrrolidinone-vinyl acetate copolymer is copovidone.

[00141] Compound 1 or a pharmaceutically acceptable salt thereof used in this invention, may be in crystalline form, amorphous form or substantially amorphous form prior to formulation of the solid dispersion. Figure 8 is a representative XRPD pattern of Compound 1 as a crystalline form.

[00142] It will be understood that any of the above embodiments may be combined to form additional embodiments.

Process for Preparing Pharmaceutical Compositions

[00143] The present invention relates to processes for the preparation of pharmaceutical compositions comprising the pan-Raf kinase inhibitor Compound 1 or a pharmaceutically acceptable salt thereof. Processes for the preparation of the pharmaceutical compositions of the invention are explained in the following.

[00144] Specifically, the processes for the preparation of the pharmaceutical compositions of the invention generally involve an extrusion process followed by a formulation process. Formation of an inactive chiral impurity was observed and determined to be directly related to the thermal production technique employed, necessitating a significant amount of work for the development of the extrusion process. Incorporation of processing additives such as poloxamer and polysorbate failed to show any significant reduction in the level of chiral impurity formation. Additionally, the processing additives appeared to compromise amorphous stability of the solid dispersion. Process optimization studies ultimately achieved a reduction of impurity formation through control of the extrusion conditions related to melt residence time.

[00145] The extrusion process involves the addition of vinylpyrrolidinone-vinyl acetate copolymer e.g., Kollidon® VA 64 to Compound 1 to form a solid dispersion extrudate. The

formulation process involves the addition of microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate to the solid dispersion extrudate produced by the extrusion process to form a pharmaceutical composition of the invention. Figure 1A is a flow diagram illustrating a representative process for the preparation of the pharmaceutical compositions of the invention according to Example 1, 2, and 3. In Figure 1, pre-extrusion mixing, melt extrusion, and milling are steps in the extrusion process and pre-blending and final blending are steps in the formulation process. Figure 1B is a flow diagram illustrating a representative process for the preparation of the pharmaceutical compositions of the invention produced according to Example 1, 4, 5, and 6. In Figure 1B, pre-extrusion mixing, melt extrusion, and milling are steps in the extrusion process and pre-blending, final blending, tablet compression and coating are steps in the formulation process.

[00146] Compound 1 and a vinylpyrrolidinone-vinyl acetate copolymer e.g., copovidone are ingredients of the extrusion process. Microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate are ingredients of the formulation process to be added to the resulting solid dispersion extrudate produced by the extrusion process. OPADRY® as film-coating agent is an ingredient of the formulation process to be added to core tablets with the final blended powder.

[00147] Specifically, in the extrusion process, Compound 1 and vinylpyrrolidinone-vinyl acetate copolymer e.g., copovidone are accurately weighed, screened and mixed using high shear mixing to form a pre-extrusion powder mixture.

[00148] A suitable hot melt extruder (e.g. twin screw, Leistritz Nano-16 mm or Micro-18 mm) is set up with the appropriate supporting equipment, including a cooling conveyor (e.g., Dorner model 220M060600D0169 or Nara TBC-309-DC) and feeder with auger (e.g., K-Tron Gravimetric Feeder e.g., with dual flight 20 mm auger). Example processing parameters are as follows: feed rate: 2.0 kg/hr; screw speed: 250 rpm; and barrel temperature: 170, 140, 90, 50 °C or 1.0 kg/hr; screw speed: 275 rpm; and barrel temperature: 175, 140, 90, 50 °C. Compound 1 exhibits a relatively high melting point at 204 °C and thermal gravimetric analysis (TGA) showed Compound 1 to be relatively stable at elevated temperatures below 200 °C.

[00149] The powder mixture is fed into the hot melt extruder, and the resulting solid dispersion extrudate is cooled and milled using a suitable impact mill with hammer forward configuration (e.g., Fizmill L1A hammer mill) or multi pin rotor (e.g., NARA Sample mill SAM). The milled extrudate may be screened using a suitable screen (e.g., 20 mesh operated at 9,000 rpm) to remove oversize material and then screened through a second suitable screen (e.g., 60 mesh). The resulting solid dispersion extrudate is taken forward to the formulation process.

Alternatively, only part of the resulting solid dispersion extrude is taken forward to the formulation process.

[00150] In one aspect of the formulation process e.g., Figure 1A, the ingredients are added sequentially to the solid dispersion extrudate: microcrystalline cellulose (e.g., Avicel PH 102, FMC Biopolymer), croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymer), and may be screened using a suitable screen (e.g., 18-mesh). Colloidal silicon dioxide (Aerosil 200, Evonik) is added and may be screened using a suitable screen (e.g., 40-mesh) to produce a pre-blend, which is blended e.g., for about 20 minutes using a diffusion class blender. Magnesium stearate (Mallinckrodt) is accurately weighed, may be screened with a suitable screen (e.g., 30-mesh) and blended with the pre-blend to produce the final blend. Blend e.g., for 20 minutes using a diffusion class blender. In one aspect, the final blend is compressed on a tablet press into tablets. In another aspect, the final blend is loaded into a capsule.

[00151] In another aspect of the formulation process e.g., Figure 1B, the ingredients are added sequentially to the solid dispersion extrudate: microcrystalline cellulose (e.g., Avicel PH 101, FMC Biopolymer), croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymer) and colloidal silicon dioxide (Aerosil 200, Evonik) are added to produce a pre-blend, which is blended e.g., for about 15 minutes using a diffusion class blender. Magnesium stearate (Mallinckrodt) is accurately weighed, may be screened with a suitable screen (e.g., sieve size 1.0 mm) and blended with the pre-blend to produce the final blend. Blend e.g., for 5 minutes using a diffusion class blender. The final blend is compressed on a tablet press into core tablets. The core tablets are charged into a suitable film coating machine (e.g. Driacoater Vario 500/600) and are coated with the spray suspension with premix film coating agent (e.g. OPADRY®, Colorcon).

[00152] The present invention includes the following embodiments:

[00153] Embodiment [96]: A process for preparing a pharmaceutical composition, which comprises the steps of:

- (i) extruding a mixture of Compound 1 or a pharmaceutically acceptable salt thereof and vinylpyrrolidone-vinyl acetate copolymer to form a solid dispersion extrudate;
- (ii) blending the resulting solid dispersion extrudate with one or more pharmaceutically acceptable excipients.

[00154] Embodiment [97]: A process for preparing a pharmaceutical composition, which comprises the steps of:

- (i) extruding a mixture of Compound 1 or a pharmaceutically acceptable salt thereof and vinylpyrrolidinone-vinyl acetate copolymer to form a solid dispersion extrudate;
- (ii) blending the resulting solid dispersion extrudate with a filler, disintegrant, and glidant to form a pre-blend; and
- (iii) blending a lubricant with the resulting pre-blend.

[00155] Embodiment [98]: The process of any one of embodiments [96] through [97], wherein the process further comprises the step of (iv-A) compressing the pharmaceutical composition resulting from steps (i), (ii), and (iii) into tablet form or loading the pharmaceutical composition from steps (i), (ii), and (iii) into capsule form.

[00156] Embodiment [99]: The process of any one of embodiments [96] through [98], wherein the process further comprises the step of (iv-A) compressing the pharmaceutical composition resulting from steps (i), (ii), and (iii) into tablet form. In one aspect, tablet form provides improved bioavailability.

[00157] Embodiment [100]: The process of any one of embodiments [96] through [99], wherein the process further comprises the step of (v) coating the pharmaceutical composition resulting from step (iv) into a film coated tablet form. In one aspect, the film coated tablet form provides improved bioavailability.

[00158] Embodiment [101]: The process of any one of embodiments [96] through [98], wherein the process further comprises the step of (iv-B) loading the pharmaceutical composition resulting from steps (i), (ii), and (iii) into capsule form.

[00159] Embodiment [102]: The process of any one of embodiments [96] through [101], wherein the mixture in step (i) is Compound 1 and vinylpyrrolidinone-vinyl acetate copolymer.

[00160] Embodiment [103]: The process of any one of embodiments [96] through [101], wherein the mixture in step (i) is the pharmaceutically acceptable salt of Compound 1 and vinylpyrrolidinone-vinyl acetate copolymer.

[00161] Embodiment [104]: The process of any one of embodiments [96] through [103], wherein the vinylpyrrolidinone-vinyl acetate copolymer is copovidone. In one aspect, the copovidone is Kollidon® VA 64. In one aspect, the vinylpyrrolidinone-vinyl acetate copolymer is pre-dried. In one aspect, copovidone is pre-dried at 60 °C for about 8 hours.

[00162] Embodiment [105]: The process of any one of embodiments [96] through [104], wherein the amount of Compound 1 is from about 3% to about 17% w/w.

[00163] Embodiment [106]: The process of any one of embodiments [96] through [105], wherein the amount of Compound 1 is from about 7% to about 17% w/w.

[00164] Embodiment [107]: The process of any one of embodiments [96] through [106], wherein the amount of Compound 1 is from about 8% to about 16% w/w.

[00165] Embodiment [108]: The process of any one of embodiments [96] through [105] for preparing a composition comprising a 5 mg tablet or capsule, wherein the amount of Compound 1 is about 4% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00166] Embodiment [109]: The process of any one of embodiments [96] through [107] for preparing a composition comprising a 20 mg tablet or capsule, wherein the amount of Compound 1 is about 8% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00167] Embodiment [110]: The process of any one of embodiments [96] through [107] for preparing a composition comprising a 70 mg tablet or capsule, wherein the amount of Compound 1 is about 13% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00168] Embodiment [111]: The process of any one of embodiments [96] through [107] for preparing a composition comprising a 100 mg tablet or capsule, wherein the amount of Compound 1 is about 16% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00169] Embodiment [112]: The process of any one of embodiments [96] through [111], wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer is from about 5% to about 25% w/w. In one aspect, the copolymer is copovidone. In one aspect, the amount of copovidone is from about 5% to about 25% w/w.

[00170] Embodiment [113]: The process of any one of embodiments [96] through [112], wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer is from about 12% to about 24% w/w. In one aspect, the copolymer is copovidone. In one aspect, the amount of copovidone is from about 12% to about 24% w/w.

[00171] Embodiment [114]: The process of any one of embodiments [96] through [105], [108], or [112] through [113], for preparing a composition comprising a 5 mg tablet or capsule, wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer is about 6% w/w. In one aspect, the copolymer is copovidone. In one aspect, the amount of copovidone is about 6% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00172] Embodiment [115]: The process of any one of embodiments [96] through [107], [109], or [112] through [113], for preparing a composition comprising a 20 mg tablet or capsule, wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer is about 12% w/w. In one aspect, the copolymer is copovidone. In one aspect, the amount of copovidone is about 12% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00173] Embodiment [116]: The process of any one of embodiments [96] through [107], [110], or [112] through [113], for preparing a composition comprising a 70 mg tablet or capsule, wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer about 19% w/w. In one aspect, the copolymer is copovidone. In one aspect, the amount of copovidone is about 19% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00174] Embodiment [117]: The process of any one of embodiments [96] through [107] or [111] through [113], for preparing a composition comprising a 100 mg tablet or capsule, wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer is about 24% w/w. In one aspect, the copolymer is copovidone. In one aspect, the amount of copovidone is about 24% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00175] Embodiment [118]: The process of any one of embodiments [96] through [117], wherein the process further comprises the step of (i-A) cooling and milling the resulting extrudate prior to step (ii).

[00176] Embodiment [119]: The process of any one of embodiments [96] through [118], wherein the process further comprises the step of (i-A) cooling and milling the resulting extrudate prior to step (ii) and the step of (i-B) screening the milled extrudate after step (i-A) and prior to step (ii).

[00177] Embodiment [120]: The process of any one of embodiments [96] through [119], wherein the process further comprises before step (i) providing a mixture wherein high shear mixing is used to prepare the mixture of Compound I or a pharmaceutically acceptable salt thereof and vinylpyrrolidinone-vinyl acetate copolymer.

[00178] High shear mixing can minimize potency variations (Figure 5).

[00179] Embodiment [121]: The process of any one of embodiments [96] through [120], wherein the extruding is carried out in an extruder operating at a screw speed of from about 225 rpm to about 350 rpm.

[00180] Embodiment [122]: The process of any one of embodiments [96] through [121], wherein the extruding is carried out in an extruder operating at a screw speed of about 250 rpm.

[00181] Embodiment [123]: The process of any one of embodiments [96] through [121], wherein the extruding is carried out in an extruder operating at a screw speed of about 275 rpm.

[00182] Embodiment [124]: The process of any one of embodiments [96] through [123], wherein the extruding is carried out in an extruder after the mixture is fed into the extruder at a feed rate of from about 0.5 kg/hr to about 2.5 kg/hr. The feeding section of the extruder transfers the feed stock into the barrel of the extruder.

[00183] Embodiment [125]: The process of any one of embodiments [96] through [124], wherein the extruding is carried out in an extruder after the mixture is fed into the extruder at a feed rate of from about 1.0 kg/hr to about 2.0 kg/hr.

[00184] Embodiment [126]: The process of any one of embodiments [96] through [125], wherein the extruding is carried out in an extruder after the mixture is fed into the extruder at a feed rate of about 1.0 kg/hr.

[00185] Embodiment [127]: The process of any one of embodiments [96] through [126], wherein the extruding is carried out in an extruder operating with a barrel temperature comprising a gradient temperature profile ranging from about room temperature to about 180 °C. In one aspect, implementation of a gradient temperature profile yields a significant reduction in chiral impurity levels during manufacture. For example, increasing the temperature provides a decrease in residual crystalline form of the extrudate.

[00186] Embodiment [128]: The process of any one of embodiments [96] through [127], wherein the extruding is carried out in an extruder operating with a barrel temperature comprising a gradient temperature profile ranging from about 50 °C to about 170 °C.

[00187] Embodiment [129]: The process of any one of embodiments [96] through [128], wherein the extruding is carried out in an extruder operating with a barrel temperature comprising a gradient temperature profile comprising four temperature zones from (1) about 50 °C, (2) about 90 °C, (3) about 140 °C and (4) about 170 °C to about 175 °C. In one aspect, lower barrel temperatures yields compositions with lower chiral impurity levels.

[00188] Embodiment [130]: The process of any one of embodiments [96] through [129], wherein the extruding is carried out in an extruder operating with a barrel temperature comprising a gradient temperature profile comprising four temperature zones from (1) about 50 °C, (2) about 90 °C, (3) about 140 °C and (4) about 170 °C. In one aspect, lower barrel temperatures yields compositions with lower chiral impurity levels.

[00189] Embodiment [131]: The process of any one of embodiments [96] through [129], wherein the extruding is carried out in an extruder operating with a barrel temperature comprising a gradient temperature profile comprising four temperature zones from (1) about 50 °C, (2) about 90 °C, (3) about 140 °C and (4) about 175 °C. In one aspect, lower barrel temperatures yields compositions with lower chiral impurity levels.

[00190] Embodiment [132]: The process of any one of embodiments [96] through [131], wherein the solid dispersion extrudate in step (i) is amorphous. For example, the solid dispersion extrudate is amorphous as detected by XRPD (Figure 6). In another aspect, the amorphous

character of the solid dispersion extrudate can be detected using differential scanning calorimetry (DSC).

[00191] Embodiment [133]: The process of any one of embodiments [96] through [132], wherein the loading of extrudate is from about 10% to about 50% w/w.

[00192] Embodiment [134]: The process of any one of embodiment [96] through [133], wherein the loading of the extrudate is from about 10% to about 40% w/w.

[00193] Embodiment [135]: The process of any one of embodiment [96] through [134], wherein, the loading of extrudate is about from about 40% to about 50% w/w. In one aspect, the loading of the extrudate is important for disintegration rate. In one aspect, a tablet form prepared at about 40% solid dispersion exhibits rapid dissolution, and achieves full release in less than 10 minutes.

[00194] Embodiment [136]: The process of any one of embodiments [96] through [105], [108], [112] through [114], [118] through [134] for preparing a composition comprising a 5 mg tablet or capsule comprising about 10% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) about 90% w/w of one or more pharmaceutically acceptable excipients. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00195] Embodiment [137]: The process of any one of embodiments [96] through [107], [109], [112] through [113], [115], or [118] through [134] for preparing a composition comprising a 20 mg tablet or capsule comprising about 20% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) about 80% w/w of one or more pharmaceutically acceptable excipients. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00196] Embodiment [138]: The process of any one of embodiments [96] through [107], [110], [112] through [113], [116], or [118] through [134], for preparing a composition comprising a 70 mg tablet or capsule comprising about 32% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) about 68% w/w of one or more pharmaceutically acceptable excipients. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00197] Embodiment [139]: The process of any one of embodiments [96] through [107], [111] through [113] or [117] through [135] for preparing a composition of a 100 mg tablet or capsule comprising about 40% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2)

about 60% w/w of one or more pharmaceutically acceptable excipients. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00198] Embodiment [140]: The process of any one of embodiments [96] through [139], wherein one or more pharmaceutically acceptable excipients comprises a disintegrant and wherein the disintegrant comprises croscarmellose sodium. In one aspect, croscarmellose sodium serves as a disintegrant for immediate release. In one aspect, disintegration is a function of the type of superdisintegrant and solid dispersion loading within the formulation.

[00199] Embodiment [141]: The process of any one of embodiments [96] through [140], wherein one or more pharmaceutically acceptable excipients comprises a disintegrant and wherein the disintegrant is croscarmellose sodium and the amount of croscarmellose sodium is from about 4% to about 9% w/w.

[00200] Embodiment [142]: The process of any one of embodiments [96] through [141], wherein one or more pharmaceutically acceptable excipients comprises a disintegrant and wherein the disintegrant is croscarmellose sodium and the amount of croscarmellose sodium is from about 5% to about 8% w/w.

