

**STABLE 4-(AMINOMETHYL)-6-(PHENYLPYRAZOLYL)PHTHALAZINONE
COMPOSITIONS AND PROCESSES FOR PREPARATION THEREOF**Cross-Reference to Related Applications

[0001] This application claims priority from U.S. Provisional Application No. 63/583,775, filed September 19, 2023, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] This invention relates to a granulated composition of 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1h-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile, pharmaceutical compositions including the granulated composition, and methods for making the same. The granulated compositions are useful in the treatment and/or prevention of diseases and/or conditions related to cell proliferation, such as cancer. In particular, the granulated compositions provide therapeutic benefits as MTA-cooperative inhibitors of Protein Arginine N-Methyl Transferase 5 (PRMT5).

BACKGROUND OF THE INVENTION

[0003] Protein Arginine N-Methyl Transferase (PRMT5) is a Form II arginine methyltransferase that catalyzes the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to an omega-nitrogen of the guanidino function of protein L-arginine residues (omega-monomethylation) and the transfer of a second methyl group to the other omega-nitrogen, yielding symmetric dimethylarginine (sDMA). PRMT5 forms a complex with MEP50 (methylosome protein 50), which is required for substrate recognition and orientation and is also required for PRMT5-catalyzed histone 2A and histone 4 methyltransferase activity (e.g., see Ho et al., (2013) PLOS ONE 8(8): 10.1371/annotation/e6b5348e-9052-44ab-8f06-90d01dc88fc2).

[0004] Homozygous deletions of p16/CDKN2a are prevalent in cancer and these mutations commonly involve the co-deletion of adjacent genes, including the gene encoding methylthioadenosine phosphorylase (MTAP). It is estimated that approximately 15% of all human cancers have a homozygous deletion of the MTAP gene (e.g., see Firestone & Schramm (2017) J. Am. Chem. Soc. 139(39):13754-13760. doi: 10.1021/jacs.7b05803. Epub 2017 Sep 20).

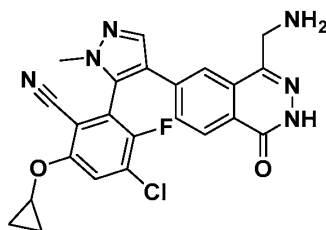
[0005] Cells lacking MTAP activity have elevated levels of the MTAP substrate, methylthioadenosine (MTA), which is a potent inhibitor of PRMT5. Inhibition of PRMT5 activity results in reduced methylation activity and increased sensitivity of cellular proliferation to PRMT5 depletion or loss of activity. Hence, the loss of MTAP activity reduces methylation activity of PRMT5 making the cells selectively dependent on PRMT5 activity.

[0006] Thus, MTA-cooperative inhibition of PRMT5 activity in MTAP deleted cancers can provide therapeutic benefit for a wide range of cancers. The compounds of the invention provide this therapeutic benefit as MTA-cooperative inhibitors of PRMT5 that negatively modulate the activity of MTA-bound PRMT5 in a cell, particularly an MTAP-deficient cell, or for treating various forms of MTAP-associated cancer.

[0007] In particular, 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1h-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile, is a potent and selective inhibitors of PRMT5 and has been found to be pharmacologically active. Here, granulated compositions of 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1h-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile have been found that are suitable for use in pharmaceutical compositions.

SUMMARY OF THE INVENTION

[0008] In one aspect, this disclosure provides granulated compositions of 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1h-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile, shown below, and hereinafter Compound 1.



Compound 1

[0009] Accordingly, in one aspect, this disclosure provides a granulated composition of Compound 1 comprising:

a crystalline form or solid form of 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1h-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile comprising

a first chiral crystalline form present in an amount of at least 85 wt%, based on the weight of the crystalline form or solid form;

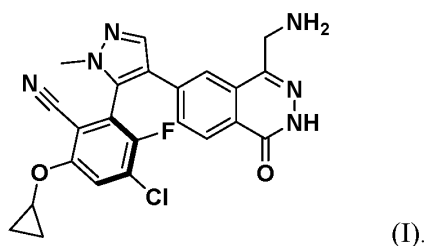
optionally, a second chiral form (e.g., crystalline or amorphous) present in an amount of no more than 5 wt%, based on the weight of the crystalline form or solid form; and

optionally, an amorphous form present in an amount of no more than 10 wt%, based on the weight of the crystalline form or solid form;

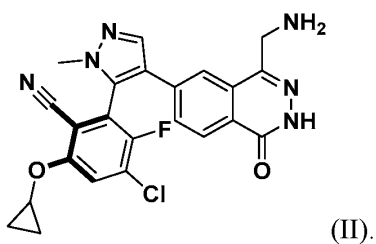
a filler; and

optionally, an organic acid.

[00010] In certain embodiments, the first chiral crystalline form is a crystalline form of a compound of Formula (I):



[00011] In certain embodiments, the second chiral form is a crystalline or an amorphous form of a compound of Formula (II):



[00012] In another aspect, the present disclosure provides a pharmaceutical composition comprising the granulated composition as described herein.

[00013] In another aspect, the present disclosure provides methods of making the granulated composition as described herein. The method comprises:

providing a crystalline form of 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile comprising at least 95 wt% of a first chiral crystalline form;

providing a filler;

mixing the crystalline form and the filler in a weight ratio of at least 1:10;

subjecting the mixture to a granulating method selected from fluid bed granulation, high or low shear granulation, and dry granulation to provide a granulated composition;

wherein the granulated composition has no more than 10 wt% of an amorphous form of 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile;

and

wherein the granulated composition has no more than 5 wt% of a second chiral form of 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile.

BRIEF DESCRIPTION OF THE FIGURES

[00014] The accompanying drawings are included to provide a further understanding of the methods of the disclosure, and are incorporated in and constitute a part of this specification. The drawings are not necessarily to scale, and sizes of various elements may be distorted for clarity. The drawings illustrate one or more embodiment(s) of the disclosure and together with the description serve to explain the principles and operation of the disclosure.

[00015] **Fig. 1** is a graph of the % dissolution vs time of drug in capsule compositions of Compound 1 as described herein.

[00016] **Fig. 2** is a flowchart of a dry granulation process as described herein.

[00017] **Fig. 3A** is a graph of the compressibility of dry granulation compositions of Compound 1 as described herein.

[00018] **Fig. 3B** is a graph of the tabletability of dry granulation compositions of Compound 1 as described herein.

[00019] **Fig. 3C** is a graph of the compactibility of dry granulation compositions of Compound 1 as described herein.

[00020] **Fig. 4A** is a graph of the particle size distribution of granules of a granulated composition of Compound 1, as described herein.

[00021] **Fig. 4B** is a graph of the particle size distribution of granules of a granulated composition of Compound 1, as described herein.

[00022] **Fig. 4C** is a graph of the particle size distribution of granules of a granulated composition of Compound 1, as described herein.

[00023] **Fig. 4D** is a graph of the particle size distribution of granules of a granulated composition of Compound 1, as described herein.

[00024] **Fig. 5A** is a graph of the compressibility of granulated compositions of Compound 1, as described herein.

[00025] **Fig. 5B** is a graph of the tabletability of granulated compositions of Compound 1, as described herein.

[00026] **Fig. 5C** is a graph of the compactibility of granulated compositions of Compound 1, as described herein.

[00027] **Fig. 6A** is a graph of the compressibility of final blends of Compound 1, as described herein.

[00028] **Fig. 6B** is a graph of the tabletability of final blends of Compound 1, as described herein.

[00029] **Fig. 6C** is a graph of the compactibility of final blends of Compound 1, as described herein.

[00030] **Fig. 7A** is a graph of the tabletability of tablets of Compound 1 with different tensile strengths.

[00031] **Fig. 7B** is a graph of the tabletability of tablets of Compound 1 with different tensile strengths.

[00032] **Fig. 8A** is a graph of the compressibility of acidified compositions of Compound 1, as described herein.

[00033] **Fig. 8B** is a graph of the tableability of acidified compositions of Compound 1, as described herein.

[00034] **Fig. 8C** is a graph of the compactibility of acidified compositions of Compound 1, as described herein.

[00035] **Fig. 9** is a graph of the particle size distribution of granules of Compound 1, as described herein.

[00036] **Fig. 10A** is a graph of the dissolution profile of granulated compositions of Compound 1 as 50 mg coated tablets.

[00037] **Fig. 10B** is a graph of the dissolution profile of granulated compositions of Compound 1 as 200 mg coated tablets.

[00038] **Fig. 11** is a graph of the dissolution profile of granulated compositions of Compound 1 as coated tablets.

[00039] **Fig. 12** is a graph of the particle size distribution of granules of Compound 1 as described herein.

[00040] **Fig. 13** is a graph of the dissolution profile of granulated compositions of Compound 1 as coated tablets.

[00041] **Fig. 14** is a graph of the dissolution profile of granulated compositions of Compound 1 as coated tables.

[00042] **Fig. 15A** is a graph of the dissolution profile of crystalline forms and amorphous forms of Compound 1.

[00043] **Fig. 15B** is a graph of the dissolution profile of crystalline forms and amorphous forms of Compound 1.

[00044] **Fig. 16** is a schematic of the proposed formation of chiral impurities in tablets of granulated compositions described herein.

[00045] **Fig. 17** is a graph of the amorphous content of Compound 1 in a power form, when compressed at 1 kN and 6kN compaction force.

[00046] **Fig. 18** is a graph of chiral growth of granulated compositions of Compound 1 at different drug loadings, when compressed at 2 kN, 6 kN, and 16 kN.

[00047] **Fig. 19** is a graph of chiral growth of granulated compositions of Compound 1 with different fillers, when compressed at 2 kN, 6 kN, and 16 kN.

[00048] **Fig. 20A** is a graph of chiral growth of granules, capsules, and tablets of granulated compositions of Compound 1 prepared by different methods.

[00049] **Fig. 20B** is a graph of chiral growth of capsules and tablets of granulated compositions of Compound 1 prepared by different granulation methods.

DETAILED DESCRIPTION OF THE INVENTION

[00050] The present disclosure is concerned with granulated compositions of Compound 1 and methods of making the same. As described above, Compound 1 is a potent and selective inhibitor of PRMT5 and has been found to be pharmacologically active. However, not all forms of Compound 1 have the same degree of pharmacological activity. In particular, it is the first chiral crystalline form of Compound 1 as described herein that is the most potent form, while the second chiral form is 250-fold less potent. The amorphous form of Compound 1 has a potency similar to that of the first chiral crystalline form but tends to convert more rapidly to the second chiral form (which may be amorphous or crystalline) than does the first chiral crystalline form; this conversion results in the amorphous material becoming less potent. Thus, it is advantageous to provide granulated compositions with low to no amounts of the amorphous form and chiral impurities. It has been found that the granulation method greatly impacts the amount of chiral impurities present in the granulated composition. Additionally, as noted above, it has been surprisingly found that it is often the presence of the amorphous form of Compound 1 that can lead to subsequent growth of the second chiral form. As such, it has been found that low-stress methods of granulation provide granulated compositions with high amounts of chiral purity.

[00051] Accordingly, in one embodiment, the present disclosure provides a granulated composition of Compound 1 comprising a crystalline form or solid form of Compound 1, a filler, and optionally, an organic acid. The crystalline form or solid form of Compound 1 in the granulated composition as described herein includes a first chiral crystalline form present in an amount of at least 85 wt%, based on the weight of the crystalline form or solid form, optionally,

a second chiral form present in an amount of no more than 5 wt%, based on the weight of the crystalline form or solid form, and optionally, an amorphous form present in an amount of no more than 10 wt%, based on the weight of the crystalline form or solid form.

