(19) DANMARK

(10) DK/EP 2464337 T4

(12) Oversættelse af ændret europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *A 61 K 9/14 (2006.01)* *A 61 K 31/44 (2006.01)* *A 61 K 31/47 (2006.01)* *A 61 K 45/06 (2006.01)* *A 61 P 19/00 (2006.01)* *A 61 P 19/10 (2006.01)* *A 61 P 43/00 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2024-07-22**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om opretholdelse af patentet i ændret form: **2024-06-26**

(86) Europæisk ansøgning nr.: **10708442.8**

(86) Europæisk indleveringsdag: **2010-02-18**

(87) Den europæiske ansøgnings publiceringsdag: **2012-06-20**

(86) International ansøgning nr.: **US2010024609**

(87) Internationalt publikationsnr.: **WO2011019413**

(30) Prioritet: **2009-08-13 US 583066** **2009-08-13 WO PCT/US2009/000462**

(84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK SM TR**

(73) Patenthaver: **Vertex Pharmaceuticals Incorporated, 50 Northern Avenue, Boston, MA 02210, USA**

(72) Opfinder: **ROWE, William, 770 Highland Avenue, Medford MA 02155, USA**
HURTER, Patricia, 49 Tahanto Trail, Harvard, MA 01451, USA
YOUNG, Christopher, R., 42 Francis Street, Unit 1, Waltham, MA 02451, USA
DINEHART, Kirk, 60 Hemlock Drive, Holliston, MA 01746, USA
VERWIJS, Marinus, Jacobus, 4 Carter Drive, Framingham, MA 01701, USA
OVERHOFF, Kirk, 47 Alder Street, 25, Waltham, MA 02453, USA
GROOTENHUIS, Peter, D.J., 4801 Riding Ridge Road, San Diego, CA 92130, USA
BOTFIELD, Martyn, 47 Walden Terrace, Concord, MA 01742, USA
GROSSI, Alfredo, 102 Tern Hills Road, Somerville, MA 02145, USA
ZLOKARNIK, Gregor, 2754 Palomino Circle, La Jolla, CA 92037, USA
VAN GOOR, Fredrick F., 832 Ormond Court, San Diego, CA 92109, USA

(74) Fuldmægtig i Danmark: **Plougmann Vingtoft A/S, Strandvejen 70, 2900 Hellerup, Danmark**

(54) Benævnelse: **Tabletformulering af N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinolin-3-carboxamid til anvendelse til behandling af cystisk fibrose**

(56) Fremdragne publikationer:
WO-A2-2007/079139
WO-A2-2009/023509
WO-A2-2010/019239
ON BEHALF OF THE VX-770 STUDY INVESTIGATORS ET AL: "Final results of a 14- and 28-day study of VX-770 in subjects with CF" JOURNAL OF CYSTIC FIBROSIS, ELSEVIER, vol. 8, 1 June 2009 (2009-06-01), page S25, XP026192272 ISSN: 1569-1993 [retrieved on 2009-06-01]

Fortsættes ...

VAN GOOR F ET AL: "Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770" JOURNAL OF CYSTIC FIBROSIS, ELSEVIER, vol. 8, 1 June 2009 (2009-06-01), page S17, XP026192243 ISSN: 1569-1993 [retrieved on 2009-06-01]
CLUNES M T ET AL: "Front-runners for pharmacotherapeutic correction of the airway ion transport defect in cystic fibrosis" CURRENT OPINION IN PHARMACOLOGY, ELSEVIER SCIENCE PUBLISHERS, NL LNKD-DOI:10.1016/J.COPH.2008.04.006, vol. 8, no. 3, 1 June 2008 (2008-06-01), pages 292-299, XP022711870 ISSN: 1471-4892 [retrieved on 2008-05-28]
A. VESTNER ET AL.: "Neue Therapieansätze bei Cystischer Fibrose" PHARMAZIE UNSERER ZEIT, vol. 37, no. 5, 2008, pages 354-355, XP002581329
ANONYMOUS: "Vertex Pharmaceuticals initiates Phase I development for VX-770 in Cystic Fibrosis" INTERNET CITATION 17 May 2006 (2006-05-17), pages 1-2, XP002528469 Retrieved from the Internet: URL:http://files.shareholder.com/downloads /VRTX/641260063x0x84745/fc8ddd6 d-3713-48bb-b689-0444fc7ad623/VRTX_News_20 06_5_17_General.pdf> [retrieved on 2009-05-18]

DESCRIPTION

Description

FIELD OF THE INVENTION

[0001] The present invention relates to pharmaceutical compositions comprising a solid dispersion of N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide as defined in the appended claims for use in treating or lessening the severity of cystic fibrosis in a patient; wherein said use comprises administering the pharmaceutical composition concurrently with, prior to, or subsequent to one or more other desired therapeutics ; wherein the patient possesses a cystic fibrosis transmembrane receptor (CFTR) with a ΔF508 mutation on both alleles; and wherein the other desired therapeutic is a CFTR modulator other than compound 1.

BACKGROUND

[0002] Cystic fibrosis (CF) is a recessive genetic disease that affects approximately 30,000 children and adults in the United States and approximately 30,000 children and adults in Europe. Despite progress in the treatment of CF, there is no cure.

[0003] CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that encodes an epithelial chloride ion channel responsible for aiding in the regulation of salt and water absorption and secretion in various tissues. Small molecule drugs, known as potentiators that increase the probability of CFTR channel opening represent one potential therapeutic strategy to treat CF.

[0004] Specifically, CFTR is a cAMP/ATP-mediated anion channel that is expressed in a variety of cells types, including absorptive and secretory epithelia cells, where it regulates anion flux across the membrane, as well as the activity of other ion channels and proteins. In epithelia cells, normal functioning of CFTR is critical for the maintenance of electrolyte transport throughout the body, including respiratory and digestive tissue. CFTR is composed of approximately 1480 amino acids that encode a protein made up of a tandem repeat of transmembrane domains, each containing six transmembrane helices and a nucleotide binding domain. The two transmembrane domains are linked by a large, polar, regulatory (R)-domain with multiple phosphorylation sites that regulate channel activity and cellular trafficking.

[0005] The gene encoding CFTR has been identified and sequenced (See Gregory, R. J. et al.

(1990) Nature 347:382-386; Rich, D. P. et al. (1990) Nature 347:358-362), (Riordan, J. R. et al. (1989) Science 245:1066-1073). A defect in this gene causes mutations in CFTR resulting in cystic fibrosis ("CF"), the most common fatal genetic disease in humans. Cystic fibrosis affects approximately one in every 2,500 infants in the United States. Within the general United States population, up to 10 million people carry a single copy of the defective gene without apparent ill effects. In contrast, individuals with two copies of the CF associated gene suffer from the debilitating and fatal effects of CF, including chronic lung disease.

[0006] In patients with CF, mutations in CFTR endogenously expressed in respiratory epithelia leads to reduced apical anion secretion causing an imbalance in ion and fluid transport. The resulting decrease in anion transport contributes to enhanced mucus accumulation in the lung and the accompanying microbial infections that ultimately cause death in CF patients. In addition to respiratory disease, CF patients typically suffer from gastrointestinal problems and pancreatic insufficiency that, if left untreated, results in death. In addition, the majority of males with cystic fibrosis are infertile and fertility is decreased among females with cystic fibrosis. In contrast to the severe effects of two copies of the CF associated gene, individuals with a single copy of the CF associated gene exhibit increased resistance to cholera and to dehydration resulting from diarrhea - perhaps explaining the relatively high frequency of the CF gene within the population.

[0007] Sequence analysis of the CFTR gene of CF chromosomes has revealed a variety of disease causing mutations (Cutting, G. R. et al. (1990) Nature 346:366-369; Dean, M. et al. (1990) Cell 61:863:870; and Kerem, B-S. et al. (1989) Science 245:1073-1080; Kerem, B-S et al. (1990) Proc. Natl. Acad. Sci. USA 87:8447-8451). To date, > 1000 disease causing mutations in the CF gene have been identified (http://www.genet.sickkids.on.ca/cftr/). The most prevalent mutation is a deletion of phenylalanine at position 508 of the CFTR amino acid sequence, and is commonly referred to as ΔF508-CFTR. This mutation occurs in approximately 70% of the cases of cystic fibrosis and is associated with a severe disease.

[0008] The deletion of residue 508 in ΔF508-CFTR prevents the nascent protein from folding correctly. This results in the inability of the mutant protein to exit the ER, and traffic to the plasma membrane. As a result, the number of channels present in the membrane is far less than observed in cells expressing wild-type CFTR. In addition to impaired trafficking, the mutation results in defective channel gating. Together, the reduced number of channels in the membrane and the defective gating lead to reduced anion transport across epithelia leading to defective ion and fluid transport. (Quinton, P. M. (1990), FASEB J. 4: 2709-2727). Studies have shown, however, that the reduced numbers of ΔF508-CFTR in the membrane are functional, albeit less than wild-type CFTR. (Dalemans et al. (1991), Nature Lond. 354: 526-528; Denning et al., supra; Pasyk and Foskett (1995), J. Cell. Biochem. 270: 12347-50). In addition to ΔF508-CFTR, other disease causing mutations in CFTR that result in defective trafficking, synthesis, and/or channel gating could be up- or down-regulated to alter anion secretion and modify disease progression and/or severity.

[0009] Although CFTR transports a variety of molecules in addition to anions, it is clear that

this role (the transport of anions) represents one element in an important mechanism of transporting ions and water across the epithelium. The other elements include the epithelial Na+ channel, ENaC, Na+/2Cl-/K+co-transporter, Na+-K+-ATPase pump and the basolateral membrane K+ channels, that are responsible for the uptake of chloride into the cell.

[0010] These elements work together to achieve directional transport across the epithelium via their selective expression and localization within the cell. Chloride absorption takes place by the coordinated activity of ENaC and CFTR present on the apical membrane and the Na+-K+-ATPase pump and Cl ion channels expressed on the basolateral surface of the cell. Secondary active transport of chloride from the luminal side leads to the accumulation of intracellular chloride, which can then passively leave the cell via Cl- channels, resulting in a vectorial transport. Arrangement of Na+/2Cl-/K+ co-transporter, Na+-K+-ATPase pump and the basolateral membrane K+ channels on the basolateral surface and CFTR on the luminal side coordinate the secretion of chloride via CFTR on the luminal side. Because water is probably never actively transported itself, its flow across epithelia depends on tiny transepithelial osmotic gradients generated by the bulk flow of sodium and chloride.

[0011] As discussed above, it is believed that the deletion of residue 508 in ΔF508-CFTR prevents the nascent protein from folding correctly, resulting in the inability of this mutant protein to exit the ER, and traffic to the plasma membrane. As a result, insufficient amounts of the mature protein are present at the plasma membrane and chloride transport within epithelial tissues is significantly reduced. In fact, this cellular phenomenon of defective ER processing of ABC transporters by the ER machinery has been shown to be the underlying basis not only for CF disease, but for a wide range of other isolated and inherited diseases.

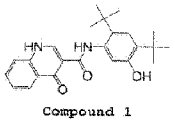
[0012] N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide is a potent and selective CFTR potentiator of wild-type and mutant (including e.g., ΔF508, R117H, and G551D) forms of human CFTR. N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide is useful for treatment of adult patients with cystic fibrosis and at least one G551D-CFTR allele.

[0013] Accordingly, there is a need for stable bioavailable pharmaceutical compositions of N[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide useful for treating patients suffering from CF and methods of administering the same. WO 2007/079139 A2 discloses "solid state forms of N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3 - carboxamide (Compound 1), pharmaceutical compositions thereof and methods therewith".

SUMMARY OF THE INVENTION

[0014] The invention relates to a pharmaceutical composition comprising about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises 80 wt% of substantially amorphous or amorphous N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-

dihydro-4-oxoquinoline-3-carboxamide (Compound 1):



Compound 1

by weight of the dispersion, 19.5 wt% of HPMCAS by weight of the dispersion, and 0.5 wt% SLS by weight of the dispersion; about 30.5 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.5 wt% of colloidal silicon dioxide by weight of the composition; about 1 wt% of magnesium stearate by weight of the composition; wherein the pharmaceutical composition is made into a tablet; for use in treating or lessening the severity of cystic fibrosis in a patient, wherein said use comprises administering the pharmaceutical composition concurrently with, prior to, or subsequent to one or more other desired therapeutics; wherein the patient possesses a cystic fibrosis transmembrane receptor (CFTR) with a ΔF508 mutation on both alleles; and wherein the other desired therapeutic is a CFTR modulator other than compound 1. The pharmaceutical compositions include one or more of the following excipients: a filler, a disintegrant, a glidant, a lubricant, a binder, and a surfactant.

[0015] In one embodiment, the present invention provides a phamaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 15 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 15 mg of substantially amorphous Compound 1.

[0016] In one embodiment, the present invention provides a phamaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 25 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 25 mg of substantially amorphous Compound 1.

[0017] In one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 50 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 50 mg of substantially amorphous Compound 1.

[0018] In one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 75 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 75 mg of substantially amorphous Compound 1.

[0019] In one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 100 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 100 mg of substantially amorphous Compound 1.

[0020] In one embodiment, the present invention provides a pharmaceutical composition

comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 150 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 150 mg of substantially amorphous Compound 1.

[0021] In one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 250 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises about 250 mg of substantially amorphous Compound 1.

[0022] In one embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises up to about 5 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises to about 5 mg of substantially amorphous Compound 1. For instance, the solid dispersion comprises 0.5 mg, 0.75 mg, 1 mg, 2 mg, 3 mg, 4 mg, or 5 mg of amorphous or substantially amorphous Compound 1.

[0023] In another embodiment, the present invention provides a pharmaceutical composition comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises up to about 1 mg of amorphous Compound 1. In certain embodiments, the solid dispersion comprises to about 1 mg of substantially amorphous Compound 1. For instance, the solid dispersion comprises 0.5 mg, 0.75 mg, or 1 mg of amorphous or substantially amorphous Compound 1.

[0024] The solid form of Compound 1 in the pharmaceutical composition is a solid dispersion comprising substantially amorphous or amorphous Compound 1 and hydroxypropylmethylcellulose (HPMC). Embodiments of this aspect include one or more of the following: The solid dispersion is a powder having mean particle diameter of greater than about 5 μm or the solid dispersion has a bulk density of about 0.10 g/cc or greater.

[0025] The pharmaceutical compositions also comprise a filler (e.g., lactose, sorbitol, celluloses, calcium phosphates, starches, sugars (e.g., mannitol, sucrose, or the like) or any combination thereof) in concentrations of at least about 10 wt% by weight of the composition; a disintegrant (e.g., sodium croscarmellose, sodium starch glycolate, or a combination thereof) in concentrations of about 10 wt% or less by weight of the composition; a surfactant (e.g., sodium lauryl sulfate, sodium stearyl fumarate (SSF), polyoxyethylene 20 sorbitan mono-oleate, or any combination thereof) in concentrations of about 10 wt% or less by weight of the composition; a binder (e.g., microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn (maize) starch, modified cellulose (e.g., hydroxymethyl cellulose), or any combination thereof) in concentrations of at least about 1 wt% by weight of the composition; a glidant (e.g., colloidal silicon dioxide, talc, or a combination thereof) in concentrations of about 2 wt% or less by weight of the composition; and a lubricant (e.g., magnesium stearate, stearic acid, hydrogenated oil, sodium stearyl fumarate, or any combination thereof) in concentrations of about 2 wt% or less by weight of the composition.

[0026] Such pharmaceutical compositions can optionally comprise one or more colorants, fragrances, and/or flavors to enhance its visual appeal, taste, and scent.

[0027] The pharmaceutical composition consisting of a tablet as defined in the claims for use as defined in the claims comprises a solid dispersion, a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the tablet optionally has a dissolution of at least about 50% in about 30 minutes, and the solid dispersion comprises substantially amorphous Compound 1. As noted below, dissolution is measured with a standard USP Type II apparatus that employs a dissolution media of 0.6% sodium lauryl sulfate dissolved in 900 mL of DI water (or a volume of media having the same ratio of SLS to DI water) at a temperature of about 37 °C. A single experimental tablet is tested in each test vessel of the apparatus. Dissolution can also be measured with a standard USP Type II apparatus that employs a dissolution media of 0.7% sodium lauryl sulfate dissolved in 900 mL of 50 mM sodium phosphate buffer (pH 6.8) at a temperature of about 37 °C. Dissolution can also be measured with a standard USP Type II apparatus that employs a dissolution media of 0.5% sodium lauryl sulfate dissolved in 900 mL of 50 mM sodium phosphate buffer (pH 6.8) at a temperature of about 37 °C. A single experimental tablet is tested in each test vessel of the apparatus.

[0028] The pharmaceutical composition consisting of a tablet as defined in the claims for use as defined in the claims comprises a solid dispersion comprising amorphous or substantially amorphous Compound 1 and HPMCAS; and, a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the tablet optionally has a hardness of at least about 5 Kp.