[00201] Embodiment [143]: The process of any one of embodiments [96] through [109], [112] through [115], [118] through [134], [136] through [137], or [140] through [142] for preparing a composition comprising a 5 mg or 20 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a disintegrant and wherein the disintegrant is croscarmellose sodium and the amount of croscarmellose sodium is about 5% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00202] Embodiment [144]: The process of any one of embodiments [96] through [107], [110], [112] through [113], [116], [118] through [134], [138], or [140] through [142], for preparing a composition comprising a 70 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a disintegrant and wherein the disintegrant is croscarmellose sodium and the amount of croscarmellose sodium is about 8% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00203] Embodiment [145]: The process of any one of embodiments [96] through [107], [111] through [113], [117] through [135], or [139] through [142], for preparing a composition comprising a 100 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a disintegrant and wherein the disintegrant is croscarmellose sodium and the amount of croscarmellose sodium is about 8% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00204] Embodiment [146]: The process of any one of embodiments [96] through [145], wherein one or more pharmaceutically acceptable excipients comprises a glidant and wherein the glidant comprises colloidal silicon dioxide. In one aspect, the colloidal silicon dioxide aids the flow property of the formulation blend.

[00205] Embodiment [147]: The process of any one of embodiments [96] through [146], wherein one or more pharmaceutically acceptable excipients comprises a glidant and wherein the glidant is colloidal silicon dioxide and the amount of colloidal silicon dioxide is from about 0.5% to about 6% w/w.

[00206] Embodiment [148]: The process of any one of embodiments [96] through [147], wherein one or more pharmaceutically acceptable excipients comprises a glidant and wherein the glidant is colloidal silicon dioxide and the amount of colloidal silicon dioxide is from about 3% to about 6% w/w.

[00207] Embodiment [149]: The process of any one of embodiments [96] through [146], wherein one or more pharmaceutically acceptable excipients comprises a glidant and wherein the glidant is colloidal silicon dioxide and the amount of colloidal silicon dioxide is from about 3.5 % to about 4.5% w/w.

[00208] Embodiment [150]: The process of any one of embodiments [96] through [146], wherein one or more pharmaceutically acceptable excipients comprises a glidant and wherein the glidant is colloidal silicon dioxide and the amount of colloidal silicon dioxide is from about 0.5 % to about 5% w/w.

[00209] Embodiment [151]: The process of any one of embodiments [96] through [146], wherein one or more pharmaceutically acceptable excipients comprises a glidant and wherein the glidant is colloidal silicon dioxide and the amount of colloidal silicon dioxide is from about 0.5 % to about 2% w/w.

[00210] Embodiment [152]: The process of any one of embodiments [96] through [109], [111] through [115], [117] through [137], [139] through [143], or [145] through [150], for preparing a composition comprising a 5, 20, or 100 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a glidant and wherein the amount of colloidal silicon dioxide is about 4.5% w/w. In one aspect, the form is capsule. In one aspect, the form is tablet.

[00211] Embodiment [153]: The process of any one of embodiments [96] through [107], [109] through [113], [115] through [135], [135] through [151], for preparing a composition comprising a 20, 70 or 100 mg tablet or capsule, wherein one or more pharmaceutically

acceptable excipients comprises a glidant and wherein the amount of colloidal silicon dioxide is about 0.5% w/w. In one aspect, the form is capsule. In one aspect, the form is tablet.

[00212] Embodiment [154]: The process of any one of embodiments [96] through [153], wherein one or more pharmaceutically acceptable excipients comprises a filler and wherein the filler is microcrystalline cellulose.

[00213] Embodiment [155]: The process of any one of embodiments [54] through [154], wherein one or more pharmaceutically acceptable excipients comprises a filler and wherein the filler is microcrystalline cellulose and the amount of microcrystalline cellulose is from about 46% to about 81% w/w.

[00214] Embodiment [156]: The process of any one of embodiments [96] through [155], wherein one or more pharmaceutically acceptable excipients comprises a filler and wherein the filler is microcrystalline cellulose and the amount of microcrystalline cellulose is from about 40% to about 80% w/w.

[00215] Embodiment [157]: The process of any one of embodiments [96] through [156], wherein one or more pharmaceutically acceptable excipients comprises a filler and wherein the filler is microcrystalline cellulose and the amount of microcrystalline cellulose is from about 51% to about 74% w/w.

[00216] Embodiment [158]: The process of any one of embodiments [96] through [157], wherein one or more pharmaceutically acceptable excipients comprises a filler and wherein the filler is microcrystalline cellulose and the amount of microcrystalline cellulose is from about 47% to about 70% w/w.

[00217] Embodiment [159]: The process of any one of embodiments [96] through [105], [108], [112] through [114], [118] through [133], [136], [140] through [143], [146] through [152], or [154] through [156] for preparing a composition comprising a 5 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler and wherein the filler is microcrystalline cellulose and the amount of microcrystalline cellulose is about 80% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00218] Embodiment [160]: The process of any one of embodiments [96] through [107], [109], [112] through [113], [115], [118] through [134], [137], [140] through [143], or [146] through [158], for preparing a composition comprising a 20 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler and wherein the filler is microcrystalline cellulose and the amount of microcrystalline cellulose is from about 74% to about 70% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00219] Embodiment [161]: The process of any one of embodiments [96] through [107], [109], [112] through [113], [115], [118] through [134], [137], [140] through [143], or [146] through [158], for preparing a composition comprising a 20 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler and wherein the filler is microcrystalline cellulose and the amount of microcrystalline cellulose is about 70% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00220] Embodiment [162]: The process of any one of embodiments [96] through [107], [109], [112] through [113], [115], [118] through [134], [137], [140] through [143], or [146] through [158], for preparing a composition comprising a 20 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler and wherein the filler is microcrystalline cellulose and the amount of microcrystalline cellulose is about 74% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00221] Embodiment [163]: The process of any one of embodiments [96] through [107], [110], [112] through [113], [116], [118] through [134], [138], [140] through [142], [144], or [146] through [151], or [154] through [158], for preparing a composition comprising a 70 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler and wherein the filler is microcrystalline cellulose and the amount of microcrystalline cellulose is about 59% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00222] Embodiment [164]: The process of any one of embodiments [96] through [107], [111] through [113], [117] through [135], [139] through [142], [145] through [151], [153] through [156], or [158], for preparing a composition comprising a 100 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a filler and wherein the filler is microcrystalline cellulose and the amount of microcrystalline cellulose is about 47% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00223] Embodiment [165]: The process of any one of embodiments [96] through [164], wherein one or more pharmaceutically acceptable excipients comprises a lubricant and wherein the lubricant comprises magnesium stearate. In one aspect, the magnesium stearate provides lubrication of the formulation during compression.

[00224] Embodiment [166]: The process of any one of embodiments [96] through [165], wherein one or more pharmaceutically acceptable excipients comprises a lubricant and wherein the lubricant is magnesium stearate and the amount of magnesium stearate is from about 0.3% to about 0.7% w/w.

[00225] Embodiment [167]: The process of any one of embodiments [96] through [166], wherein one or more pharmaceutically acceptable excipients comprises a lubricant and wherein

the lubricant is magnesium stearate and the amount of magnesium stearate is from about 0.4% to about 0.5% w/w.

[00226] Embodiment [168]: The process of any one of embodiments [96] through [167], wherein one or more pharmaceutically acceptable excipients comprises a lubricant and wherein the lubricant is magnesium stearate and the amount of magnesium stearate is about 0.5% w/w.

[00227] Embodiment [169]: The process of any one of embodiments [96] through [107], [109] through [113], [118] through [135], [137] through [143], [146] through [158], or [160] through [168], for preparing a composition comprising a 20, 70, or 100 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a lubricant and wherein the lubricant is magnesium stearate and the amount of magnesium stearate is about 0.5% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00228] Embodiment [170]: The process of embodiment any one of embodiments [96] through [109], [111] through [114], [116] through [135], [137] through [151], [153] through [156], [158], or [165] through [168], for preparing a composition comprising a 5, 20, or 100 mg tablet or capsule, wherein one or more pharmaceutically acceptable excipients comprises a lubricant and wherein the lubricant is magnesium stearate and the amount of magnesium stearate is about 0.5% w/w. In one aspect, the form is tablet. In one aspect, the form is capsule.

[00229] Embodiment [171]: The process of any one of embodiments [96] through [170], wherein one or more pharmaceutically acceptable excipients comprises a film coating agent. In one aspect, the film coating agent comprises OPADRY®.

[00230] Embodiment [172]: The process of any one of embodiments [96] through [171], wherein one or more pharmaceutically acceptable excipients comprises a film coating agent and wherein the film coating agent comprises OPADRY® and wherein the amount of OPADRY® is from about 0.5% to about 5% w/w.

[00231] Embodiment [173]: The process of any one of embodiments [96] through [172], wherein one or more pharmaceutically acceptable excipients comprises a film coating agent and wherein the film coating agent comprises OPADRY® and the amount of OPADRY® is from about 3.3% to about 4.2 % w/w.

[00232] Embodiment [174]: The process of any one of embodiments [96] through [173] for preparing a composition comprising a 20 mg tablet, wherein one or more pharmaceutically acceptable excipients comprises a film coating agent and wherein the film coating agent is OPADRY® and the amount of OPADRY® is about 4.2 % w/w.

[00233] Embodiment [175]: The process of any one of embodiments [96] through [173] for preparing a composition comprising a 70 mg tablet, wherein one or more pharmaceutically

acceptable excipients comprises a film coating agent and wherein the film coating agent is OPADRY® and the amount of OPADRY® is about 3.3% w/w.

Embodiment [176]: The process of any one of embodiments [96] through [173] for preparing a composition comprising a 100 mg tablet, wherein one or more pharmaceutically acceptable excipients comprises a film coating agent and wherein the film coating agent is OPADRY® and the amount of OPADRY® is about 3.4% w/w.

[00234] Embodiment [177]: A process for preparing a pharmaceutical composition, which comprises the steps of:

- (i) extruding a mixture of Compound 1 or a pharmaceutically acceptable salt thereof and vinylpyrrolidinone-vinyl acetate copolymer to form a solid dispersion extrudate;
- (ii) blending the resulting solid dispersion extrudate with filler, disintegrant, and glidant to form a pre-blend; and
- (iii) blending a lubricant with the resulting pre-blend;

wherein the pharmaceutical composition prepared comprises:

- from about 3% to about 17% w/w Compound 1 or a pharmaceutically acceptable salt thereof;
- from about 5% to about 25% w/w vinylpyrrolidinone-vinyl acetate copolymer;
- from about 4% to about 9% w/w disintegrant;
- from about 3% to about 6% w/w glidant;
- from about 46% to about 81% w/w filler; and
- from about 0.3% to about 0.7% w/w lubricant.

Embodiment [178]: A process for preparing a pharmaceutical composition, which comprises the steps of: (i) extruding a mixture of Compound 1 and copovidone to form a solid dispersion extrudate;

- (ii) blending the resulting solid dispersion extrudate with filler, disintegrant, and glidant to form a pre-blend; and
- (iii) blending a lubricant with the resulting pre-blend;

wherein the pharmaceutical composition prepared comprises:

- from about 3% to about 17% w/w Compound 1;
- from about 5% to about 25% w/w copovidone;
- from about 4% to about 9% w/w croscarmellose;
- from about 3% to about 6% w/w glidant;
- from about 46% to about 81% w/w filler; and

from about 0.3% to about 0.7% w/w lubricant.

[00235] Embodiment [179]: A process for preparing a pharmaceutical composition, which comprises the steps of:

- (i) extruding a mixture of Compound 1 or a pharmaceutically acceptable salt thereof and vinylpyrrolidinone-vinyl acetate copolymer to form a solid dispersion extrudate;
- (ii) blending the resulting solid dispersion extrudate with filler, disintegrant, and glidant to form a pre-blend; and
- (iii) blending a lubricant with the resulting pre-blend;
- (iv) compressing the resulting final blend to form core tablets;
- (v) coating the core tablets with a film-coating agent;

wherein the pharmaceutical composition prepared comprises:

from about 3% to about 17% w/w Compound 1 or a pharmaceutically acceptable salt thereof;

from about 5% to about 25% w/w vinylpyrrolidinone-vinyl acetate copolymer;

from about 4% to about 9% w/w disintegrant;

from about 0.1% to about 5% w/w glidant;

from about 40% to about 80% w/w filler; and

from about 0.3% to about 0.7% w/w lubricant

from about 0.5% to about 5% w/w film-coating agent.

[00236] Embodiment [180]: A process for preparing a pharmaceutical composition, which comprises the steps of:

- (i) extruding a mixture of Compound 1 and copovidone to form a solid dispersion extrudate;
- (ii) blending the resulting solid dispersion extrudate with filler, disintegrant, and glidant to form a pre-blend; and
- (iii) blending a lubricant with the resulting pre-blend;
- (iv) compressing the resulting final blend to form core tablets;
- (v) coating the core tablets with a film-coating agent;

wherein the pharmaceutical composition prepared comprises:

from about 3% to about 17% w/w Compound 1;

from about 5% to about 25% w/w copovidone;

from about 4% to about 9% w/w croscarmellose;

from about 3% to about 6% w/w glidant;

from about 46% to about 81% w/w filler; and

from about 0.3% to about 0.7% w/w lubricant
from about 0.5% to about 5% w/w coating agent.

[00237] Embodiment [181]: A pharmaceutical composition prepared by the process of any of embodiments [96] through [180].

[00238] Embodiment [182]: A pharmaceutical composition prepared by a process comprising the steps of:

- (i) extruding a mixture of Compound 1 or a pharmaceutically acceptable salt thereof and vinylpyrrolidinone-vinyl acetate copolymer to form a solid dispersion extrudate;
- (ii) blending the resulting solid dispersion extrudate with one or more pharmaceutically acceptable excipients.

[00239] Embodiment [183]: A pharmaceutical composition prepared by a process comprising the steps of:

- (i) extruding a mixture of Compound 1 or a pharmaceutically acceptable salt thereof and vinylpyrrolidinone-vinyl acetate copolymer to form a solid dispersion extrudate;
- (ii) blending the resulting solid dispersion extrudate with filler, disintegrant, and glidant to form a pre-blend; and
- (iii) blending a lubricant with the resulting pre-blend.

[00240] Embodiment [184]: A pharmaceutical composition prepared by a process comprising the steps of:

- (i) extruding a mixture of Compound 1 and copovidone to form a solid dispersion extrudate;
- (ii) blending the resulting solid dispersion extrudate with filler, disintegrant, and glidant to form a pre-blend; and
- (iii) blending a lubricant with the resulting pre-blend;

wherein the pharmaceutical composition prepared comprises:

from about 3% to about 17% w/w Compound 1;
from about 5% to about 25% w/w copovidone;
from about 4% to about 9% w/w croscarmellose;
from about 3% to about 6% w/w glidant;
from about 46% to about 81% w/w filler; and
from about 0.3% to about 0.7% w/w lubricant.

[00241] Embodiment [185]: The pharmaceutical composition of any one of embodiments [181] or [184], wherein the pharmaceutical composition is substantially amorphous. In one aspect, the substantially amorphous pharmaceutical composition comprises an amount of crystalline Compound 1 or a pharmaceutically acceptable salt thereof. In one aspect, the amount of crystalline Compound 1 is less than about 30%, less than about 29%, less than about 28%, less than about 27%, less than about 26%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 4%.

[00242] Embodiment [186]: A pharmaceutical composition comprising as an active ingredient Compound 1 or a pharmaceutically acceptable salt thereof, wherein the active ingredient is in a solid dispersion form comprising vinylpyrrolidinone-vinyl acetate copolymer.

[00243] Embodiment [187]: The pharmaceutical composition of embodiment [186], wherein the copolymer is copovidone.

[00244] Embodiment [188]: The pharmaceutical composition of embodiments [186] or [187], wherein the pharmaceutical composition is substantially amorphous. In one aspect, the substantially amorphous pharmaceutical composition comprises an amount of crystalline Compound 1 or a pharmaceutically acceptable salt thereof. In one aspect, the amount of crystalline Compound 1 is less than about 30%, less than about 29%, less than about 28%, less than about 27%, less than about 26%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 4%.

[00245] Embodiment [188A]: A method of improving the absorption of Compound 1 or a pharmaceutically acceptable salt thereof, by combining with a vinylpyrrolidinone-vinyl acetate copolymer to form an amorphous system.

[00246] Embodiment [188B]: The method of embodiment [188A], wherein the vinylpyrrolidinone-vinyl acetate copolymer is copovidone.

[00247] It will be understood that any of the above embodiments may be combined to form additional embodiments.

Utility of the Pharmaceutical Compositions of the Invention

[00248] The MAP kinase pathway is a central signal transduction pathway that is dysregulated in a large number of cancers and developmental disorders. Normally, binding of a growth factor to its receptor switches on RAS, which, in turn, activates one or more of the RAF

kinase family members, ARAF, BRAF and CRAF (Raf-1). RAF kinases perpetuate the signal by phosphorylating and activating MEK, another kinase that phosphorylates a third kinase, ERK. ERK then phosphorylates a number of key growth-, survival-, or differentiation-promoting targets.

[00249] Of the proteins in the cascade, RAF kinases have the most complex regulatory mechanisms, including the ability to form dimers. RAF dimerization is acknowledged to be a required step for RAF signaling in multiple cellular contexts including normal RAS-dependent RAF activation. Furthermore in some oncogenic settings, RAF dimerization contributes to the pathogenic role of the pathway. Specifically, RAF signals as a dimer in settings where oncogenic mutations affect NRAS as well as in settings where there are point mutations of the BRAF protein that do not target the amino acid V600 or K601.

[00250] RAF dimerization has also been found to alter the therapeutic response and disease progression in patients treated with type-1 BRAF ATP-competitive inhibitors (such as vemurafenib). In these settings there is inhibitor-induced RAF heterodimerization that leads to the inadvertent activation of the downstream pathway. This phenomenon is known as paradoxical activation of the MAP kinase pathway and is thought to be the mechanism by which type-1 BRAF inhibitors induce certain adverse events, including the formation of squamous cell carcinomas (SCC). It is for this reason that treatment with type-1 BRAF inhibitors may be contraindicated in cancer settings where mutations in the RAS family or the V600 or K601 BRAF mutations occur.

[00251] Type-1 BRAF ATP-competitive inhibitors have been developed to target BRAF V600* mutations (such as V600E) that occur in melanoma, thyroid, colon cancer and NSCLC. These type-1 BRAF inhibitors have demonstrated clinical benefit for patients with this mutation. The responses observed in these patients can be explained by differences in RAF signaling. In these settings, BRAF functions as a RAF monomer rather than as a RAF dimer. This RAF monomer, signals independent of upstream growth stimuli and leads to constitutive activation of the BRAF monomeric protein. As discussed above, type-1 BRAF inhibitors may be withheld for cancers in the RAF dimer setting. Whereas, a pan-RAF inhibitor such as Compound 1 could in principle work in settings of RAF dimerization in distinct mutant contexts, e.g., BRAF and NRAS.