[00052] As described above, Compound 1 may be present in the composition as a crystalline form or as a solid form. In certain embodiments as described herein, the crystalline form of Compound 1 is a hydrochloride salt. In certain other embodiments as described herein, the crystalline form of Compound 1 is a free base. These crystalline forms have been previously described in published international applications WO/2024/173207 and WO/2024/173215, each of which is hereby incorporated herein by reference in its entirety. In other embodiments, the Compound 1 is present in a solid form. The solid form of Compound 1 may include both crystalline form, an amorphous form, or combinations thereof.

[00053] The crystalline form or solid form of Compound 1 may be present in the granulated composition in various amounts. In some embodiments as described herein, the crystalline form is present in an amount of at least 10 wt%, based on the weight of the granulated composition. For example, in various embodiments, the crystalline form is present in an amount of at least 20 wt%, at least 30 wt%, at least 40 wt%, or at least 50 wt%, based on the weight of the granulated composition. In some embodiments as described herein, the crystalline form is present in an amount in the range of 10-90 wt%, based on the weight of the granulated composition. For example, in various embodiments as described herein, the crystalline form is present in an amount in the range of 10-70 wt%, or 10-50 wt%, or 30-90 wt%, or 30-70 wt%, or 30-50 wt%, based on the weight of granulated composition.

[00054] As described above, the granulated composition also includes a filler. The filler may be selected from any suitable pharmaceutical carrier, diluents, excipients, auxiliaries, or combinations thereof, which facilitate processing of Compound 1 into preparations which can be used pharmaceutically. For example, in various embodiments as described herein, the filler is selected from colloidal silicon dioxide, croscarmellose sodium, polyvinylpyrrolidone, dibasic calcium phosphate, sodium lauryl sulphate, hydroxypropyl cellulose (e.g., hydroxypropyl methylcellulose), lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, pregelatinized starch, crospovidone, sodium starch glycolate, sodium stearyl fumarate, or combinations thereof.

[00055] The filler may be present in the granulated composition in various amounts. In some embodiments as described herein, the filler is present in an amount of at least 10 wt%, based on the weight of the granulated composition. For example, in various embodiments, the filler is present in an amount of at least 20 wt%, at least 30 wt%, at least 40 wt%, or at least 50 wt%, based on the weight of the granulated composition. In certain embodiments as described herein, the filled is present in the granulated composition in an amount in the range of 10-90 wt%, based on the weight of the granulated composition. For example, in various embodiments as described herein, the filler is present in an amount in the range of 10-70 wt%, or 10-50 wt%, or 30-90 wt%, or 30-70 wt%, or 30-50 wt%, based on the weight of the granulated composition.

[00056] In certain embodiments as described herein, the filler comprises microcrystalline cellulose, mannitol, croscarmellose sodium, sodium lauryl sulphate, colloidal silicon dioxide, and magnesium stearate. In certain embodiments as described herein wherein the filler comprises microcrystalline cellulose, the microcrystalline cellulose may be present in an amount of at least 20 wt%, based on the weight of the granulated composition. For example, in various embodiments as described herein, the microcrystalline cellulose is present in an amount of at least 30 wt%, at least 40 wt%, or at least 50 wt%, based on the weight of the granulated composition. In certain embodiments as described herein wherein the filler comprises mannitol, the mannitol may be present in an amount of at least 10 wt%, based on the weight of the granulated composition. For example, in various embodiments as described herein, the microcrystalline cellulose is present in an amount of at least 15 wt%, or at least 20 wt%, based on the weight of the granulated composition. In certain embodiments as described herein wherein the filler comprises croscarmellose sodium, sodium lauryl sulphate, colloidal silicon dioxide, and magnesium stearate, the croscarmellose sodium, sodium lauryl sulphate, colloidal silicon dioxide, and magnesium stearate may be present in an amount of no more than 15 wt%, based on the weight of the granulated composition. For example, in various embodiments as described herein, the croscarmellose sodium, sodium lauryl sulphate, colloidal silicon dioxide, and magnesium stearate are present in an amount of no more than 12 wt%, or no more than 10 wt%, or no more than 8 wt%, based on the weight of the granulated composition. As such, in certain embodiments, the granulated composition comprises the following components in the amounts described in the following table:

Component	Weight % per Composition
Crystalline Form of Compound 1	10-80%
Microcrystalline Cellulose	15.0-95.0%
Mannitol	0.0-40.0%
Croscarmellose Sodium	0.5-10.0%
Sodium Lauryl Sulphate	0.0-2.0%
Colloidal Silicon Dioxide	0.0-3.0 %
Magnesium Stearate	0.0-4.0%
Core Tablet Weight	100.0%

[00057] In certain other embodiments as described herein, the filler comprises microcrystalline cellulose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. In certain embodiments wherein the filler comprises microcrystalline cellulose, the microcrystalline cellulose is present in an amount of at least 5 wt%, based on the weight of the granulated composition. For example, in various embodiments as described herein, the microcrystalline cellulose is present in an amount of at least 10 wt%, at least 15 wt%, at least 20 wt%, or at least 25 wt%, based on the weight of the granulated composition. In certain embodiments wherein the filler comprises croscarmellose sodium, the croscarmellose sodium is present in an amount of at least 4 wt%, based on the weight of the granulated composition. For example, in various embodiments as described herein, the microcrystalline cellulose is present in an amount of at least 6 wt%, or at least 8 wt%, based on the weight of the granulated composition. In certain embodiments wherein the filler comprises hydroxypropyl methylcellulose and magnesium stearate, the hydroxypropyl methylcellulose and magnesium stearate may be present in an amount of no more than 10 wt%, based on the weight of the granulated composition. For example, in various embodiments as described herein, the hydroxypropyl methylcellulose and magnesium stearate are present in an amount of no more than 5 wt%, based on the weight of the granulated composition. As such, in certain embodiments, the granulated composition comprises the following components in the amounts described in the following table:

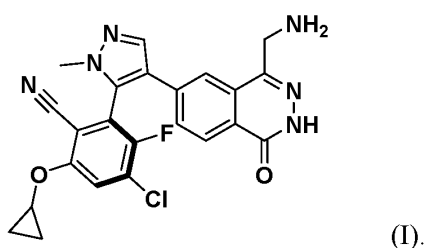
Component	Weight % per Composition
Crystalline Form of Compound 1	10-90%
Microcrystalline Cellulose	5.0-90%
Croscarmellose Sodium	4.0-10.0%
Hydroxypropyl methylcellulose	0.0-5.0%
Magnesium Stearate	0.0-5.0%
Core Tablet Weight	100.0%

[00058] In certain embodiments as described herein, the filler comprises microcrystalline cellulose, polyvinyl pyrrolidone, croscarmellose sodium, and magnesium stearate. In certain embodiments wherein the filler comprises microcrystalline cellulose, the microcrystalline cellulose is present in an amount of at least 5 wt%, based on the weight of the granulated composition. For example, in various embodiments as described herein, the microcrystalline cellulose is present in an amount of at least 10 wt%, at least 15 wt%, at least 20 wt%, or at least 25 wt%, based on the weight of the granulated composition. In certain embodiments wherein the filler comprises croscarmellose sodium, the croscarmellose sodium is present in an amount of at least 4 wt%, based on the weight of the granulated composition. For example, in various embodiments as described herein, the microcrystalline cellulose is present in an amount of at least 6 wt%, or at least 8 wt%, based on the weight of the granulated composition. In certain embodiments wherein the filler comprises polyvinyl pyrrolidone and magnesium stearate, the polyvinyl pyrrolidone and magnesium stearate may be present in an amount of no more than 10 wt%, based on the weight of the granulated composition. For example, in various embodiments as described herein, the polyvinyl pyrrolidone and magnesium stearate are present in an amount of no more than 5 wt%, based on the weight of the granulated composition. As such, in certain embodiments, the granulated composition comprises the following components in the amounts described in the following table:

Component	Weight % per Composition
Crystalline Form of Compound 1	10-90%
Microcrystalline Cellulose	5.0-90%
Croscarmellose Sodium	4.0-10.0%
Polyvinyl pyrrolidone	0.0-5.0%
Magnesium Stearate	0.0-5.0%
Core Tablet Weight	100.0%

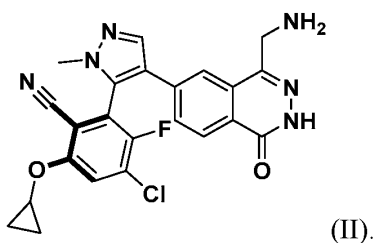
[00059] In some embodiments as described herein, the weight ratio of the crystalline form of Compound 1 to the filler is at least 1:10. For example, in various embodiments as described herein, the weight ratio of the crystalline form to the filler is in the range of 1:10 to 10:1, or 1:10 to 5:1, or 1:10 to 2:1, or 1:10 to 1:1, or 1:5 to 10:1, or 1:5 to 5:1, or 1:5 to 2:1, or 1:5 to 1:1, or 2:1 to 10:1, or 2:1 to 5:1, or 2:1 to 2:1, or 2:1 to 1:1.

[00060] As described above, the crystalline form of Compound 1 includes a first chiral crystalline form, present in an amount of at least 85 wt%, based on the weight of the crystalline form. In certain embodiments as described herein, the first chiral crystalline form is a compound of Formula (I):



This first chiral crystalline form has particularly high pharmaceutical activity, especially when compared to other chiral forms of Compound 1. As such, it is particularly advantageous to have high amounts of the first chiral crystalline form present in the granulated composition. According, in certain embodiments, the first chiral crystalline form is present in an amount of at least 90 wt%, based on the weight of the crystalline form. For example, in various embodiments as described herein, the first chiral crystalline form is present in an amount of at least 92 wt%, at least 94 wt%, or at least 96 wt%, based on the weight of the crystalline form.

[00061] In some embodiments as described herein, the crystalline form of Compound 1 may optionally include a second chiral form present in an amount of no more than 5 wt%, based on the weight of the crystalline form. In certain embodiments where the second chiral form is present, the second chiral form is a compound of Formula (II):



This second chiral form is an atropisomer of the first chiral crystalline form that is brought about by rotation of the C-C bond linking the N-methylpyrazole and phenyl rings. It has been found that the second chiral form is 250-fold less potent than that of the first chiral crystalline form. Additionally, any amorphous form present in the composition has been found to more readily convert to the second chiral form, leading to an overall less potent composition. As such, it is advantageous to provide compositions that have low amounts (or no amounts) of the second chiral form. According, in certain embodiments, the second chiral form is present in an amount of no more than 3 wt%, based on the weight of the crystalline form. For example, in various embodiments as described herein, the second chiral form is present in an amount of no more than 2 wt%, or no more than 1 wt%, based on the weight of the crystalline form. The second chiral form may be present in either a crystalline form, an amorphous form, or combinations thereof. For example, in some embodiments as described herein, the second chiral form is present in a crystalline form. In other embodiments, the second chiral form is present in an amorphous form.

[00062] As described above, the crystalline form of Compound 1 may also optionally include an amorphous form present in an amount of no more than 10 wt%, based on the weight of the crystalline form. As described above, the amorphous form of Compound 1 has a potency similar to that of the first chiral crystalline form but tends to convert more rapidly to the second chiral form; this conversion results in amorphous material becoming less potent. Thus, it is advantageous to provide compositions that have low amounts (or no amounts) of the amorphous form. For example, in various embodiments as described herein, the amorphous form is present in an amount of no more than 8 wt%, no more than 5 wt% or no more than 3 wt%, based on the weight of the crystalline form.

[00063] In certain embodiments as described herein, the granulated composition includes an organic acid. It has been found that the inclusion of an organic acid can advantageously improve the *in vitro* dissolution for the compositions in neutral media. In some embodiments as described herein, the organic acid is selected from citric acid, fumaric acid, DL-tartaric acid, maleic acid, DL-malic acid, or succinic acid. When the organic acid is present in the granulated composition, it may be present in an amount of at least 5 wt%, based on the weight of the granulated composition. For example, in various embodiments as described herein, the organic acid is present in an amount of at least 10 wt%, or at least 12 wt%, or at least 15 wt%, based on the weight of the granulated composition. In various embodiments as described herein, the

organic acid is present in an amount in the range of 5-30 wt%, or 5-25 wt%, or 5-20 wt%, or 10-30 wt%, or 10-25 wt%, or 10-20 wt%, based on the weight of the granulated composition.