[0029] In yet another aspect, the tablets described herein are coated.

[0030] In another aspect, the coated tablets described herein are colored.

[0031] In still another aspect, the colored, coated tablets include text or images. For instance, the text or images can be printed on the colored, coated tablet.

[0032] In still other aspects, the colored, coated tablets include about 3 wt% of a film coating comprising a blue colorant, such as OPADRY® II. In some embodiments, the colored tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a black ink, such as Opacode® WB or Opacode® S-1-17823. In still further embodiments, the colored, coated tablets are coated with a colorant, waxed, and then labeled with a logo, other image, and/or text using a suitable ink. In some embodiments, the tablets are coated with about 3 wt% of colorant, and waxed with Carnauba wax powder weighed out in the amount of about 0.01% w/w of the starting tablet core weight. The waxed tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a suitable ink.

[0033] Disclosed herein is a method of producing a pharmaceutical composition comprising the steps of providing an admixture of a solid dispersion of amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, and compressing the admixture

into a tablet having a dissolution of at least about 50% in about 30 minutes. In one example, the admixture is compressed to a hardness of at least about 5 Kp.

[0034] Disclosed herein is a method of producing a pharmaceutical composition comprising the steps of providing an admixture of a solid dispersion of amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, and compressing the admixture into a tablet having a dissolution of at least about 70% in about 30 minutes.

[0035] The pharmaceutical composition as defined in the appended claims for use as defined in the appended claims can be orally administered to a patient at least once per day, wherein the solid dispersion comprises at least about 25 mg of substantially amorphous or amorphous Compound 1. In some embodiments, the tablet is orally administered to the patient once per day. Other tablets useful in this method comprise a solid dispersion containing at least about 50 mg of substantially amorphous or amorphous Compound 1. Some tablets useful in this method comprise a solid dispersion containing at least about 75 mg of substantially amorphous or amorphous Compound 1. Other tablets useful in this method comprise a solid dispersion containing at least about 100 mg of substantially amorphous or amorphous Compound 1. Yet other tablets useful in this method comprise a solid dispersion containing at least about 150 mg of substantially amorphous or amorphous Compound 1. In another method, the administration comprises orally administering to a patient at least once per day at least one tablet comprising a solid dispersion of substantially amorphous or amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, in which the solid dispersion contains at least about 250 mg of substantially amorphous or amorphous Compound 1.

[0036] The pharmaceutical composition used in the invention can be orally administered to a patient at least once per day, wherein which the solid dispersion comprises up to about 5 mg of substantially amorphous or amorphous Compound 1. For instance the solid dispersion comprises 0.5 mg, 0.75 mg, 1 mg, 2 mg, 3 mg, 4 mg, or 5 mg of substantially amorphous or amorphous Compound 1. In some embodiments, the tablet for use as defined in the claims is orally administered to the patient once per day.

[0037] The pharmaceutical composition used in the invention can be orally administering to a patient at least once per day, wherein the solid dispersion comprises up to about 1 mg of substantially amorphous or amorphous Compound 1. For instance the solid dispersion comprises 0.5 mg, 0.75 mg, or 1 mg of substantially amorphous or amorphous Compound 1. In some embodiments, the tablet for use as defined in the claims is orally administered to the patient once per day.

[0038] The pharmaceutical compositions used in the invention can be orally administered at least once a day. In other embodiments, the pharmaceutical composition used in the invention can be orally administered once a day. In some embodiments, the pharmaceutical composition used in the invention can be orally administered twice a day.

BRIEF DESCRIPTION OF THE FIGURES

[0039] Figure 1 presents a graphical illustration of the dissolution profiles of exemplary tablets according to the present invention.

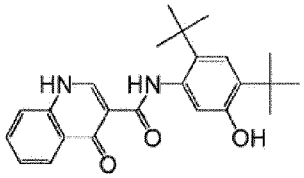
DETAILED DESCRIPTION

[0040] The present invention provides a pharmaceutical composition comprising about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises 80 wt% of substantially amorphous or amorphous N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide (Compound 1) by weight of the dispersion, 19.5 wt% of HPMCAS by weight of the dispersion, and 0.5 wt% SLS by weight of the dispersion; about 30.5 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.5 wt% of colloidal silicon dioxide by weight of the composition; about 1 wt% of magnesium stearate by weight of the composition; wherein the pharmaceutical composition is made into a tablet; for use in treating or lessening the severity of cystic fibrosis in a patient; wherein said use comprises administering the pharmaceutical composition concurrently with, prior to, or subsequent to one or more other desired therapeutics; wherein the patient possesses a cystic fibrosis transmembrane receptor (CFTR) with a ΔF508 mutation on both alleles; and wherein the other desired therapeutic is a CFTR modulator other than compound 1. A method of manufacturing a pharmaceutical composition comprising N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide, and a method of administering a pharmaceutical composition comprising a solid form of N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide are disclosed herein.

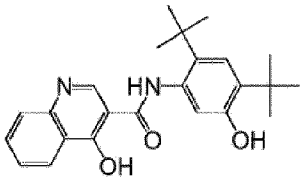
I. DEFINITIONS

[0041] As used herein, the term "active pharmaceutical ingredient" or "API" refers to a biologically active compound. Exemplary APIs include a CF potentiator (e.g., N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide).

[0042] As used herein, the term "Compound 1" is used interchangeably with "N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide", which has the following structure:



[0043] "Compound 1" also means tautomeric forms such as:



[0044] As used herein, the term "amorphous" refers to a solid material having no long range order in the position of its molecules. Amorphous solids are generally supercooled liquids in which the molecules are arranged in a random manner so that there is no well-defined arrangement, e.g., molecular packing, and no long range order. Amorphous solids are generally isotropic, i.e. exhibit similar properties in all directions and do not have definite melting points. For example, an amorphous material is a solid material having no sharp characteristic crystalline peak(s) in its X-ray power diffraction (XRPD) pattern (i.e., is not crystalline as determined by XRPD). Instead, one or several broad peaks (e.g., halos) appear in its XRPD pattern. Broad peaks are characteristic of an amorphous solid. See, US 2004/0006237 for a comparison of XRPDs of an amorphous material and crystalline material.

[0045] 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, substantially amorphous materials have less than about 15% crystallinity (e.g., less than about 10% crystallinity or less than about 5% crystallinity). It is also noted that the term 'substantially amorphous' includes the descriptor, 'amorphous', which refers to materials having no (0%) crystallinity.

[0046] As used herein, the term "dispersion" refers to a disperse system in which one substance, the dispersed phase, is distributed, in discrete units, throughout a second substance (the continuous phase or vehicle). The size of the dispersed phase can vary considerably (e.g. single molecules, colloidal particles of nanometer dimension, to multiple microns in size). In general, the dispersed phases can be solids, liquids, or gases. In the case of a solid dispersion, the dispersed and continuous phases are both solids. In pharmaceutical applications, a solid dispersion can include: an amorphous drug in an amorphous polymer; an amorphous drug in crystalline polymer; a crystalline drug in an amorphous polymer; or a crystalline drug in crystalline polymer. In this invention, a solid dispersion can include an amorphous drug in an amorphous polymer or an amorphous drug in crystalline polymer. In some embodiments, a solid dispersion includes the polymer constituting the dispersed phase, and the drug constitutes the continuous phase. Or, a solid dispersion includes the drug constituting the dispersed phase, and the polymer constitutes the continuous phase.

[0047] As used herein, the term "solid dispersion" generally refers to a solid dispersion of two or more components, usually one or more drugs (e.g., one drug (e.g., Compound 1)) and polymer, but possibly containing other components such as surfactants or other pharmaceutical excipients, where the drug(s) (e.g., Compound 1) is substantially amorphous

(e.g., having about 15% or less (e.g., about 10% or less, or about 5% or less)) of crystalline drug (e.g., N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide) or amorphous (i.e., having no crystalline drug), and the physical stability and/or dissolution and/or solubility of the substantially amorphous or amorphous drug is enhanced by the other components. Solid dispersions typically include a compound dispersed in an appropriate carrier medium, such as a solid state carrier. For example, a carrier comprises a polymer (e.g., a water-soluble polymer or a partially water-soluble polymer) and can include optional excipients such as functional excipients (e.g., one or more surfactants) or nonfunctional excipients (e.g., one or more fillers). Another exemplary solid dispersion is a co-precipitate or a co-melt of N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide with at least one polymer.

[0048] A "Co-precipitate" is a product after dissolving a drug and a polymer in a solvent or solvent mixture followed by the removal of the solvent or solvent mixture. Sometimes the polymer can be suspended in the solvent or solvent mixture. The solvent or solvent mixture includes organic solvents and supercritical fluids. A "co-melt" is a product after heating a drug and a polymer to melt, optionally in the presence of a solvent or solvent mixture, followed by mixing, removal of at least a portion of the solvent if applicable, and cooling to room temperature at a selected rate.

[0049] As used herein, "crystallinity" refers to the degree of structural order in a solid. For example, Compound 1, which is substantially amorphous, has less than about 15% crystallinity, or its solid state structure is less than about 15% crystalline. In another example, Compound 1, which is amorphous, has zero (0%) crystallinity.

[0050] As used herein, a "CF potentiator" refers to a compound that exhibits biological activity characterized by increasing gating functionality of the mutant CFTR protein present in the cell surface to approximately wild type levels.

[0051] As used herein, an "excipient" is an inactive ingredient in a pharmaceutical composition. Examples of excipients include fillers or diluents, surfactants, binders, glidants, lubricants, disintegrants, and the like.

[0052] As used herein, a "disintegrant" is an excipient that hydrates a pharmaceutical composition and aids in tablet dispersion. Examples of disintegrants include sodium croscarmellose and/or sodium starch glycolate.

[0053] As used herein, a "diluent" or "filler" is an excipient that adds bulkiness to a pharmaceutical composition. Examples of fillers include lactose, sorbitol, celluloses, calcium phosphates, starches, sugars (e.g., mannitol, sucrose, or the like) or any combination thereof.

[0054] As used herein, a "surfactant" is an excipient that imparts pharmaceutical compositions with enhanced solubility and/or wetability. Examples of surfactants include sodium lauryl sulfate (SLS), sodium stearyl fumarate (SSF), polyoxyethylene 20 sorbitan mono-oleate (e.g.,

Tween™), or any combination thereof.

[0055] As used herein, a "binder" is an excipient that imparts a pharmaceutical composition with enhanced cohesion or tensile strength (e.g., hardness). Examples of binders include dibasic calcium phosphate, sucrose, corn (maize) starch, microcrystalline cellulose, and modified cellulose (e.g., hydroxymethyl cellulose).

[0056] As used herein, a "glidant" is an excipient that imparts a pharmaceutical compositions with enhanced flow properties. Examples of glidants include colloidal silica and/or talc.

[0057] As used herein, a "colorant" is an excipient that imparts a pharmaceutical composition with a desired color. Examples of colorants include commercially available pigments such as FD&C Blue # 1 Aluminum Lake, FD&C Blue #2, other FD&C Blue colors, titanium dioxide, iron oxide, and/or combinations thereof.

[0058] As used herein, a "lubricant" is an excipient that is added to pharmaceutical compositions that are pressed into tablets. The lubricant aids in compaction of granules into tablets and ejection of a tablet of a pharmaceutical composition from a die press. Examples of lubricants include magnesium stearate, stearic acid (stearin), hydrogenated oil, sodium stearyl fumarate, or any combination thereof.

[0059] As used herein, "friability" refers to the property of a tablet to remain intact and withhold its form despite an external force of pressure. Friability can be quantified using the mathematical expression presented in equation 1:

$$\%\,friabiliy = 100 \times \frac{(W_0 - W_f)}{W_0} \qquad (1)$$

wherein W_0 is the original weight of the tablet and W_f is the final weight of the tablet after it is put through the friabilator.

[0060] Friability is measured using a standard USP testing apparatus that tumbles experimental tablets for 100 revolutions. Some tablets of the present invention have a friability of less than about 1 % (e.g., less than about 0.75%, less than about 0.50%, or less than about 0.30%)

[0061] As used herein, "mean particle diameter" is the average particle diameter as measured using techniques such as laser light scattering, image analysis, or sieve analysis.

[0062] As used herein, "bulk density" is the mass of particles of material divided by the total volume the particles occupy. The total volume includes particle volume, inter-particle void volume and internal pore volume. Bulk density is not an intrinsic property of a material; it can change depending on how the material is processed.

[0063] 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 or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof.

[0064] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19. Pharmaceutically acceptable salts of the compounds of this invention 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.

[0065] Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, edisylate (ethanedisulfonate), 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+(C1-4alkyl)4 salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. 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.

II. PHARMACEUTICAL COMPOSITION

[0066] The present invention provides a pharmaceutical composition comprising about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises 80 wt% of substantially amorphous or amorphous Compound 1 by weight of the dispersion, 19.5 wt% of HPMCAS by weight of the dispersion, and 0.5 wt% SLS by weight of the dispersion; about 30.5 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.5 wt% of colloidal

silicon dioxide by weight of the composition; about 1 wt% of magnesium stearate by weight of the composition; wherein the pharmaceutical composition is made into a tablet; for use in treating or lessening the severity of cystic fibrosis in a patient; wherein said use comprises administering the pharmaceutical composition concurrently with, prior to, or subsequent to one or more other desired therapeutics; wherein the patient possesses a cystic fibrosis transmembrane receptor (CFTR) with a ΔF508 mutation on both alleles; and wherein the other desired therapeutic is a CFTR modulator other than compound 1.

[0067] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1, wherein the solid dispersion comprises up to about 1 mg of substantially amorphous Compound 1, for use as defined in the appended claims. For instance, the solid dispersion comprises about 0.5 mg, about 0.75, or about 1 mg of substantially amorphous Compound 1.

[0068] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1, wherein the solid dispersion comprises up to about 5 mg of substantially amorphous Compound 1, for use as defined in the appended claims. For instance, the solid dispersion comprises about 0.5 mg, about 0.75, about 1 mg, about 2 mg, about 3 mg, about 4 mg, or about 5 mg of substantially amorphous Compound 1.

[0069] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1, wherein the solid dispersion comprises about 15 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0070] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1, wherein the solid dispersion comprises about 25 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0071] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1, wherein the solid dispersion comprises about 50 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0072] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1, wherein the solid dispersion comprises about 75 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0073] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous

Compound 1, wherein the solid dispersion comprises about 100 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0074] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1, wherein the solid dispersion comprises about 150 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0075] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1, wherein the solid dispersion comprises about 250 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0076] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1, wherein the solid dispersion comprises up to about 1 mg of amorphous Compound 1, for use as defined in the appended claims. For instance, the solid dispersion comprises about 0.5 mg, about 0.75, or about 1 mg of amorphous Compound 1.

[0077] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1, wherein the solid dispersion comprises up to about 5 mg of amorphous Compound 1, for use as defined in the appended claims. For instance, the solid dispersion comprises about 0.5 mg, about 0.75, about 1 mg, about 2 mg, about 3 mg, about 4 mg, or about 5 mg of amorphous Compound 1.

[0078] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 15 mg of amorphous Compound 1, for use as defined in the appended claims.

[0079] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 25 mg of amorphous Compound 1, for use as defined in the appended claims.

[0080] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 50 mg of amorphous Compound 1, for use as defined in the appended claims.

[0081] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 75 mg of amorphous Compound 1, for use as

defined in the appended claims.

[0082] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 100 mg of amorphous Compound 1, for use as defined in the appended claims.

[0083] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 150 mg of amorphous Compound 1, for use as defined in the appended claims.

[0084] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1, wherein the solid dispersion comprises about 250 mg of amorphous Compound 1, for use as defined in the appended claims.

[0085] Another aspect of the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of Compound 1 in which the solid dispersion comprises a polymer, for use as defined in the appended claims.

[0086] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises up to about 1 mg of substantially amorphous Compound 1, for use as defined in the appended claims. For instance, the solid dispersion comprises about 0.5 mg, about 0.75, or about 1 mg of substantially amorphous Compound 1.

[0087] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises up to about 5 mg of substantially amorphous Compound 1, for use as defined in the appended claims. For instance, the solid dispersion comprises about 0.5 mg, about 0.75, about 1 mg, about 2 mg, about 3 mg, about 4 mg, or about 5 mg of substantially amorphous Compound 1.

[0088] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 15 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0089] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 25 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0090] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 50 mg of substantially amorphous Compound 1, as for use as defined in the appended claims.

[0091] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 75 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0092] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 100 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0093] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 150 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0094] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 250 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0095] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises up to about 1 mg of substantially amorphous Compound 1, for use as defined in the appended claims. For instance, the solid dispersion comprises about 0.5 mg, about 0.75, or about 1 mg of substantially amorphous Compound 1.

[0096] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of substantially amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises up to about 5 mg of amorphous Compound 1, for use as defined in the appended claims. For instance, the solid dispersion comprises about 0.5 mg, about 0.75, about 1 mg, about 2 mg, about 3 mg, about 4 mg, or about 5 mg of amorphous Compound 1.