[00252] Preclinical models have suggested that a higher maximum tolerated dose of Compound 1 may achieve better stasis or tumor regression. Pharmacodynamic effects of Compound 1 in melanoma tumor tissues further support this hypothesis. Accordingly, it has now been discovered that the pharmaceutical compositions of the present invention comprising

Compound 1 can be administered so as to achieve a higher maximum tolerated dose, and thus a higher effective amount, if it is administered using an intermittent dosing regimen.

[00253] Accordingly, the present invention relates to methods of treating cancer in settings of RAF dimerization in the context of BRAF and NRAS positive-mutated cancers, comprising administering such pharmaceutical compositions described herein to a patient according to an intermittent dosing regimen and to the use of such pharmaceutical compositions described herein in the manufacture of medicaments.

[00254] The present invention includes the following embodiments:

[00255] Embodiment [189]: A method for the treatment of cancer in a patient in need of such treatment, comprising administering an effective amount of a pharmaceutical composition as described herein, for example, the pharmaceutical compositions described in embodiments [1] through [89] or [181] through [188] to the patient according to an intermittent dosing regimen, wherein the dosing regimen comprises administering the composition once or twice a week and the amount of the composition administered each week is from about 400 mg to about 1000 mg.

[00256] Embodiment [190]: A method for the treatment of cancer in a patient in need of such treatment, comprising administering an effective amount of a pharmaceutical composition, wherein the pharmaceutical composition comprises (1) a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) one or more pharmaceutically acceptable excipients, to the patient according to an intermittent dosing regimen, wherein the dosing regimen comprises administering the composition once or twice a week and the amount of the composition administered each week is from about 400 mg to about 1000 mg.

[00257] Embodiment [191]: The method of embodiment [190], wherein the pharmaceutical composition comprises (1) a solid dispersion extrudate comprising Compound 1 and a vinylpyrrolidinone-vinyl acetate copolymer and (2) one or more pharmaceutically acceptable excipients.

[00258] Embodiment [192]: The method of embodiment [191], wherein the pharmaceutical composition comprises (1) a solid dispersion extrudate comprising Compound 1 and copovidone and (2) one or more pharmaceutically acceptable excipients.

[00259] Embodiment [193]: The method of any one of embodiments [189] through [192], wherein the dosing regimen comprises administering to the patient the composition once a week with a rest period of 6 days between each administration.

[00260] Embodiment [194]: The method of any one of embodiments [189] through [193], wherein the dosing regimen comprises administering the composition in a single dose. For example, the amount of the composition to be administered for the week is administered a single dose on days 1, 8, 15, and 22 of a 28-day cycle.

[00261] Embodiment [195]: The method of any one of embodiments [189] through [194], wherein the dosing regimen comprises administering the composition in a split dose. For example, “administering the composition in a split dose” means administering at one time point half of the composition to be administered for the week and administering at a later time point the remaining half of the composition. In one aspect, the two half doses are administered on the same day e.g., days 1, 8, 15, and 22 of a 28-day cycle. In one aspect, the two half doses are administered at different time points that are about 12 hours apart. In one aspect, the two half doses are administered at different time points that are 12 hours apart.

[00262] Embodiment [196]: The method of embodiment [195], wherein dosing regimen comprises administering the composition in a split dose on two different days. For example, the two half doses are administered on two different days e.g., days 1 and 2, days 8 and 9, days 15 and 16, and days 22 and 23 of a 28-day cycle.

[00263] Embodiment [197]: The method of any one of embodiments [189] through [196], wherein the amount of the composition administered each week is from about 800 mg to about 1000 mg.

[00264] Embodiment [198]: The method of any one of embodiments [189] through [196], wherein the amount of the composition administered each week is from about 400 mg to about 900 mg.

[00265] Embodiment [199]: The method of any one of embodiments [189] through [196], wherein the amount administered each week is from about 500 mg to about 900 mg.

[00266] Embodiment [200]: The method of any one of embodiments [189] through [196], wherein the amount administered each week is from about 600 mg to about 800 mg.

[00267] Embodiment [201]: The method of any one of embodiments [189] through [196], wherein the amount administered each week is from about 400 mg to about 600 mg.

[00268] Embodiment [202]: The method of any one of embodiments [189] through [196], wherein the amount administered each week is from about 400 mg to about 700 mg.

[00269] Embodiment [203]: The method of any one of embodiments [189] through [196], wherein the amount administered each week is from about 600 mg to about 700 mg.

[00270] Embodiment [204]: The method of any one of embodiments [189] through [196], wherein the amount administered each week is about 300 mg.

[00271] Embodiment [205]: The method of any one of embodiments [189] through [196], wherein the amount administered each week is about 400 mg.

[00272] Embodiment [206]: The method of any one of embodiments [189] through [196], wherein the amount administered each week is about 500 mg.

[00273] Embodiment [207]: The method of any one of embodiments [189] through [196], wherein the amount administered each week is about 600 mg.

[00274] Embodiment [208]: The method of any one of embodiments [189] through [196], wherein the amount administered each week is about 700 mg.

[00275] Embodiment [209]: The method of any one of embodiments [189] through [196], wherein the amount administered each week is about 800 mg.

[00276] Embodiment [210]: The method of any one of embodiments [189] through [196], wherein the amount administered each week is about 900 mg.

[00277] Embodiment [211]: The method of any one of embodiments [189] through [196], wherein the cancer is a solid tumor cancer.

[00278] Embodiment [212]: The method of any one of embodiments [189] through [196], wherein the cancer is relapsed.

[00279] Embodiment [213]: The method of any one of embodiments [189] through [196], wherein the cancer is refractory.

[00280] Embodiment [214]: The method any one of embodiments [189] through [213], wherein the cancer is BRAF and/or NRAS positive cancer.

[00281] As used herein, "BRAF" refers to B-Raf proto-oncogene, serine/threonine kinase, the gene associated with the mRNA sequence assigned as GenBank Accession No. NM_004333, SEQ ID NO:1 (open reading frame is SEQ ID NO:2, nucleotides 62 to 2362 of SEQ ID NO:1), encoding GenPept Accession No. NP_004324, SEQ ID NO:3). Other names for BRAF include rafB1 and Noonan Syndrome 7 (NS7). BRAF functions as a serine/threonine kinase, has a role in regulating the MAP kinase/ERKs signaling pathway and can be found on chromosome 7q.

[00282] As used herein, "NRAS" refers to neuroblastoma RAS viral (v-ras) oncogene homolog, the gene associated with the mRNA sequence assigned as GenBank Accession No. NM_002524, SEQ ID NO:4 (open reading frame is SEQ ID NO:5, nucleotides 255 to 824 of SEQ ID NO:4), encoding GenPept Accession No. NP_002515, SEQ ID NO:6). Other names for NRAS include Autoimmune Lymphoproliferative Syndrome type IV (ALPS4), NRAS1, and

Noonan Syndrome 6 (NS6). NRAS functions as an oncogene with GTPase activity and can be found on chromosome 1p. NRAS interacts with the cell membrane and various effector proteins, such as Raf and RhoA, which carry out its signaling function through the cytoskeleton and effects on cell adhesion (Fotiadou et al. (2007) *Mol. Cel. Biol.* 27:6742-6755).

[00283] As used herein, the phrase “BRAF positive cancer,” “BRAF mutation-positive cancer,” “BRAF positive-mutation cancer,” or “BRAF positive-mutation cancer” means the cancer has one or more mutations in BRAF gene. As used herein “NRAS positive cancer,” “NRAS mutation-positive cancer,” “NRAS positive-mutated cancer,” or “NRAS positive mutation cancer” means the cancer has one or more mutations in NRAS gene. In one aspect, the cancer is BRAF wild type and has one or more mutations in NRAS gene. In one aspect, the cancer is NRAS wild type and has one or more mutations in BRAF gene. In one aspect, the cancer has one or more mutations in both BRAF gene and NRAS gene.

[00284] Embodiment [215]: The method of any one of embodiments [189] through [214], wherein the cancer is BRAF mutation-positive cancer.

[00285] Embodiment [216]: The method of any one of embodiments [189] through [215], wherein the one or more BRAF mutation is in exon 15 or 11.

[00286] Embodiment [217]: The method of any one of embodiments [189] through [216], wherein the one or more BRAF mutation is in codon 464-469, 600 or 601.

[00287] Embodiment [218]: The method of any one of embodiments [189] through [217], wherein the BRAF mutation is V600 mutation. In one aspect, the V600 mutation is V600E, V600G, V600A, or V600K; V600E, V600D, or V600K; or V600E, V600D, V600M, V600G, V600A, V600R, or V600K. In one aspect, the BRAF mutation is V600E. In one aspect, the BRAF mutation is V600D. In one aspect, the BRAF mutation is V600K. “V600E mutation” means substitution of glutamic acid for valine at the amino acid position of 600. “V600K mutation” means substitution of lysine for valine at the amino acid position of 600. “V600D mutation” means substitution of aspartic acid for valine at the amino acid position of 600. “V600G mutation” means substitution of glycine for valine at the amino acid position of 600. “V600A mutation” means substitution of alanine for valine at the amino acid position of 600. “V600M mutation” means substitution of methionine for valine at the amino acid position of 600. “V600R mutation” means substitution of arginine for valine at the amino acid position of 600.

[00288] Embodiment [219]: The method of any one of embodiments [189] through [218], wherein the one or more BRAF mutation is non-V600E mutation. In one aspect, one or more non-V600E mutation is G466A, G466V, N581S, D594H, R146W, L613F, D565_splice, S394*, P367R, G469A, G469V, G469*, G466V, G464V, G397S, S113I, A762E, G469L, D594N,

G596S, G596R, D594N, D594H, or G327_splice. In one aspect, one or more non-V600E mutations are G469R, R95T, A621_splice, V639I, Q609H, G464V, or G466V. The asterisk "*" means a stop codon.

[00289] Embodiment [220]: The method of any one of embodiments [189] through [219], wherein the cancer is NRAS mutation-positive cancer.

[00290] Embodiment [221]: The method of any one of embodiments [189] through [220], wherein one or more NRAS mutation is in exon 3 or exon 4.

[00291] Embodiment [222]: The method of any one of embodiments [189] through [221], wherein one or more NRAS mutation is in codon 59, 61, 117, or 146.

[00292] Embodiment [223]: The method of any one of embodiments [189] through [222], wherein NRAS mutation is Q61. In one aspect, NRAS mutation is Q61R, Q61K, Q61L, Q61H, or Q61P. In one aspect, NRAS mutation is Q61R.

[00293] Embodiment [224]: The method of any one of embodiments [189] through [223], wherein the cancer is skin, ocular, gastrointestinal, thyroid, breast, ovarian, lung, brain, laryngeal, cervical, lymphatic system, genitourinary tract, or bone cancer.

[00294] Embodiment [225]: The method of any one of embodiments [189] through [224], wherein the cancer is skin cancer.

[00295] Embodiment [226]: The method of any one of embodiments [189] through [224], wherein the cancer is ocular cancer.

[00296] Embodiment [227]: The method of any one of embodiments [189] through [224], wherein the cancer is thyroid cancer.

[00297] Embodiment [228]: The method of any one of embodiments [189] through [224], wherein the cancer is breast cancer.

[00298] Embodiment [229]: The method of any one of embodiments [189] through [224], wherein the cancer is ovarian cancer.

[00299] Embodiment [230]: The method of any one of embodiments [189] through [224], wherein the cancer is lung cancer.

[00300] Embodiment [231]: The method of any one of embodiments [189] through [224], wherein the cancer is brain cancer.

[00301] Embodiment [232]: The method of any one of embodiments [189] through [224], wherein the cancer is laryngeal cancer.

[00302] Embodiment [233]: The method of any one of embodiments [189] through [224], wherein the cancer is gastrointestinal cancer.

[00303] Embodiment [234]: The method of any one of embodiments [189] through [224], wherein the cancer is cervical cancer.

[00304] Embodiment [235]: The method of any one of embodiments [189] through [224], wherein the cancer is lymphatic system cancer.

[00305] Embodiment [236]: The method of any one of embodiments [189] through [224], wherein the cancer is genitourinary tract cancer.

[00306] Embodiment [237]: The method of any one of embodiments [189] through [224], wherein the cancer is bone cancer. In one aspect, the bone cancer is multiple myeloma.

[00307] Embodiment [238]: The method of any one of embodiments [189] through [225], wherein the cancer is skin cancer. In one aspect, the skin cancer is melanoma. In one aspect, the melanoma is locally advanced, metastatic and/or unresectable melanoma. In one aspect, the melanoma is locally advanced. In one aspect, the melanoma is metastatic. In aspect, the melanoma is unresectable melanoma. In one aspect, the melanoma is BRAF mutation-positive melanoma. In one aspect, the melanoma is BRAF mutation-positive cutaneous melanoma. In one aspect, BRAF mutation is selected from V600E, V600K, and V600D mutation. In one aspect, BRAF mutation is V600E. In one aspect, BRAF mutation is V600K. In one aspect, BRAF mutation is V600D. In one aspect, the melanoma is NRAS mutation-positive melanoma. In one aspect, the melanoma is NRAS mutation-positive cutaneous melanoma. In one aspect, the melanoma is BRAF/NRAS mutation negative cutaneous melanoma (wild type). In one aspect, the melanoma is of cutaneous, uveal, or mucosal origin. In one aspect, the melanoma is of cutaneous origin. In one aspect, the melanoma is of uveal origin. In one aspect, the melanoma is of mucosal origina.

[00308] Embodiment [239]: The method any one of embodiments [189] through [224], wherein the cancer is ocular cancer. In one aspect, the ocular cancer is ocular melanoma.

[00309] Embodiment [240]: The method of any one of embodiments [189] through [224], wherein the cancer is brain cancer. In one aspect, the brain cancer is glioma, neuroblastoma or astrocytoma. In one aspect, the brain cancer is glioma. In one aspect, the brain cancer is neuroblastoma. In one aspect, the cancer is astrocytoma.

[00310] Embodiment [241]: The method of any one of embodiments [189] through [224], wherein the cancer is genitourinary tract cancer. In one aspect, the genitourinary tract cancer is bladder or prostate cancer. In one aspect, the cancer is bladder cancer. In one aspect, the cancer is prostate cancer.

[00311] Embodiment [242]: The method of any one of embodiments [189] through [224], wherein the cancer is papillary thyroid cancer.

[00312] Embodiment [243]: The method of any one of embodiments [189] through [224], wherein the cancer is a gastrointestinal cancer. In one aspect, the gastrointestinal cancer is esophageal, stomach, colorectal, liver, renal, pancreatic, or gallbladder cancer. In one aspect the gastrointestinal cancer is esophageal cancer. In one aspect the gastrointestinal cancer is stomach cancer. In one aspect the gastrointestinal cancer is colorectal cancer. In one aspect the gastrointestinal cancer is liver cancer. In one aspect the gastrointestinal cancer is renal cancer. In one aspect, the gastrointestinal cancer is pancreatic cancer. In one aspect the gastrointestinal cancer is gallbladder cancer.

[00313] Embodiment [244]: A method for the treatment of melanoma in a patient in need of such treatment, comprising administering an effective amount of a pharmaceutical composition according to any one of embodiments [1] through [89] or [181] through [188] to the patient according to an intermittent dosing regimen, wherein the dosing regimen comprises administering the composition once weekly and the amount of the composition administered each week is from about 400 mg to about 700 mg, wherein the melanoma is BRAF wild type and has a mutation in NRAS gene. In one aspect, NRAS mutation is in exon 3 or 4. In one aspect, NRAS mutation is Q61. In one aspect, the melanoma is relapsed and/or refractory.

[00314] Embodiment [245]: A method for the treatment of melanoma in a patient in need of such treatment, comprising administering an effective amount of a pharmaceutical composition according to any one of embodiments [1] through [89] or [181] through [188] to the patient according to an intermittent dosing regimen, wherein the dosing regimen comprises administering the composition once weekly and the amount of the composition administered each week is from about 400 mg to about 700 mg, wherein the melanoma has a mutation in BRAF gene. In one aspect, BRAF mutation is in exon 15 or 11. In one aspect, BRAF mutation is V600. In one aspect, BRAF mutation is V600E. In one aspect, the melanoma is relapsed and/or refractory.

[00315] Embodiment [246]: A method for the treatment of colorectal cancer in a patient in need of such treatment, comprising administering an effective amount of a pharmaceutical composition according to any one of embodiments [1] through [89] or [181] through [188] to the patient according to an intermittent dosing regimen, wherein the dosing regimen comprises administering the composition once weekly and the amount of the composition administered each week is from about 400 mg to about 700 mg, wherein the colorectal cancer has a mutation in BRAF gene. In one aspect, BRAF mutation is in exon 15 or 11. In one aspect, the BRAF mutation is V600. In one aspect, BRAF mutation is V600E.

[00316] Embodiment [247]: A method for the treatment of non-small cell lung cancer in a patient in need of such treatment, comprising administering an effective amount of a

pharmaceutical composition according to any one of embodiments [1] through [89] or [181] through [188] to the patient according to an intermittent dosing regimen, wherein the dosing regimen comprises administering the composition once weekly and the amount of the composition administered each week is from about 400 mg to about 700 mg, wherein the non-small cell lung cancer has a mutation in BRAF gene. In one aspect, BRAF mutation is non-V600E. In one aspect, BRAF mutation is in exon 15 or 11. In one aspect, the BRAF mutation is V600. In one aspect, BRAF mutation is V600E.

[00317] Embodiment [248]: A method for the treatment of colorectal cancer in a patient in need of such treatment, comprising administering an effective amount of a pharmaceutical composition according to any one of embodiments [1] through [89] or [181] through [188] to the patient according to an intermittent dosing regimen, wherein the dosing regimen comprises administering the composition once weekly and the amount of the composition administered each week is from about 400 mg to about 700 mg, wherein the colorectal cancer has a mutation in NRAS gene. In one aspect, NRAS mutation is in exon 3 or 4. In one aspect, NRAS mutation is in codon 59, 61, 117, or 146.