[00064] The granulated composition as described herein may be prepared to provide a desired porosity and pore size to provide the desired dissolution of the composition. In some embodiments as described herein, the granulated composition has a porosity in the range of 5-40%. For example, in various embodiments, the granulated composition has a porosity in the range of 5-35%, or 5-30%, or 10-40%, or 10-35%, or 10-30%. In certain embodiments as described herein, the granulated composition has a porosity of 28%. In certain other embodiments, the granulated composition has a porosity of 11%. The porosity ε , may be calculated using the following equation:

$$\varepsilon = 1 - \frac{\rho_{envelope}}{\rho_{true}} \times 100$$

Where ρ_{true} is the true density of a material that was obtained by helium pycnometer or calculated from a room temperature crystal structure. For helium pycnometry measurements, a helium pycnometer (Ultracyc 1200e or AccuPyc) can be used, with approximately 75% of the sample cell volume filled by the sample. After helium is introduced to the sample chamber to reach a pressure of ~ 17 Pa, the system is given 300 seconds to stabilize before a valve is open to allow helium diffuse into an expansion chamber to establish a new pressure. From the pressures before and after the expansion of helium gas, the volume of the solid sample can be calculated. This process can be repeated until the volume standard deviation (VSD) of last five runs is smaller than 0.005% or a total of 100 runs have been performed. The average of the last five values may be taken as sample volume, which can be used to calculate true density using sample weight.

[00065] In various embodiments as described herein, the granulated composition has an average particle size of at least about 250 μm , and typically from about 250 μm to about 1 mm. Suitable average particle sizes are about 250 μm , about 300 μm , about 400 μm , about 500 μm , about 600 μm , about 700 μm , about 800 μm , about 900 μm , and about 1000 μm . Suitable granulated compositions may have a narrow average particle size distribution or a relatively wide average particle size distribution within the range of about 250 μm to about 1 mm. As used herein, “particle size” is the largest dimension of the particle. Conventional methods known in the art may be used to measure the particle size distribution of the composition.

[00066] Another aspect of the present disclosure provides a pharmaceutical composition including the granulated composition as described herein. Pharmaceutical compositions comprising the granulated compositions of Compound 1 may be manufactured by various granulation processes.

[00067] In particular embodiments as described herein, the pharmaceutical composition is in a form suitable for oral administration. For oral administration, the pharmaceutical compositions may take the form of, for example, lozenges, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulfate). The tablets may be coated by methods well known in the art with, for example, sugars, films or enteric coatings.

[00068] In certain embodiments as described herein, the pharmaceutical composition is in the form of a tablet. In certain other embodiments, the tablet is a coated tablet. When the pharmaceutical composition is present as a coated tablet, the granulated composition as described herein is present as the core composition of the tablet. A coating agent may be applied to the core composition of the tablet to provide the coated tablet. The coating agent may be selected from various agents known in the art. For example, the coating agent may be selected from hydroxypropyl methylcellulose, titanium dioxide, polydextrose, talc, maltodextrin, medium chain triglycerides, polyethylene glycol (PEG), mono-glycerides of caprylic/capric acid, di-glycerides of caprylic/capric acid, polyvinyl alcohol, carmine, iron oxide, or combinations thereof. In certain embodiments as described herein, the coating agent is as described in the following table:

Component	Quantity(% w/w)
Hypromellose	15-35
Titanium Dioxide	15-30
Polydextrose	15-30
Talc	5-10
Maltodextrin	2.5-10
Medium Chain Triglyceride	2-5

[00069] In certain embodiments as described herein, the coating agent is as described in the following table:

Component	Quantity (% w/w)
Polyethylene Glycol (PEG)	30-50
Talc	5-30
Titanium Dioxide	15-25
Mono- and Diglycerides of Caprylic/Capric Acid (GMDCC)	2-5
Polyvinyl Alcohol (PVA)	0-5
Carmines	0-5
Iron Oxide	0-10

[00070] The coating agent may be applied to the core composition (e.g., the granulated composition of Compound 1 as described herein) in various amounts. For example, in certain embodiments as described herein, the coating agent is present on the tablet in an amount of at least 1 wt%, based on the weight of the tablet. For example, in various embodiments as described herein, the coating agent is present in an amount of at least 2 wt%, at least 3 wt%, or at least 5 wt%, based on the weight of the tablet. In various embodiments as described herein, the coating agent is present in an amount in the range of 1-50 wt%, or 1-45 wt%, or 1-40 wt%, or 3-50 wt%, or 3-45 wt%, or 3-50 wt%, based on the weight of the tablet.

[00071] The pharmaceutical compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the compound(s). The pack may, for example, comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

[00072] Another aspect of the present disclosure provides a method of making the granulated compositions as described herein. The methods includes providing a crystalline form of Compound 1 comprising at least 95 wt% of a first chiral crystalline form; providing a filler; mixing the crystalline form and the filler in a weight ratio of at least 1:10; subjecting the mixture to a granulating method selected from fluid bed granulation, high or low shear granulation, and dry granulation to provide a granulated composition; wherein the granulated composition has no more than 10 wt% of an amorphous form of Compound 1; and wherein the granulated composition has no more than 5 wt% of a second chiral form of Compound 1.

[00073] Conventional methods of fluid bed granulation, high or low shear granulation, and dry granulation may be used to provide the granulated composition. However, as discussed above, it can be advantageous to use a granulation method that avoids high-stress to prevent amorphization and growth of chiral impurities of Compound 1. Accordingly, in certain embodiments as described herein, the granulating method is fluid bed granulation. In certain

other embodiments, the granulating method is shear granulation. In certain other embodiments, the granulating method involves low shear granulation, such as low shear granulation carried out using a planetary mixer.

[00074] As described above, it is advantageous for the granulated composition to have a low amount of chiral impurities. The granulated compositions and methods for making the same provide compositions that maintain their chiral purity overtime. In certain embodiments, the crystalline form in the granulated composition comprises a second chiral form in an amount of no more than 5 wt%, or no more than 2 wt%, or no more than 1 wt%, after two weeks of storage at 55°C, based on the weight of the crystalline form. In certain embodiments, the crystalline form in the granulated composition comprises a second chiral form in an amount of no more than 5 wt%, or no more than 2 wt%, or no more than 1 wt%, after three months of storage at 40°C and 75% relative humidity, based on the weight of the crystalline form. In certain embodiments, the crystalline form in the granulated composition comprises an amorphous form in an amount of no more than 10 wt%, or no more than 8 wt%, or no more than 6 wt%, after two weeks of storage at 55°C, based on the weight of the crystalline form. In certain embodiments, the crystalline form in the granulated composition comprises an amorphous form in an amount of no more than 10 wt%, or no more than 8 wt%, or no more than 6 wt%, after three months of storage at 40°C and 75% relative humidity, based on the weight of the crystalline form.

[00075] The granulated compositions described herein, will generally be used in an amount effective to achieve the intended result, for example in an amount effective to treat or prevent the particular disease being treated. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated and/or eradication or amelioration of one or more of the symptoms associated with the underlying disorder such that the patient reports an improvement in feeling or condition, notwithstanding that the patient may still be afflicted with the underlying disorder. Therapeutic benefit also generally includes halting or slowing the progression of the disease, regardless of whether improvement is realized.

[00076] In yet another aspect, the invention provides for methods for inhibiting PRMT5 activity in a cell, comprising contacting the cell in which inhibition of PRMT5 activity is desired in vitro with an effective amount of a crystalline forms of Compound 1 as described herein or pharmaceutical compositions containing the crystalline forms of Compound 1 as described herein. In one embodiment, the cell is an MTAP-deficient cell.

[00077] The compositions and methods provided herein are particularly deemed useful for inhibiting PRMT5 activity in a cell in vivo. In one embodiment, a cell in which inhibition of PRMT5 activity is desired is contacted in vivo with a therapeutically effective amount of crystalline forms of Compound 1 as described herein or pharmaceutical compositions containing the crystalline forms of Compound 1 as described herein. In one embodiment, the cell is an MTAP-deficient cell. In one embodiment, the negatively modulating the activity of PRMT5 occurs in the presence of bound MTA.

[00078] By negatively modulating the activity of PRMT5, particularly in cases for cells that lack MTAP activity, the methods are designed to inhibit PRMT5 activity to block cellular proliferation. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to affect the desired negative modulation of PRMT5. The degree PRMT5 inhibition may be monitored in vitro against the enzyme in the presence and absence of MTA and in the cell using well known methods, including those described in Example B below, to assess the effectiveness of treatment and dosages.

[00079] In another aspect, methods of treating cancer comprising administering to a patient having cancer a therapeutically effective amount of crystalline forms of Compound 1 as described herein or pharmaceutical compositions containing the crystalline forms of Compound 1 as described herein. In one embodiment, the cancer is an MTAP-associated cancer.

[00080] The compositions and methods provided herein may be used for the treatment of a wide variety of cancer including tumors such as prostate, breast, brain, skin, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compositions and methods of the invention include, but are not limited to tumor types such as astrocytic, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatocellular, laryngeal, lung, oral, ovarian, prostate and thyroid carcinomas and sarcomas. More specifically, these compounds can be used to treat: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma,

lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. In certain embodiments, the cancer is diffuse large B-cell lymphoma (DLBCL).

[00081] In one embodiment, the cancer is an MTAP-associated cancer selected from hepatocellular carcinoma, breast cancer, skin cancer, bladder cancer, liver cancer, pancreatic cancer, and head and neck cancer.

[00082] The concentration and route of administration to the patient will vary depending on the cancer to be treated. The granulated composition of Compound 1 as described herein or pharmaceutical compositions containing the granulated composition of Compound 1 as described herein also may be co-administered with other anti-neoplastic compounds, e.g., chemotherapy, or used in combination with other treatments, such as radiation or surgical intervention, either as an adjuvant prior to surgery or post-operatively.

EXAMPLES

[00083] The Examples that follow are illustrative of specific embodiments of the composition and methods of the disclosure. They are set forth for explanatory purposes only, and are not to be taken as limiting the scope of the disclosure.

[00084] Example 1. Drug in Capsule Preparation

[00085] Five drug in capsule formulations of Compound 1 were formed and tested for their dissolution. The amounts of Compound 1, either as a free base or HCl salt, was corrected for its chiral purity, filled into suitable capsules (sizes 00-4) at unit dose strengths ranging from 10 mg to 300 mg. The capsules used were hypromellose, but gelatin or k-carrageenan can also be used. The drug in capsule formulations are recited in Table 1.

[00086] Table 1.

Drug in Capsule Formulation No.	Ingredient	Function	Unit Formula	
			%(w/w)	Weight (mg)
1	Compound 1 Free Base	Active Ingredient	100.0	100.0
		Total	100.0	100.0
	White Opaque Size 0 Hypromellose Empty Capsules	Capsule Shell	N/A	95.6
2	Compound 1 Free Base	Active Ingredient	100.0	25.0
		Total	100.0	25.0
	Swedish Orange Opaque Size 1 Hypromellose Empty Capsules	Capsule Shell	N/A	72.5

3	Compound 1 Free Base	Active Ingredient	100.0	10.0
		Total	100.0	10.0
	Swedish Orange Opaque Size 3 Hypromellose Empty Capsules	Capsule Shell	N/A	48.0
4	Compound 1 HCl Salt	Active Ingredient	100.0	107.3
		Total	100.0	107.3
	White Opaque Size 0 Hypromellose Empty Capsules	Capsule Shell	N/A	95.6
5	Compound 1 HCl Salt	Active Ingredient	100.0	26.8
		Total	100.0	26.8
	White Opaque Size 1 Hypromellose Empty Capsules	Capsule Shell	N/A	48.0

[00087] The dissolution of the drug in capsules was evaluated using USP <711> Type II apparatus with 50 rpm stirring speed in a simulated fasted gastric fluid for the first 30 minutes and then the pH was changed to pH 6.8 to simulate fasted intestinal fluid for the next 90 minutes. The dissolution for the drug in capsule formulations was also evaluated in a fasted simulated intestinal fluid for comparison. These results are shown in Fig. 1. As shown in Fig. 1, both the free base and HCl salt drug in capsule formulations of Compound 1 exhibited significant parachute effect (slower precipitation) when the pH was changed from pH 1.2 (FaSSGF) to pH 6.8 (FaSSIF). Additionally, all of the capsules tested disintegrated within 6 minutes in DI water at 37 °C.