[0097] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 15 mg of amorphous Compound 1, for use as defined in the appended claims.

[0098] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 25 mg of amorphous Compound 1, for use as defined in the appended claims.

[0099] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 50 mg of amorphous Compound 1, for use as defined in the appended claims.

[0100] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 75 mg of amorphous Compound 1, for use as defined in the appended claims.

[0101] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 100 mg of amorphous Compound 1, for use as defined in the appended claims.

[0102] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 150 mg of amorphous Compound 1, for use as defined in the appended claims.

[0103] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising a solid dispersion of amorphous Compound 1 and HPMCAS, wherein the solid dispersion comprises about 250 mg of amorphous Compound 1, for use as defined in the appended claims.

[0104] One aspect of the present invention provides a pharmaceutical composition as defined in the appended claims comprising a CF potentiator API (e.g., a solid dispersion of Compound 1) and other excipients (e.g., a filler, a disintegrant, a surfactant, a binder, a glidant, a colorant, a lubricant, or any combination thereof) for use as defined in the appended claims.

[0105] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and

7. g. a lubricant,

wherein the solid dispersion comprises up to about 1 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0106] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises up to about 5 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0107] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 15 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0108] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 25 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0109] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 50 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0110] In another embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 75 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0111] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 100 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0112] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and a polymer;

2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 150 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0113] In another embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 250 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0114] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises up to about 1 mg of amorphous Compound 1, for use as defined in the appended claims.

[0115] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;

6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises up to about 5 mg of amorphous Compound 1, for use as defined in the appended claims.

[0116] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 15 mg of amorphous Compound 1, for use as defined in the appended claims.

[0117] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 25 mg of amorphous Compound 1, for use as defined in the appended claims.

[0118] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 50 mg of amorphous Compound 1, for use as

defined in the appended claims.

[0119] In another embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 75 mg of amorphous Compound 1, for use as defined in the appended claims.

[0120] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 100 mg of amorphous Compound 1, for use as defined in the appended claims.

[0121] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 150 mg of amorphous Compound 1, for use as defined in the appended claims.

[0122] In another embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and a polymer;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 250 mg of amorphous Compound 1, for use as defined in the appended claims.

[0123] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises up to about 1 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0124] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises up to about 5 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0125] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;

5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 15 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0126] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 25 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0127] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 50 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0128] In another embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 75 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0129] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 100 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0130] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 150 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0131] In another embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of substantially amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 250 mg of substantially amorphous Compound 1, for use as defined in the appended claims.

[0132] In one embodiment, the present invention provides a pharmaceutical composition as

defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises up to about 1 mg of amorphous Compound 1, for use as defined in the appended claims.

[0133] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises up to about 5 mg of amorphous Compound 1, for use as defined in the appended claims.

[0134] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 15 mg of amorphous Compound 1, for use as defined in the appended claims.

[0135] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and HPMCAS;
2. b. a filler;

3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 25 mg of amorphous Compound 1, for use as defined in the appended claims.

[0136] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 50 mg of amorphous Compound 1, for use as defined in the appended claims.

[0137] In another embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 75 mg of amorphous Compound 1, for use as defined in the appended claims.

[0138] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and

7. g. a lubricant,

wherein the solid dispersion comprises about 100 mg of amorphous Compound 1, for use as defined in the appended claims.

[0139] In one embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 150 mg of amorphous Compound 1, for use as defined in the appended claims.

[0140] In another embodiment, the present invention provides a pharmaceutical composition as defined in the appended claims comprising:

1. a. a solid dispersion of amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant,

wherein the solid dispersion comprises about 250 mg of amorphous Compound 1, for use as defined in the appended claims.

[0141] In one embodiment, the pharmaceutical composition as defined in the appended claims comprises a solid dispersion, a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the solid dispersion comprises Compound 1 and a polymer, for use as defined in the appended claims.

[0142] The pharmaceutical composition used in the invention is defined in the appended claims and comprises a solid dispersion a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the solid dispersion comprises 80 wt% of Compound 1 by weight of the dispersion and a polymer.

[0143] Suitable solid dispersions of Compound 1, i.e., N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide, include, without limitation, those dispersions described in PCT publication no. WO 2007/079139.

[0144] The pharmaceutical composition used in the present invention comprises a solid dispersion of Compound 1. For example, the solid dispersion comprises substantially amorphous Compound 1, where Compound 1 is less than about 15% (e.g., less than about 10% or less than about 5%) crystalline, and at least one polymer. In another example, the solid dispersion comprises amorphous Compound 1, i.e., Compound 1 has about 0% crystallinity. The concentration of Compound 1 in the solid dispersion depends on several factors such as the amount of pharmaceutical composition needed to provide a desired amount of Compound 1 and the desired dissolution profile of the pharmaceutical composition.

[0145] Polymers useful in these solid dispersions are inert, pharmaceutically acceptable polymers that are at least partially soluble in water or biological fluids. Polymers can include homopolymers (e.g., polysaccharides) or copolymers (e.g., block copolymers). The solid dispersion comprises substantially amorphous or amorphous N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide and hydroxypropylmethylcellulose acetate succinate (HPMCAS).

[0146] In another embodiment, the pharmaceutical composition comprises a solid dispersion that contains substantially amorphous Compound 1 and HPMCAS, in which the solid dispersion has a mean particle diameter, measured by light scattering (e.g., using a Malvern Mastersizer available from Malvern Instruments in England) of greater than about 5 μm (e.g., greater than about 6 μm, greater than about 7 μm, greater than about 8 μm, or greater than about 10 μm). For example, the pharmaceutical composition comprises a solid dispersion that contains amorphous Compound 1 and HPMCAS, in which the solid dispersion has a mean particle diameter, measured by light scattering, of greater than about 5 μm (e.g., greater than about 6 μm, greater than about 7 μm, greater than about 8 μm, or greater than about 10 μm). In another example, the pharmaceutical composition comprises a solid dispersion comprising substantially amorphous Compound 1 and HPMCAS, in which the solid dispersion has a mean particle diameter, measured by light scattering, of from about 7 μm to about 25 μm. For instance, the pharmaceutical composition comprises a solid dispersion comprising amorphous Compound 1 and HPMCAS, in which the solid dispersion has a mean particle diameter, measured by light scattering, of from about 7 μm to about 25 μm. In yet another example, the pharmaceutical composition comprises a solid dispersion comprising substantially amorphous Compound 1 and HPMCAS, in which the solid dispersion has a mean particle diameter, measured by light scattering, of from about 10 μm to about 35 μm. For instance, the pharmaceutical composition comprises a solid dispersion comprising amorphous Compound 1 and HPMCAS, in which the solid dispersion has a mean particle diameter, measured by light scattering, of from about 10 μm to about 35 μm. In another example, the pharmaceutical composition comprises a solid dispersion comprising substantially amorphous Compound 1 and HPMCAS, in which the solid dispersion has a bulk density of about 0.10 g/cc or greater (e.g., 0.15 g/cc or greater, 0.17 g/cc or greater). For instance, the pharmaceutical composition comprising a solid dispersion comprising amorphous Compound 1 and HPMCAS, in which the solid dispersion has a bulk density of about 0.10 g/cc or greater (e.g., 0.15 g/cc or greater, 0.17 g/cc or greater). In another instance, the pharmaceutical composition comprises a solid

dispersion that comprises substantially amorphous Compound 1 and HPMCAS, in which the solid dispersion has a bulk density of from about 0.10 g/cc to about 0.45 g/cc (e.g., from about 0.15 g/cc to about 0.42 g/cc, or from about 0.17 g/cc to about 0.40 g/cc). In still another instance, the pharmaceutical composition comprises a solid dispersion that includes amorphous Compound 1 and HPMCAS, in which the solid dispersion has a bulk density of from about 0.10 g/cc to about 0.45 g/cc (e.g., from about 0.15 g/cc to about 0.42 g/cc, or from about 0.17 g/cc to about 0.40 g/cc). In another example, the pharmaceutical composition comprises a solid dispersion that comprises substantially amorphous Compound 1 and HPMCAS, in which the solid dispersion has a bulk density of from about 0.10 g/cc to about 0.45 g/cc (e.g., from about 0.15 g/cc to about 0.42 g/cc, or from about 0.17 g/cc to about 0.40 g/cc). For instance, the pharmaceutical composition includes a solid dispersion that comprises amorphous Compound 1 and HPMCAS, in which the solid dispersion has a bulk density of from about 0.10 g/cc to about 0.45 g/cc (e.g., from about 0.15 g/cc to about 0.42 g/cc, or from about 0.17 g/cc to about 0.40 g/cc).

[0147] Solid dispersions used in the present invention comprise sodium lauryl sulfate (SLS)

[0148] The solid dispersion used in the invention contains 80 wt% of substantially amorphous or amorphous Compound 1, 19.5 wt% of HPMCAS, and 0.5 wt% of SLS.

[0149] In addition to the solid dispersion of Compound 1, pharmaceutical compositions used in the present invention also comprise one or more excipients such as fillers, disintegrants, surfactants, binders, glidants, lubricants, colorants, or fragrances.

[0150] Fillers suitable for the present invention are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the hardness, the chemical stability, the physical stability, or the biological activity of the pharmaceutical composition. Exemplary fillers include lactose, sorbitol, celluloses, calcium phosphates, starches, sugars (e.g., mannitol, sucrose, or the like), or any combination thereof. In one embodiment, the pharmaceutical composition comprises at least one filler in an amount of at least about 10 wt% (e.g., at least about 20 wt%, at least about 25 wt%, or at least about 27 wt%) by weight of the composition. For example, the pharmaceutical composition comprises from about 10 wt% to about 60 wt% (e.g., from about 20 wt% to about 55 wt%, from about 25 wt% to about 50 wt%, or from about 27 wt% to about 45 wt%) of filler, by weight of the composition. In another example, the pharmaceutical composition comprises at least about 20 wt% (e.g., at least 25 wt% or at least 27 wt%) of lactose, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 20 wt% to about 60 wt% (e.g., from about 25 wt% to about 55 wt% or from about 27 wt% to about 45 wt%) of lactose, by weight of the composition.

[0151] Disintegrants suitable for the present invention enhance the dispersal of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition.

Exemplary disintegrants include sodium croscarmellose, sodium starch glycolate, or a combination thereof. In one embodiment, the pharmaceutical composition comprises disintegrant in an amount of about 10 wt% or less (e.g., about 7 wt% or less, about 6 wt% or less, or about 5 wt% or less) by weight of the composition. For example, the pharmaceutical composition comprises from about 1 wt% to about 10 wt% (e.g., from about 1.5 wt% to about 7.5 wt% or from about 2.5 wt% to about 6 wt%) of disintegrant, by weight of the composition. In another example, the pharmaceutical composition comprises about 10 wt% or less (e.g., 7 wt% or less, 6 wt% or less, or 5 wt% or less) of sodium croscarmellose, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 1 wt% to about 10 wt% (e.g., from about 1.5 wt% to about 7.5 wt% or from about 2.5 wt% to about 6 wt%) of sodium croscarmellose, by weight of the composition. In some examples, the pharmaceutical composition comprises from about 0.1% to about 10 wt% (e.g., from about 0.5 wt% to about 7.5 wt% or from about 1.5 wt% to about 6 wt%) of disintegrant, by weight of the composition. In still other examples, the pharmaceutical composition comprises from about 0.5% to about 10 wt% (e.g., from about 1.5 wt% to about 7.5 wt% or from about 2.5 wt% to about 6 wt%) of disintegrant, by weight of the composition.

[0152] Surfactants suitable for the present invention enhance the solubility of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition. Exemplary surfactants include sodium lauryl sulfate (SLS), sodium stearyl fumarate (SSF), polyoxyethylene 20 sorbitan mono-oleate (e.g., Tween™), any combination thereof, or the like. In one embodiment, the pharmaceutical composition comprises a surfactant in an amount of about 10 wt% or less (e.g., about 5 wt% or less, about 2 wt% or less, about 1 wt% or less, about 0.8 wt% or less, or about 0.6 wt% or less) by weight of the composition. For example, the pharmaceutical composition includes from about 10 wt% to about 0.1 wt% (e.g., from about 5 wt% to about 0.2 wt% or from about 2 wt% to about 0.3 wt%) of surfactant, by weight of the composition. In another example, the pharmaceutical composition comprises 10 wt% or less (e.g., about 5 wt% or less, about 2 wt% or less, about 1 wt% or less, about 0.8 wt% or less, or about 0.6 wt% or less) of sodium lauryl sulfate, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 10 wt% to about 0.1 wt% (e.g., from about 5 wt% to about 0.2 wt% or from about 2 wt% to about 0.3 wt%) of sodium lauryl sulfate, by weight of the composition.

[0153] Binders suitable for the present invention enhance the tablet strength of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the chemical stability, the physical stability, or the biological activity of the pharmaceutical composition. Exemplary binders include microcrystalline cellulose, dibasic calcium phosphate, sucrose, corn (maize) starch, modified cellulose (e.g., hydroxymethyl cellulose), or any combination thereof. In one embodiment, the pharmaceutical composition comprises a binder in an amount of at least about 1 wt% (e.g., at least about 10 wt%, at least about 15 wt%, at least about 20 wt%, or at least about 22 wt%) by weight of the composition. For example, the pharmaceutical composition comprises from about

5 wt% to about 50 wt% (e.g., from about 10 wt% to about 45 wt% or from about 20 wt% to about 45 wt%) of binder, by weight of the composition. In another example, the pharmaceutical composition comprises at least about 1 wt% (e.g., at least about 10 wt%, at least about 15 wt%, at least about 20 wt%, or at least about 22 wt%) of microcrystalline cellulose, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 5 wt% to about 50 wt% (e.g., from about 10 wt% to about 45 wt% or from about 20 wt% to about 45 wt%) of microcrystalline cellulose, by weight of the composition.

[0154] Glidants suitable for the present invention enhance the flow properties of the pharmaceutical composition and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the hardness, the chemical stability, the physical stability, or the biological activity of the pharmaceutical composition. Exemplary glidants include colloidal silicon dioxide, talc, or a combination thereof. In one embodiment, the pharmaceutical composition comprises a glidant in an amount of 2 wt% or less (e.g., 1.75 wt%, 1.25 wt% or less, or 1.00 wt% or less) by weight of the composition. For example, the pharmaceutical composition comprises from about 2 wt% to about 0.05 wt% (e.g., from about 1.5 wt% to about 0.07 wt% or from about 1.0 wt% to about 0.09 wt%) of glidant, by weight of the composition. In another example, the pharmaceutical composition comprises 2 wt% or less (e.g., 1.75 wt%, 1.25 wt% or less, or 1.00 wt% or less) of colloidal silicon dioxide, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 2 wt% to about 0.05 wt% (e.g., from about 1.5 wt% to about 0.07 wt% or from about 1.0 wt% to about 0.09 wt%) of colloidal silicon dioxide, by weight of the composition.

[0155] Lubricants suitable for the present invention improve the compression and ejection of compressed pharmaceutical compositions from a die press and are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the hardness, or the biological activity of the pharmaceutical composition. Exemplary lubricants include magnesium stearate, stearic acid (stearin), hydrogenated oil, sodium stearyl fumarate, or any combination thereof. In one embodiment, the pharmaceutical composition comprises a lubricant in an amount of 2 wt% or less (e.g., 1.75 wt%, 1.25 wt% or less, or 1.00 wt% or less) by weight of the composition. For example, the pharmaceutical composition comprises from about 2 wt% to about 0.10 wt% (e.g., from about 1.5 wt% to about 0.15 wt% or from about 1.3 wt% to about 0.30 wt%) of lubricant, by weight of the composition. In another example, the pharmaceutical composition comprises 2 wt% or less (e.g., 1.75 wt%, 1.25 wt% or less, or 1.00 wt% or less) of magnesium stearate, by weight of the composition. In yet another example, the pharmaceutical composition comprises from about 2 wt% to about 0.10 wt% (e.g., from about 1.5 wt% to about 0.15 wt% or from about 1.3 wt% to about 0.30 wt%) of magnesium stearate, by weight of the composition.

[0156] Pharmaceutical compositions of the present invention can optionally comprise one or more colorants, flavors, and/or fragrances to enhance the visual appeal, taste, and/or scent of the composition. Suitable colorants, flavors, or fragrances are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the

chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition. In one embodiment, the pharmaceutical composition comprises a colorant, a flavor, and/or a fragrance. For example, the pharmaceutical composition comprises less than about 1 wt% (e.g., less than about 0.75 wt% or less than about 0.5 wt%) of each optionally ingredient, i.e., colorant, flavor and/or fragrance, by weight of the composition. In another example, the pharmaceutical composition comprises less than about 1 wt% (e.g., less than about 0.75 wt% or less than about 0.5 wt%) of a colorant. In still another example, the pharmaceutical composition comprises less than about 1 wt% (e.g., less than about 0.75 wt% or less than about 0.5 wt%) of a blue colorant (e.g., FD&C Blue #1 and/or FD&C Blue #2 Aluminum Lake, commercially available from Colorcon, Inc. of West Point, PA.)