[00318] Embodiment [249]: A method for the treatment of thyroid cancer in a patient in need of such treatment, comprising administering an effective amount of a pharmaceutical composition according to any one of embodiments [1] through [89] or [181] through [188] to the patient according to an intermittent dosing regimen, wherein the dosing regimen comprises administering the composition once weekly and the amount of the composition administered each week is from about 400 mg to about 700 mg, wherein the thyroid cancer has a mutation in BRAF gene. In one aspect, the BRAF mutation is in exon 15 or 11. In one aspect, the BRAF mutation is V600. In one aspect, the BRAF mutation is V600E.

[00319] Embodiment [250]: The method of any one of embodiments [189] through [249], wherein the patient is naïve to prior therapy with one or more RAF and/or MEK inhibitors.

[00320] Embodiment [251]: The method of any one of embodiments [189] through [249], wherein the patient's response to previous treatment with RAF inhibitors and/or MEK inhibitors has 1) relapsed following an objective response, 2) failed to demonstrate an objective response, and/or 3) could not tolerate such a regimen due to unacceptable toxicity.

[00321] Embodiment [252]: The method of any one of embodiments [189] through [249], wherein the patient has received at least one line of prior anticancer therapy. In one aspect, the method is for treating a patient after failure of at least one standard chemotherapy.

[00322] Embodiment [253]: The method any one of embodiments [189] through [249], wherein the patient is naïve to any prior anticancer treatment except for treatment with ipilimumab, anti-PD-1, and/or anti-PDL-1 mAbs.

[00323] Embodiment [254]: A method for determining whether to treat a patient with a pharmaceutical composition of any one of embodiments [1] through [89] or [181] through [188] comprising:

- a) measuring at least one characteristic of at least one or more BRAF and/or NRAS markers associated with gene mutation in a patient sample comprising tumor cells;
- b) identifying whether the at least one characteristic measured in step a) is informative for outcome upon treatment with the pharmaceutical composition; and
- c) determining to treat the patient with the pharmaceutical composition if the informative characteristic indicates that the tumor cells comprise at least one marker gene with a BRAF and/or NRAS mutational status that indicates a favorable outcome to treatment with the pharmaceutical composition.

[00324] Embodiment [255]: The method of embodiment [254], wherein the at least one characteristic is sequence.

[00325] Embodiment [256]: The method of embodiment [254] or [255], wherein the mutational status of at least one of the BRAF and/or NRAS markers is mutant.

[00326] Embodiment [257]: The method of any one of embodiments [254] through [256], wherein the mutational status of the BRAF marker is mutant.

[00327] Embodiment [258]: The method of any one of embodiments [254] through [257], wherein the BRAF mutation is in exon 15 or 11.

[00328] Embodiment [259]: The method of any one of embodiments [254] through [258], wherein the one or more BRAF mutation is in codon 464-469, 600 or 601.

[00329] Embodiment [260]: The method of any one of embodiments [254] through [259], wherein the BRAF mutation is V600 mutation. In one aspect, the V600 mutation is V600E, V600G, V600A, or V600K; V600E, V600D, or V600K; or V600E, V600D, V600M, V600G, V600A, V600R, or V600K. In one aspect, the BRAF mutation is V600E.

[00330] Embodiment [261]: The method of any one of embodiments [254] through [260], wherein the BRAF mutation is a non-V600E mutation.

[00331] Embodiment [262]: The method of any one of embodiments [254] through [261], wherein the mutational status of the NRAS marker is mutant.

[00332] Embodiment [263]: The method of any one of embodiments [254] through [262], wherein the one or more NRAS mutation is in exon 3 or exon 4.

[00333] Embodiment [264]: The method of any one of embodiments [254] through [263], wherein the one or more NRAS mutation is in codon 59, 61, 117, or 146.

[00334] Embodiment [265]: The method of any one of embodiments [254] through [264], wherein the NRAS mutation is Q61. In one aspect, the NRAS mutation is Q61R, Q61K, Q61L, Q61H, or Q61P. In one aspect, the NRAS mutation is Q61R.

[00335] Embodiment [266]: A method for determining an increased likelihood of pharmacological effectiveness of treatment by a pharmaceutical composition as described herein in an patient diagnosed with cancer (particularly a cancer selected from those cancers described herein), said method comprising

subjecting a nucleic acid sample from a cancer (tumor) sample from the patient to BRAF or NRAS mutational testing or PCR, wherein the presence of at least one mutation in BRAF or NRAS gene, such as e.g., one or more of those mutations described herein, indicates an increased likelihood of pharmacological effectiveness of the treatment.

[00336] Embodiment [267]: A method of treating a patient having cancer (particularly a cancer described herein), said method comprising:

- i) obtaining a nucleic acid sample from a cancer sample from said patient;
- ii) subjecting the sample to BRAF or NRAS mutational testing or PCR and identifying the presence of at least one mutation in BRAF or NRAS gene (such as e.g., one or more of those mutations described herein); and
- iii) administering an effective amount of a pharmaceutical composition as described herein to the patient in whose sample the presence of at least one mutation in BRAF or NRAS gene (such as e.g., one or more of those mutations described herein) is identified.

[00337]

[00338]

[00339] It will be understood that any of the above embodiments may be combined to form additional embodiments.

General Procedures

[00340] In some embodiments, a mutation in a marker can be identified by sequencing a nucleic acid, e.g., a DNA, RNA, cDNA or a protein correlated with the marker gene, e.g., a

genotype marker gene, e.g., BRAF or NRAS. There are several sequencing methods known in the art to sequence nucleic acids. A nucleic acid primer can be designed to bind to a region comprising a potential mutation site or can be designed to complement the mutated sequence rather than the wild type sequence. Primer pairs can be designed to bracket a region comprising a potential mutation in a marker gene. A primer or primer pair can be used for sequencing one or both strands of DNA corresponding to the marker gene. A primer can be used in conjunction with a probe, e.g., a nucleic acid probe, e.g., a hybridization probe, to amplify a region of interest prior to sequencing to boost sequence amounts for detection of a mutation in a marker gene. Examples of regions which can be sequenced include an entire gene, transcripts of the gene and a fragment of the gene or the transcript, e.g., one or more of exons or untranslated regions or a portion of a marker comprising a mutation site. Examples of mutations to target for primer selection and sequence or composition analysis can be found in public databases which collect mutation information, such as Database of Genotypes and Phenotypes (dbGaP) maintained by the National Center for Biotechnology Information (Bethesda, MD) and Catalogue of Somatic Mutations in Cancer (COSMIC) database maintained by the Wellcome Trust Sanger Institute (Cambridge, UK).

[00341] Sequencing methods are known to one skilled in the art. Examples of methods include the Sanger method, the SEQUENOM™ method and Next Generation Sequencing (NGS) methods. The Sanger method, comprising using electrophoresis, e.g., capillary electrophoresis to separate primer-elongated labeled DNA fragments, can be automated for high-throughput applications. The primer extension sequencing can be performed after PCR amplification of regions of interest. Software can assist with sequence base calling and with mutation identification. SEQUENOM™ MASSARRAY® sequencing analysis (San Diego, CA) is a mass-spectrometry method which compares actual mass to expected mass of particular fragments of interest to identify mutations. NGS technology (also called “massively parallel sequencing” and “second generation sequencing”) in general provides for much higher throughput than previous methods and uses a variety of approaches (reviewed in Zhang et al. (2011) *J. Genet. Genomics* 38:95-109 and Shendure and Hanlee (2008) *Nature Biotech.* 26:1135-1145). NGS methods can identify low frequency mutations in a marker in a sample. Some NGS methods (see, e.g., GS-FLX Genome Sequencer (Roche Applied Science, Branford, CT), Genome analyzer (Illumina, Inc. San Diego, CA) SOLID™ analyzer (Applied Biosystems, Carlsbad, CA), Polonator G.007 (Dover Systems, Salem, NH), HELISCOPE™ (Helicos Biosciences Corp., Cambridge, MA)) use cyclic array sequencing, with or without clonal amplification of PCR products spatially separated in a flow cell and various schemes to detect the labeled modified nucleotide that is incorporated

by the sequencing enzyme (e.g., polymerase or ligase). In one NGS method, primer pairs can be used in PCR reactions to amplify regions of interest. Amplified regions can be ligated into a concatenated product. Clonal libraries are generated in the flow cell from the PCR or ligated products and further amplified (“bridge” or “cluster” PCR) for single-end sequencing as the polymerase adds a labeled, reversibly terminated base that is imaged in one of four channels, depending on the identity of the labeled base and then removed for the next cycle. Software can aid in the comparison to genomic sequences to identify mutations. Another NGS method is exome sequencing, which focuses on sequencing exons of all genes in the genome. As with other NGS methods, exons can be enriched by capture methods or amplification methods.

[00342] In some embodiments, DNA, e.g., genomic DNA corresponding to the wild type or mutated marker can be analyzed both by *in situ* and by *in vitro* formats in a biological sample using methods known in the art. DNA can be directly isolated from the sample or isolated after isolating another cellular component, e.g., RNA or protein. Kits are available for DNA isolation, e.g., QIAAMP® DNA Micro Kit (Qiagen, Valencia, CA). DNA also can be amplified using such kits.

[00343] In another embodiment, mRNA corresponding to the marker can be analyzed both by *in situ* and by *in vitro* formats in a biological sample using methods known in the art. Many expression detection methods use isolated RNA. For *in vitro* methods, any RNA isolation technique that does not select against the isolation of mRNA can be utilized for the purification of RNA from tumor cells (see, e.g., Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York 1987-1999). Additionally, large numbers of tissue samples can readily be processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski (1989, U.S. Patent No. 4,843,155). RNA can be isolated using standard procedures (see e.g., Chomczynski and Sacchi (1987) *Anal. Biochem.* 162:156-159), solutions (e.g., trizol, TRI REAGENT® (Molecular Research Center, Inc., Cincinnati, OH; see U.S. Patent No. 5,346,994) or kits (e.g., a QIAGEN® Group RNEASY® isolation kit (Valencia, CA) or LEUKOLOCK™ Total RNA Isolation System, Ambion division of Applied Biosystems, Austin, TX).

[00344] Additional steps may be employed to remove DNA from RNA samples. Cell lysis can be accomplished with a nonionic detergent, followed by microcentrifugation to remove the nuclei and hence the bulk of the cellular DNA. DNA subsequently can be isolated from the nuclei for DNA analysis. In one embodiment, RNA is extracted from cells of the various types of interest using guanidinium thiocyanate lysis followed by CsCl centrifugation to separate the RNA from DNA (Chirgwin *et al.* (1979) *Biochemistry* 18:5294-99). Poly(A)+RNA is selected by

selection with oligo-dT cellulose (see Sambrook *et al.* (1989) *Molecular Cloning--A Laboratory Manual* (2nd ed.), Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.). Alternatively, separation of RNA from DNA can be accomplished by organic extraction, for example, with hot phenol or phenol/chloroform/isoamyl alcohol. If desired, RNase inhibitors may be added to the lysis buffer. Likewise, for certain cell types, it may be desirable to add a protein denaturation/digestion step to the protocol. For many applications, it is desirable to enrich mRNA with respect to other cellular RNAs, such as transfer RNA (tRNA) and ribosomal RNA (rRNA). Most mRNAs contain a poly(A) tail at their 3' end. This allows them to be enriched by affinity chromatography, for example, using oligo(dT) or poly(U) coupled to a solid support, such as cellulose or SEPHADEX.R™. medium (see Ausubel *et al.* (1994) *Current Protocols In Molecular Biology*, vol. 2, Current Protocols Publishing, New York). Once bound, poly(A)+mRNA is eluted from the affinity column using 2 mM EDTA/0.1% SDS.

[00345] A characteristic of a marker of the invention in a sample, e.g., after obtaining a sample (e.g., a tumor biopsy) from a test subject, can be assessed by any of a wide variety of well known methods for detecting or measuring the characteristic, e.g., of a marker or plurality of markers, e.g., of a nucleic acid (e.g., RNA, mRNA, genomic DNA, or cDNA) and/or translated protein. Non-limiting examples of such methods include immunological methods for detection of secreted, cell-surface, cytoplasmic, or nuclear proteins, protein purification methods, protein function or activity assays, nucleic acid hybridization methods, optionally including "mismatch cleavage" steps (Myers, *et al.* (1985) *Science* 230:1242) to digest mismatched, i.e. mutant or variant, regions and separation and identification of the mutant or variant from the resulting digested fragments, nucleic acid reverse transcription methods, and nucleic acid amplification methods and analysis of amplified products. These methods include gene array/chip technology, RT-PCR, TAQMAN® gene expression assays (Applied Biosystems, Foster City, CA), e.g., under GLP approved laboratory conditions, *in situ* hybridization, immunohistochemistry, immunoblotting, FISH (fluorescence *in situ* hybridization), FACS analyses, northern blot, southern blot, INFINIUM® DNA analysis Bead Chips (Illumina, Inc., San Diego, CA), quantitative PCR, bacterial artificial chromosome arrays, single nucleotide polymorphism (SNP) arrays (Affymetrix, Santa Clara, CA) or cytogenetic analyses.

[00346] Examples of techniques for detecting differences of at least one nucleotide between two nucleic acids include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide probes can be prepared in which the known polymorphic nucleotide is placed centrally (allele- or mutant-specific probes) and then hybridized to target DNA under conditions which permit hybridization

only if a perfect match is found (Saiki *et al.* (1986) *Nature* 324:163); Saiki *et al.* (1989) *Proc. Natl Acad. Sci USA* 86:6230; and Wallace *et al.* (1979) *Nucl. Acids Res.* 6:3543). Such allele specific oligonucleotide hybridization techniques can be used for the simultaneous detection of several nucleotide changes in different polymorphic or mutated regions of NRAS. For example, oligonucleotides having nucleotide sequences of specific allelic variants or mutants are attached to a solid support, e.g., a hybridizing membrane and this support, e.g., membrane, is then hybridized with labeled sample nucleic acid. Analysis of the hybridization signal thus can reveal the identity of the nucleotides of the sample nucleic acid.

EXPERIMENTAL PROCEDURES

[00347] The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitations on the scope of the invention.

[00348] Manufacture of multi-component pharmaceutical dosage forms with pharmaceutically acceptable polymeric compositions as described herein.

Example 1: Experimental Procedure for Preparation of Solid Dispersion Extrudate

Table A. Solid Dispersion Extrudate

Solid Dispersion Extrudate Formulation	Procedure 1	Procedure 2	Procedure 3	
	Weight (g) for Example 2 and 3A	Weight (g) for Example 3B	Weight (g) for Example 4, 5 and 6	(% w/w)
Compound 1	1200g x 3batches =3600g	2000g x 2batches =4000g	4400g	40
copovidone	1800g x 3batches =5400g	3000g x 2batches =6000g	6600g	60

Procedure 1:

[00349] 1,200 grams of Compound 1 and 1,800 grams of copovidone (e.g., Kollidon VA64, BASF) were accurately weighed, screened with a suitable sieve (e.g. 12 mesh) and mixed using a high shear mixer (e.g., Vector GMX-25 high share mixer) operated at 325 rpm \pm 25rpm for about five minutes to form a pre-extrusion blended powder.

[00350] A suitable twin screw hot melt extruder (e.g. Leistritz ZSE-18HP) was set up with appropriate supporting equipment, including a cooling conveyor (e.g., Dorner Cooling Conveyor) and feeder with auger (e.g., K-Tron Gravimetric Feeder). The processing parameters were as follows:

Feed rate: 1.0 kg/hr (Range: 0.5~1.5 kg/hr);

Screw speed: 250 rpm (Range: 225~275 rpm);

Barrel temperature: zone1: 50 ±5 °C, zone2: 90 ±5 °C, zone3: 140±5 °C, zone4: 170±5 °C, Die heater: 165±10 °C

[00351] Three batches of the pre-extrusion blended powder were fed into the Hot Melt Extruder, and the resulting extrudate was cooled and milled using a suitable impact mill with hammer forward configuration (e.g., Fizmill model L1A) operated at 9,000±1,000 rpm. The milled extrudate was passed through a suitable screen (e.g., 60 mesh) manually.

Procedure 2:

[00352] 2,000 grams of Compound 1 and 3,000 grams of copovidone (e.g., Kollidon VA64, BASF) were accurately weighed, screened with a suitable sieve (e.g. 12 mesh) and mixed using high shear mixing (e.g. POWREX VG-50 high share vertical granulator) operated at 325 rpm ±25rpm for about ten minutes to form a pre-extrusion blended powder.

[00353] A suitable twin screw hot melt extruder (e.g. Leistritz ZSE-18HP) was set up with appropriate supporting equipment, including a cooling conveyor (e.g., Dorner End Drive Conveyor) and feeder with auger (e.g., K-Tron Gravimetric Feeder). Processing parameters were as follows:

Feed rate: 1.0 kg/hr (Range: 0.5~1.5 kg/hr);

Screw speed: 250 rpm (Range: 225~275 rpm);

Barrel temperature: zone1: 50 ±5 °C, zone2: 90 ±5 °C, zone3: 140±5 °C, zone4: 170±5 °C, Die heater: 165±10 °C;

[00354] Two batches of the pre-extrusion blended powder were fed into the Hot Melt Extruder, and the resulting extrudate was cooled and milled using a suitable impact mill with hammer forward configuration (e.g., Fizmill model M5A) operated at 6,000 rpm ±100rpm. The milled extrudate was passed through a suitable screen (e.g., 60 mesh) manually or using automatic sieve shaker (e.g., Kason sieve shaker).

Procedure 3:

[00355] 4,400 grams of Compound 1 and 6,600 grams of copovidone (e.g., Kollidon VA64, BASF) were accurately weighed and mixed using high shear mixing (e.g. Diosna P100 high share vertical granulator) operated at 200 rpm for about ten minutes to form a pre-extrusion blended powder.

[00356] A suitable twin screw hot melt extruder (e.g. Leistritz ZSE-18HP) was set up with appropriate supporting equipment, including a cooling conveyor (e.g., Nara TBC-309-DC) and feeder with auger (e.g., K-Tron Gravimetric Feeder). Processing parameters were as follows:
 Feed rate: 1.0 kg/hr (Range: 0.5~1.5 kg/hr);
 Screw speed: 275 rpm (Range: 250~300 rpm);
 Barrel temperature: zone1: 50 ±10 °C, zone2: 90 ±10 °C, zone3: 140±10 °C, zone4: 175±10 °C,
 Die heater: 175±10 °C;

[00357] The pre-extrusion blended powder was fed into the Hot Melt Extruder, and the resulting extrudate was cooled and milled using a suitable pulverizer with multi pin rotor and suitable screen (e.g., NARA Sample mill SAM with 0.5mm screen) operated at 10,000 rpm.