[00088] Example 2. Dry Granulation Formulations

[00089] *Preparation of Dry Granulation Formulations*

[00090] Three tablet formulations of Compound 1 free base, using a dry granulation process, were prepared and evaluated for their physical properties. The process of dry granulation is shown in Fig. 2. The three formulation differ mainly in their drug loadings (DL). The dry granulation tablet formulations are shown in Table 2. Two dose amounts, 50 mg and 200 mg, were prepared for each formulation, and are identifies as “A” or “B” respectively in the table below.

[00091] Table 2.

Dry Granulation Formulation No.	Description	Component	Function	Quantity per tablet (mg)	Weight% per tablet
1A	Compound 1 Freebase (20% drug loading), 50 mg	Compound 1 Freebase Substance	Drug Substance	50.0	20%
		Microcrystalline Cellulose	Diluent	130.0	52%
		Mannitol	Diluent	50.0	20%
		Croscarmellose Sodium	Disintegrant	12.5	5%
		Sodium Lauryl Sulphate	Surfactant	2.5	1%
		Colloidal Silicon Dioxide	Glidant	2.5	1%
		Magnesium Stearate	Lubricant	2.5	1%
		Core Tablet Weight	-	250.0	100%
1B	Compound 1 Freebase (20% drug loading), 200 mg	Compound 1 Freebase Substance	Drug Substance	200.0	20%
		Microcrystalline Cellulose	Diluent	520.0	52%
		Mannitol	Diluent	200.0	20%
		Croscarmellose Sodium	Disintegrant	50.0	5%
		Sodium Lauryl Sulphate	Surfactant	10.0	1%
		Colloidal Silicon Dioxide	Glidant	10.0	1%
		Magnesium Stearate	Lubricant	10.0	1%
		Core Tablet Weight	-	1000.0	100%
2A	Compound 1 Freebase (35% drug loading), 50 mg	Compound 1 Freebase Substance	Drug Substance	50.0	35%
		Microcrystalline Cellulose	Diluent	60.0	42%
		Mannitol	Diluent	21.4	15%
		Croscarmellose Sodium	Disintegrant	7.1	5%
		Sodium Lauryl Sulphate	Surfactant	1.4	1%

		Colloidal Silicon Dioxide	Glidant	1.4	1%
		Magnesium Stearate	Lubricant	1.4	1%
		Core Tablet Weight	-	142.9	100%
2B	Compound 1 Freebase (35% drug loading), 200 mg	Compound 1 Freebase Substance	Drug Substance	200.0	35%
		Microcrystalline Cellulose	Diluent	240.0	42%
		Mannitol	Diluent	85.7	15%
		Croscarmellose Sodium	Disintegrant	28.6	5%
		Sodium Lauryl Sulphate	Surfactant	5.7	1%
		Colloidal Silicon Dioxide	Glidant	5.7	1%
		Magnesium Stearate	Lubricant	5.7	1%
		Core Tablet Weight	-	571.4	100%
3A	Compound 1 Freebase (50% drug loading), 50 mg	Compound 1 Freebase Substance	Drug Substance	50.0	50%
		Microcrystalline Cellulose	Diluent	32.0	32%
		Mannitol	Diluent	10.0	10%
		Croscarmellose Sodium	Disintegrant	5.0	5%
		Sodium Lauryl Sulphate	Surfactant	1.0	1%
		Colloidal Silicon Dioxide	Glidant	1.0	1%
		Magnesium Stearate	Lubricant	1.0	1%
		Core Tablet Weight	-	100.0	100%
3B	Compound 1 Freebase (50% drug loading), 200 mg	Compound 1 Freebase Substance	Drug Substance	200	50%
		Microcrystalline Cellulose	Diluent	128.0	32%
		Mannitol	Diluent	40.0	10%
		Croscarmellose Sodium	Disintegrant	20.0	5%
		Sodium Lauryl Sulphate	Surfactant	4.0	1%

		Colloidal Silicon Dioxide	Glidant	4.0	1%
		Magnesium Stearate	Lubricant	4.0	1%
		Core Tablet Weight	-	400.0	100%

[00092] Preparing and Characterization of Intragranular Blends

[00093] Intragranular (IG) blends of formulations 1, 2, and 3 were prepared and their compressibility, tabletability, and compactability profiles were determined. The intragranular formulation blends were prepared by individually weighting the required amount of each component and mixing by a Turbula mixer (Glen Mills Inc., Clifton, NJ) at 49 rpm. The mixing was firstly conducted for all the other components except magnesium stearate for 10 min, and then magnesium stearate was mixed with the mixture of all other ingredients for 2 min. This is to avoid over lubrication of magnesium stearate, which might deteriorate the compaction property of the blends. In the mixing process, 1/3 – 1/2 headspace of the mixing container was maintained.

[00094] The compressibility, tabletability, and compactability profiles are shown in Figs. 3A, 3B, and 3C, respectively. The changes in the drug loading only lead to minor changes in these profiles.

[00095] Preparation and Characterization of Granules Using Dry Granulation

[00096] Compaction stress in the range of 50-200 MPa were found to be suitable to prepare ribbons with different tensile strengths and porosities of 28% and 11% with formulation 1 (DL 20%) and formulation 3 (DL 50%). Ribbons were then manufactured at 28% porosity and 11% porosity for both formulations. Ribbons were manufactured using a slugging technique.

[00097] Ribbons (16 x 9 mm rectangular shape) were prepared by a compaction simulator (Styl'One Evolution; MedelPharm, Beynost, France), using force-controlled cycle at 2% speed. Ribbons with ~450 mg were milled in the granulator unit of a roller compactor (Alexanderwerk WP 120, Germany), with screen sizes of 3.15 mm and 1.25 mm. Alternatively, ribbons can be manufactured using roller compactors such as Alexanderwerk WP120 or WP200 or Gerteis Mini Pactor or Macropactor or Fitzpatrick Chilsonator or similar equipment to obtain

the desired porosity. The ribbons were milled using Alexanderwerk WP120 roller compactor and passed through two screens to obtain desired particle size distribution. Particle size distribution (PSD) for the granules were measured along with compressibility, tabletability, and compactibility profiles. Particle size distribution was obtained using a sonic sifter (AdvanTech, New Berlin, WI) equipped with U.S. no. 25, 35, 45, 60, 80, 120, 170, 230 screens (710, 500, 354, 250, 177, 125, 88, 63 μm openings). Powders were sieved under sift/pulse mode with amplitude of 4 and duration time of 5 min. Fractions retained on screens and undersize fractions were weighed to determine particle size distributions. The results of the particle size distribution are shown in Figs. 4A-4D and the compressibility, tabletability, and compactibility profiles are shown in Figs. 5A, 5B, and 5C, respectively.

[00098] Additionally, the flowability of these granules were evaluated using a Shear Cell test and a Flodex test. For the Shear cell test, a ring shear tester RST-XS (Dietmar Schulze, Wolfenbüttel, Germany), equipped with a XS-Mr cell (~30 mL) was used for flow properties measurement at 3 kPa preshear normal stress. A powder was overfilled and, using a spatula, excess powder was gently scraped off without compacting the powder to achieve a flat surface flush with the upper edge of the shear cell. Shear strength of the powder was tested under five progressively increasing normal stresses (0.23, 1, 1.5, 2, 2.5, 0.23 kPa) to construct a yield locus. Mohr's circles were drawn to obtain the unconfined yield strength (f_c) and major principal stress (σ_n) from each yield locus. The powder flowability index, $ffc = \sigma_n/f_c$, was calculated. For the Flodex test, the minimum orifice diameter that a powder can fall out freely was determined with Flodex (Teledyne Hanson Research, Chatsworth, CA), consisting of a loading funnel, a cylinder assembly with changeable stainless steel discs with holes of different diameters at the center, and a shutter covering the hole. The sample was first loaded into the cylinder by passing through a funnel with the shutter closed. After filling the stainless steel cylinder, the powder bed was allowed to settle before the shutter was opened. The powder bed was observed from above to determine whether or not an open hole was visible in it. By repeating the experiment using stainless steel discs with different opening sizes, the minimal diameter (d_{min}) of the orifice that allows the powder to pass through was recorded ($n = 1$). The flowability of the intragranular blends and granules of formulation 1 and formulation 3 determined by shear cell testing and Flodex testing are shown in Tables 3 and 4, respectively.

[00099] Table 3.

Dry Granulation Formulation No.	Drug Loading	Description	Flowability Index				
			1	2	3	AVE	SD
1	20%	IG Blend	5.55	6.44	4.91	5.63	0.63
		28% Porosity	5.27	5.51	5.3	5.36	0.11
		11% Porosity	8.26	8.6	7.64	8.17	0.40
3	50%	IG Blend	3.9	2.85	2.93	3.23	0.48
		28% Porosity	5.56	5.84	5.62	5.70	0.14
		11% Porosity	14.92	24.78	10.84	19.85	4.93

[000100] Table 4.

Dry Granulation Formulation No.	Drug Loading	Description	Minimum orifice diameter
1	20%	28% Porosity	14 mm
		11% Porosity	8 mm
3	50%	28% Porosity	16 mm
		11% Porosity	10 mm

[000101] Granules prepared from ribbons compacted at 28% porosity contained more fines than those at 11% porosity for both formulations which had a significant impact on its flowability. Drug loading was identified as the critical factor for flowability and granulation process improved the flowability of both formulations.

[000102] *Preparation and Characterization of the Final Blend*

[000103] Final blends were prepared using granules from formulation 1 and formulation 3 at both 11% and 28% porosity, as described above. The granules were mixed with an extragranular mixture of microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, and croscarmellose sodium. These blends were prepared as described with respect to the intragranular blend. These final blends were evaluated for their flowability, compaction properties, and disintegration. The disintegration times for these final blends were all not more than 5 minutes. The flowability was measured using both the shear cell test and Flodex test as described above. These results are shown in Tables 5 and 6, respectively.

[000104] Table 5.

Dry Granulation Formulation No.	Description	Flowability Index				
		1	2	3	AVE	SD
1	Final Blend (DL 20%), 11% Porosity	9.04	8.08	8.73	8.62	0.40
	Final Blend (DL 20%), 28% Porosity	9.7	20.35	12.86	14.30	4.47
3	Final Blend (DL 50%), 11% Porosity	8.35	8.65	8.51	8.50	0.15
	Final Blend (DL 50%), 28% Porosity	8.01	14.04	16.49	12.85	4.36

[000105] Table 6.

Dry Granulation Formulation No.	Description	Minimum orifice diameter
1	Final Blend (DL 20%), 28% Porosity	12 mm
	Final Blend (DL 20%), 11% Porosity	9 mm
3	Final Blend (DL 50%), 28% Porosity	16 mm
	Final Blend (DL 50%), 11% Porosity	10 mm

[000106] After mixing with the extragranular excipients, all blends exhibited good flowability based on their flowability index. Values between 4 and 10 indicate easy flowing, while values of greater than 10 indicate free flowing. Among them, the blends containing granules made with 11% porosity showed better flowability than 28% porosity granules and this is consistent with the respectively different flowability of corresponding granules.