[0157] The pharmaceutical composition is made into tablets. The tablets can be coated with a colorant and optionally labeled with a logo, other image and/or text using a suitable ink. In still other embodiments, the pharmaceutical composition can be made into tablets and the tablets can be coated with a colorant, waxed, and optionally labeled with a logo, other image and/or text using a suitable ink. Suitable colorants and inks are compatible with the ingredients of the pharmaceutical composition, i.e., they do not substantially reduce the solubility, the chemical stability, the physical stability, the hardness, or the biological activity of the pharmaceutical composition. The suitable colorants and inks can be any color and are water based or solvent based. In one embodiment, tablets made from the pharmaceutical composition are coated with a colorant and then labeled with a logo, other image, and/or text using a suitable ink. For example, tablets comprising pharmaceutical composition as described herein can be coated with about 3 wt% (e.g., less than about 6 wt% or less than about 4 wt%) of film coating comprising a colorant. The colored tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a suitable ink. In another example, tablets comprising pharmaceutical composition as described herein can be coated with about 3 wt% (e.g., less than about 6 wt% or less than about 4 wt%) of a film coating comprising a blue colorant (e.g., OPADRY® II, commercially available from Colorcon, Inc. of West Point, PA.). The colored tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a black ink (e.g., Opacode® WB, commercially available from Colorcon, Inc. of West Point, PA.). In another embodiment, tablets made from the pharmaceutical composition are coated with a colorant, waxed, and then labeled with a logo, other image, and/or text using a suitable ink. For example, tablets comprising pharmaceutical composition as described herein can be coated with about 3 wt% (e.g., less than about 6 wt% or less than about 4 wt%) of film coating comprising a colorant. The colored tablets can be waxed with Carnauba wax powder weighed out in the amount of about 0.01% w/w of the starting tablet core weight. The waxed tablets can be labeled with a logo and text indicating the strength of the active ingredient in the tablet using a suitable ink. In another example, tablets comprising pharmaceutical composition as described herein can be coated with about 3 wt% (e.g., less than about 6 wt% or less than about 4 wt%) of a film coating comprising a blue colorant (e.g., OPADRY® II, commercially available from Colorcon, Inc. of West Point, PA.). The colored tablets can be waxed with Carnauba wax powder weighed out in the amount of about 0.01% w/w of the starting tablet core weight. The waxed tablets can be labeled with a logo and

text indicating the strength of the active ingredient in the tablet using a black ink (e.g., Opacode® S-1-17823 - a solvent based ink, commercially available from Colorcon, Inc. of West Point, PA.).

[0158] A pharmaceutical composition disclosed herein comprises about 34.5 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30 wt% of microcrystalline cellulose by weight of the composition; about 30 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; about 1 wt% of magnesium stearate by weight of the composition.

[0159] A pharmaceutical composition disclosed herein is a caplet shaped pharmaceutical tablet composition having a hardness of 9.5 Kp ± 15 percent comprises about 34 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30 wt% of microcrystalline cellulose by weight of the composition; about 30 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In certain embodiments, the caplet shaped pharmaceutical tablet contains 150 mg of Compound 1. In certain embodiments, the caplet shaped pharmaceutical tablet contains 100 mg of Compound 1.

[0160] Disclosed herein is a caplet shaped pharmaceutical tablet composition having an initial hardness of 11 Kp ± 20 percent comprises about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In some aspects, the caplet shaped pharmaceutical tablet composition contains 100 mg of Compound 1. In other aspects, the caplet shaped pharmaceutical tablet composition includes a colorant coating and a printed logo or text. In some embodiments of this aspect, the caplet shaped pharmaceutical tablet composition includes a blue OPADRY® II coating and a water or solvent based ink logo or text. In certain embodiments, the caplet shaped pharmaceutical tablet contains 150 mg of Compound 1.

[0161] The pharmaceutical composition used in the present invention can optionally be a caplet shaped pharmaceutical tablet composition having an initial hardness of between about 6

and 16 Kp comprises about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30.5 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.5 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In some aspects, the caplet shaped pharmaceutical tablet composition contains 100 mg of Compound 1. In some further aspects, the caplet shaped pharmaceutical tablet composition comprises a colorant coated, a wax coating, and a printed logo or text. In some embodiments of this aspect, the caplet shaped pharmaceutical tablet includes a blue OPADRY® II coating and a water or solvent based ink logo or text. In some instances, the colorant coating is blue OPADRY® II. In some instances, the wax coating comprises Carnauba wax. In certain aspects, the ink for the printed logo or text is a solvent based ink. In some aspects, the caplet shaped pharmaceutical tablet composition contains 150 mg of Compound 1.

[0162] The pharmaceutical composition used in the present invention can optionally be a pharmaceutical tablet composition having an initial hardness of between about 9 and 21 Kp comprises about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30.5 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.5 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In some embodiments, the caplet shaped pharmaceutical tablet composition contains 150 mg of Compound 1. In some aspects, the caplet shaped pharmaceutical tablet composition further comprises a colorant coated, a wax coating, and a printed logo or text. In some instances, the tablet includes a blue OPADRY® II coating and a water or solvent based ink logo or text. In still other instances, the wax coating comprises Carnauba wax. In some embodiments, the ink for the printed logo or text is a solvent based ink. In some aspects, the caplet shaped pharmaceutical tablet composition contains 100 mg of Compound 1.

[0163] Disclosed herein is a pharmaceutical composition comprises about 34 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30 wt% of microcrystalline cellulose by weight of the composition; about 30 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In

certain embodiments, the pharmaceutical composition contains 150 mg of Compound 1. In other embodiments, the pharmaceutical composition contains 100 mg of Compound 1.

[0164] Disclosed herein is a pharmaceutical composition comprises about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 1 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In some aspects, the pharmaceutical composition contains 100 mg of Compound 1. In other embodiments, the pharmaceutical composition contains 150 mg of Compound 1. In other aspects, the pharmaceutical composition is formed as a tablet composition that includes a colorant coating and a printed logo or text. In some embodiments of this aspect, the pharmaceutical tablet composition includes a blue OPADRY® II coating and a water or solvent based ink logo or text.

[0165] In another pharmaceutical composition used in the present invention, a pharmaceutical composition comprises about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30.5 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.5 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In some aspects, the pharmaceutical tablet contains 100 mg of Compound 1. In other embodiments, the pharmaceutical composition contains 150 mg of Compound 1. In some further aspects, the pharmaceutical composition is formed as a tablet and comprises a colorant coated, a wax coating, and a printed logo or text. In some embodiments of this aspect, the pharmaceutical tablet includes a blue OPADRY® II coating and a water or solvent based ink logo or text. In some instances, the colorant coating is blue OPADRY® II. In some instances, the wax coating comprises Carnauba wax. In certain aspects, the ink for the printed logo or text is a solvent based ink.

[0166] Disclosed herein is a pharmaceutical composition consisting of a tablet that includes a CF potentiator API (e.g., a solid dispersion of N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide) and other excipients (e.g., a filler, a disintegrant, a surfactant, a binder, a glidant, a colorant, a lubricant, or any combination thereof), each of which is described above and in the Examples below, wherein the tablet has a dissolution of at least about 50% (e.g., at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 99%) in about 30 minutes. In one example, the

pharmaceutical composition consists of a tablet that includes a CF potentiator API (e.g., a solid dispersion of Compound 1) and other excipients (e.g., a filler, a disintegrant, a surfactant, a binder, a glidant, a colorant, a lubricant, or any combination thereof), each of which is described above and in the Examples below, wherein the tablet has a dissolution of from about 50% to about 100% (e.g., from about 55% to about 95% or from about 60% to about 90%) in about 30 minutes. In another example, the pharmaceutical composition consists of a tablet that comprises a solid dispersion comprising substantially amorphous or amorphous Compound 1 and HPMCAS or PVP/VA; and, a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the tablet has a dissolution of at least about 50% (e.g., at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 99%) in about 30 minutes. In still another example, the pharmaceutical composition consists of a tablet that comprises a solid dispersion comprising substantially amorphous or amorphous Compound 1 and HPMCAS or PVP/VA; and, a filler, a disintegrant, a surfactant, a binder, a glidant, and a lubricant, wherein the tablet has a dissolution of from about 50% to about 100% (e.g., from about 55% to about 95% or from about 60% to about 90%) in about 30 minutes.

[0167] In another embodiment, the tablet comprises a solid dispersion comprising at least about 25 mg (e.g., at least about 30 mg, at least about 40 mg, at least about 50 mg, at least about 100 mg, or at least 150 mg) of substantially amorphous or amorphous Compound 1; and HPMCAS and SLS.

[0168] Dissolution can be measured with a standard USP Type II apparatus that employs a dissolution media of 0.6% sodium lauryl sulfate dissolved in 900 mL of DI water, stirring at about 50-75 rpm at a temperature of about 37 °C. A single experimental tablet is tested in each test vessel of the apparatus. Dissolution can also be measured with a standard USP Type II apparatus that employs a dissolution media of 0.7% sodium lauryl sulfate dissolved in 900 mL of 50 mM sodium phosphate buffer (pH 6.8), stirring at about 65 rpm at a temperature of about 37 °C. A single experimental tablet is tested in each test vessel of the apparatus. Dissolution can also be measured with a standard USP Type II apparatus that employs a dissolution media of 0.5% sodium lauryl sulfate dissolved in 900 mL of 50 mM sodium phosphate buffer (pH 6.8), stirring at about 65 rpm at a temperature of about 37 °C. A single experimental tablet is tested in each test vessel of the apparatus.

[0169] Disclosed herein is a pharmaceutical composition consisting of a tablet that comprises a CF potentiator API (e.g., a solid dispersion of Compound 1) and other excipients (e.g., a filler, a disintegrant, a surfactant, a binder, a glidant, a colorant, a lubricant, or any combination thereof), each of which is described above and in the Examples below, wherein the tablet has a hardness of at least about 5 Kp. In one example, the pharmaceutical composition consists of a tablet that comprises a CF potentiator API (e.g., a solid dispersion of Compound 1) and other excipients (e.g., a filler, a disintegrant, a surfactant, a binder, a glidant, a colorant, a lubricant, or any combination thereof), each of which is described above and in the Examples below, wherein the tablet has a hardness of at least about 5 Kp (e.g., at least about 5.5, at least about 6 Kp, or at least about 7 Kp).

III. METHOD OF PRODUCING A PHARMACEUTICAL COMPOSITION

[0170] Disclosed herein is a method of producing a pharmaceutical composition comprising providing an admixture of a solid dispersion of substantially amorphous or amorphous N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, and compressing the admixture into a tablet having a dissolution of at least about 50% in about 30 minutes.

[0171] Each of the ingredients of this admixture is described above and in the Examples below. Furthermore, the admixture can comprise optional additives such as one or more colorants, one or more flavors, and/or one or more fragrances as described above and in the Examples below. And, the relative concentrations (e.g., wt%) of each of these ingredients (and any optional additives) in the admixture is also presented above and in the Examples below. The ingredients constituting the admixture can be provided sequentially or in any combination of additions; and, the ingredients or combination of ingredients can be provided in any order. In one embodiment the lubricant is the last component added to the admixture.

[0172] In one embodiment, the admixture comprises a solid dispersion of substantially amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, wherein each of these ingredients is provided in a powder form (e.g., provided as particles having a mean diameter, measured by light scattering, of 250 μm or less (e.g., 150 μm or less, 100 μm or less, 50 μm or less, 45 μm or less, 40 μm or less, or 35 μm or less)). For instance, the admixture comprises a solid dispersion of amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, wherein each of these ingredients is provided in a powder form (e.g., provided as particles having a mean diameter, measured by light scattering, of 250 μm or less (e.g., 150 μm or less, 100 μm or less, 50 μm or less, 45 μm or less, 40 μm or less, or 35 μm or less)).

[0173] In another embodiment, the admixture comprises a solid dispersion of substantially amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, wherein each of these ingredients is substantially free of water. Each of the ingredients comprises less than 5 wt% (e.g., less than 2 wt%, less than 1 wt%, less than 0.75 wt%, less than 0.5 wt%, or less than 0.25 wt%) of water by weight of the ingredient. For instance, the admixture comprises a solid dispersion of amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler, wherein each of these ingredients is substantially free of water. Each of the ingredients comprises less than 5 wt% (e.g., less than 2 wt%, less than 1 wt%, less than 0.75 wt%, less than 0.5 wt%, or less than 0.25 wt%) of water by weight of the ingredient.

[0174] In another embodiment, compressing the admixture into a tablet is accomplished by filling a form (e.g., a mold) with the admixture and applying pressure to admixture. This can be accomplished using a die press or other similar apparatus. It is also noted that the application

of pressure to the admixture in the form can be repeated using the same pressure during each compression or using different pressures during the compressions. In another example, the admixture is compressed using a die press that applies sufficient pressure to form a tablet having a dissolution of about 50% or more at about 30 minutes (e.g., about 55% or more at about 30 minutes or about 60% or more at about 30 minutes). For instance, the admixture is compressed using a die press to produce a tablet hardness of at least about 5 Kp (at least about 5.5 Kp, at least about 6 Kp, at least about 7 Kp, at least about 11 Kp, or at least 21Kp). In some instances, the admixture is compressed to produce a tablet hardness of between about 6 and 21 Kp.

[0175] In some embodiments, tablets comprising a pharmaceutical composition as described herein can be coated with about 3.0 wt% of a film coating comprising a colorant by weight of the tablet. In certain instances, the colorant suspension or solution used to coat the tablets comprises about 20%w/w of solids by weight of the colorant suspension or solution. In still further instances, the coated tablets can be labeled with a logo, other image or text.

[0176] In another embodiment, the method of producing a pharmaceutical composition comprises providing an admixture of a solid dispersion of substantially amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler; mixing the admixture until the admixture is substantially homogenous, and compressing the admixture into a tablet as described above or in the Examples below. Or, the method of producing a pharmaceutical composition comprises providing an admixture of a solid dispersion of amorphous Compound 1, a binder, a glidant, a surfactant, a lubricant, a disintegrant, and a filler; mixing the admixture until the admixture is substantially homogenous, and compressing the admixture into a tablet as described above or in the Examples below. For example, the admixture is mixed by stirring, blending, shaking, or the like using hand mixing, a mixer, a blender, any combination thereof, or the like. When ingredients or combinations of ingredients are added sequentially, mixing can occur between successive additions, continuously throughout the ingredient addition, after the addition of all of the ingredients or combinations of ingredients, or any combination thereof. The admixture is mixed until it has a substantially homogenous composition.

IV. ADMINISTRATION OF A PHARMACEUTICAL FORMULATION

[0177] The invention provides a pharmaceutical composition as defined in the appended claims for use as defined in the appended claims.

[0178] The pharmaceutical composition as defined in the appended claims is used to treat or lessen the severity of cystic fibrosis in a patient possessing the ΔF508 mutation of human CFTR on both alleles

[0179] The pharmaceutical composition used in the invention is made into a tablet and comprises about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises 80 wt% of substantially amorphous or amorphous Compound 1 by weight

of the dispersion, 19.5 wt% of HPMCAS by weight of the dispersion, and 0.5 wt% SLS by weight of the dispersion; about 30.5 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.5 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In some aspects, the pharmaceutical composition contains 100 mg of Compound 1. In other embodiments, the pharmaceutical composition contains 150 mg of Compound 1. In some further aspects, the pharmaceutical composition is formed as a tablet and comprises a colorant coated, a wax coating, and a printed logo or text. In some embodiments of this aspect, the pharmaceutical tablet includes a blue OPADRY® II coating and a water or solvent based ink logo or text. In some instances, the colorant coating is blue OPADRY® II. In some instances, the wax coating comprises Carnauba wax. In certain aspects, the ink for the printed logo or text is a solvent based ink.

[0180] The use defined in the appended claims comprises lessening the severity of cystic fibrosis in a patient possessing the ΔF508 mutation of human CFTR on both alleles, wherein the use comprises administering to said patient one of the compositions as defined herein.

[0181] The pharmaceutical composition used in the invention can be used to lessen the severity of cystic fibrosis in a patient. The pharmaceutical composition used in the invention is made into a tablet and comprises about 34.1 wt% of a solid dispersion by weight of the composition, wherein the dispersion comprises about 80 wt% of substantially amorphous or amorphous Compound 1 by weight of the dispersion, about 19.5 wt% of HPMCAS by weight of the dispersion, and about 0.5 wt% SLS by weight of the dispersion; about 30.5 wt% of microcrystalline cellulose by weight of the composition; about 30.4 wt% of lactose by weight of the composition; about 3 wt% of sodium croscarmellose by weight of the composition; about 0.5 wt% of SLS by weight of the composition; about 0.5 wt% of colloidal silicon dioxide by weight of the composition; and about 1 wt% of magnesium stearate by weight of the composition. In some aspects, the pharmaceutical composition contains 100 mg of Compound 1. In other embodiments, the pharmaceutical composition contains 150 mg of Compound 1. In some further aspects, the pharmaceutical composition is formed as a tablet and comprises a colorant coated, a wax coating, and a printed logo or text. In some embodiments of this aspect, the pharmaceutical tablet includes a blue OPADRY® II coating and a water or solvent based ink logo or text. In some instances, the colorant coating is blue OPADRY® II. In some instances, the wax coating comprises Carnauba wax. In certain aspects, the ink for the printed logo or text is a solvent based ink.