Example 2: Experimental Procedure for Composition of Compound 1, 20 mg Tablet

Table B. 20 mg Tablet Formulation

Pharmaceutical Composition Formulation	(% w/w)
Solid Dispersion Extrudate	20.0
microcrystalline cellulose	70.0
croscarmellose sodium	5.0
colloidal silicon dioxide	4.5
magnesium stearate	0.5

[00358] 1,700 grams of the sieved Extrudate (from Procedure 1), 5,950 grams of microcrystalline cellulose (e.g., Avicel PH 102, FMC Biopolymer), 425.0 grams of croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymer) and 382.5 grams of colloidal silicon dioxide were accurately weighed. The extrudate, croscarmellose sodium and approximately half of the microcrystalline cellulose were charged into a diffusion mixer (e.g. Bohle LM40 Bin Blender). The colloidal silicon dioxide was combined with the remaining microcrystalline cellulose and screened through a suitable screen (e.g. 40 mesh) and charged into the mixer. And

then the powders were blended for 10 minutes at 25 rpm to produce the pre-blend powder. 42.5 grams of magnesium stearate (Mallinckrodt) were accurately weighed, screened with a suitable screen (e.g., 30 mesh) and blended with the pre-blend for 5 minutes at 25 rpm to produce the final blended powder. The final blended powder was compressed by a rotary tablet-making machine (e.g., Stokes B2 16 station tablet press) using 9mm round punch to produce tablets which weight is 250 mg.

Example 3: Experimental Procedures for Composition of Compound 1, 100 mg Tablet

Table C. 100 mg Tablet Formulation

Pharmaceutical Composition Formulation	(% w/w)
Solid Dispersion Extrudate	40
microcrystalline cellulose	47.0
croscarmellose sodium	8.0
colloidal silicon dioxide	4.5
Magnesium stearate	0.5

[00359] 3,400 grams of the sieved Extrudate (from Procedure 1), 3,995 grams of Microcrystalline cellulose (e.g., Avicel PH 102, FMC Biopolymer), 680.0 grams of croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymer) and 382.5 grams of colloidal silicon dioxide were accurately weighed. The extrudate, croscarmellose sodium and approximately half of the microcrystalline cellulose were charged into a diffusion mixer (e.g. Bohle LM40 Bin Blender). The colloidal silicon dioxide was combined with the remaining microcrystalline cellulose and screened through a suitable screen (e.g. 40 mesh) and charged into the mixer. And then the powders were blended for 10 minutes at 25 rpm to produce the pre-blend powder. 42.5 grams of Magnesium stearate (Mallinckrodt) was accurately weighed, screened with a suitable screen (e.g., 30 mesh) and blended with the pre-blend for 5 minutes at 25 rpm to produce the final blended powder. The final blended powder was compressed by a rotary tablet-making machine (e.g., Stokes B2 16 station tablet press) 8mm by 18 mm caplet punch to produce tablets which weight is 625 mg.

Table D. 100 mg Tablet Formulation

Pharmaceutical Composition Formulation	(% w/w)
Solid Dispersion Extrudate	40
microcrystalline cellulose	47.0
croscarmellose sodium	8.0
colloidal silicon dioxide	4.5
Magnesium stearate	0.5

[00360] 6,600 grams of the sieved Extrudate (from Procedure 2), 7,755 grams of microcrystalline cellulose (e.g., Avicel PH 102, FMC Biopolymer), 1,320 grams of croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymer) and 742.5 grams of colloidal silicon dioxide (e.g., Aerosil 200, Evonik) were accurately weighed. The extrudate and the croscarmellose sodium were charged into a diffusion mixer (e.g. Showa Kagaku Kikai Kosakusho TM-60S). The colloidal silicon dioxide was combined with the microcrystalline cellulose and screened through a suitable screen (e.g. 30 mesh) and charged into the mixer. And then the powders were blended for 5 minutes at 15 rpm to produce the pre-blended powder. 82.5 grams of Magnesium stearate (Mallinckrodt) was accurately weighed, screened with a suitable screen (e.g., 30 mesh), and blended with the pre-blended powder for 2 minutes at 15 rpm to produce the final blended powder. The final blended powder was compressed by a rotary tablet-making machine (e.g. Kikusui Seisakusho, Ltd AQUARIUS) using 8mm by 18 mm caplet punch to produce tablets which weight was 625 mg.

Example 4: Experimental Procedures for Composition of Compound 1, 20 mg Film Coated Tablet

Table E. 20 mg Film Coated Tablet Formulation

Pharmaceutical Composition Formulation	(% w/w)
Solid Dispersion Extrudate	20.0
microcrystalline cellulose	74.0
croscarmellose sodium	5.0
colloidal silicon dioxide	0.5

magnesium stearate	0.5
total core tablet	100.0
OPADRY® Red (% of core tablet weight)	4.2

[00361] 2,000 grams of the extrudate (from Procedure 3), 7,400 grams of microcrystalline cellulose (e.g., Avicel PH 101, FMC Biopolymer), 500.0 grams of croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymer) and 50.0 grams of colloidal silicon dioxide were accurately weighed. The colloidal silicon dioxide and a part of the microcrystalline cellulose were charged into a diffusion mixer (e.g. Bohle LM40 Bin Blender with 10L mixing container) and blended for 5 min at 6 rpm. The powders were screened through a suitable screen (e.g. sieve size 0.5 mm) and charged into a suitable diffusion mixer (e.g. Bohle LM40 Bin Blender with 40L mixing container). The extrudate, croscarmellose sodium and the remaining microcrystalline cellulose were charged into the mixer. The powders were blended for 15 min at 6 rpm to produce the pre-blend powder. 50.0 grams of magnesium stearate (Mallinckrodt) were accurately weighed, screened with a suitable screen (e.g., sieve size 1.0 mm) and blended with the pre-blend for 5 minutes at 6 rpm to produce the final blended powder. The final blended powder was compressed by a rotary tablet-making machine (e.g., Korsch XL 100) using 9mm round punch to produce core tablets which weight is 250 mg. Subsequently, 840.0 gram of OPADRY® RED 03F45081 and 6,160 grams of purified water were added into a tank and the spray suspension was prepared by stirring. The core tablets were charged into a suitable film coating machine (e.g. Driacoater Vario 500/600) and were coated with the spray suspension until the coating amount per tablet reached 10.5mg.

Example 5: Experimental Procedures for Composition of Compound 1, 70 mg Film Coated Tablet

Table F. 70 mg Film Coated Tablet Formulation

Pharmaceutical Composition Formulation	(% w/w)
Solid Dispersion Extrudate	32.4
microcrystalline cellulose	58.6
croscarmellose sodium	8.0
colloidal silicon dioxide	0.5

magnesium stearate	0.5
total core tablet	100.0
OPADRY® Yellow (% of core tablet weight)	3.3

[00362] 3,241 grams of the extrudate (from Procedure 3), 5,859 grams of microcrystalline cellulose (e.g., Avicel PH 101, FMC Biopolymer), 800.0 grams of croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymer) and 50.0 grams of colloidal silicon dioxide were accurately weighed. The colloidal silicon dioxide and a part of the microcrystalline cellulose were charged into a diffusion mixer (e.g. Bohle LM40 Bin Blender with 10L mixing container) and blended for 5 min at 6 rpm. The powders were screened through a suitable screen (e.g. seive size 0.5 mm) and charged into a suitable diffusion mixer (e.g. Bohle LM40 Bin Blender with 40L mixing container). The extrudate, croscarmellose sodium and the remaining microcrystalline cellulose were charged into the mixer. The powders were blended for 15 min at 6 rpm to produce the pre-blend powder. 50.0 grams of magnesium stearate (Mallinckrodt) were accurately weighed, screened with a suitable screen (e.g., seive size 1.0 mm) and blended with the pre-blend for 5 min at 6 rpm to produce the final blended powder. The final blended powder was compressed by a rotary tablet-making machine (e.g., Korsch XL 100) using a 9mm by 14mm oblong punch to produce core tablets which weighed 540 mg. Subsequently, 667.0 gram of OPADRY® Yellow 03F42240 and 4,889 grams of purified water were added into a tank and the spray suspension was prepared by stirring. The core tablets were charged into a suitable film coating machine (e.g. Driacoater Vario 500/600) and were coated with the spray suspension until the coating amount per tablet reached 18.0 mg.

Example 6: Experimental Procedures for Composition of Compound 1, 100 mg Film Coated Tablet

Table G. 100 mg Film Coated Tablet Formulation

Pharmaceutical Composition Formulation	(% w/w)
Solid Dispersion Extrudate	40.0
microcrystalline cellulose	51.0
croscarmellose sodium	8.0

colloidal silicon dioxide	0.5
magnesium stearate	0.5
total core tablet	100.0
OPADRY® Red (% of core tablet weight)	1.12
OPADRY® Yellow (% of core tablet weight)	2.24

[00363] 4,000 grams of the extrudate (from Procedure 3), 5,100 grams of microcrystalline cellulose (e.g., Avicel PH 101, FMC Biopolymer), 800.0 grams of croscarmellose sodium (Ac-Di-Sol®, FMC Biopolymer) and 50.0 grams of colloidal silicon dioxide were accurately weighed. The colloidal silicon dioxide and a part of the microcrystalline cellulose were charged into a diffusion mixer (e.g. Bohle LM40 Bin Blender with 10L mixing container) and blended for 5 min 6 rpm. The powders were screened through a suitable screen (e.g. sieve size 0.5 mm) and charged into a suitable diffusion mixer (e.g. Bohle LM40 Bin Blender with 40L mixing container). The extrudate, croscarmellose sodium and the remaining microcrystalline cellulose were charged into the mixer. The powders were blended for 15 min at 6 rpm to produce the pre-blend powder. 50.0 grams of magnesium stearate (Mallinckrodt) were accurately weighed, screened with a suitable screen (e.g., sieve size 1.0 mm) and blended with the pre-blend for 5 min at 6 rpm to produce the final blended powder. The final blended powder was compressed by a rotary tablet-making machine (e.g., Korsch XL 100) using a 9mm by 16mm oval punch to produce core tablets which weight is 625 mg. Subsequently, 224.0 grams of OPADRY® RED 03F45081, 448.0 grams of OPADRY® Yellow 03F42240 and 4,928 grams of purified water were added into a tank and the spray suspension was prepared by stirring. The core tablets were charged into a suitable film coating machine (e.g. Driacoater Vario 500/600) and were coated with the spray suspension until the coating amount per tablet reached 21.0 mg.

Example 7: Hot Melt Extrusion Solid Dispersion Carrier Development

[00364] Due to the limited solubility of Compound 1, an extensive amount of development work was required to produce the pharmaceutical composition of the present invention. Pre-formulation studies, including significant testing related to solubility, dissolution, and stability led to the initial identification of solid dispersion as a strategy for formulation development. Following the pre-formulation work, several different types of solid dispersions were evaluated. For example, complexes with resins were tried in an effort to combine slow release of drug

substance without precipitation, and compositions comprising many different types of polymers (solid-based and non-solid based), surfactants, and plasticizers were also prepared, and dissolution characteristics and stability were studied. These solid dispersions were initially prepared by solvent evaporation. Later, hot melted extrusion was tried to avoid the use of solvents in manufacture.

[00365] Melt extrusion was identified as the preferred method of manufacture for solid dispersion of Compound 1 due to the improved oral bioavailability provided by the material. Further feasibility studies were carried out to investigate additional polymer types and other excipients. Optimization of polymer type and drug load during hot melt extrusion was critical in order to avoid racemization and crystallization of drug substance. Critical process parameters such as feed rate and zone temperature were also found to have a significant impact on critical product attributes (amorphous nature, chiral purity) of the solid dispersion.

[00366] Studies indicated that high levels of a chiral impurity (the S-enantiomer of Compound 1) were observed when hot melt extrusion was used for production of the solid dispersion extrudates of Compound 1. Incorporation of processing additives such as poloxamer and polysorbate failed to show any significant reduction in the level of chiral impurity formation. Table E shows the results of one study that was carried out to evaluate the potency, chiral purity, non-sink dissolution, and glass transition values of several solid dispersion compositions. Copovidone (Kollidon® VA 64) was selected as the primary polymer for dispersion due to the low level of formation of chiral impurity. The amount of Compound 1 (the desired R-isomer) was measured by high performance liquid chromatography.

Table E. Potency, Chiral Purity, Non-Sink Dissolution and Glass Transition (TG) Values of Screening Study Batches

Batch Number	Composition	Potency (%)	Chiral Impurity (%)	Glass Transition (°C)	Non-Sink AUC _{0→6} (µg·hr/ml)
1	Compound 1: Copovidone (45:55)	99.2	9.49	111	366.102
2	Compound 1: Copovidone (45:55)	97.0	4.37	111	3,375.595
3	Compound 1: Copovidone: Tween 80 (45:55:10)	NA	NA	NA	NA
4	Compound 1: Copovidone: Tween 80 (30:60:10)	99.2	7.61	84	6,216.536
5	Compound 1: Copovidone: Tween 80 (40:50:10)	99.2	6.07	81	4,613.41
6	Compound 1: Copovidone: Tween 80 (40:50:10)	99.3	17.91	85	NA
7	Compound 1: Eudragit® L100-	99.3	50.54	61	8,794.975

	55:Triethyl Citrate (20:64:16)				
8	Compound 1: Eudragit® L100-55:Triethyl Citrate (40:54:6)	98.8	50.45	86	4,409.724
9	Compound 1:HPMCAS-M (20:80)	100.8	49.29	93	4,489.699
10	Compound 1:HPMCAS-M (40:60)	97.0	45.62	92	4,088.841
11	Compound 1:Eudragit® E PO (30:70)	94.5	48.14	NA	11,687.956 *
12	Compound 1:Copovidone: Poloxamer 407 (40:50:10)	96.8	5.68	109	3,130.347
13	Compound 1:Copovidone:Sodium Lauryl Sulfate (40:56:4)	98.4	49.32	NA	5,253.017
14	Compound 1:Copovidone:Tween 80 (5:85:10)	101.2	15.45	NA	10,726.54

*Dissolution testing conducted in simulated gastric fluid

NT = not tested

HPMCAS-M = hypromellose acetate succinate

[00367] Non-sink dissolution testing was performed using a modified centrifuge method with biosimilar media. Briefly, approximately 4.0 mg of Compound 1 equivalent solid dispersion was accurately weighed and dispersed into a centrifuge vial with 0.5% w/w bile salt (NaTC, POPC), pH 6.5 phosphate media and stored under shaking at 250 rpm. At predetermined time points the centrifuge vial was spun at 13,000 rpm and 25 microliters of supernatant sampled without replacement for analysis by HPLC. The remaining material was briefly vortex mixed prior to returning to the incubated shaker system maintained at 37 °C in order to re-suspend material.

[00368] Samples were analyzed by differential scanning calorimetry (DSC) using a Diamond DSC. All samples were analyzed from 25 °C to 225 °C using a ramp rate of 10 °C/min and sample size of approximately 8 mg. Natural glass transition temperatures were obtained by analysis of the second heating cycle.

Example 8: Processing Additives

[00369] Selected formulations from Table E (Batch 2, 5, and 12) using the Kollidon® VA 64 carrier were placed on an accelerated (40 °C/75% RH) open dish stability for one month and examined by scanning electron microscopy to assess potential surface recrystallization. Surface images of compositions containing processing additives such as Tween 80 and Poloxamer 407

showed indications of recrystallization. The magnitude of this behavior was significantly influenced by the type of additive selected. Compositions containing Poloxamer 407 exhibited substantial surface recrystallization over the storage period, while formulations using Tween 80 showed only the minimal potential recrystallization. Solid dispersion produced without a processing aid exhibited excellent amorphous stability, showing no indications of recrystallization.

[00370] Kollidon® VA 64 compositions with and without a non-ionic surfactant, Poloxamer 407, from Table E (Batch 2 and 12) were also evaluated for oral bioavailability enhancement in cynomolgus monkeys. The compositions were administered to achieve a target dose of 25 mg/kg body weight of the Compound 1 (R-enantiomer). Formulation development results showed that these compositions provided similar physicochemical properties and also yielded similar non-sink dissolution behavior. A second batch containing Poloxamer 407 was produced for this dosing experiment using a ZSE-18 mm extruder (the original batches were produced using a Nano-16 extruder). Additionally, to enhance disintegration of the compositions, all dosed capsules contained Polyplasdone XL-10 (Crospovidone) at a loading of 4.0%. This second batch yielded similar potency and chiral impurity levels as previously described for equivalent formulations; however presented a significantly reduced oral bioavailability in comparison to the Poloxamer 407 free formulation (Batch 2). The formulations studied presented relative oral bioavailabilities of $104\% \pm 33\%$ and $38\% \pm 19\%$ for the Poloxamer 407 free and Poloxamer 407 containing formulations respectively.

Example 9: Bioavailability Study

[00371] Tablet and capsule dosage forms were prepared to support oral bioavailability in cynomologus monkeys. Formulations for each batch are presented in Table F below along with composition attributes.

Table F.

Material	Compound 1 Tablets, 100 mg	Compound 1 Capsules, 100 mg
Extrudate 400 mg/g	40.0%	86.24%
Microcrystalline cellulose, Avicel PH 102	45.0%	6.76%
Polyplasdone XL	--	5.0%
Croscarmellose Sodium, Ac-Di-Sol	10.0%	--
Colloidal Silicon Dioxide, Aerosil 200	4.5%	2.00

Magnesium Stearate	0.5%	--

Table G.