[000107] The results of the final blend compressibility, tabletability, and compactibility are shown in Figs. 6A, 6B, and 6C, respectively. Similar to that observed in IG granules, the final blends using granules with 11% porosity had lower tabletability than that made with 11% porosity for both formulations. From the compressibility, tabletability, and compactibility profiles for the final blends, tablet porosity and tensile strength at different compaction forces could be clearly known. Hence, tablets with different tensile strength were selected for further characterizations. Tablets with tensile strengths of 1.75, 2.0 and 2.25 MPa were prepared at two

different compaction stresses (35 MPa and 210 MPa) from both formulation 1 and 3 for further analysis. These results are shown in Table 7 and Figs. 7A and 7B.

[000108] Table 7.

Dry Granulation Formulation No.	Description	Tensile strength (MPa)	Compaction Stress (MPa)
1	Final Blend (DL 20%), 28% Porosity, Compacted at 35 MPa	1.75	70
		2	80
		2.25	90
	Final Blend (DL 50%), 11% Porosity, Compacted at 210 MPa	1.75	100
		2	110
		2.25	125
3	Final Blend (DL 50%), 28% Porosity, Compacted at 35 MPa	1.75	50
		2	60
		2.25	70
	Final Blend (DL 50%), 11% Porosity, Compacted at 210 MPa	1.75	100
		2	130
		2.25	150

[000109] Tablet friability and disintegration time of these tablets showed that all the tablets exhibited < 1.0 % friability and all tablets disintegrated within 5 min in DI water at 37 °C. Tablet friability profile, i.e., tablet weight loss as a function of compaction force, of each formulation was carried out using an expedited method. A batch of tablets prepared under different compression forces was individually coded and then loaded into a friabilator. Tablets were weighed before and after the test to calculate the percentage weight loss for individual tablets (% friability), which was plotted against compaction force. Disintegration times (DT) of the tablets were measured using a USP disintegration tester (Di 200; Pharma Alliance Group, Valencia, CA) (Pharmacopeia). For each formulation, DT was recorded for three tablets. Tablets were individually placed into each tube of a disintegration apparatus, which was immersed into a beaker containing 900 mL of DI water. The temperature of the unit was maintained at 37°C.

[000110] The drug loading and granulation parameters (Roll force, roll speed, mill speed etc.) were subsequently optimized in the subsequent formulations to produce granules with the desired flow and compressibility. The optimized formulations did not have undesired flow or compaction parameters.

[000111] Example 3. Acidified Formulations

[000112] *Preparation and Characterization of Acidified Formulations*

[000113] To improve the *in vitro* dissolution in neutral media, 15% of Compound 1 freebase form of formulation 3 was replaced by organic acids. Citric acid, DL-malic acid and succinic acid were selected to cover the entire range of the tableability of organic acid. These formulations were prepared using dry granulation process and evaluations for their physical properties, as described above. These acidified formulations are shown in Table 8.

[000114] Table 8.

Acidified Formulation no.	Description	Component	Function	Quantity per Tablet (mg)	Weight % per Tablet
4	Compound 1 Freebase (35% drug loading), 50 mg citric acid	Compound 1 Freebase Substance	Drug Substance	50.0	35%
		Microcrystalline Cellulose	Diluent	45.7	32%
		Citric Acid	Local pH modifier	21.4	15%
		Mannitol	Diluent	14.3	10%
		Croscarmellose Sodium	Disintegrant	7.1	5%
		Sodium Lauryl Sulphate	Surfactant	1.4	1%
		Colloidal Silicon Dioxide	Glidant	1.4	1%
		Magnesium Stearate	Lubricant	1.4	1%
		Core Tablet Weight	-	142.9	100%
5	Compound 1 Freebase (35% drug loading), 50 mg succinic acid	Compound 1 Freebase Substance	Drug Substance	50.0	35%
		Microcrystalline Cellulose	Diluent	45.7	32%
		Succinic Acid	Local pH modifier	21.4	15%

6	Compound 1 Freebase (35% drug loading), 50 mg DL-malic acid	Mannitol	Diluent	14.3	10%
		Croscarmellose Sodium	Disintegrant	7.1	5%
		Sodium Lauryl Sulphate	Surfactant	1.4	1%
		Colloidal Silicon Dioxide	Glidant	1.4	1%
		Magnesium Stearate	Lubricant	1.4	1%
		Core Tablet Weight	-	142.9	100%
		Compound 1 Freebase Substance	Drug Substance	50.0	35%
		Microcrystalline Cellulose	Diluent	45.7	32%
		DL-Malic Acid	Local pH modifier	21.4	15%
		Mannitol	Diluent	14.3	10%
		Croscarmellose Sodium	Disintegrant	7.1	5%
		Sodium Lauryl Sulphate	Surfactant	1.4	1%
		Colloidal Silicon Dioxide	Glidant	1.4	1%
		Magnesium Stearate	Lubricant	1.4	1%
		Core Tablet Weight	-	142.9	100%
		Compound 1 Freebase Substance	Drug Substance	50.0	35%
		Microcrystalline Cellulose	Diluent	45.7	32%
		DL-Malic Acid	Local pH modifier	21.4	15%
		Mannitol	Diluent	14.3	10%
		Croscarmellose Sodium	Disintegrant	7.1	5%

[000115] The compressibility, tabletability, and compactibility of formulations 4, 5, and 6 are shown in Figs. 8A, 8B, and 8C, respectively.

[000116] Example 4. Dry Granulation Formulations with Coating

[000117] *Preparation of Dry Granulation Formulations with Coating*

[000118] Two tablet formulations of Compound 1 free base, using a dry granulation process, were prepared with a coating and evaluated for their physical properties. The dry granulation tablet formulations with a coating are shown in Table 9. Two dose amounts, 50 mg and 200 mg, were prepared for each formulation and are identified as “A” and “B”, respectively, in the table below.

[000119] Table 9.

Dry Granulation with Coating Formulation no.	Description	Component	Function	Quantity per Tablet (mg)	Weight % per Tablet
7A	Compound 1 freebase (40% drug loading), 50 mg	Compound 1 Freebase Substance	Drug Substance	50.0	40.0%
		Microcrystalline Cellulose	Diluent	41.9	33.5%
		Mannitol	Diluent	18.8	15.0%
		Croscarmellose Sodium	Disintegrant	7.5	6.0%
		Sodium Lauryl Sulphate	Surfactant	2.5	2.0%
		Colloidal Silicon Dioxide	Glidant	1.9	1.50%
		Magnesium Stearate	Lubricant	2.5	2.0%
		Core Tablet Weight	-	125.0	100.0%
		Coating Agent	Coating Agent	3.8	3.0%
		Coated Tablet Weight	-	128.8	103.0%
7B	Compound 1 freebase (40% drug loading), 200 mg	Compound 1 Freebase Substance	Drug Substance	200.0	40.0%
		Microcrystalline Cellulose	Diluent	167.5	33.5%
		Mannitol	Diluent	75.0	15.0%
		Croscarmellose Sodium	Disintegrant	30.0	6.0%
		Sodium Lauryl Sulphate	Surfactant	10.0	2.0%
		Colloidal Silicon Dioxide	Glidant	7.5	1.50%
		Magnesium Stearate	Lubricant	10.0	2.0%
		Core Tablet Weight	-	500.0	100.0%
		Coating Agent	Coating Agent	15.0	3.0%
		Coated Tablet Weight	-	515.0	103.0%

8A	Compound 1 freebase (40% drug loading), 50 mg	Compound 1 Freebase Substance	Drug Substance	50.0	40.0%
		Microcrystalline Cellulose	Diluent	50.9	40.75%
		Mannitol	Diluent	12.5	10.0%
		Croscarmellose Sodium	Disintegrant	6.3	5.0%
		Sodium Lauryl Sulphate	Surfactant	1.9	1.50%
		Colloidal Silicon Dioxide	Glidant	1.6	1.25%
		Magnesium Stearate	Lubricant	1.9	1.5%
		Core Tablet Weight	-	125.0	100.0%
		Coating Agent	Coating Agent	3.8	3.0%
		Coated Tablet Weight	-	128.8	103.0%
8B	Compound 1 freebase (40% drug loading), 200 mg	Compound 1 Freebase Substance	Drug Substance	200.0	40.0%
		Microcrystalline Cellulose	Diluent	203.8	40.75%
		Mannitol	Diluent	50.0	10.0%
		Croscarmellose Sodium	Disintegrant	25.0	5.0%
		Sodium Lauryl Sulphate	Surfactant	7.5	1.50%
		Colloidal Silicon Dioxide	Glidant	6.3	1.25%
		Magnesium Stearate	Lubricant	7.5	1.5%
		Core Tablet Weight	-	500.0	100.0%
		Coating Agent	Coating Agent	15.0	3.0%
		Coated Tablet Weight	-	515.0	103.0%

[000120] Intragranular blending was performed using a blend/de-lump/blend process. De-lumping was performed by Comil U5 with 024R (610 µm) screen and round impeller at 1750 rpm to break up agglomerates and produce a homogenous blend. The pre-blend was roller compacted according at a roll pressure of 3 MPa, a gap of 2.0 mm and a roll speed of 5 rpm using an Alexanderwerk WP120 roller compactor. Ribbons produced were milled on two

different screens (2.0 mm and 1.0 mm) and the granules were characterized for bulk density, tapped density, angle of repose, and particle size distribution by sieve analysis. The Carr index and Hausner Ratio of pre-blend and granules was calculated. These results are shown in Table 10. The particle size distribution results are shown in Fig. 9.

[000121] Table 10.

Batch No	Formulation 7 (40% Drug Loading)		Formulation 8 (40% Drug Loading)	
	Pre-Blend	Granules	Pre-Blend	Granules
Powder weight (g)	19.77	27.3	19.51	20.2
Powder initial volume (mL)	58	55	56	39
Bulk Density (g/mL)	0.341	0.496	0.348	0.518
The final tapped volume (mL)	34	38.5	33	27
Tapped Density (g/mL)	0.581	0.709	0.591	0.748
Carr Index %	41	30	41	31
Hausner Ratio	1.70	1.43	1.70	1.44
Angle of repose (Avg.)	-	18.8°	-	20.9°

[000122] Based on this result, there was a significant improvement of blend flowability by roller compaction. Comparing PSD results between Formula 7 and Formula 8, although Formula 8 had a higher fraction of particles above 500-microns than Formula 7, there was no significant difference in flowability.

[000123] The final blend was compressed by Korsch XL100 with 2 active stations. Tablets were characterized for hardness, thickness, weight, disintegration, and friability. Tablet friability and disintegration time of these tablets showed that all the tablets exhibited < 0.5 % friability and all tablets disintegrated within 5 min in DI water at 37 °C. Opadry II 85F18422, white was used as coating material for 50 mg and 200 mg tablets, using the Vector LDCS-Plus Coater assembled with 4 L pan. Coated tablets showed elegant appearance and no scuffing was observed. Dissolution testing was conducted using USP Type II dissolution apparatus in a pH 6.8 buffer media containing surfactant at 37 °C and 75 RPM. The dissolution parameters used are shown in Table 11 and the dissolution profiles for formulations 7 and 8, for both the 50 mg (A) and 200 mg (B) coated tablets, are shown in Figs. 10A and 10B, respectively.

[000124] Table 11.

Dissolution Parameters	Value
Dissolution Medium	0.5% SLS in 50mM Sodium Phosphate Monobasic, pH 6.8
Medium Volume	900mL
Medium Temperature	37.0°C (±0.5°C)
Stirring Rate	75 rpm, 250 rpm (60-75min)
Dissolution Apparatus	USP Type 2

[000125] More than 75% of the drug was released within 45 minutes from both the formulations. No difference in dissolution was observed between 50 and 200 mg dose strengths.