[0182] The pharmaceutical composition used in the invention can be orally administered to a patient at least once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises up to about 1 mg of substantially amorphous or amorphous Compound 1.

[0183] The pharmaceutical composition used in the invention can be orally administered to a patient at least once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises up to about 5 mg of substantially amorphous or amorphous Compound 1.

[0184] The pharmaceutical composition used in the invention can be orally administered to a patient at least once per day, wherein the solid dispersion comprises at least about 15 mg of substantially amorphous or amorphous Compound 1.

[0185] The pharmaceutical composition used in the invention can be orally administered to a patient at least once per day the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 25 mg of substantially amorphous or amorphous Compound 1.

[0186] The pharmaceutical composition used in the invention can be orally administered to a patient at least once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 50 mg of substantially amorphous or amorphous Compound 1.

[0187] The pharmaceutical composition used in the invention can be orally administered to a patient at least once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 75 mg of substantially amorphous or amorphous Compound 1.

[0188] The pharmaceutical composition used in the invention can be orally administered to a patient at least once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 100mg of substantially amorphous or amorphous Compound 1.

[0189] The pharmaceutical composition used in the invention can be orally administered to a patient at least once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 150 mg of substantially amorphous or amorphous Compound 1.

[0190] The pharmaceutical composition used in the invention can be orally administered to a patient at least once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 250 mg of substantially amorphous or amorphous Compound 1.

[0191] The pharmaceutical composition used in the invention can be orally administered to a patient twice per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises up to about 1 mg of substantially amorphous or amorphous Compound 1.

[0192] The pharmaceutical composition used in the invention can be orally administered to a patient twice per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises up to about 5 mg of substantially amorphous or amorphous Compound 1.

[0193] The pharmaceutical composition used in the invention can be orally administered to a patient twice per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 15 mg of substantially amorphous or amorphous Compound 1.

[0194] The pharmaceutical composition used in the invention can be orally administered to a patient twice per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 25 mg of substantially amorphous or amorphous Compound 1.

[0195] The pharmaceutical composition used in the invention can be orally administered to a patient twice per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 50 mg of substantially amorphous or amorphous Compound 1.

[0196] The pharmaceutical composition used in the invention can be orally administered to a patient twice per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 75 mg of substantially amorphous or amorphous Compound 1.

[0197] The pharmaceutical composition used in the invention can be orally administered to a patient twice per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 100 mg of substantially amorphous or amorphous Compound 1.

[0198] The pharmaceutical composition used in the invention can be orally administered to a patient twice per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 150 mg of substantially amorphous or amorphous Compound 1.

[0199] The pharmaceutical composition used in the invention can be orally administered to a patient twice per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 250 mg of substantially amorphous or amorphous Compound 1.

[0200] The pharmaceutical composition used in the invention can be orally administered to a patient once every 12 hours. The composition comprises a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises up to about 1 mg of substantially amorphous or amorphous Compound 1.

[0201] The pharmaceutical composition used in the invention can be orally administered to a patient once every 12 hours. The composition comprises a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises up to about 5 mg of substantially amorphous or amorphous Compound 1.

[0202] The pharmaceutical composition used in the invention can be orally administered to a patient once every 12 hours. The composition comprises a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 15 mg of substantially amorphous or amorphous Compound 1.

[0203] The pharmaceutical composition used in the invention can be orally administered to a patient once every 12 hours. The composition comprises a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 25 mg of substantially amorphous or amorphous Compound 1.

[0204] The pharmaceutical composition used in the invention can be by orally administered to a patient once every 12 hours. The composition comprises a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 50 mg of substantially amorphous or amorphous Compound 1.

[0205] The pharmaceutical composition used in the invention can be orally administered to a patient once every 12 hours. The composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 75 mg of substantially amorphous or amorphous Compound 1.

[0206] The pharmaceutical composition used in the invention can be orally administered to a patient once every 12 hours. The composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 100 mg of substantially amorphous or amorphous Compound 1.

[0207] The pharmaceutical composition used in the invention can be orally administered to a patient once every 12 hours. The composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 150 mg of substantially amorphous or amorphous Compound 1.

[0208] The pharmaceutical composition used in the invention can be orally administered to a patient once every 12 hours. The composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 250 mg of substantially amorphous or amorphous Compound 1.

[0209] The pharmaceutical composition used in the invention is orally administered to a patient once every 24 hours.

[0210] The pharmaceutical composition defined in the appended claims for use as defined in the appended claims can be orally administered to a patient once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 15 mg of substantially amorphous or amorphous Compound 1.

[0211] The pharmaceutical composition used in the invention can be orally administered to a patient once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 25 mg of substantially amorphous or amorphous Compound 1.

[0212] The pharmaceutical composition used in the invention can be orally administered to a patient once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 50 mg of substantially amorphous or amorphous Compound 1.

[0213] The pharmaceutical composition used in the invention can be orally administered to a patient once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 75 mg of substantially amorphous or amorphous Compound 1.

[0214] The pharmaceutical composition used in the invention can be orally administered to a patient once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 100 mg of substantially amorphous or amorphous Compound 1.

[0215] The pharmaceutical composition used in the invention can be orally administered to a patient once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 150 mg of substantially amorphous or amorphous Compound 1.

[0216] The pharmaceutical composition used in the invention can be orally administered to a patient once per day, the composition comprising a solid dispersion of substantially amorphous or amorphous Compound 1, in which the solid dispersion comprises at least about 250 mg of substantially amorphous or amorphous Compound 1.

[0217] The pharmaceutical composition defined in the appended claims for use as defined in the appended claims is provided, wherein the uses comprises orally administering to a patient at least once per day at least one tablet comprising the pharmaceutical composition defined in the appended claims, wherein the solid dispersion comprises up to about 1 mg (e.g., about 0.5 mg, about 0.75 mg, or about 1 mg) of substantially amorphous Compound 1.

[0218] The pharmaceutical composition defined in the appended claims for use as defined in the appended claims is provided, wherein the use comprises orally administering to a patient at

least once per day at least one tablet comprising the pharmaceutical composition containing defined in the appended claims, wherein the solid dispersion comprises up to about 5 mg (e.g., about 0.5 mg, about 0.75 mg, about 1 mg, about 2, mg, about 3 mg, about 4 mg, or about 5 mg) of substantially amorphous Compound 1.

[0219] The pharmaceutical composition defined in the appended claims for use as defined in the appended claims is provided, wherein the use comprises orally administering to a patient at least once per day at least one tablet comprising the pharmaceutical composition defined in the appended claims, wherein the solid dispersion comprises at least 15 mg (e.g., at least 25 mg, at least 35 mg, at least 40 mg, or at least 45 mg) of substantially amorphous Compound 1.

[0220] In some embodiments, the present invention provides a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 15 mg of substantially amorphous or amorphous Compound 1;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0221] In some embodiments, the present invention provides a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 25 mg of substantially amorphous or amorphous Compound 1;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0222] In some embodiments, the present invention provides a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 50 mg of substantially amorphous or amorphous

Compound 1;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0223] In some embodiments, the present invention provides a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 75 mg of substantially amorphous or amorphous Compound 1;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0224] In some embodiments, the present invention provides a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 100 mg of substantially amorphous or amorphous Compound 1;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0225] In some embodiments, the present invention provides a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 150 mg of substantially amorphous or amorphous Compound 1;

2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0226] In some embodiments, the present invention provides a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 250 mg of substantially amorphous or amorphous Compound 1;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0227] In some embodiments, the present invention provides a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 25 mg of substantially amorphous or amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0228] In some embodiments, the present invention provides a a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 15 mg of substantially amorphous or amorphous Compound 1 and HPMCAS;
2. b. a filler;

3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0229] In some embodiments, the present invention provides a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 50 mg of substantially amorphous or amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0230] In some embodiments, the present invention provides a a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 75 mg of substantially amorphous or amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0231] In some embodiments, the present invention provides a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 100 mg of substantially amorphous or amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;

4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0232] In some embodiments, the present invention provides a a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 150 mg of substantially amorphous or amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0233] In some embodiments, the present invention provides a a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least one tablet comprising:

1. a. a solid dispersion comprising about 250 mg of substantially amorphous or amorphous Compound 1 and HPMCAS;
2. b. a filler;
3. c. a disintegrant;
4. d. a surfactant;
5. e. a binder;
6. f. a glidant; and
7. g. a lubricant.

[0234] In some embodiments, the pharmaceutical composition used in the invention can be orally administered once a day. In other embodiments, the pharmaceutical composition used in the invention can be orally administered twice a day.

[0235] Another aspect of the present invention provides a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least once per day at least one tablet which is defined in the appended claims, in which the solid dispersion comprises at least about 25 mg of substantially amorphous or amorphous Compound 1. In some embodiments, the

tablet is orally administered to the patient once per day. In another method, the use comprises orally administering to a patient twice per day at least one tablet which is defined in the appended claims, in which the solid dispersion contains at least about 25 mg of substantially amorphous or amorphous Compound 1. Some tablets useful in this method comprise a solid dispersion containing at least about 50 mg of substantially amorphous or amorphous Compound 1. In another method, the administration includes orally administering to a patient twice per day at least one tablet which is defined in the appended claims, in which the solid dispersion contains at least about 50 mg of substantially amorphous or amorphous Compound 1. Some tablets useful in this method comprise a solid dispersion containing at least about 75 mg of substantially amorphous or amorphous Compound 1. In another method, the administration includes orally administering to a patient twice per day at least one tablet which is defined in the appended claims, in which the solid dispersion contains at least about 75 mg of substantially amorphous or amorphous Compound 1. Another aspect of the present invention provides a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, wherein the use further comprises orally administering to a patient at least once per day at least one tablet which is defined in the appended claims, in which the solid dispersion comprises at least about 100 mg of substantially amorphous or amorphous Compound 1. In some embodiments, the tablet is orally administered to the patient once per day. In another method, the administration comprises orally administering to a patient twice per day at least one tablet which is defined in the appended claims, in which the solid dispersion contains at least about 100 mg of substantially amorphous or amorphous Compound 1. Other tablets useful in this method comprise a solid dispersion containing at least about 150 mg of substantially amorphous or amorphous Compound 1. In another method, the administration includes orally administering to a patient twice per day at least one tablet which is defined in the appended claims, in which the solid dispersion contains at least about 150 mg of substantially amorphous or amorphous Compound 1. In another method, the administration includes orally administering to a patient at least once per day at least one tablet which is defined in the appended claims, in which the solid dispersion contains at least about 250 mg of substantially amorphous or amorphous Compound 1. In another method, the administration includes orally administering to a patient once per day at least one tablet which is defined in the appended claims, in which the solid dispersion contains at least about 250 mg of substantially amorphous or amorphous Compound 1. In another method, the administration includes orally administering to a patient twice per day at least one tablet which is defined in the appended claims, in which the solid dispersion contains at least about 250 mg of substantially amorphous or amorphous Compound 1.

[0236] In one embodiment, a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, is provided, wherein the use further comprises orally administering to a patient at least once per day at least one tablet including a pharmaceutical composition which is defined in the appended claims, wherein the solid dispersion comprises at least 15 mg (e.g., at least 25 mg, at least 35 mg, at least 40 mg, or at least 45 mg) of substantially amorphous Compound 1.

[0237] In one embodiment, a pharmaceutical composition which is defined in the appended

claims, for use as defined in the appended claims, is provided, wherein the use further comprises orally administering to a patient at least once per day at least one tablet comprising a pharmaceutical composition which is defined in the appended claims, wherein the solid dispersion comprises from about 30 mg to about 300 mg (e.g., from about 40 mg to about 280 mg or from about 45 mg to about 260 mg, or from about 50 mg to about 200 mg) of substantially amorphous Compound 1. Or, the method of administering a pharmaceutical composition includes orally administering to a patient at least once per day at least one tablet comprising a pharmaceutical composition containing a solid dispersion of amorphous Compound 1, a filler, a binder, a glidant, a disintegrant, a surfactant, and a lubricant, wherein the solid dispersion comprises from about 30 mg to about 300 mg (e.g., from about 40 mg to about 280 mg or from about 45 mg to about 260 mg, or from about 50 mg to about 200 mg) of amorphous Compound 1.

[0238] In another embodiment, a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, is provided, wherein the use further comprises orally administering to a patient once per day at least one tablet comprising a pharmaceutical composition which is defined in the appended claims, wherein the solid dispersion comprises at least 15 mg (e.g., at least 25 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 75 mg, at least about 100 mg, at least about 150 mg, or at least 250 mg,) of substantially amorphous Compound 1 or amorphous Compound 1. For example, the use further comprises administering the pharmaceutical composition orally administering to a patient once per day one tablet comprising a pharmaceutical composition which is defined in the appended claims, wherein the solid dispersion comprises at least 75 mg (e.g., at least 100 mg, at least 125 mg, at least 140 mg, at least 150 mg, or at least 250 mg) of substantially amorphous Compound 1 or amorphous Compound 1. In another example, the use further comprises administering the pharmaceutical composition orally to a patient once per day a plurality of tablets (e.g., two tablets, three tablets, four or five tablets), wherein each tablet comprises a pharmaceutical composition which is defined in the appended claims, wherein the solid dispersion comprises at least 15 mg (e.g., at least 25 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 75 mg, at least about 150 mg, or at least 250 mg,) of substantially amorphous Compound 1 or amorphous Compound 1.

[0239] In another embodiment, a pharmaceutical composition which is defined in the appended claims, for use as defined in the appended claims, is provided, wherein the use further comprises orally administering to a patient twice per day at least one tablet comprising a pharmaceutical composition which is defined in the appended claims, wherein the solid dispersion comprises at least 15 mg (e.g., at least 25 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 75 mg, at least about 150 mg, or at least 250 mg,) of substantially amorphous Compound 1 or amorphous Compound 1. For example, the use further comprises orally administering to a patient twice per day one tablet comprising a pharmaceutical composition which is defined in the appended claims, wherein the solid dispersion comprises at least 75 mg (e.g., at least 100 mg, at least 125 mg, at least 140 mg, at least 150 mg, or at least 250 mg) of substantially amorphous Compound 1 or amorphous Compound 1. In another example, the use further comprises orally administering to a patient

twice per day a plurality of tablets (e.g., two tablets, three tablets, four or five tablets), wherein each tablet comprises a pharmaceutical composition which is defined in the appended claims, wherein the solid dispersion comprises at least 15 mg (e.g., at least 25 mg, at least 35 mg, at least 40 mg, at least 45 mg, at least 50 mg, at least 75 mg, at least about 150 mg, or at least 250 mg,) of substantially amorphous Compound 1 or amorphous Compound 1.

[0240] It is noted that the uses of the present invention according to claim 1 can optionally include orally administering a beverage (water, milk, or the like), food, and/or additional pharmaceutical compositions including additional APIs. When the use includes orally administering a beverage (water, milk, or the like), food (including a standard high fat high calorie CF meal or snack), and/or additional pharmaceutical compositions including additional APIs, the oral administration of the beverage, food, and/or additional API can occur concurrently with the oral administration of the tablet, prior to the oral administration of the tablet, and/or after the administration of the tablet. In the invention, the pharmaceutical composition defined in claim 1 for use as in claim 1 is administered concurrently with, prior to, or subsequent to one or more other desired therapeutics. For instance, in one example, the use includes orally administering to a patient at least once per day at least one tablet comprising a pharmaceutical composition which is defined in the appended claims, and a second API as defined in the claims. In another example, the use includes orally administering to a patient at least once per day at least one tablet comprising a pharmaceutical composition which is defined in the appended claims, wherein the solid dispersion comprises at least 15 mg (e.g., at least 25 mg, at least 35 mg, at least 45 mg, or at least 50 mg) of substantially amorphous Compound 1 or amorphous Compound 1, and orally administering to a patient at least once per day a second pharmaceutical composition comprising a second API as defined in the claims. In still other examples, the use as defined in the claims includes orally administering to a patient every 12 hours at least one tablet comprising a pharmaceutical composition as described in the appended claims, in which the tablet is administered about 30 minutes after consuming a high fat, high calorie CF meal or snack.

[0241] The pharmaceutically acceptable compositions of the present invention are employed in combination therapies, that is, the pharmaceutically acceptable compositions defined in claim 1 are administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics, wherein the other desired therapeutic is a CFTR modulator other than compound 1.