Solid Dispersion Composition Attributes		
Metric	Compound 1 Tablets, 100 mg Value	Compound 1 Capsules, 100 mg Value
Potency	104.7%	103.9%
Total Impurities	0.66%	0.66%
RRT 0.79	0.16%	0.16%
RRT 0.84	0.05%	0.05%
RRT 0.84	0.027%	0.027%
Chiral Impurity	3.47%	3.5%
Amorphous Character	Amorphous	Amorphous

[00372] Tablets prepared to support the animal trial were adjusted based on the measured potency and chiral purity of the extrudate to achieve a target delivery of 100 mg of Compound 1. Potency values for both the tablet and capsule tested at approximately 103.5% to account for the measured chiral impurity level of the extrudate. The composition attributes (Table G) associated with the chemical purity indicated that the dosage forms produced provided a robust product with no significant decomposition induced by the manufacturing process.

[00373] The amorphous nature of the solid dispersion compositions was assessed by XRPD, with representative diffraction patterns for each constituent raw material and the respective dosage forms presented in Figure 2. Results show that only magnesium stearate and crystalline Compound 1 produced characteristic peaks indicative of their crystalline nature. Other materials in the composition were shown to be amorphous due to the absence of characteristic peaks associated with crystalline structure. Testing of both compositions showed that the materials prepared for the study were amorphous, demonstrating amorphous halos characteristic of the major amorphous excipients in the formulations. Based on these results, compositions prepared were shown to be amorphous.

[00374] Dissolution behavior of the compositions produced was also assessed using sink dissolution, with profiles presented in Figure 3 (diamond = tablet; square = capsule). Compound 1 tablets showed rapid dissolution. Capsule formulations showed muted release relative to the tablet formulation.

[00375] Preclinical bioavailability studies were conducted in cynomolgus monkeys (n = 3) at an approximate dose of 25 mg/kg to assess oral bioavailability of tablet and capsule dosage forms prepared by hot melt extrusion and spray drying. Melt extruded compositions were shown to provide superior AUC values compared to spray dried formulations. Mean plasma profiles for each of the formulations are presented in Figure 4.

Example 10: High Shear Mixing Reduces Potency Variation

[00376] Due to the continuous nature of the extrusion process potency variation must be kept to a minimum to yield a robust manufacturing procedure. During the initial development runs significant intra-batch potency variation was observed that could not be accounted for based on a mass balance and suggested heterogeneity of the feed stock during processing. For the preparation of the initial development batches a bag blending procedure was used where Compound 1 and Kollidon® VA 64 were added into a polyethylene bag and manually agitated for a period of up to 5 minutes. Once potency variability within batches was observed, a procedural change was made to prepare feed stock material by screening both components through an 18-mesh screen and mixing in a high shear mixer for two minutes at 1,500 rpm. A retroactive comparison of the potency values, presented in Figure 5, showed that the use of high shear mixing significantly reduced potency variation.

Example 11: Tablet Disintegration

[00377] For the preliminary disintegration study tablets were manually prepared at 100 mg strength using 10.0 mm round, standard concave tooling at compression forces of 4.8, 6.9, 6.2 and 13.9 kN, respectively from blend batches having extrudate levels of 62.5% and 80%. Forces used for compression were selected to yield tablets with approximate hardness values of 10.0 ± 5.0 kP. Disintegration testing was conducted using simulated gastric fluid to assess performance. Results from testing the prototype batches showed limited disintegration, with measured times greater than 180 min for the samples selected. Additional optimization was conducted by sequentially reducing the solid dispersion loading and also modifying the grade of diluent and superdisintegrant used. For this study, four formulation modifications and two tooling types were investigated, as presented in Table H. Results showed that reductions in solid dispersion loading from 62.5% to 50% provided a significant improvement in disintegration performance, with further improvement observed when further reducing to 40%.

Table H. Disintegration Optimization Studies for Compound Tablets, 100 mg

Sample No.	Formulation Variation	Force (kN)	Hardness (kP)	Disintegration Time (min)
1	62.5% extrudate; 22.5% MCC, 10% XL10 10 mm round, standard concave	4.8	14.7	>180
2	50% extrudate; 35% MCC, 10% XL10 10 mm round, standard concave	6.4	10.1	21.3
3	50% extrudate; 35% MCC, 10% Ac-Di-Sol 10 mm round, standard concave	6.4	9.2	0.3
4	50% extrudate; 35% MCC:S1500, 10% XL10 10 mm round, standard concave	7.7	8.7	24.8
5	40% extrudate; 45% MCC, 10% Ac-Di-Sol 8 x 18 mm Caplet Shaped Tooling	3.5	8.6	0.3
6	50% extrudate; 35% MCC, 10% Ac-Di-Sol 8 x 18 mm Caplet Shaped Tooling	6.4	11.5	0.4

Example 12: Compression Optimization

[00378] Compression robustness of each formulation was studied using a manual tablet press to assess the impact of critical process parameters (dwell time and compression force) and disintegration time and tablet hardness. For this study a two level factorial design was implemented, varying the levels of each critical process parameter as shown in Table I.

[00379] Critical product attributes for each formulation condition were evaluated and the results are presented in Table I. Both formulations exhibited tablet hardness values that were dependent on both compression force and dwell time. Disintegration behavior for both formulations was rapid, with measured disintegration times less than 5 min for all tablets studied.

Table I. Compression Optimization Study of 100 mg Tablets

Formulation	50% solid dispersion extrudate 35% avicel PH 102 10% Ac-Di-Sol 4.5% Colloidal Silicon Dioxide 0.5% Magnesium Stearate		40% solid dispersion extrudate 45% avicel PH 102 10% Ac-Di-Sol 4.5% Colloidal Silicon Dioxide 0.5% Magnesium Stearate	
Run #	Dwell Time (s)	Compression Force (kN/psi)	Dwell Time (s)	Compression Force (kN)
1	0	6.4 / 1,700	0	3.5 / 1,000
2	0	8.5 / 2,200	0	5.6 / 1,500
3	0	6.4 / 1,700	5	3.5 / 1,000

4	0	8.5 / 2,200	5	5.6 / 1,500
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Example 13: Treatment of Patients

[00380] “An Open-Label, Phase I, Dose Escalation Study of Compound 1 in Patients With Relapsed or Refractory Solid Tumors Followed by a Dose Expansion Phase in Patients with Metastatic Melanoma.”

[00381] This is a phase 1, multicenter, nonrandomized, open-label, dose escalation study. This study is conducted in patients ≥ 18 years of age with advanced solid tumors (excluding lymphoma) (Dose Escalation and PK Expansion cohort) or locally advanced, metastatic, and/or unresectable melanoma (melanoma expansion cohorts) and additional solid tumors.

[00382] The QW arm tests an initial Compound 1 dose of 400 mg once weekly (on Days 1, 8, 15, and 22) in a 28-day cycle. Patients will fast (with the exception of water) for at least 2 hours before and at least 2 hours after taking their dose of Compound 1. Patients may continue treatment for additional cycles until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. The maximum duration of treatment will be 12 months unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

[00383] QW Dose Expansion Phase: Once the MTD and/or RP2D of QW Compound 1 has been determined, the study will continue to a QW Dose Expansion phase. The Dose Expansion phase will enroll approximately 16 patients (up to 16 patients per cohort), one cohort of patients with locally advanced, metastatic, and/or unresectable NRAS mutation positive melanoma naive to MEK or RAF inhibitors, and one cohort of patients with BRAF mutation positive thyroid, colorectal or non-small cell lung cancers. Individual Dose Expansion cohorts may be opened or closed sequentially or in parallel at the sponsor’s discretion, based on emerging data.

[00384] Patients in the QW Dose Expansion phase will take Compound 1 orally QW for a 28-day cycle until disease progression, unacceptable toxicity, or the patient discontinues for any other reason. The maximum duration of treatment will be 1 year unless it is determined that a patient would derive benefit from continued therapy beyond 12 months.

Example 14: Methods for measuring BRAF and/or NRAS markers

[00385] BRAF PCR based Assay (Vendor: Qiagen; Catalog#: 870801)

The BRAF RGQ PCR Kit v2 combines two technologies, ARMS® and Scorpions®, to detect mutations in real-time PCR assays. This assay detects BRAFV600 mutations V600E (GAG) and V600E complex (GAA), V600D (GAT), V600K (AAG), V600R (AGG). The kit detects the

presence of the V600E (GAG) and V600E complex (GAA) but does not distinguish between them.

ARMS

Specific mutated sequences are selectively amplified by allele specific primer designed to match a mutated DNA.

Scorpions

Detection of amplification is performed using Scorpions. Scorpions are PCR primer covalently linked to a fluorescently labeled probe (*i.e.* FAM™ or HEX™) and a quencher. During PCR when the probe is bound to the amplicon, the fluorophore and quencher become separated resulting in an increase in fluorescence signal.

Procedure

The BRAF RGQ PCR Kit v2 comprises a two-step procedure. In the first step, the control assay is performed to assess the total amplifiable BRAF DNA in a sample. In the second step, both the mutation and control assays are performed to determine the presence or absence of mutant DNA.

- **Control assay**

The control assay, labeled with FAM, is used to assess the total amplifiable BRAF DNA in a sample. The control assay amplifies a region of exon 3 of the BRAF gene. The primers and Scorpion probe are designed to amplify independently of any known BRAF polymorphisms.

- **Mutation assays**

Each mutation assay contains a FAM-labeled Scorpion probe and an ARMS primer for discrimination between the wild-type DNA and a specific mutant DNA.

Data Analysis: Δ Ct Method

Scorpions real-time assays uses the number of PCR cycles necessary to detect a fluorescent signal above a background signal as a measure of the target molecules present at the beginning of the reaction. The point at which the signal is detected above background fluorescence is called the 'cycle threshold' (Ct).

Sample ΔCt values are calculated as the difference between the mutation assay Ct and control assay Ct from the same sample. Samples are classed as mutation positive if they give a ΔCt less than the Cut-Off ΔCt value for that assay. Above this value, the sample either contains less than the percentage of mutation able to be detected by the kit (beyond the limit of the assays), or the sample is mutation negative.

When using ARMS primers some inefficient priming could occur, giving a very late background Ct from DNA not containing a mutation. All ΔCt values calculated from background amplification are greater than the cut off ΔCt values and the sample is classed mutation negative.

For each sample, the ΔCt values are calculated as follows, ensuring that the mutation and control Ct values are from the same sample:

$$\Delta Ct = \{\text{sample mutation Ct}\} - \{\text{sample control Ct}\}$$

Sample control Ct can range between 27-33

Sample mutation Ct can range between 15-40

Acceptable ΔCt for the mutant call is <6 or 7

Methods for measuring NRAS mutations are similar to those described above for BRAF. Qiagen NRAS assay for the detection of NRAS Q61 mutations includes:

Q61K (181 C>A)

Q61R (182 A>G)

CLAIMS

What is claimed:

1. A pharmaceutical composition comprising (1) a solid dispersion extrudate comprising (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) one or more pharmaceutically acceptable excipients.
2. The pharmaceutical composition of claim 1, comprising (1) from about 10% to about 50% w/w of a solid dispersion extrudate comprising Compound 1 or a pharmaceutically acceptable salt thereof and a vinylpyrrolidinone-vinyl acetate copolymer and (2) from about 50% to about 90% w/w of one or more pharmaceutically acceptable excipients comprising a filler, disintegrant, glidant and lubricant.
3. The pharmaceutical composition of claims 1 or 2, wherein the vinylpyrrolidinone-vinyl acetate copolymer is copovidone.
4. The pharmaceutical composition of any one of claims 1-3, wherein the solid dispersion extrudate comprises <3% w/w of the S-enantiomer of 2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)- N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide.
5. The pharmaceutical composition of any one of claims 1-4, wherein the solid dispersion extrudate is amorphous.
6. The pharmaceutical composition of any one of claims 1-5, wherein the glass transition temperature (TG) of the solid dispersion extrudate is from about 45 °C to about 120 °C.
7. The pharmaceutical composition of any one of claims 1-6, wherein the amount of Compound 1 is from about 3% to about 17% w/w.
8. The pharmaceutical composition of any one of claims 1-7, wherein the amount of vinylpyrrolidinone-vinyl acetate copolymer is from about 5% to about 25% w/w.
9. The pharmaceutical composition of any one of claims 1-8, which comprises croscarmellose sodium.
10. The pharmaceutical composition of any one of claims 1-9, wherein the amount of croscarmellose sodium is from about 4% to about 9% w/w.
11. The pharmaceutical composition of any one of claims 1-10, which comprises colloidal silicon dioxide.
12. The pharmaceutical composition of any one of claims 1-11, wherein the amount of colloidal silicon dioxide is from about 0.5 % to about 6% w/w.

13. The pharmaceutical composition of any one of claims 1-12, which comprises magnesium stearate.
14. The pharmaceutical composition of any one of claims 1-13, wherein the amount of magnesium stearate is from about 0.3% to about 0.7% w/w.
15. The pharmaceutical composition of any one of claims 1-14, which comprises microcrystalline cellulose.
16. The pharmaceutical composition of any one of claims 1-15, wherein the amount of microcrystalline cellulose is from about 46% to about 81% w/w.
17. A process for preparing a pharmaceutical composition, which comprises the steps of:
 - (i) extruding a mixture of (R)-2-(1-(6-amino-5-chloropyrimidine-4-carboxamido)ethyl)-N-(5-chloro-4-(trifluoromethyl)pyridin-2-yl)thiazole-5-carboxamide or a pharmaceutically acceptable salt thereof and vinylpyrrolidinone-vinyl acetate copolymer to form a solid dispersion extrudate;
 - (ii) blending the resulting solid dispersion extrudate with one or more pharmaceutically acceptable excipients.
18. The process of claim 17, wherein the vinylpyrrolidinone-vinyl acetate copolymer is copovidone.
19. The process of claim 17 or 18, wherein the extruding is carried out in an extruder operating with a barrel temperature comprising a gradient temperature profile ranging from about room temperature to about 180 °C.
20. A method for the treatment of cancer in a patient in need of such treatment, comprising administering an effective amount of a pharmaceutical composition of any one of claims 1-16 to the patient according to an intermittent dosing regimen, wherein the dosing regimen comprises administering the composition once or twice weekly and the amount of the composition administered each week is from about 400 mg to about 1000 mg.
21. The method of claim 20, wherein the dosing regimen comprises administering the composition to the patient once a week with a rest period of 6 days between each administration.
22. The method of claim 20 or 21, wherein the cancer has one or more mutations in BRAF and/or NRAS.
23. The method of any one of claims 20-22, wherein the cancer has a V600 BRAF mutation
24. The method of any one of claims 20-23, wherein the cancer has a NRAS mutation.
25. The method of any one of claims 20-24, wherein the cancer has a non-V600E BRAF mutation.

26. The method of any one of claims 20-25, wherein the cancer is skin, ocular, gastrointestinal, thyroid, breast, ovarian, lung, brain, laryngeal, cervical, lymphatic system, genitourinary tract, or bone cancer.
27. A method for determining whether to treat a patient with a pharmaceutical composition of any one of claims 1-16 comprising:
- a) measuring at least one characteristic of at least one or more BRAF and/or NRAS markers associated with gene mutation in a patient sample comprising tumor cells;
 - b) identifying whether the at least one characteristic measured in step a) is informative for outcome upon treatment with the pharmaceutical composition; and
 - c) determining to treat the patient with the pharmaceutical composition if the informative characteristic indicates that the tumor cells comprise at least one marker gene with a BRAF and/or NRAS mutational status that indicates a favorable outcome to treatment with the pharmaceutical composition.
28. A method for determining an increased likelihood of pharmacological effectiveness of treatment by a pharmaceutical composition of any one of claims 1-16 in a patient diagnosed with cancer, said method comprising
- subjecting a nucleic acid sample from a cancer (tumor) sample from the patient to BRAF or NRAS mutational testing or PCR, wherein the presence of at least one mutation in BRAF or NRAS gene indicates an increased likelihood of pharmacological effectiveness of the treatment.
29. A method of treating a patient having cancer, said method comprising:
- iv) obtaining a nucleic acid sample from a cancer sample from said patient;
 - v) subjecting the sample to BRAF or NRAS mutational testing or PCR and identifying the presence of at least one mutation in BRAF or NRAS gene; and
 - vi) administering an effective amount of a pharmaceutical composition of any one of claims 1-16 to the patient in whose sample the presence of at least one mutation in BRAF or NRAS gene is identified.