[000126] Example 5. Effect of Surfactant in Formulations

[000127] To evaluate the impact of surfactant on the formulations as described herein, dry granulation was used to prepare a formulation without sodium lauryl sulphate. Additionally, the granulator screens were reduced from 2.0 mm and 1.0 mm to 1.6 mm and 0.8 mm to reduce the granule particle size. Table 12 describes this formulation for both 50 mg and 200 mg tablets identified as “A” and “B”, respectively, in the table below.

[000128] Table 12.

Dry Granulation with Coating Formulation no.	Description	Component	Function	Quantity per Tablet (mg)	Weight % per Tablet
9A	Compound 1 freebase (40% drug loading), 50 mg, no SLS	Compound 1 Freebase Substance	Drug Substance	50.0	40.0%
		Microcrystalline Cellulose	Diluent	44.4	35.5%
		Mannitol	Diluent	20.6	16.5%
		Croscarmellose Sodium	Disintegrant	6.3	5.0%
		Colloidal Silicon Dioxide	Glidant	1.9	1.50%
		Magnesium Stearate	Lubricant	1.9	1.50%
		Core Tablet Weight	-	125.0	100.0%

		Coating Agent	Coating Agent	3.8	3.0%
		Coated Tablet Weight	-	128.8	103.0%
9B	Compound 1 freebase (40% drug loading), 200 mg, no SLS	Compound 1 Freebase Substance	Drug Substance	200.0	40.0%
		Microcrystalline Cellulose	Diluent	177.5	35.5%
		Mannitol	Diluent	82.5	16.5%
		Croscarmellose Sodium	Disintegrant	25.0	5.0%
		Colloidal Silicon Dioxide	Glidant	7.5	1.50%
		Magnesium Stearate	Lubricant	7.5	1.50%
		Core Tablet Weight	-	500.0	100.0%
		Coating Agent	Coating Agent	15.0	3.0%
		Coated Tablet Weight	-	515.0	103.0%

[000129] The dissolution of formulations 9A and 9B were evaluated as described above. The results of the dissolution testing are shown in Table 13 and the dissolution profiles are shown in Fig. 11.

[000130] Table 13.

Batch. No.	Formulation 9A		Formulation 9B	
Time	% Drug release	%RSD	% Drug release	%RSD
0	0	0	0	0
5	41	3.8	38	2.1
10	66	2.9	64	2.4
15	79	2.7	77	2.5
20	86	2.5	84	2.5
30	93	2.4	92	2.5
45	97	2.0	96	2.2
60	99	1.7	98	1.8
90	101	1.4	101	1.0

[000131] More than 75% of the drug was released within 15 minutes from formulation 9 which was significantly faster compared to formulations 7 and 8. Dissolution can be optimized

by varying the granule particle size. The need for surfactant can be minimized by effectively managing the particle size of the granules after roller compaction

[000132] Example 6. Effect of Granule Particle Size

[000133] Granules of formulation 8, as described above, were made at a reduced size by changing the screen size during roller compaction. Both 50 mg and 200 mg coated tablets were made. These reduces size granules for the 50 mg and 200 mg tablets will be referred to as formulations 10A and 10B, respectively. The characteristics of formulation 10 are shown in Table 14.

[000134] Table 14.

Batch No	Formulation 10	
Item	Pre-Blend	Granules
Powder weight (g)	28.69	29.19
Powder initial volume (mL)	81.0	57.0
Bulk Density (g/mL)	0.354	0.512
The final tapped volume (mL)	50.5	39.0
Tapped Density (g/mL)	0.568	0.748
Carr Index	38	32
Hausner Ratio	1.60	1.46
Angle of repose (Avg.)	-	16.8°

[000135] The particle size distribution of formulation 10 is shown in Fig. 12 and the dissolution of formulations 10A and 10B is shown Fig. 13. Slower dissolution observed with Formulation 8 was not observed with Formulation 10 suggesting that the optimal dissolution can be achieved by varying the granule particle size. Interestingly, the flow properties of the blend also remained unchanged despite the reduction in the particle size.

[000136] Example 7. Effect of Mannitol on Drug Formulation

[000137] In the previous formulations described in the examples, it was the observed that the composition would stick to the rollers and that the amount of mannitol (a brittle filler) in the formulation is directly proportional to the extent of the sticking. To test the effect of mannitol on the formulation, mannitol was completely removed from formulation 10. Table 15 describes this formulation for both 50 mg and 200 mg tablets identified as “A” and “B”, respectively.

[000138] Table 15.

Dry Granulation Formulation no.	Description	Component	Function	Quantity per Tablet (mg)	Weight % per Tablet
11A	Compound 1 freebase (40% drug loading), 50 mg, no mannitol	Compound 1 Freebase Substance	Drug Substance	50.0	40.0%
		Microcrystalline Cellulose	Diluent	65.3	52.25%
		Croscarmellose Sodium	Disintegrant	6.3	5.0%
		Colloidal Silicon Dioxide	Glidant	1.6	1.25%
		Magnesium Stearate	Lubricant	1.9	1.5%
		Core Tablet Weight	-	125.0	100.0%
11B	Compound 1 freebase (40% drug loading), 200 mg, no mannitol	Compound 1 Freebase Substance	Drug Substance	200.0	40.0%
		Microcrystalline Cellulose	Diluent	261.3	52.25%
		Croscarmellose Sodium	Disintegrant	25.0	5.0%
		Colloidal Silicon Dioxide	Glidant	6.3	1.25%
		Magnesium Stearate	Lubricant	7.5	1.5%
		Core Tablet Weight	-	500.0	100.0%

[000139] Formulations with only 5% mannitol were also prepared at three strengths (50 mg, 200 mg, and 300mg) with two various coating agents. These formulations were assessed for their dissolution and stability risks. Table 16 describes these formulations and Fig. 14 shows the dissolution of the formulations with various coatings.

[000140] Table 16.

Dry Granulation with Coating Formulation no.	Description	Component	Function	Quantity per Tablet (mg)	Weight % per Tablet
12A	Compound 1 freebase (40% drug loading), 50 mg, 5% mannitol	Compound 1 Freebase Substance	Drug Substance	50.0	40.0%
		Microcrystalline Cellulose	Diluent	59.1	47.25%
		Mannitol	Diluent	6.3	5.0%
		Croscarmellose Sodium	Disintegrant	6.3	5.0%
		Colloidal Silicon Dioxide	Glidant	1.6	1.25%
		Magnesium Stearate	Lubricant	1.9	1.5%
		Core Tablet Weight	-	125.0	100.0%
		Coating Agent	-	3.8	3.0%
		Coated Tablet Weight	-	128.8	103.0%
12B	Compound 1 freebase (40% drug loading), 200 mg, 5% mannitol	Compound 1 Freebase Substance	Drug Substance	200.0	40.0%
		Microcrystalline Cellulose	Diluent	236.3	47.25%
		Mannitol	Diluent	25.0	5.0%
		Croscarmellose Sodium	Disintegrant	25.0	5.0%
		Colloidal Silicon Dioxide	Glidant	6.3	1.25%
		Magnesium Stearate	Lubricant	7.5	1.5%
		Core Tablet Weight	-	500.0	100.0%
		Coating Agent	-	15.0	3.0%
		Coated Tablet Weight	-	515.0	103.0%
12C	Compound 1 freebase (40% drug loading), 300 mg, 5% mannitol	Compound 1 Freebase Substance	Drug Substance	300.0	40.0%
		Microcrystalline Cellulose	Diluent	354.38	40.75%
		Mannitol	Diluent	37.50	10.0%
		Croscarmellose Sodium	Disintegrant	37.50	5.0%

		Colloidal Silicon Dioxide	Glidant	9.37	1.25%
		Magnesium Stearate	Lubricant	11.25	1.5%
		Core Tablet Weight	-	500.0	100.0%
		Coating Agent	-	15.0	3.0%
		Coated Tablet Weight	-	515.0	103.0%
13	Compound 1 freebase (40% drug loading), 50 mg, 5% mannitol (Opadry AMB II 88A180021 White)	Compound 1 Freebase Substance	Drug Substance	50.0	40.0%
		Microcrystalline Cellulose	Diluent	59.1	47.25%
		Mannitol	Diluent	6.3	5.0%
		Croscarmellose Sodium	Disintegrant	6.3	5.0%
		Colloidal Silicon Dioxide	Glidant	1.6	1.25%
		Magnesium Stearate	Lubricant	1.9	1.5%
		Core Tablet Weight	-	125.0	100.0%
		Opadry AMB II 88A180021	-	3.8	3.0%
		Coated Tablet Weight	-	128.8	103.0%
14	Compound 1 freebase (40% drug loading), 50 mg, 5% mannitol (Opadry II 85F18422)	Compound 1 Freebase Substance	Drug Substance	50.0	40.0%
		Microcrystalline Cellulose	Diluent	59.1	47.25%
		Mannitol	Diluent	6.3	5.0%
		Croscarmellose Sodium	Disintegrant	6.3	5.0%
		Colloidal Silicon Dioxide	Glidant	1.6	1.25%
		Magnesium Stearate	Lubricant	1.9	1.5%
		Core Tablet Weight	-	125.0	100.0%
		Opadry II 85F18422	-	3.8	3.0%
		Coated Tablet Weight	-	128.8	103.0%
15	Compound 1 freebase (40% drug loading), 50	Compound 1 Freebase Substance	Drug Substance	50.0	40.0%

	mg, 5% mannitol (Opadry QX 321A180025)	Microcrystalline Cellulose	Diluent	59.1	47.25%
		Mannitol	Diluent	6.3	5.0%
		Croscarmellose Sodium	Disintegrant	6.3	5.0%
		Colloidal Silicon Dioxide	Glidant	1.6	1.25%
		Magnesium Stearate	Lubricant	1.9	1.5%
		Core Tablet Weight	-	125.0	100.0%
		Opadry QX 321A180025	-	3.8	3.0%
		Coated Tablet Weight	-	128.8	103.0%

[000141] Example 8. Amorphous Solid Dispersion Formulations

[000142] Amorphous solid dispersions of Compound 1 were evaluated using Spray Drying Technique. The amorphous solid dispersions were prepared by dissolving the drug substance and the stabilizing polymer in a suitable solvent to form a feed solution and then spray drying the feed solution using an atomizer to form the amorphous solid dispersion as a powder. Through this technique, the crystalline form is converted into amorphous and is stabilized onto a polymer to overcome slower dissolution in intestinal media was evaluated.

[000143] Examples of suitable solvents include dichloromethane (DCM), chloroform, ethanol, methanol, 2-propanol, ethyl acetate, acetone, water or mixtures thereof. A preferred solvent is a mixture of dichloromethane and ethanol. Examples of polymers include hydroxypropyl methylcellulose phthalate (also known as HPMCP and/or hypromellose phthalate), cellulose acetate phthalate (also known as CAP), hydroxypropyl methyl cellulose acetate Succinate (also known as HPMCAS), Hypromellose (HPMC) and polymeric polymethacrylates, such as EUDRAGIT RL 100, Eudragit L100.

[000144] Visual solubility was performed with various solvents and mixtures thereof. A combination of DCM: methanol, at a ratio of 80:20, was selected due to its low boiling point and ability to solubilize commonly used spray drying polymers. Mixtures of the crystalline form of Compound 1 and different polymers (HPMCAS (LG grade), HPMCAS (HG grade), HPMC E3 and PVPVA64 were prepared at a 1:1 ratio as 5% solids in the DCM: methanol solvent mixture. The resultant solutions were sprayed using a ProCepT 4M8-Trix pharmaceutical spray

dryer. Polymers were dissolved in the solvent system followed by addition of the crystalline form.

[000145] Quantitative solubility of the crystalline form and the amorphous solid dispersions in FaSSIF media at 37 °C was determined and it was observed that the amorphous solubility ranged from 0.3-0.7 mg/mL in the presence of polymers which was higher than the crystalline solubility of 0.19 mg/mL. All samples were found to be physically stable after 1 week at 40 °C.