[0242] In another embodiment, the additional agent is (3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl) cyclopropanecarboxamido)-3-methylpyridin-2-yl)benzoic acid.

VI. EXAMPLES

[0243] In order that the invention described herein may be more fully understood, the following examples are set forth..

A. Manufacture of Tablets

Intermediate A - comparative example

[0244] A solvent system of methylethyl ketone (MEK) and DI water, formulated according to the ratio 90 wt% MEK / 10 wt% DI water, was added to a reactor equipped with a magnetic stirrer and thermal circuit. Into this solvent system, hypromellose acetate succinate polymer ((HPMCAS) HG grade, commercially available from Biddle Sawyer Corporation in New York, New York or Shin-Etsu Chemical Co. in Tokyo, Japan), sodium lauryl sulfate (SLS), and N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 49.5 wt% hypromellose acetate succinate / 0.5 wt% sodium lauryl sulfate (SLS) / 50 wt% N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 20 wt% dissolved solids. The actual amounts of ingredients and amounts of solvents used to generate this mixture are recited in Table A1, below:

Table A1: Solid Spray Dispersion Ingredients for Intermediate A

	Units	**Batch**
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	9.00
HPMCAS	Kg	8.91
SLS	Kg	0.09
Total Solids	**Kg**	**18.00**
MEK	Kg	64.80
Water	Kg	7.20
Total Solvents	**Kg**	**72.00**
Total Spray Solution Weight	**Kg**	**90.00**

[0245] The mixture was mixed at room temperature until it was substantially homogenous and all components were substantially dissolved.

[0246] A spray drier, Niro Mobile Minor Spray Dryer with extended chamber, fitted with a 1.3 mm two-fluid atomizer situated approximately 5 cm from the top of the spray drying vessel was used in accordance with the spray dry parameters in Table A2.

Table A2: Dry spray process parameters used to generate Intermediate A.

Parameter	**Value**
Atomization Flow Rate	10.5 kg/hr
Feed Flow Rate	7 kg/hr

Parameter	Value
Inlet Temperature	~105 °C
Outlet Temperature	40 °C ± 5 °C
Vacuum Dryer Temperature	55 °C
Vacuum Drying Time	24 hours

[0247] An inertial cyclone separated the product from the process gas and solvent vapors, and a filter bag collected the fine particles not separated by the cyclone. The resultant product was transferred to a vacuum tray dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate A.

Intermediate B - comparative example

[0248] A solvent system of MEK, DI water, and acetone, formulated according to the ratio 65 wt% MEK / 9 wt% DI water / 26 wt% acetone, was heated to a temperature of 20 - 30 °C in a reactor equipped with a magnetic stirrer and thermal circuit. Into this solvent system, a copolymer of vinylpyrrolidone and vinylacetatepolyvinylpyrrolidone (PVP/VA-64 commercially available from Shanghai Lite Chemical Technology Co., Ltd. Shanghai, China), SLS, and N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 19.5 wt% PV/PVA-64 / 0.5 wt% sodium lauryl sulfate / 80 wt% N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphanyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 11.5 wt% solids. The actual amounts of ingredients and solvents used to generate this mixture are recited in Table B1, below:

Table B1: Solid Spray Dispersion Ingredients for Intermediate B

	Units	Batch 1
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	24.00
PVP/VA-64	Kg	5.850
SLS	Kg	0.1500
Total Solids	**Kg**	**30.00**
MEK	Kg	150.1
Water	Kg	20.78
Acetone	Kg	60.03
Total Solvents	**Kg**	**230.9**
Total Spray Solution Weight	**Kg**	**260.9**

[0249] The mixture was maintained at a temperature of 20 - 30 °C and mixed until it was

substantially homogenous and all components were substantially dissolved.

[0250] A spray drier, Niro Production Minor Spray Dryer, fitted with pressure nozzles (Spray Systems Maximum Passage series SK-MFP having orifice size 72), was used under normal spray drying mode, following the dry spray process parameters recited in Table B2, below. The spray nozzle was situated approximately 5 cm from the top of the spray drying vessel.

Table B2: Dry spray process parameters used to generate Intermediate B.

Parameter	**Value**
Feed Pressure	30 - 100 bar
Feed Flow Rate	15 - 25 Kg/hr
Inlet Temperature	85 - 125 °C
Outlet Temperature	45 - 75 °C
Vacuum Dryer Temperature	55 °C ± 5 °C
Vacuum Drying Time	24 hours

[0251] A high efficiency cyclone separated the wet product from the spray gas and solvent vapors. The wet product was transferred to a tray vacuum dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate B.

Intermediate C:

[0252] A solvent system of MEK and DI water, formulated according to the ratio 90 wt% MEK / 10 wt% DI water, was heated to a temperature of 20 - 30 °C in a reactor, equipped with a magnetic stirrer and thermal circuit. Into this solvent system, hypromellose acetate succinate polymer (HPMCAS)(HG grade), SLS, and N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 19.5 wt% hypromellose acetate succinate / 0.5 wt% SLS / 80 wt% N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 12.5 wt% solids. The actual amounts of ingredients and solvents used to generate this mixture are recited in Table C1, below:

Table C1: Solid Spray Dispersion Ingredients for Intermediate C.

	Units	Batch
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	24.00
HPMCAS	Kg	5.850
SLS	Kg	0.1500
Total Solids	**Kg**	**30.00**
MEK	Kg	189.0

	Units	Batch
Water	Kg	21.00
Total Solvents	**Kg**	**210.0**
Total Spray Solution Weight	**Kg**	**240.0**

[0253] The mixture was maintained at a temperature of 20 - 30 °C and mixed until it was substantially homogenous and all components were substantially dissolved.

[0254] A spray drier, Niro Production Minor Spray Dryer, fitted with pressure nozzles (Spray Systems Maximum Passage series SK-MFP having orifice size 72), was used under normal spray drying mode, following the dry spray process parameters recited in Table C2, below. The spray nozzle was situated approximately 5 cm from the top of the spray drying vessel.

Table C2: Dry spray process parameters used to generate Intermediate C.

Parameter	**Target Value**
Feed Pressure	30 - 100 bar
Feed Flow Rate	15 - 25 Kg/hr
Inlet Temperature	85 - 125 °C
Outlet Temperature	45 - 75 °C
Vacuum Dryer Temperature	55 °C (+/-5 °C)
Vacuum Drying Time	24 hours

[0255] A high efficiency cyclone separated the wet product from the spray gas and solvent vapors. The wet product was transferred to a tray vacuum dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate C.

Intermediate D:

[0256] A solvent system of MEK and DI water, formulated according to the ratio 90 wt% MEK / 10 wt% DI water, was heated to a temperature of 20 - 30 °C in a reactor, equipped with a magnetic stirrer and thermal circuit. Into this solvent system, hypromellose acetate succinate polymer (HPMCAS)(HG grade), SLS, and N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 19.5 wt% hypromellose acetate succinate / 0.5 wt% SLS / 80 wt% N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 12.5 wt% solids. The actual amounts of ingredients and solvents used to generate this mixture are recited in Table D1, below:

Table D1: Solid Spray Dispersion Ingredients for Intermediate D.

	Units	Batch
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	1.60
HPMCAS	Kg	0.390
SLS	Kg	0.010
Total Solids	Kg	**2.00**
MEK	Kg	12.6
Water	Kg	1.40
Total Solvents	Kg	**14.0**
Total Spray Solution Weight	Kg	**16.0**

[0257] The mixture was maintained at a temperature of 20 - 30 °C and mixed until it was substantially homogenous and all components were substantially dissolved.

[0258] A spray drier, Niro Mobil Minor Spray Dryer fitted with a 1.0mm two fluid nozzle, was used in normal spray drying mode, following the dry spray process parameters recited in Table D2, below.

Table D2: Dry spray process parameters used to generate Intermediate D.

Parameter	**Value**
Atomization Ratio	1.5
Feed Flow Rate	4.5 - 5.0 Kg/hr
Outlet Temperature	60°C
Vacuum Dryer Temperature	55 °C (+/-5 °C)
Vacuum Drying Time	192 hours

[0259] A high efficiency cyclone separated the wet product from the spray gas and solvent vapors. The wet product contained 6.3% MEK and 0.7% Water and had a mean particle size of 7um and a bulk density of 0.23g/cc. The wet product was transferred to a tray vacuum dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate D. The dry Intermediate D contained <0.5% MEK and 0.3% Water.

Intermediate E:

[0260] A solvent system of MEK and DI water, formulated according to the ratio 90 wt% MEK / 10 wt% DI water, was heated to a temperature of 20 - 30 °C in a reactor, equipped with a magnetic stirrer and thermal circuit. Into this solvent system, hypromellose acetate succinate polymer (HPMCAS)(HG grade), SLS, and N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-

dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 19.5 wt% hypromellose acetate succinate / 0.5 wt% SLS / 80 wt% N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 10.5 wt% solids. The actual amounts of ingredients and solvents used to generate this mixture are recited in Table E1, below:

Table E1: Solid Spray Dispersion Ingredients for Intermediate E.

	Units	Batch
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	43.93
HPMCAS	Kg	10.72
SLS	Kg	0.2750
Total Solids	**Kg**	**54.93**
MEK	Kg	421.8
Water	Kg	46.90
Total Solvents	**Kg**	**468.7**
Total Spray Solution Weight	**Kg**	**523.6**

[0261] The mixture temperature was adjusted to a range of 30 - 45 °C and mixed until it was substantially homogenous and all components were substantially dissolved.

[0262] A spray drier, Niro PSD4 Commercial Spray Dryer, fitted with pressure nozzles (Spray Systems Maximum Passage series SK-MFP having orifice/core size 54/21, 53/21 or 52/21) equipped with anti-bearding cap, was used under normal spray drying mode, following the dry spray process parameters recited in Table E2, below.

Table E2: Dry spray process parameters used to generate Intermediate E.

Parameter	**Value**
Feed Pressure	20 - 40 bar
Feed Flow Rate	90 - 160 Kg/hr
Inlet Temperature	75 - 125 °C
Outlet Temperature	35 - 55 °C
Vacuum Dryer Temperature	80 °C (+/-5 °C)
Vacuum Drying Time	156 hours

[0263] A high efficiency cyclone separated the wet product from the spray gas and solvent vapors. The wet product contained 8.8 - 12.5%wt. MEK/Water a mean particle size of 16 - 24um and a bulk density of 0.28 - 0.36g/cc. The wet product was transferred to a 350L stainless steel double cone vacuum dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate E. The dry Intermediate E

contained <0.3% MEK and 0.8% Water.

Intermediate F:

[0264] A solvent system of MEK and DI water, formulated according to the ratio 90 wt% MEK / 10 wt% DI water, was heated to a temperature of 20 - 30 °C in a reactor, equipped with a magnetic stirrer and thermal circuit. Into this solvent system, hypromellose acetate succinate polymer (HPMCAS)(HG grade), SLS, and N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 19.5 wt% hypromellose acetate succinate / 0.5 wt% SLS / 80 wt% N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 10.5 wt% solids. The actual amounts of ingredients and solvents used to generate this mixture are recited in Table F1, below:

Table F1: Solid Spray Dispersion Ingredients for Intermediate F.

	Units	Batch
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	70.0
HPMCAS	Kg	17.1
SLS	Kg	0.438
Total Solids	**Kg**	**87.5**
MEK	Kg	671
Water	Kg	74.6
Total Solvents	**Kg**	**746**
Total Spray Solution Weight	**Kg**	**833**

[0265] The mixture temperature was adjusted to a range of 20 - 45 °C and mixed until it was substantially homogenous and all components were substantially dissolved.

[0266] A spray drier, Niro PSD4 Commercial Spray Dryer, fitted with pressure nozzle (Spray Systems Maximum Passage series SK-MFP having orifice/core size 54/21) equipped with anti-bearding cap, was used under normal spray drying mode, following the dry spray process parameters recited in Table F2, below.

Table F2: Dry spray process parameters used to generate Intermediate F.

Parameter	**Value**
Feed Pressure	20 bar
Feed Flow Rate	92 - 100 Kg/hr
Inlet Temperature	93 - 99 °C
Outlet Temperature	53 - 57 °C

Parameter	Value
Vacuum Dryer Temperature	80 °C for 2 hours then 110 °C (+/-5 °C)
Vacuum Drying Time	20 - 24 hours

[0267] A high efficiency cyclone separated the wet product from the spray gas and solvent vapors. The wet product contained 8.5 - 9.7% MEK and 0.56 - 0.83% Water and had a mean particle size of 17 - 19um and a bulk density of 0.27 - 0.33g/cc. The wet product was transferred to a 4000L stainless steel double cone vacuum dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate F. The dry Intermediate F contained <0.03% MEK and 0.3% Water.

Intermediate G:

[0268] A solvent system of MEK and DI water, formulated according to the ratio 90 wt% MEK / 10 wt% DI water, was heated to a temperature of 20 - 30 °C in a reactor, equipped with a magnetic stirrer and thermal circuit. Into this solvent system, hypromellose acetate succinate polymer (HPMCAS)(HG grade), SLS, and N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 19.5 wt % hypromellose acetate succinate / 0.5 wt % SLS / 80 wt% N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide. The resulting mixture contained 10.5 wt% solids. The actual amounts of ingredients and solvents used to generate this mixture are recited in Table G1, below:

Table G1: Solid Spray Dispersion Ingredients for Intermediate G.

	Units	Batch
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	24.0
HPMCAS	Kg	5.85
SLS	Kg	0.15
Total Solids	**Kg**	**30.0**
MEK	Kg	230.1
Water	Kg	25.6
Total Solvents	**Kg**	**255.7**
Total Spray Solution Weight	**Kg**	**285.7**

[0269] The mixture temperature was adjusted to a range of 20 - 45 °C and mixed until it was substantially homogenous and all components were substantially dissolved.

[0270] A spray drier, Niro Production Minor Spray Dryer, fitted with pressure nozzle (Spray

Systems Maximum Passage series SK-MFP having orifice size 72) was used under normal spray drying mode, following the dry spray process parameters recited in Table G2, below.

Table G2: Dry spray process parameters used to generate Intermediate G.

Parameter	**Value**
Feed Pressure	33 bar
Feed Flow Rate	18 - 24 Kg/hr
Inlet Temperature	82 - 84 °C
Outlet Temperature	44 - 46 °C
Vacuum Dryer Temperature	80 °C for 2 hours then 110 °C (+/-5 °C)
Vacuum Drying Time	48 hours

[0271] A high efficiency cyclone separated the wet product from the spray gas and solvent vapors. The wet product contained 10.8% MEK and 0.7% Water and had a mean particle size of 19um and a bulk density of 0.32g/cc. The wet product was transferred to a 4000L stainless steel double cone vacuum dryer for drying to reduce residual solvents to a level of less than about 5000 ppm and to generate dry Intermediate. The dry Intermediate G contained <0.05% MEK and 0.7% Water.

Intermediate H:

[0272] A solvent system of MEK and DI water, formulated according to the ratio 90 wt% MEK / 10 wt% DI water, was heated to a temperature of 20 - 30 °C in a reactor, equipped with a magnetic stirrer and thermal circuit. Into this solvent system, hypromellose acetate succinate polymer (HPMCAS)(HG grade), SLS, and N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide were added according to the ratio 19.5 wt % hypromellose acetate succinate / 0.5 wt % SLS / 80 wt% N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide. The actual amounts of ingredients and solvents used to generate this mixture are recited in Table HI, below:

Table H1: Solid Spray Dispersion Ingredients for Intermediate H.

	Units	Batch
N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide	Kg	56.0
HPMCAS	Kg	13.65
SLS	Kg	0.35
Total Solids	**Kg**	**70.0**
MEK	Kg	509.73
Water	Kg	56.64
Total Solvents	**Kg**	**566.40**

	Units	Batch
Total Spray Solution Weight	**Kg**	**636.40**

[0273] The mixture temperature was adjusted to a range of 20 - 30 °C and mixed until it was substantially homogenous and all components were substantially dissolved.

[0274] A spray drier, Niro Production Minor Spray Dryer, fitted with pressure nozzle (Spray Systems Maximum Passage series SK-MFP having orifice size # 52 or # 54, e.g., about 1.39-1.62 mm) was used under normal spray drying mode, following the dry spray process parameters recited in Table H2, below.

Table H2: Dry spray process parameters used to generate Intermediate H.

Parameter	**Value**
Feed Pressure	20-50 bar
Feed Flow Rate	18 - 24 Kg/hr
Inlet Temperature	-7 to 7 °C
Outlet Temperature	30 - 70 °C

[0275] A high efficiency cyclone separated the wet product from the spray gas and solvent vapors. The wet product contained approximately 10.8% MEK and 0.7% Water and had a mean particle size of about 19µm and a bulk density of about 0.33g/cc.