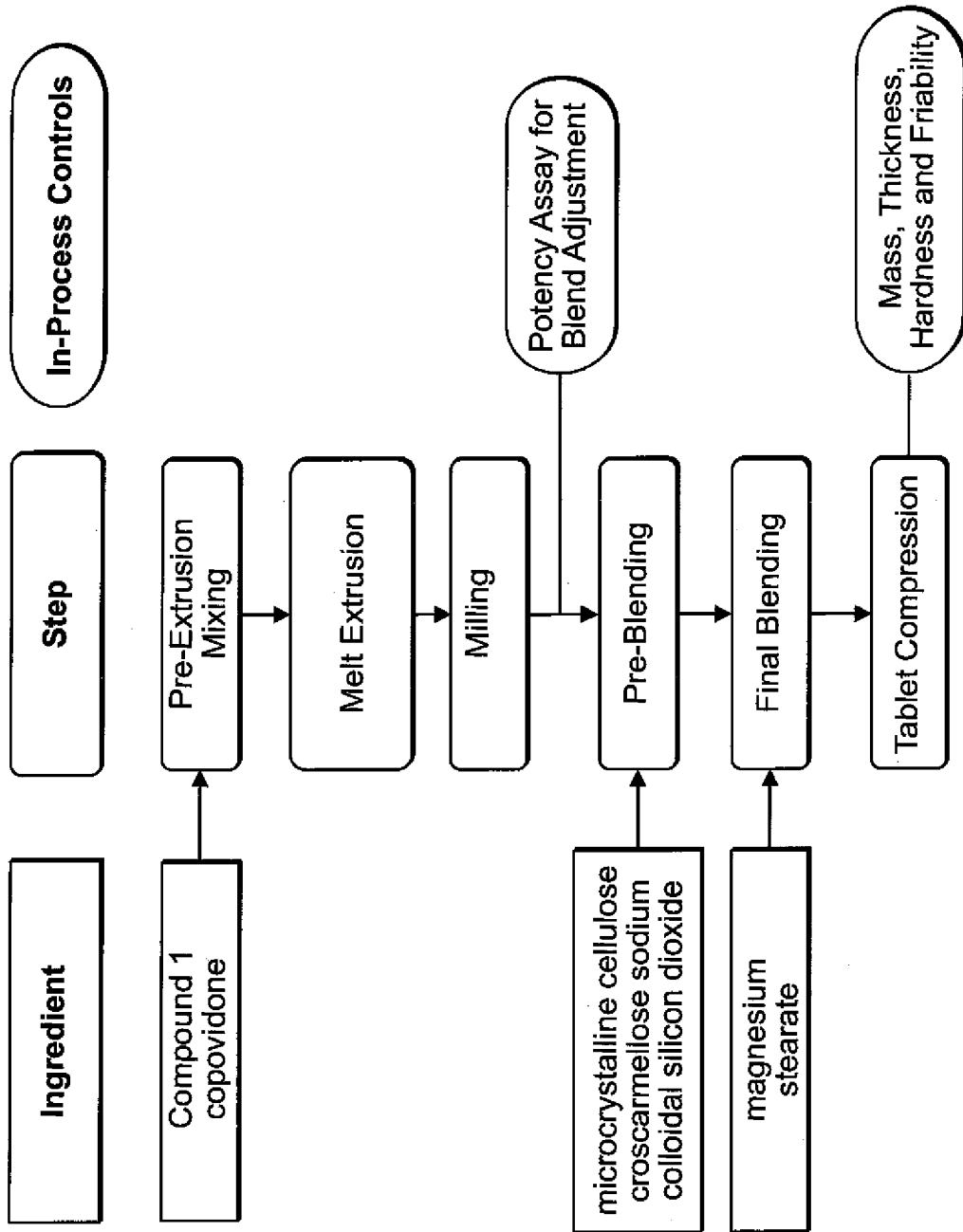


FIG. 1A

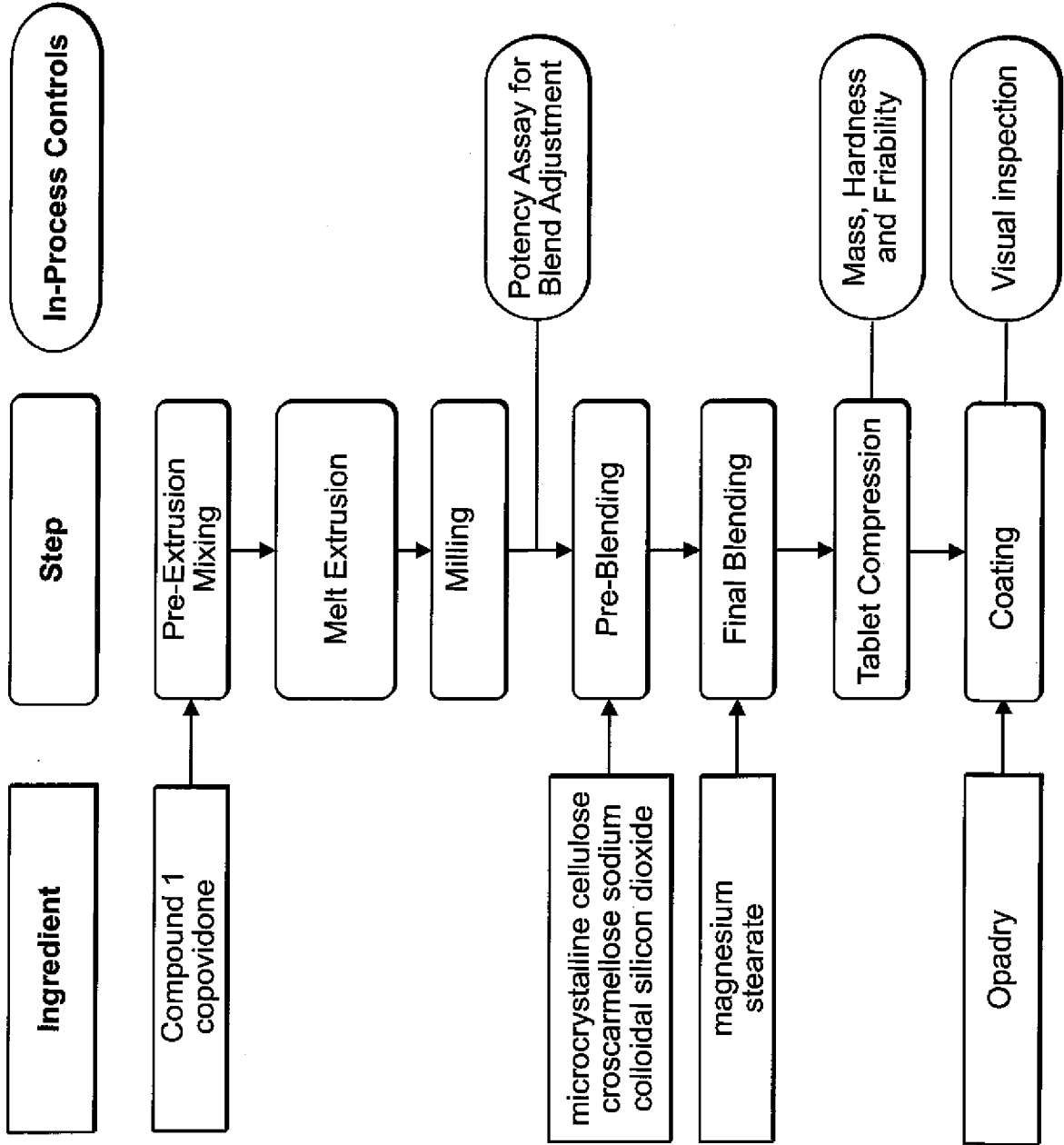


FIG. 1B

FIG. 2

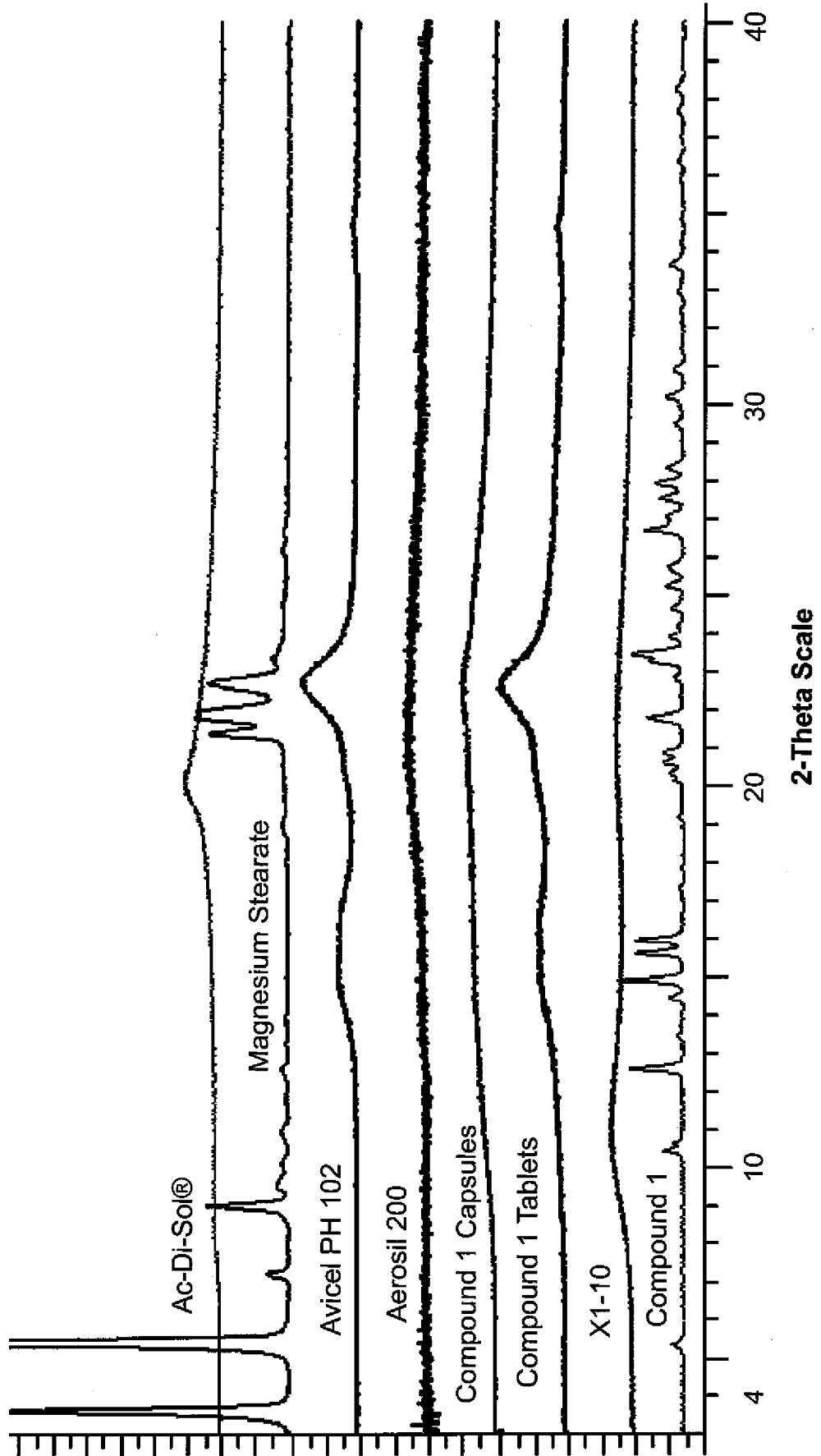


FIG. 3

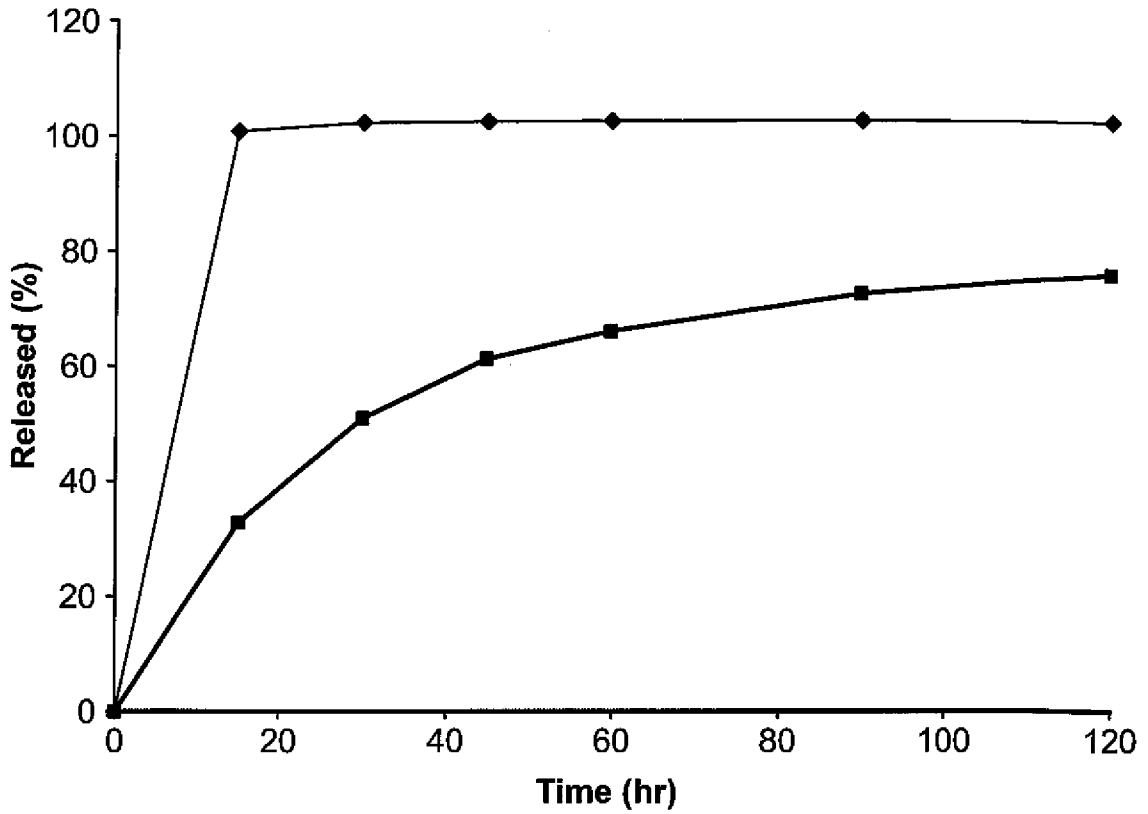
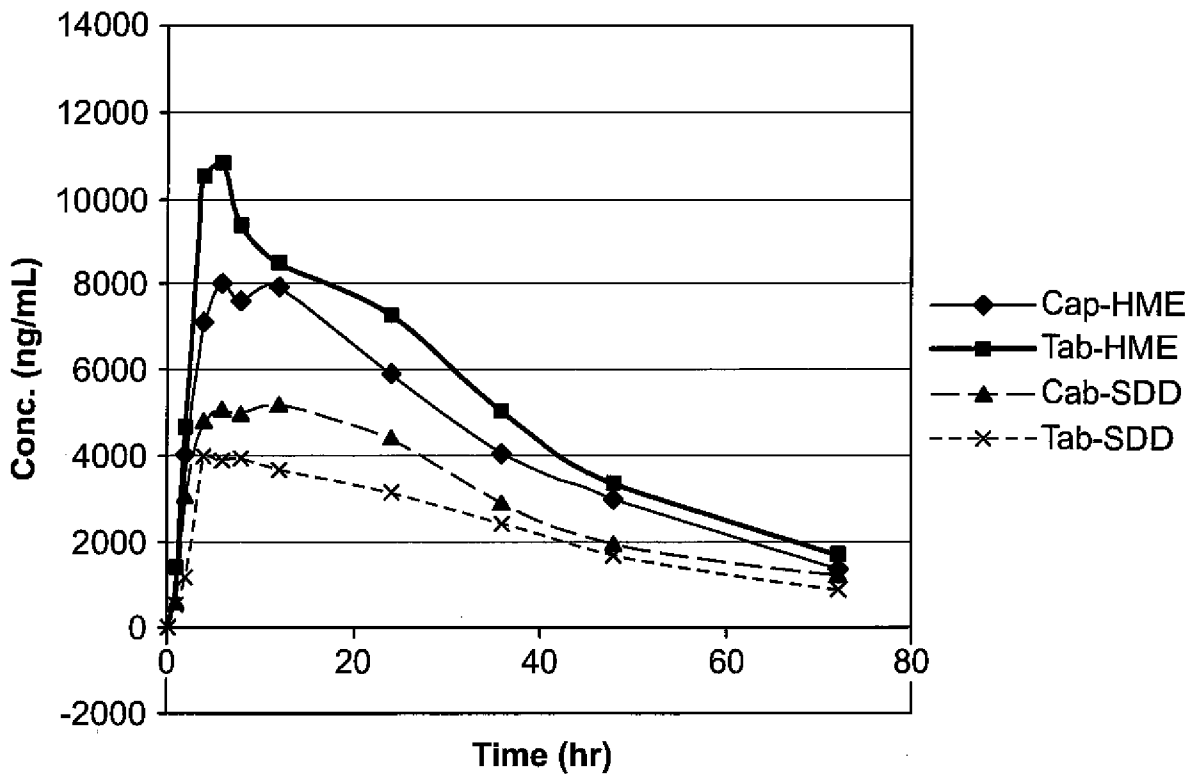