[000146] Dissolution (SSKD) studies were performed using Pion μ DISS Profiler on all the samples including the crystalline form. The studies were performed using two different two-stage dissolution media where the pH of the media is switched to intestinal pH (pH 6.8 after 30 minutes). The initial pH however was different in the two studies (pH 1.2 to simulate fasted condition and pH 5.0 to simulate fed condition). Figs. 15A and 15B show the results of the dissolution study.

[000147] From Figs. 15A and 15B, it can be seen that all the spray dried dispersions exhibited the well-established spring and parachute effect that is typical of amorphous solid dispersions. However, HPMC E3 had the least parachute effect with faster precipitation at pH 6.5. Interestingly, when pre-dissolved in both pH 1.2 and pH 5.0 the crystalline form also exhibited supersaturation (solubility higher than its theoretical solubility) in FaSSIF media similar to the amorphous solid dispersion. This is very uncommon and is an inherent property of the Compound 1 free base.

[000148] Example 9. Chiral Impurities in Tablets

[000149] *Background*

[000150] During tablet drug product development, the prototypes when stressed at accelerated conditions, showed amorphous formation during manufacture and subsequent growth of an enantiomeric impurity upon storage.

[000151] Generally, Compound 1 has an atropoenantiomeric (chiral) impurity currently at levels between 1-2%. The crystalline form of Compound 1 and drug-in-capsule formulations show no significant growth in the chiral impurity at room temperature and 40°C and 75% relative humidity. However, tablet drug product exhibits a growth at both 25°C/60% relative humidity and 40°C/75% relative humidity conditions upon storage and no growth at 2-8 °C.

[000152] Upon further investigation, it was discovered that while the crystalline form of Compound 1 has lower rate of chiral conversion, the amorphous form of Compound 1 has a significantly higher chiral conversion rate especially at higher temperatures. This suggests that some of the crystalline Compound 1 may undergo amorphization during drug product manufacturing which in turn converts to chiral impurity upon storage at elevated temperatures. Fig. 16 depicts the proposed hypothesis for the generation of the chiral impurity observed in tablets.

[000153] Solid-state NMR analysis conducted on the final blend and tablet samples suggest ~3% amorphous content in the final blend prior to compression and ~6% amorphous content in the finished tablet drug product manufactured using dry granulation. The drug product manufacturing includes dry granulation followed by compression. 3% amorphous content in the final blend suggests that the drug substance undergoes amorphization to a certain degree during roller compaction and the level increases to 6% during compression.

[000154] *Methodology*

[000155] Different common blends were manufactured using dry granulation, high shear wet granulation and fluid bed granulation with similar formulation compositions to evaluate the impact of processing conditions on amorphization and subsequent chiral growth. The common blends were filled into both capsules and tablets to differentiate the effects of granulation and tableting unit operations. The samples were also stored at 55 °C for 2 weeks and 40 °C/75%RH for 3 months to establish correlation between amorphous content and chiral growth. Tables 17 and 18 show these results.

[000156] Table 17.

Time Point	Sample	Compound 1	Chiral Impurity	Δ from Initial
Initial	100% Crystalline Free Base Compound 1	98.98	1.02%	-
	100% Amorphous Free Base Compound 1	99.03%	0.97%	-
2 Weeks	100% Crystalline Free Base Compound 1	98.96%	1.02%	0.02%
	100% Amorphous Free Base Compound 1	97.67%	2.33%	1.36%

[000157] Table 18.

	Condition	Initial	1 Month	2 Month	3 Month	6 Month
Tablets	5°C	1.3	1.3	1.3	1.3	1.3
	25°C/60%	1.3	1.4	1.4	1.4	1.5
	40°C/75%	1.3	1.5	1.7	1.8	2.1
Drug in Capsule	25°C/60%	1.4	1.4	1.4	1.4	1.4
Compound 1 (crystalline)	25°C/60%	1.6	1.7	NT	1.6	1.7
	40°C/75%	1.6	1.6	NT	1.7	1.7

[000158] *Effect of Compression Force on Amorphous Content*

[000159] The impact of compression force was evaluated by compressing 150 mg of crystalline free base using 8 mm round flat faced tooling using a Styl'One TM Compaction Simulator at 1 kN and 6 kN compression force that correlates well with the compaction stress typically experienced by the API during tableting.

[000160] Due to the lower amounts of amorphous content in the tablet drug product, quantification of % crystallinity was deemed not possible using convention XRPD techniques and ¹⁹F SSNMR was used instead.

[000161] For evaluating the amorphous content using SSNMR, one tablet was removed, placed into a clean mortar and pestle, and gently broken up to create a powder for packing into the 4mm rotor for analysis. The minimum amount of force needed to break up the tablet was used. No grinding of the sample occurred. Remaining tablet material was saved in a new 20 mL scintillation vial.

[000162] ¹⁹F Solid-state NMR experiments were acquired using a 400 MHz Bruker Avance NEO spectrometer, equipped with a Revolution NMR HF probe and 4mm magic angle spinning (MAS) module. ¹⁹F spectra were acquired using Cross Polarization (CP) experiment and was able to distinguish the sharp resonance (-117 to -118 ppm) of crystalline material from the broad resonance (-122 ppm) of amorphous material. Amorphous content determination utilized a spectral subtraction technique to determine % amorphous content present in the samples. The resulting amorphous content measured is reported in Fig. 17.

[000163] It was observed that forces as low as 1 kN also increase the amount of amorphous content in the formulation and a compaction force of 6 kN increases the amount of amorphous content closer to 3.6%.

[000164] *Effect of Drug Loading on Amorphous Content and Subsequent Chiral Growth*

[000165] A validated High-Performance Liquid Chromatography (HPLC) method was utilized to evaluate the growth of the chiral impurity in tablet and drug-in-capsule samples during the stability study. To determine whether the growth of the impurity was caused by stress-induced amorphization, crystalline Compound 1 was compressed at different compaction forces using a Styl'One™ Compaction simulator (Korsch America) and the samples were evaluated for amorphous content.

[000166] Crystalline form of Compound 1 was also co-compressed with different fillers to understand the impact of filler and drug loading. Physical mixtures of the crystalline form and MCC were evaluated at 3 different ratios and free base crystalline form was used as a control. Physical mixtures prepared were well mixed to ensure uniformity and compressed using a Styl'One™ Compaction simulator (Korsch America) at three different compactions forces (2 kN, 6 kN and 16 kN). The 16 kN force was used as an extreme case to understand the extent of amorphization and subsequent chiral conversion. After compression, the samples were stored at 55 °C for 2 weeks to correlate the amorphous content with chiral growth. These results are shown in Fig. 18.

[000167] From Fig. 18, it can be seen that the 100% crystalline form had the least amount of chiral conversion when subjected to physical stress and 20% drug loading had the highest. Even forces as low as 2 kN seem to generate amorphous content as evident by the extent of chiral growth. However, it is important to note that the values do not grow significantly from 6 to 16 kN. An optimized drug loading and compression force was determined to be critical in minimizing the amount of chiral conversion especially at higher temperatures.

[000168] *Effect of Type of Filler*

[000169] The type of filler also has an impact on the chiral conversion with plastic fillers, such as microcrystalline cellulose, having a worse effect than brittle fillers such as mannitol or lactose.

[000170] To further evaluate the effect of the fillers, Compound 1 was also co-compressed with different grades of microcrystalline cellulose with different compressibility and particle size to understand the impact of microcrystalline cellulose grade. 50:50 physical mixtures of Compound 1 and different grades of microcrystalline cellulose and other fillers were evaluated. Physical mixtures prepared were well mixed to ensure uniformity and compressed using a Styl'One™ Compaction simulator (Korsch America) at three different compactions forces (2 kN, 6 kN and 16 kN). The 16 kN force was used as an extreme case to understand the extent of amorphization and subsequent chiral conversion. After compression, the samples were stored at 55 °C for 2 weeks to correlate the amorphous content with chiral growth. Fig. 19 shows these results. It is noted that certain grades of Microcrystalline cellulose may have lower impact on amorphous conversion than others based on their particle size and compressibility

[000171] Example 10. High Shear Wet Granulation and Fluid Bed Granulation

[000172] For an effective drug formulation, crystalline Compound 1 must be granulated as the crystalline form as is has poor flow. While dry granulation can be used, amorphization was observed even during roller compaction (albeit at levels lower than the compression studies discussed in Example 9).

[000173] High shear wet granulation and fluid bed granulation were evaluated as alternative granulation technologies to avoid stress-induced amorphization. Wet granulation technologies mainly include high shear wet granulation (HSWG), low shear wet granulation using planetary mixer, twin-screw granulation (TSG), fluid-bed granulation (FBG), and fluid-

bed melt granulation. Among these methods, HSWG is one of the most widely applied granule product development technologies.

[000174] *Methodology*

[000175] The formulation composition for both high shear wet granulation and fluid bed granulation are listed in Tables 19 and 20. The compositions were similar to the dry granulation formulations with 40% drug loading and with an exception of addition of binders such as poly(vinyl pyrrolidone) or HPMC and processing with water as a wet granulation aid.

[000176] For high shear wet granulations, granulations were made in a 1L high shear unit (Vector GMXB Lab Micro Granumeist). Mixer blade speed was low (710 rpm) for pre-mix (5 min) and water infusion steps (3 min) and high (1100 rpm) for high-shear step (2 min). The chopper was run on low speed for the high-shear step. The resultant wet mass was then dried with 65°C air using a fluid-bed dryer until the product was closer to 5% moisture content.

[000177] For fluid bed granulations, granulations were made in a VFC Lab Mini Flo Coater (0.8 L). The pre-mix was initially fluidized and heated to 65°C, after which water was gradually sprayed using a top spray gun placed 8" away from the tablet bed at a spray rate of 2 g/min along with an atomization pressure of 5 psi. After the addition of water, the inlet air was increased and the resultant mass was dried until the product was closer to 5% moisture content.

[000178] Table 19.

High Shear Wet Granulation Formulation no.	Description	Component	Function	Quantity per Tablet (mg)	Weight % per Tablet
1	Compound 1 Free Base (50% drug loading), 200 mg, Intra-granular	MRTX1719 API	Active	213.90	53.48%
		Avicel PH101	Filler	114.10	28.52%
		Hypromellose, HPMC E3	Binder	16.00	4.00%
		Ac-Di-Sol	Disintegrant	12.00	3.00%
		Water	Granulating Fluid	Removed through Processing	
	Extra-granular	Intra-granular Formulation	-	356.00	89.00%
		Avicel PH102	Filler	20.00	5.00%
		Ac-Di-Sol	Disintegrant	20.00	5.00%

		Magnesium Stearate	Lubricant	4.00	1.00%
2	Compound 1 Free Base (50% drug loading, with PVP), 200 mg, Intra-granular	MRTX1719 API	Active	213.90	53.48%
		Avicel PH101	Filler	114.10	28.52%
		Poly Vinyl Pyrrolidone	Binder	16.00	4.00%
		Ac-Di-Sol	Disintegrant	12.00	3.00%
		Water	Granulating Fluid	Removed through Processing	
	Extra-granular	Intra-granular Formulation	-	356.00	89.00%
		Avicel PH102	Filler	20.00	5.00%
		Ac-Di-Sol	Disintegrant	20.00	5.00%
		Magnesium Stearate	Lubricant	4.00	1.00%
3	Compound 1 Free Base (66% drug loading), 400 mg, Intra-granular	MRTX1719 API	Active	400.00	66.67%
		Avicel PH101	Filler	80.00	13.33%
		Hypromellose, HPMC E3	Binder	36.00	6.00%
		Ac-Di-Sol	Disintegrant	18.00	3.00%
		Water	Granulating Fluid	Removed through Processing	
	Extra-granular	Intra-granular Formulation	-	534.00	89.00%
		Avicel PH102	Filler	30.00	5.00%
		Ac-Di-Sol	Disintegrant	30.00	5.00%
		Magnesium Stearate	Lubricant	6.00	1.00%
4	Compound 1 Free Base (80% drug loading), 600 mg, Intra-granular	MRTX1719 API	Active	600.00	80.00%
		Avicel PH101	Filler	45.00	6.00%
		Hypromellose, HPMC E3	Binder	60.00	8.00%
		Ac-Di-Sol	Disintegrant	18.75	2.50%
		Water	Granulating Fluid	Removed through Processing	
	Extra-granular	Intra-granular Formulation	-	723.75	96.0%
		Ac-Di-Sol	Disintegrant	18.75	2.50%
		Magnesium Stearate	Lubricant	7.50	1.00%

[000179] Table 20.