[0276] An inertial cyclone is used to separate the spray dried intermediate from the process gas and solvent vapors. Particle size is monitored on-line. The spray dried intermediate is collected in an intermediate bulk container. The process gas and solvent vapors are passed through a filter bag to collect the fine particles not separated by the cyclone. The resultant gas is condensed to remove process vapors and recycled back to the heater and spray dryer. The spray dried intermediate will be stored at less than 30°C, if secondary drying will occur in less than 24 hours or between 2-8°C, if secondary drying will occur in more than 24 hours.

[0277] Secondary drying occurs by charging a 4000-L biconical dryer having a jacket temperature between about 20-30°C with the spray dried intermediate. The vacuum pressure, jacket temperature, and nitrogen bleed are set at between about -0.8 psig and about -1.0 psig, between about 80 - 120°C, and between about 0.5 - 8.0 m^3/h, respectively. Agitation is set at lrpm. Bulk samples of the spray dried intermediate are tested for MEK (GC), every 4 hours until dry. The MEK drying rate is monitored on-line by GC-MS, calibrated for MEK concentration. Upon reaching a plateau in the drying of the residual MEK, heating in the biconical dryer is discontinued while continuing rotatation until the spray dried intermediate reaches a temperature less than or equal to 50°C.

[0278] Although Intermediates A through H are described above as being formed, in part, by

admixing the solid spray dispersion ingredients with application of heat to form a homogeneuos mixture, the solid spray dispersion ingredients can also be mixed without application of heat to form a mixture of the solid spray dispersion ingredients.

Example 1:Exemplary Tablet 1 (Formulated to have 25 mg of Compound 1) - comparative example

[0279] A batch of round core 3/8" tablets was formulated to have approximately 25 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 1, below.

Table 1: Ingredients for Exemplary Tablet 1.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate A	15.29%	51.23	512.5
Microcrystalline cellulose	35.00%	117.25	1172
Lactose	43.85%	146.00	1460
Sodium croscarmellose	5.000%	16.75	167.5
SLS	0.500%	1.675	16.75
Colloidal silicon dioxide	0.125%	0.4188	4.188
Magnesium stearate	0.50%	1.675	16.75
Total	**100%**	**335**	**3350**

[0280] Intermediate A, microcrystalline cellulose (FMC MCC Avicel® PH102, commercially available from FMC BioPolymer Corporation of Philadelphia, PA), lactose (Foremost FastFlo® Lactose #316 commercially available from Foremost Farms USA of Baraboo, WI), sodium croscarmellose (FMC Ac-Di-Sol®, commercially available from FMC BioPolymer Corporation of Philadelphia, PA), SLS, and colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide, commercially available from Cabot Corporation of Alpharetta, GA) were sieved through a 20 mesh screen to remove lumps.

[0281] Each of the sieved ingredients was added to a 16 quart V-blender in the following order:

1. 1) lactose;
2. 2) SLS;
3. 3) sodium croscarmellose;
4. 4) colloidal silicon dioxide;
5. 5) Intermediate A; and
6. 6) microcrystalline cellulose PH101

[0282] The mixture was blended for 25 minutes in a V-blender at 20-24 rpm. Magnesium stearate was sieved through a 30 mesh screen to remove lumps, and added to the mixture, which was blended for another 3 minutes.

[0283] Once the final blend has been completed, the mixture was transferred to a Piccola B-Tooling, 10 Station rotary tablet press (half tooled) for compression. Pressing the mixture into tablets generated 3/8" round tablets having approximately 25 mg of N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide.

Example 2: Exemplary Tablet 2 (Formulated to have 50 mg of Compound 1) - comparative example

[0284] A batch of round core 3/8" tablets was formulated to have about 50 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 2, below.

Table 2: Ingredients for Exemplary Tablet 2.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate A	30.60%	102.50	1025.0
Microcrystalline cellulose	25.00%	83.75	837.5
Lactose	38.28%	128.23	1282.3
Sodium croscarmellose	5.000%	16.75	167.5
SLS	0.500%	1.675	16.75
Colloidal silicon dioxide	0.125%	0.4188	4.188
Magnesium stearate	0.50%	1.675	16.75
Total	**100%**	**335**	**3350**

[0285] Intermediate A, microcrystalline cellulose, lactose, sodium croscarmellose, SLS, and colloidal silicon dioxide were sieved through a 20 mesh screen to remove lumps, and each of the sieved ingredients was added to a 16 quart V-blender in the following order:

1. 1) lactose;
2. 2) SLS;
3. 3) sodium croscarmellose;
4. 4) colloidal silicon dioxide;
5. 5) Intermediate A; and
6. 6) microcrystalline cellulose PH101

[0286] The mixture was blended for 25 minutes in a V-blender at 20-24 rpm. Magnesium stearate was sieved through a 30 mesh screen to remove lumps, and added to the mixture,

which was blended for another 3 minutes.

[0287] Once the final blend has been completed, the mixture was transferred to a Piccola B-Tooling, 10 Station rotary tablet press (half tooled) for compression. Pressing the mixture into tablets generated 3/8" round tablets having approximately 50 mg of N-[2,4-Bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinoline-3-carboxamide.

Example 3: Exemplary Tablet 3 (Formulated with PVP/VA Polymer to have 150 mg of Compound 1) - comparative example

[0288] A batch of caplet-shaped tablets was formulated to have about 150 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 3, below.

Table 3: Ingredients for Exemplary Tablet 3.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate B	40.000%	187.50	240.00
Microcrystalline cellulose	27.063%	126.86	162.38
Lactose	27.063%	126.86	162.38
Sodium croscarmellose	3.000%	14.06	18.00
SLS	0.500%	2.34	3.00
Colloidal silicon dioxide	1.000%	4.69	6.00
Coloring	0.375%	1.76	2.25
Magnesium stearate	1.000%	4.69	6.00
Total	**100%**	**469**	**600**

[0289] A glidant blend of colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide) and SLS was produced by hand mixing these two ingredients, in the amounts given in Table 3, and filtering the resulting mix through a 70 mesh screen sieve. A color blend of coloring (Colorcon Blue #1 Aluminum Lake #5516) and sodium croscarmellose (FMC Ac-Di-Sol®) was produced by hand mixing these two ingredients, in the amounts given in Table 3, and filtering the resulting mix through a 70 mesh screen sieve. The glidant blend and the color blend were hand mixed and added to a 2 L blending container. Intermediate B was added to this mixture in the 2 L blending container, and the contents 2 L blending container were hand mixed and filtered through a 30 mesh screen sieve. The resulting mixture was mixed on a Turbula mixer for 20 minutes at a rate of 22 rpm.

[0290] The microcrystalline cellulose (FMC MCC Avicel® PH102) and lactose (Foremost FastFlo® Lactose #316) were each filtered through a 30 mesh screen sieve and added to the blending container. The resulting mixture was mixed on a Turbula mixer for 20 minutes at a

rate of 22 rpm.

[0291] Magnesium Stearate was filtered through a 70 mesh screen sieve and added to the mixture in the blending container, and the resulting mixture was mixed for 5 minutes at a rate of 22 rpm.

[0292] The resulting mixture was compressed into tablets using a gravity fed boot tooled with 0.64" × 0.32" caplet type B tooling set to produce a tablet having an initial hardness of about 8 Kp ± 15%.

Example 4: Exemplary Tablet 4 (Formulated with HPMCAS Polymer to have 150 mg of Compound 1)

[0293] A batch of caplet-shaped tablets was formulated to have about 150 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 4, below.

Table 4: Ingredients for Exemplary Tablet 4.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate C	34.091%	187.50	204.55
Microcrystalline cellulose	30.017%	165.09	180.10
Lactose	30.017%	165.09	180.10
Sodium croscarmellose	3.000%	16.50	18.00
SLS	0.500%	2.75	3.00
Colloidal silicon dioxide	1.000%	5.50	6.00
Coloring	0.375%	2.06	2.25
Magnesium stearate	1.000%	5.50	6.00
Total	100%	550	600

[0294] A glidant blend of colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide) and SLS was produced by hand mixing these two ingredients, in the amounts given in Table 4, and filtering the resulting mix through a 70 mesh screen sieve. A color blend including coloring (Colorcon Blue #1 Aluminum Lake #5516) and sodium croscarmellose (FMC Ac-Di-Sol®) was produced by hand mixing these two ingredients, in the amounts given in Table 4, and filtering the resulting mix through a 70 mesh screen sieve. The glidant blend and the color blend were hand mixed and added to a 2 L blending container. Intermediate C was added to this mixture in the 2 L blending container, and the contents 2 L blending container were hand mixed and filtered through a 30 mesh screen sieve. The resulting mixture was mixed on a Turbula mixer for 20 minutes at a rate of 22 rpm.

[0295] The microcrystalline cellulose (FMC MCC Avicel® PH102) and lactose (Foremost

FastFlo® Lactose #316) were each filtered through a 30 mesh screen sieve and added to the blending container. The resulting mixture was mixed on a Turbula mixer for 20 minutes at a rate of 22 rpm.

[0296] Magnesium stearate was filtered through a 70 mesh screen sieve and added to the mixture in the blending container, and the resulting mixture was mixed for 5 minutes at a rate of 22 rpm.

[0297] The resulting mixture was compressed into tablets using a tablet press tooled with 0.64" × 0.32" caplet type B tooling set to produce a tablet having an initial hardness of about 9.5 Kp ± 15%.

Example 5: Exemplary Tablet 5 (Formulated with HPMCAS Polymer to have 150 mg of Compound 1)

[0298] A batch of caplet-shaped tablets was formulated to have about 150 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 5, below.

Table 5: Ingredients for Exemplary Tablet 5.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate G	34.564%	190.10	21000.00
Microcrystalline cellulose	29.968%	164.82	18207.62
Lactose	29.968%	164.82	18207.62
Sodium croscarmellose	3.000%	16.50	1822.71
SLS	0.500%	2.75	303.78
Colloidal silicon dioxide	1.000%	5.50	607.57
Magnesium stearate	1.000%	5.50	607.57
Total	**100%**	**550**	**607560**

[0299] A blend of colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide), SLS, sodium croscarmellose (FMC Ac-Di-Sol®), and approximately 10% of the lactose (Foremost FastFlo® Lactose #316) given in Table 5 was produced by mixing these ingredients in a V-blender to provide about 125 inversions. This mixture, Preblend 1, was cone-milled through a 40 mesh screen sieve, collected and stored for subsequent use.

[0300] Approximately 20% of the lactose (Foremost FastFlo® Lactose #316) given in Table 5 was cone-milled through a 30 mesh screen sieve, collected and stored for subsequent use as Preblend 2. Intermediate G was filtered through a 30 mesh screen, collected and stored for subsequent use as Preblend 3. The microcrystalline cellulose (FMC MCC Avicel® PH102) was

filtered through a 30 mesh screen, collected and stored for subsequent use as Preblend 4.

[0301] A V-blender was charged with Preblend 2, the remaining 70% of the lactose (Foremost FastFlo® Lactose #316) given in Table 3, Preblend 3, Preblend 1, and Preblend 4, in that order, and blended for about 500 inversions. The blended mixture was tested for uniformity.

[0302] Magnesium Stearate was filtered through a 70 mesh screen sieve and added to the mixture in the blending container, and the resulting mixture was mixed to provide about 125 inversions.

[0303] The resulting mixture was compressed into tablets using a Killian T100 press tooled with 0.64" × 0.32" caplet type B tooling set to produce a tablet having an initial hardness of about 11 Kp ± 20%.

Example 6: Exemplary Tablet 6 (Formulated with HPMCAS Polymer to have 100 mg of Compound 1)

[0304] A batch of caplet-shaped tablets was formulated to have about 100 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 6, below.

Table 6: Ingredients for Exemplary Tablet 6.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate G	34.564%	126.73	9000.06
Microcrystalline cellulose	29.968%	109.88	7803.32
Lactose	29.968%	109.88	7803.32
Sodium croscarmellose	3.000%	11.00	781.17
SLS	0.500%	1.83	130.19
Colloidal silicon dioxide	1.000%	3.67	260.39
Magnesium stearate	1.000%	3.67	260.39
Total	**100%**	**367**	**26040**

[0305] A blend of colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide), SLS, sodium croscarmellose (FMC Ac-Di-Sol®), and approximately 10% of the lactose (Foremost FastFlo® Lactose #316) given in Table 6 was produced by mixing these ingredients in a V-blender to provide about 125 inversions. This mixture, Preblend 1, was cone-milled through a 40 mesh screen sieve, collected and stored for subsequent use.

[0306] Approximately 20% of the lactose (Foremost FastFlo® Lactose #316) given in Table 6 was cone-milled through a 30 mesh screen sieve, collected and stored for subsequent use as

Preblend 2. Intermediate G was filtered through a 30 mesh screen, collected and stored for subsequent use as Preblend 3. The microcrystalline cellulose (FMC MCC Avicel® PH102) was filtered through a 30 mesh screen, collected and stored for subsequent use as Preblend 4.

[0307] A V-blender was charged with Preblend 2, the remaining 70% of the lactose (Foremost FastFlo® Lactose #316) given in Table 3, Preblend 3, Preblend 1, and Preblend 4, in that order, and blended for about 500 inversions. The blended mixture was tested for uniformity.

[0308] Magnesium Stearate was filtered through a 70 mesh screen sieve and added to the mixture in the blending container, and the resulting mixture was mixed to provide about 125 inversions.

[0309] The resulting mixture was compressed into tablets using a Killian T100 press tooled with 0.64" × 0.32" caplet type B tooling set to produce a tablet having an initial hardness of about 11 Kp ± 20%.

Example 7: Exemplary Tablets 7 and 8 (Tablet 5 and 6 with Spray-Coating

[0310] A batch of caplet-shaped tablets from Example 5 and 6 was spray-coated with OPADRY® II (Blue, Colorcon) to a weight gain of about 3.0% using a 24" coating pan configured with the parameters in Table 7 followed by logo printing using Opacode® WB (Black, Colorcon).

Table 7: Spray-Coating Process Parameters

Coating Parameters 24" Pan	Target
Pan Load (kg)	15
Inlet Temperature (°C)*	*
Pan Speed (rpm)	14
Jog Time	TBD
# of Spray Guns	2
Solids Content (%w/w)	20
Gun to Bed Distance (inches)	6
Inlet Air Flow (cfm)	250, 300**
Spray Rate (g/min)	70
Exhaust Temperature (°C)	50
Atomization Pressure (psi)	25
Pattern Pressure (psi)	25
* Inlet temperature is monitored to achieve target exhaust temperature. Initial inlet temperature should be set at about 75°C to achieve target exhaust temp.	

Coating Parameters 24" Pan	Target
** The target Inlet Air Flow was 250, 300 for Tablet 7 and Tablet 8, respectively.	

[0311] The OPADRY® II suspension was prepared by measuring an amount of deionized water which when combined with OPADRY® II would produce a total solids content of 20 %w/w. The water is mixed to a vortex followed by addition of OPADRY® II over a period of approximately 5 minutes. Once the OPADRY® II powder was wetted, mixing was continued to ensure that all solid material is well-dispersed. The suspension is then charged into a Thomas 24" pan coating instrument using coating conditions outlined in Table 7.

[0312] Core tablets are placed into the coating pan and pre-warmed. The inlet temperature was increased from room temperature to about 55°C and then increased as necessary to provide the exhaust temperature in Table 7. The coating process was performed with 20% w/w OPADRY® II (85 Series Blue) coating dispersion to obtain a target weight gain of about 3%. The coated tablets were then allowed to tumble for about 2 minutes without spraying. The bed temperature was then allowed to cool to about 35°C.

[0313] Once coated with OPADRY® II, the tablets are then labeled using a Hartnett Delta tablet printer charged with Opacode® WB.

Example 8: Exemplary Tablet 9 (Formulated with HPMCAS Polymer to have 100 mg of Compound 1)

[0314] A batch of caplet-shaped tablets was formulated to have about 100 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 8, below.

Table 8: Ingredients for Exemplary Tablet 9.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate F	34.09%	125.1	23.86
Microcrystalline cellulose	30.51%	112.0	21.36
Lactose	30.40%	111.6	21.28
Sodium croscarmellose	3.000%	11.01	2.100
SLS	0.500%	1.835	0.3500
Colloidal silicon dioxide	0.500%	1.835	0.3500
Magnesium stearate	1.000%	3.670	0.7000
Total	**100%**	**367**	**70**

[0315] The colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide) and the microcrystalline cellulose (FMC MCC Avicel® PH102) were passed through a 30 mesh screen.

[0316] The sodium croscarmellose (FMC Ac-Di-Sol®), SLS, Intermediate F, and lactose (Foremost FastFlo® Lactose #316) were also passed, individually in the preceding order, through the same 30 mesh screen. A nitrogen purge was used when screening Intermediate F. The screened components were loaded into a 10 cubic feet V-blender, which was purged with nitrogen, and blended for about 180 (+/- 10) inversions.

[0317] The Magnesium Stearate was filtered through a 40 mesh screen sieve into the blending container and mixed to provide about 54 inversions.