FIG. 4



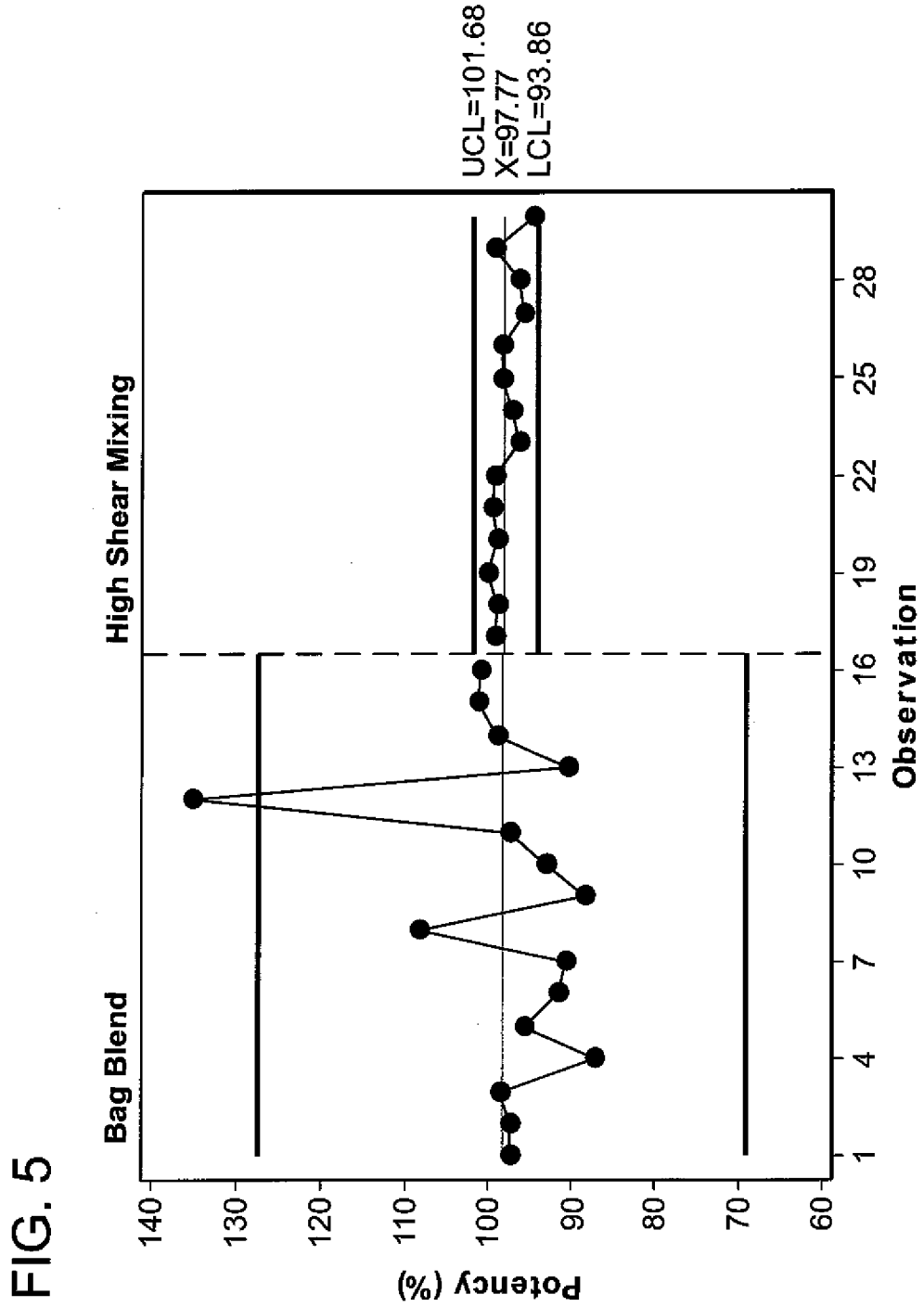


FIG. 6

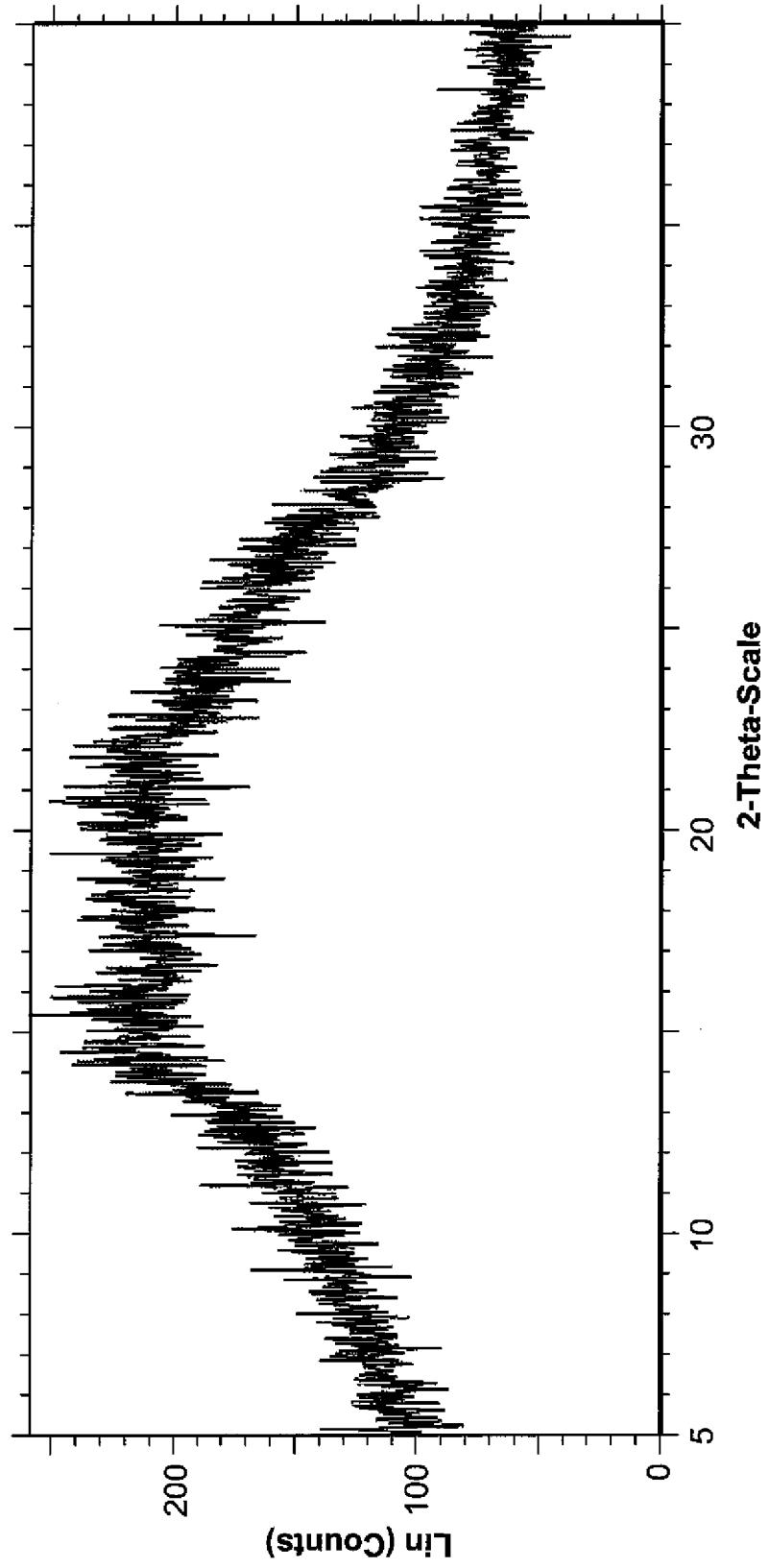


FIG. 7A

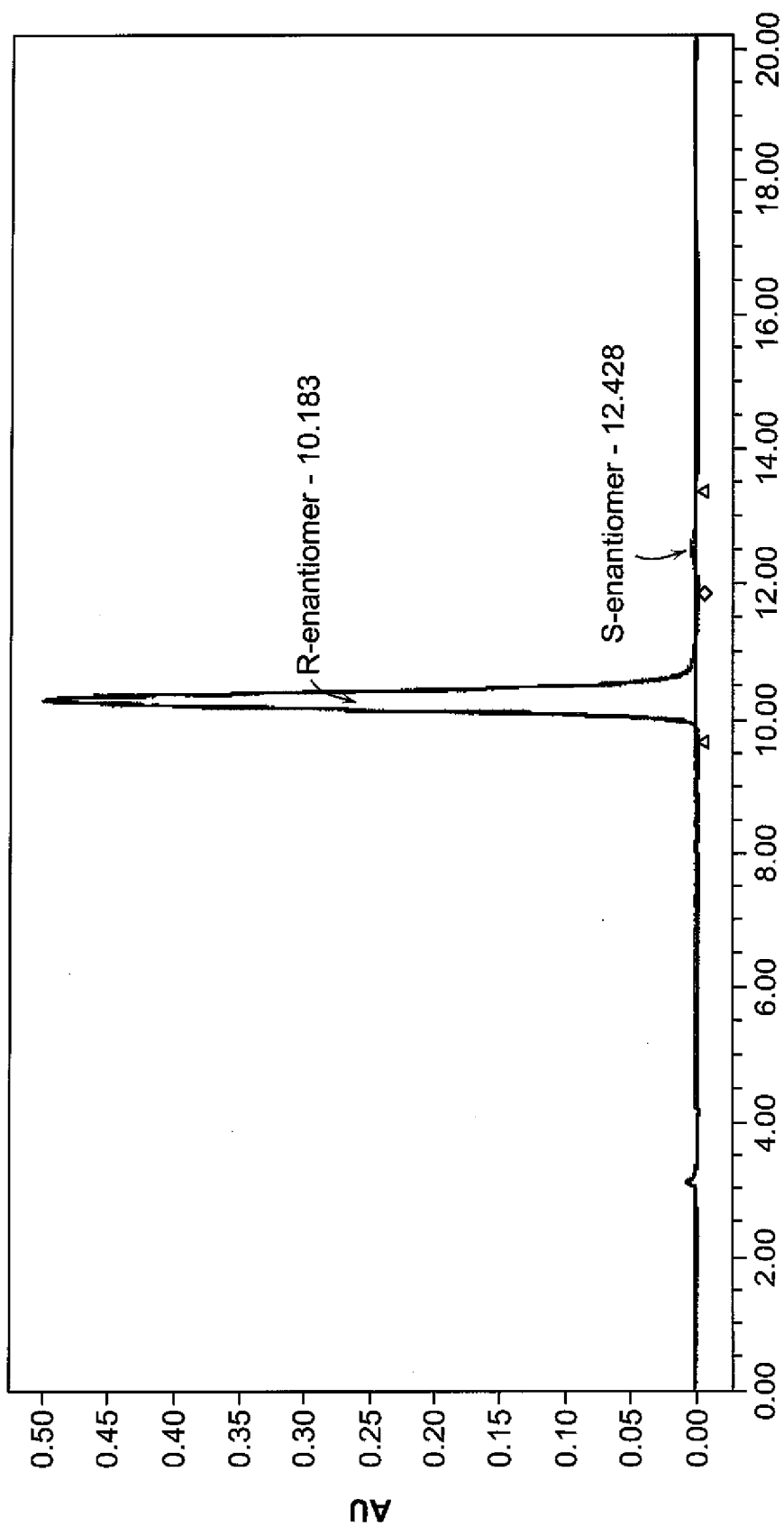
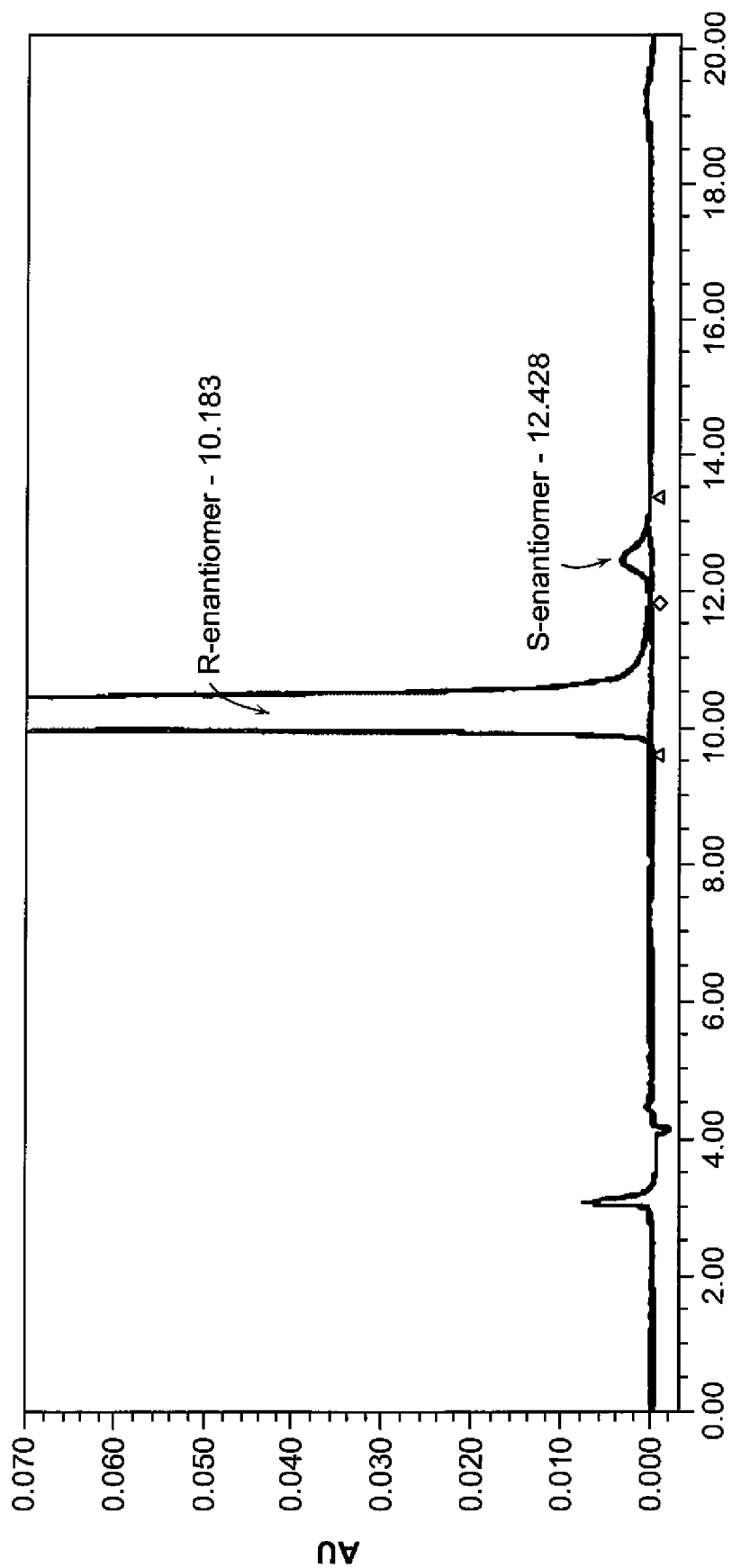


FIG. 7B



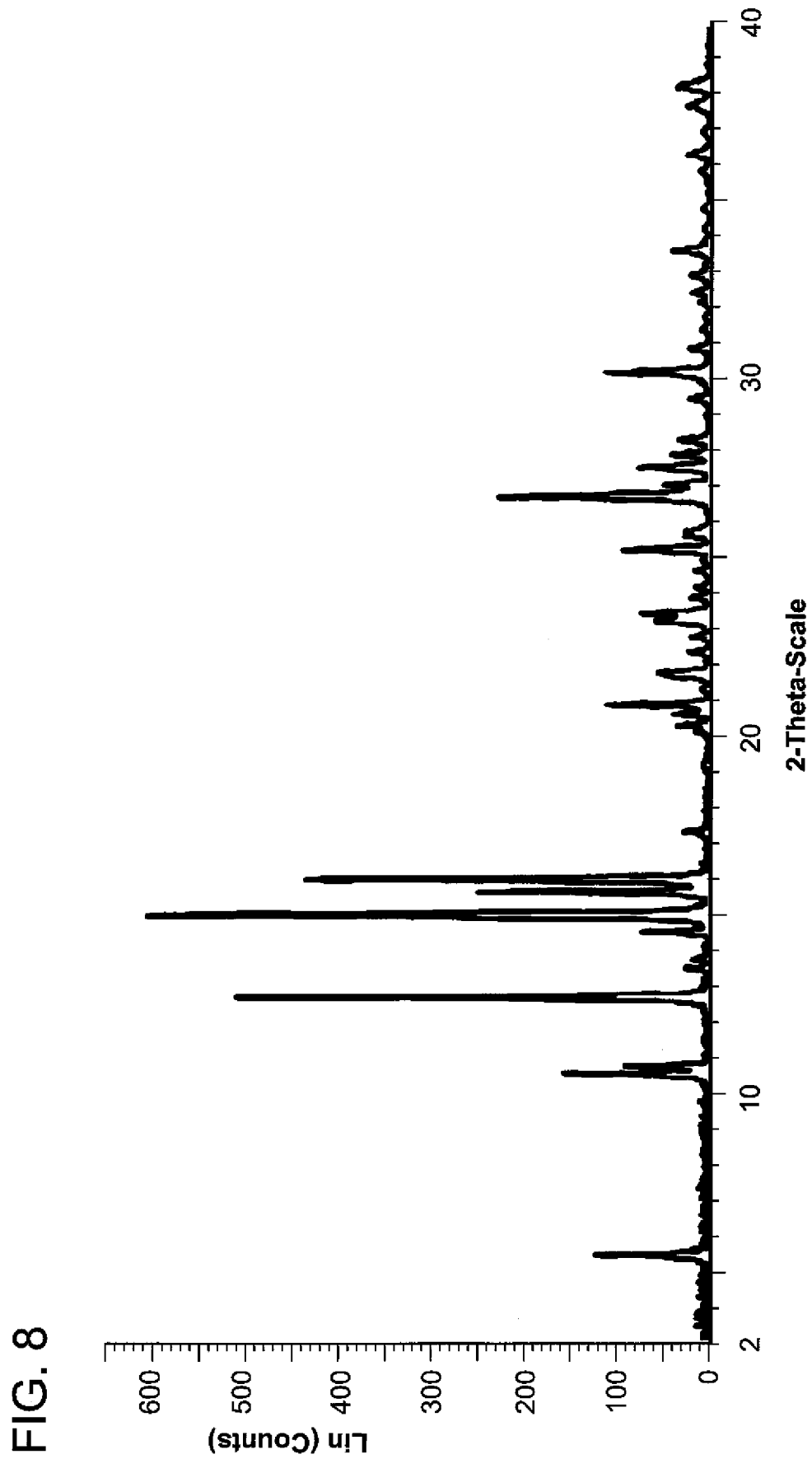


FIG. 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/022792

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14 A61K9/20 C12Q1/68
ADD. A61K9/28

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)
A61K C12Q

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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/006389 A2 (SUNESIS PHARMACEUTICALS INC [US]; CHEN WEIRONG [US]; COSSROW JENNIER []) 8 January 2009 (2009-01-08) cited in the application paragraph [0010] - paragraph [0012] paragraph [0107] - paragraph [0123] compounds 10D, 10Da, 10Db on page 168 paragraph [0379] - paragraph [0382]	1-29
X	WO 2013/144923 A1 (TAKEDA PHARMACEUTICAL [JP]) 3 October 2013 (2013-10-03) cited in the application paragraph [0004] - paragraph [0007] paragraph [0032] - paragraph [0045] claims 1-4, 7-11, 14	27, 28
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Further documents are listed in the continuation of Box C.

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 9 June 2015	Date of mailing of the international search report 22/06/2015
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Marchand, Petra
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/022792

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>MACAULEY D ET AL: "American Association for Cancer Research (AACR) 103<rd> Annual Meeting Chicago, Illinois, USA - March 31-April 4, 2012", DRUGS OF THE FUTURE, PROUS SCIENCE, ES, vol. 37, no. 6, 1 June 2012 (2012-06-01), pages 451-455, XP009173753, ISSN: 0377-8282, DOI: 10.1358/DOF.2012.37.6.1820866 page 453, line 1 - line 24</p> <p style="text-align: center;">-----</p>	27,28
X	<p>ZIAI JAMES ET AL: "BRAF mutation testing in clinical practice", EXPERT REVIEW OF MOLECULAR DIAGNOSTICS, EXPERT REVIEWS LTD, GB, vol. 12, no. 2, 1 March 2012 (2012-03-01), pages 127-138, XP008176589, ISSN: 1744-8352, DOI: 10.1586/ERM.12.1 the whole document page 130, left-hand column, last paragraph - page 131, left-hand column, last paragraph</p> <p style="text-align: center;">-----</p>	27,28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2015/022792

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
WO 2009006389	A2	08-01-2009	AR 067354 A1	07-10-2009
			AU 2008273002 A1	08-01-2009
			BR PI0813499 A2	06-01-2015
			CA 2693182 A1	08-01-2009
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			CN 104370828 A	25-02-2015
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			JP 5649445 B2	07-01-2015
			JP 2010532380 A	07-10-2010
			JP 2013256534 A	26-12-2013
			KR 20100033384 A	29-03-2010
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