[0318] The resulting mixture was compressed into tablets using a fully tooled 36 Fette 2090 press with 0.568" × 0.2885" caplet type B tooling set to produce a tablet having an initial target hardness of about 10 Kp ± 20%.

Example 9: Exemplary Tablet 10 (Tablet 9 with Spray-Coating)

[0319] A batch of caplet-shaped tablets from Example 8 was spray-coated with OPADRY® II (Blue, Colorcon) to a weight gain of about 3.0% using a 24" coating pan configured with the parameters in Table 9 followed by wax coating and then printing using Opacode® S-1-17823 (Solvent based Black, Colorcon).

Table 9: Spray-Coating Process Parameters

Coating Parameters 24" Pan	Target
Pan Load (kg)	14
Inlet Temperature (°C)*	*
Pan Speed (rpm)	10
Jog Time (sec)	
# of Spray Guns	2
Solids Content (%w/w)	20
Gun to Bed Distance (inches)	6
Inlet Air Flow (cfm)	300
Spray Rate (g/min)	35
Exhaust Temperature (°C)	50
Atomization Pressure (psi)	42
* Inlet temperature is monitored to achieve target exhaust temperature. Initial inlet temperature should be set at about 75°C to achieve target exhaust temp.	

[0320] The OPADRY® II suspension was prepared by measuring an amount of deionized water which when combined with OPADRY® II would produce a total solids content of 20 %w/w. The water is mixed to a vortex followed by addition of OPADRY® II over a period of approximately 5 minutes. Once the OPADRY® II powder was wetted, mixing was continued to ensure that all solid material is well-dispersed. The suspension is then charged into a Thomas 24" pan coating instrument using coating conditions outlined in Table 9.

[0321] Uncoated tablets are placed into the coating pan and pre-warmed. The inlet was increased from room temperature to about 55°C and then increased as necessary to provide the exhaust temperature in Table 9. The coating process was performed with 20% w/w OPADRY® II (85 Series Blue) coating dispersion to obtain a target weight gain of about 3%. The coated tablets were then allowed to tumble for about 2 minutes without spraying. The bed temperature was then allowed to cool to about 35°C.

[0322] Upon cooling, the Carnauba wax powder was weighed out in the amount of about 0.01% w/w of the starting tablet core weight. With the air flow off, the carnauba wax powder was sprinkled evenly on the tablet bed. The pan bed was turned on to the speed indicated in Table 9. After 5 minutes, the air flow was turned on (without heating) to the setting indicated in Table 9. After about one minute the air flow and pan were turned off.

[0323] Once coated with OPADRY® II, the tablets are then labeled using a Hartnett Delta tablet printer charged with Opacode® S-1-17823.

Example 10: Exemplary Tablet 11 (Formulated with HPMCAS Polymer to have 150 mg of Compound 1)

[0324] A batch of caplet-shaped tablets was formulated to have about 150 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 11, below.

Table 10: Ingredients for Exemplary Tablet 11.

Tablet Formulation	Percent Dose %Wt./Wt.	Dose (mg)	Batch (g)
Intermediate F	34.09%	187.5	23.86
Microcrystalline cellulose	30.51 %	167.8	21.36
Lactose	30.40%	167.2	21.28
Sodium croscarmellose	3.000%	16.50	2.100
SLS	0.500%	2.750	0.3500
Colloidal silicon dioxide	0.500%	2.750	0.3500
Magnesium stearate	1.000%	5.500	0.7000
Total	**100%**	**550**	**70**

[0325] The colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide) and the microcrystalline cellulose (FMC MCC Avicel® PH102) were passed through a 30 mesh screen.

[0326] The sodium croscarmellose (FMC Ac-Di-Sol®), SLS, Intermediate F, and lactose (Foremost FastFlo® Lactose #316) were also passed, individually in the preceding order, through the same 30 mesh screen. A nitrogen purge was used when screening Intermediate F. The screened components were loaded into a 10 cubic feet V-blender, which was purged with nitrogen, and blended for about 180 (+/- 10) inversions.

[0327] The Magnesium Stearate was filtered through a 40 mesh screen sieve into the blending container and mixed to provide about 54 inversions.

[0328] The resulting mixture was compressed into tablets using a fully tooled 36 Fette 2090 press with 0.568" × 0.2885" caplet type B tooling set to produce a tablet having an initial target hardness of about 10 Kp ± 20%.

Example 11: Exemplary Tablet 12 (Tablet 11 with Spray-Coating)

[0329] A batch of caplet-shaped tablets from Example 10 was spray-coated with OPADRY® II (Blue, Colorcon) to a weight gain of about 3.0% using a 24" coating pan configured with the parameters in Table 11 followed by wax coating and then printing using Opacode® S-1-17823 (Solvent based Black, Colorcon).

Table 11: Spray-Coating Process Parameters

Coating Parameters 24" Pan	Target
Pan Load (kg)	14
Inlet Temperature (°C)*	*
Pan Speed (rpm)	10
Jog Time (sec)	2-5 sec every 60 sec
# of Spray Guns	2
Solids Content (%w/w)	20
Gun to Bed Distance (inches)	6
Inlet Air Flow (cfm)	300
Spray Rate (g/min)	35
Exhaust Temperature (°C)	50
Atomization Pressure (psi)	42
* Inlet temperature is monitored to achieve target exhaust temperature. Initial inlet temperature should be set at about 75°C to achieve target exhaust temp.	

[0330] The OPADRY® II suspension was prepared by measuring an amount of deionized water which when combined with OPADRY® II would produce a total solids content of 20 %w/w. The water is mixed to a vortex followed by addition of OPADRY® II over a period of approximately 5 minutes. Once the OPADRY® II powder was wetted, mixing was continued to ensure that all solid material is well-dispersed. The suspension is then charged into a Thomas 24" pan coating instrument using coating conditions outlined in Table 11.

[0331] Uncoated tablets are placed into the coating pan and pre-warmed. The inlet was increased from room temperature to about 55°C and then increased as necessary to provide the exhaust temperature in Table 11. The coating process was performed with 20% w/w OPADRY® II (85 Series Blue) coating dispersion to obtain a target weight gain of about 3%. The coated tablets were then allowed to tumble for about 2 minutes without spraying. The bed temperature was then allowed to cool to about 35°C.

[0332] Upon cooling, the Carnauba wax powder was weighed out in the amount of about 0.01% w/w of the starting tablet core weight. With the air flow off, the carnauba wax powder was sprinkled evenly on the tablet bed. The pan bed was turned on to the speed indicated in Table 11. After 5 minutes, the air flow was turned on (without heating) to the setting indicated in Table 11. After about one minute the air flow and pan were turned off.

[0333] Once coated with OPADRY® II, the tablets are then labeled using a Hartnett Delta tablet printer charged with Opacode® S-1-17823.

Example 12: Exemplary Tablet 13 (Formulated with HPMCAS Polymer to have 150 mg of Compound 1)

[0334] A batch of caplet-shaped tablets is formulated to have about 150 mg of Compound 1 per tablet using the amounts of ingredients recited in Table 12, below.

Table 12: Ingredients for Exemplary Tablet 13.

Tablet Formulation	Percent Dose %Wt./Wt.
Intermediate H	34.1%
Microcrystalline cellulose	30.5%
Lactose	30.4%
Sodium croscarmellose	3.000%
SLS	0.500%
Colloidal silicon dioxide	0.500%
Magnesium stearate	1.000%

Tablet Formulation	Percent Dose %Wt./Wt.
Total	**100%**

[0335] The colloidal silicon dioxide (Cabot Cab-O-Sil® M-5P Fumed Silicon Dioxide) and the microcrystalline cellulose (FMC MCC Avicel® PH102) are passed through a 30 mesh screen.

[0336] The sodium croscarmellose (FMC Ac-Di-Sol®), SLS, Intermediate H, and lactose (Foremost FastFlo® Lactose #316) are also passed, individually in the preceding order, through the same 30 mesh screen. A nitrogen purge is used when screening Intermediate H. The screened components are loaded into a 10 cubic feet V-blender, which is purged with nitrogen, and blended for about 180 (+/- 10) inversions.

[0337] The Magnesium Stearate is filtered through a 40 mesh screen sieve into the blending container and mixed to provide about 54 inversions.

[0338] The resulting mixture is compressed into tablets using a fully tooled 36 Fette 2090 press with 0.568" x 0.2885" caplet type B tooling set to produce a tablet having an initial target hardness of about 10 Kp ± 20%.

Example 13: Exemplary Tablet 14 (Tablet 13 with Spray-Coating)

[0339] A batch of caplet-shaped tablets from Example 12 is spray-coated with OPADRY® II (Blue, Colorcon) to a weight gain of about 3.0% using a Thomas 48" coating pan configured with the parameters in Table 13 followed by wax coating and then printing using Opacode® S-1-17823 (Solvent based Black, Colorcon).

Table 13: Spray-Coating Process Parameters

Coating Parameters 48" Pan	**Target**
Pan Load (kg)	up to 120
Inlet Temperature (°C)*	*
# of Spray Guns	4
Solids Content (%w/w)	20
Gun to Bed Distance (inches)	7-7.5
Inlet Air Flow (cfm)	1050-2400
Spray Rate (ml/min)	203-290
Exhaust Temperature (°C)	40-65
Atomization Pressure (slpm)	145
* Inlet temperature is monitored to achieve target exhaust temperature. Initial inlet	

Coating Parameters 48" Pan	Target
temperature should be set at about 50-75°C to achieve target exhaust temp.	

[0340] The OPADRY® II suspension is prepared by measuring an amount of deionized water which when combined with OPADRY® II would produce a total solids content of 20 %w/w. The water is mixed to a vortex followed by addition of OPADRY® II over a period of approximately 5 minutes. Once the OPADRY® II powder is wetted, mixing is continued to ensure that all solid material is well-dispersed. The suspension is then charged into a Thomas 48" pan coating instrument using coating conditions outlined in Table 13. In other examples, the suspension can be coated with a Thomas 24" pan coating instrument.

[0341] Uncoated tablets are placed into the coating pan and pre-warmed. The inlet is increased from room temperature to about 55°C and then increased as necessary to provide the exhaust temperature in Table 13. The coating process is performed with 20% w/w OPADRY® II (85 Series Blue) coating dispersion to obtain a target weight gain of about 3%. The coated tablets are then allowed to tumble for about 2 minutes without spraying. The bed temperature is then allowed to cool to about 35°C.

[0342] Upon cooling, the Carnauba wax powder is weighed out in the amount of about 0.01% w/w of the starting tablet core weight. With the air flow off, the carnauba wax powder is sprinkled evenly on the tablet bed. The pan bed is turned on to the speed indicated in Table 13. After 5 minutes, the air flow is turned on (without heating) to the setting indicated in Table 13. After about one minute the air flow and pan is turned off.

[0343] Once coated with OPADRY® II, the tablets are then labeled using a Hartnett Delta tablet printer charged with Opacode® S-1-17823.

B. Administration of Pharmaceutical Formulations

Example 14: Exemplary Administration A

[0344] Human patients are orally administered a pharmaceutical formulation according to Table 14:

Table 14: Exemplary administration A of pharmaceutical formulations of the present invention.

Frequency of dosing (per day)	Tablet Description	Conditions
One administration	3×50 mg Tablets of Example 2	Administered with 240 mL of water under fasting conditions
One administration	150 mg Tablet of Example 3	Administered with 240 mL of water under fasting conditions
One administration	150 mg Tablet of Example 3	Administered with 240 mL of water, 30 minutes after start of a high fat breakfast
One administration	150 mg Tablet of Example 4	Administered with 240 mL of water under fasting conditions
One administration	150 mg Tablet of Example 4	Administered with 240 mL of water, 30 minutes after start of a high fat breakfast

[0345] The pharmaceutical formulations are administered to subjects between 7:00 AM and 9:00 AM, and the pharmaceutical formulation is given at approximately the same time (within a 1-hour window) on each dosing occasion. For administrations that occur under patient fasting, food is allowed 4 hours after the pharmaceutical formulation is administered. For administrations that permit feeding, breakfast is given about 30 minutes prior to the dosing time and is consumed in about 25 minutes. In each of these administrations, the patient is instructed not to lie down for 4 hours after taking the study drug.

Example 15: Exemplary Administration B

[0346] Human patients are orally administered a pharmaceutical formulation according to Table 15:

Table 15: Exemplary administration B of pharmaceutical formulations of the present invention.

Frequency of dosing	Dosage
12 hr. intervals	25 mg Tablet of Example 1
12 hr. intervals	1×25 mg Tablet of Example 1, and 1×50 mg Tablet of Example 2
12 hr. intervals	3×50 mg Tablet of Example 2
12 hr. intervals	5×50 mg Tablet of Example 2
12 hr. intervals	150 mg Tablet of Example 5
12 hr. intervals	100 mg Tablet of Example 6

[0347] The pharmaceutical formulations are administered to patients approximately every 12 hours.

Example 16: Dissolution Profile of Several Exemplary Tablets

[0348] Referring to Figure 1, the dissolution profiles of several exemplary tablets are graphically illustrated. It is noted that each of the exemplary tablets illustrated in Figure 1 are at least 50% dissolved at about 30 minutes.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO2007079139A2 [0013]
- US20040006237A [0044]
- WO2007079139A [0143]

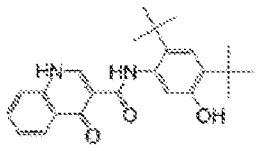
Non-patent literature cited in the description

- **GREGORY, R. J et al.**Nature, 1990, vol. 347, 382-386 [0005]
- **RICH, D. P. et al.**Nature, 1990, vol. 347, 358-362 [0005]
- **RIORDAN, J. R. et al.**Science, 1989, vol. 245, 1066-1073 [0005]
- **CUTTING, G. R. et al.**Nature, 1990, vol. 346, 366-369 [0007]
- **DEAN, M. et al.**Cell, 1990, vol. 61, 863-870 [0007]
- **KEREM, B-S. et al.**Science, 1989, vol. 245, 1073-1080 [0007]
- **KEREM, B-S et al.**Proc. Natl. Acad. Sci. USA, 1990, vol. 87, 8447-8451 [0007]
- **QUINTON, P. M.**FASEB J., 1990, vol. 4, 2709-2727 [0008]
- **DALEMANS et al.**Nature Lond., 1991, vol. 354, 526-528 [0008]
- **PASYKFOSKETT**J. Cell. Biochem., 1995, vol. 270, 12347-50 [0008]

- **S. M. BERGE et al.**describes pharmaceutically acceptable salts in detailJ. Pharmaceutical Sciences, 1977, vol. 66, 1-19 [0064]

Patentkrav

1. Farmaceutisk sammensætning omfattende ca. 34,1 vægtprocent af en fast dispersion efter vægt af sammensætningen, hvor dispersionen omfatter 80 vægtprocent af i alt væsentligt amorf eller amorf N-[2,4-bis(1,1-dimethylethyl)-5-hydroxyphenyl]-1,4-dihydro-4-oxoquinolin-3-carboxamid (forbindelse 1)



Forbindelse 1

efter vægt af dispersionen, 19,5 vægtprocent HPMCAS efter vægt af dispersionen, og 0,5 vægtprocent SLS efter vægt af dispersionen; ca. 30,5 vægtprocent mikrokrystallinsk cellulose efter vægt af sammensætningen; ca. 30,4 vægtprocent lactose efter vægt af sammensætningen; ca. 3 vægtprocent natriumcroscarmellose efter vægt af sammensætningen; ca. 0,5 vægtprocent SLS efter vægt af sammensætningen; ca. 0,5 vægtprocent kolloid siliciumdioxid efter vægt af sammensætningen; ca. 1 vægtprocent magnesiumstearat efter vægt af sammensætningen;

hvor den farmaceutiske sammensætning laves til en tablet;

til anvendelse til behandling eller formindskelse af graden af cystisk fibrose hos en patient;

hvor anvendelsen omfatter indgivelse af den farmaceutiske sammensætning samtidigt med, forud for, eller efter et eller flere ønskede terapeutiske midler;

hvor patienten har en cystisk fibrose transmembranreceptor (CFTR) med en ΔF508 mutation på begge alleler; og

hvor det andet ønskede terapeutiske middel er en CFTR-modulator forskellig fra forbindelse 1.

2. Farmaceutisk sammensætning til anvendelse ifølge krav 1, hvor den farmaceutiske sammensætning indeholder 150 mg af forbindelse 1.

3. Farmaceutisk sammensætning til anvendelse ifølge krav 1, hvor den farmaceutiske sammensætning indeholder 100 mg af forbindelse 1.

4. Farmaceutisk sammensætning til anvendelse ifølge krav 1, hvor det andet ønskede terapeutiske middel er (3-(6-(1-(2,2-difluorbenzo[d][1,3]dioxol-5-yl) cyclopropancarboxamido)-3-methylpyridin-2-yl)benzoesyre.

DRAWINGS

Drawing

FIGURE 1