Fluid Bed Granulation Formulation no.	Description	Component	Function	Quantity per Tablet (mg)	Weight % per Tablet
1	Compound 1 Free Base (50% drug loading), 200 mg, Intra-granular	MRTX1719 API	Active	213.90	53.48%
		Avicel PH101	Filler	114.10	28.52%
		Hypromellose, HPMC E3	Binder	16.00	4.00%
		Ac-Di-Sol	Disintegrant	12.00	3.00%
		Water	Granulating Fluid	Removed through Processing	
	Extra-granular	Intra-granular Formulation	-	356.00	89.00%
		Avicel PH102	Filler	20.00	5.00%
		Ac-Di-Sol	Disintegrant	20.00	5.00%
		Magnesium Stearate	Lubricant	4.00	1.00%
2	Compound 1 Free Base (50% drug loading, with PVP), 200 mg, Intra-granular	MRTX1719 API	Active	213.90	53.48%
		Avicel PH101	Filler	114.10	28.52%
		Poly Vinyl Pyrrolidone	Binder	16.00	4.00%
		Ac-Di-Sol	Disintegrant	12.00	3.00%
		Water	Granulating Fluid	Removed through Processing	
	Extra-granular	Intra-granular Formulation	-	356.00	89.00%
		Avicel PH102	Filler	20.00	5.00%
		Ac-Di-Sol	Disintegrant	20.00	5.00%
		Magnesium Stearate	Lubricant	4.00	1.00%

[000180] The resultant granules from both high shear granulation and fluid bed granulation were milled using an appropriate screen and then added to extragranular components including a lubricant to form a final blend. The final blend was encapsulated into size 00 capsules at a unit dose strength of 200 mg and was also compressed into tablets at the same unit dose strength. The capsules and tablets were then evaluated for amorphous content using solid state NMR and the tablets were also subjected to storage at 55 °C for 2 weeks and 40 °C/75%RH for 3 months to evaluate the chiral growth. The SSNMR method used was the same as described in Example 9. The results were compared with tablets and capsules

manufactured using dry granulation. These results are shown in Table 21 and Figures 20A and 20B.

[000181] Table 21.

Sample	Chiral Impurity Growth		Amorphous Content by ssNMR
	55°C – 2 weeks	40°C/75% RH – 3 Months	
Fluid Bed Capsules	0.05%	0.01%	0.8%
HCl Salt Capsules	0.11%	0.01%	0.7%
HCl Salt Tablets	0.11%	0.11%	1.5%
High Shear Capsules	0.19%	0.12%	2.2%
Fluid Bed Tablets	0.23%	0.17%	3.4%
Dry Granulation Capsules	0.39%	0.31%	3.7%
High Shear Tablets	0.35%	0.28%	5.4%
Dry Granulation Tablets	0.47%	0.51%	7.5%

[000182] From these results, it can be seen that all formulations exhibited chiral growth upon storage at accelerated conditions albeit at different levels. Fluid bed granulation had the least chiral growth among all the technologies evaluated after granulation. No changes were observed in the amount of chiral growth between granules and capsules suggesting no impact of encapsulation on amorphous content. A combination of high shear granulation with higher drug load can be employed to manufacture capsules and tablets with lower degree of amorphization. HSWG and Fluid Bed Granulation are influenced by multiple formulation and process parameters that can be optimized to lower the amount of amorphous content. The final blend can be filled into capsules instead of tablets and the chiral impurity growth is reduced due to lower extent of amorphization in capsules.

* * *

[000183] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from this disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

We claim:

1. A granulated composition of 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1h-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile comprising:
a crystalline form of 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1h-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile comprising
a first chiral crystalline form present in an amount of at least 85 wt%, based on
the weight of the crystalline form;
optionally, a second chiral form present in an amount of no more than 5 wt%,
based on the weight of the crystalline form; and
optionally, an amorphous form present in an amount of no more than 10 wt%,
based on the weight of the crystalline form;
filler; and
optionally, an organic acid.
2. The granulated composition of claim 1, wherein the crystalline form is a hydrochloride salt.
3. The granulated composition of claim 1, wherein the crystalline composition is a free base.
4. The granulated composition of any of claims 1 to 3, wherein the crystalline form is present in an amount of at least 10 wt% (e.g., at least 20 wt%, at least 30 wt%, at least 40 wt%, or at least 50 wt%), based on the weight of the granulated composition.
5. The granulated composition of any of claims 1 to 4, wherein the crystalline form is present in an amount in the range of 10-90 wt% (e.g., in the range of 10-70 wt%, or 10-50 wt%, or 30-90 wt%, or 30-70 wt%, or 30-50 wt%), based on the weight of the granulated composition.
6. The granulated composition of any of claims 1 to 5, wherein the filler is selected from colloidal silicon dioxide, croscarmellose sodium, polyvinylpyrrolidinone, dibasic calcium phosphate, sodium lauryl sulphate, hydroxypropyl cellulose (e.g., hydroxypropyl

methylcellulose), lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, sodium stearyl fumarate, or combinations thereof.

7. The granulated composition of any of claims 1 to 6, wherein the filler comprises microcrystalline cellulose, mannitol, croscarmellose sodium, sodium lauryl sulphate, colloidal silicon dioxide, and magnesium stearate.

8. The granulated composition of claim 7, wherein the microcrystalline cellulose is present in an amount of at least 20 wt% (e.g., at least 30 wt%, at least 40 wt%, or at least 50 wt%), based on the weight of the granulated composition.

9. The granulated composition of claim 7 or claim 8, wherein the mannitol is present in an amount of at least 10 wt% (e.g., at least 15 wt%, or at least 20 wt%), based on the weight of the granulated composition.

10. The granulated composition of any of claims 7 to 9, wherein croscarmellose sodium, sodium lauryl sulphate, colloidal silicon dioxide, and magnesium stearate are present in an amount of no more than 15 wt% (e.g. no more than 12 wt%, or no more than 10 wt%, or no more than 8 wt%), based on the weight of the granulated composition.

11. The granulated composition of any of claims 1 to 6, wherein the filler comprises microcrystalline cellulose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate.

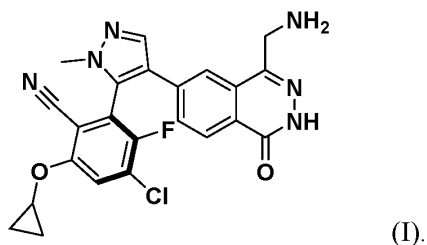
12. The granulated composition of claim 11, wherein the microcrystalline cellulose is present in an amount of at least 5 wt% (e.g., at least 10 wt%, at least 15 wt%, at least 20 wt%, or at least 25 wt%), based on the weight of the granulated composition.

13. The granulated composition of claim 11 or claim 12, wherein the croscarmellose sodium is present in an amount of at least 4 wt% (e.g., at least 6 wt% or at least 8 wt%), based on the weight of the granulated composition.

14. The granulated composition of any of claims 11 to 13, wherein hydroxypropyl methylcellulose and magnesium stearate are present in an amount of no more than 10 wt% (e.g., no more than 5 wt%).
15. The granulated composition of any of claims 1 to 6, wherein the filler comprises microcrystalline cellulose, polyvinyl pyrrolidone, croscarmellose sodium, and magnesium stearate.
16. The granulated composition of claim 15, wherein the microcrystalline cellulose is present in an amount of at least 5 wt% (e.g., at least 10 wt%, at least 15 wt%, at least 20 wt%, or at least 25 wt%), based on the weight of the granulated composition.
17. The granulated composition of claim 15 or claim 16, wherein the croscarmellose sodium is present in an amount of at least 4 wt% (e.g., at least 6 wt% or at least 8 wt%), based on the weight of the granulated composition.
18. The granulated composition of any of claims 15 to 17, wherein polyvinyl pyrrolidone and magnesium stearate are present in an amount of no more than 10 wt% (e.g., no more than 5 wt%), based on the weight of the granulated composition.
19. The granulated composition of any of claims 1 to 18, wherein the filler is present in an amount of at least 10 wt% (e.g., at least 20 wt%, at least 30 wt%, at least 40 wt%, or at least 50 wt%), based on the weight of the granulated composition.
20. The granulated composition of any of claims 1 to 19, wherein the filler is present in an amount in the range of 10-90 wt% (e.g., in the range of 10-70 wt%, or 10-50 wt%, or 30-90 wt%, or 30-70 wt%, or 30-50 wt%), based on the weight of the granulated composition.
21. The granulated composition of any of claims 1 to 20, wherein the weight ratio of the crystalline form to the filler is at least 1:10.
22. The granulated composition of any of claims 1 to 21, wherein the weight ratio of the crystalline form to the filler is in the range of 1:10 to 10:1 (e.g., in the range of 1:10 to 5:1, or

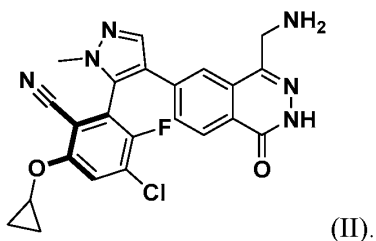
1:10 to 2:1, or 1:10 to 1:1, or 1:5 to 10:1, or 1:5 to 5:1, or 1:5 to 2:1, or 1:5 to 1:1, or 2:1 to 10:1, or 2:1 to 5:1, or 2:1 to 2:1, or 2:1 to 1:1).

23. The granulated composition of any of claims 1 to 22, wherein the first chiral crystalline form is a compound having Formula (I):



24. The granulated composition of any of claims 1 to 23, wherein the first chiral crystalline form is present in an amount of at least 90 wt% (e.g., at least 92 wt%, at least 94 wt%, or at least 96 wt%), based on the weight of the crystalline form.

25. The granulated composition of any of claims 1 to 24, wherein the second chiral form is a compound having Formula (II):



26. The granulated composition of any of claims 1 to 25, wherein the second chiral form is present in an amount of no more than 3 wt% (e.g., no more than 2 wt%, or no more than 1 wt%), based on the weight of the crystalline form.

27. The granulated composition of any of claims 1 to 26, wherein the second chiral form is present in a crystalline form.

28. The granulated composition of any of claims 1 to 26, wherein the second chiral form is present in an amorphous form.
29. The granulated composition of any of claims 1 to 28, wherein the amorphous form is present in an amount of no more than 8 wt% (e.g., no more than 5 wt% or no more than 3 wt%), based on the weight of the crystalline form.
30. The granulated composition of any of claims 1 to 29 comprising the organic acid.
31. The granulated composition of claim 30, wherein the organic acid is selected from citric acid, fumaric acid, DL-tartaric acid, maleic acid, DL-malic acid, or succinic acid.
32. The granulated composition of claim 30 or claim 31, wherein the organic acid is present in an amount of at least 5 wt% (e.g., at least 10 wt%, or at least 12 wt%, or at least 15 wt%), based on the weight of the granulated composition.
33. The granulated composition of any of claims 1 to 32 having a porosity in the range of 5-40 % (e.g., in the range of 5-35%, or 5-30%, or 10-40%, or 10-35%, or 10-30%).
34. The granulated composition of any of claims 1 to 33 having a porosity of 28%.
35. The granulated composition of any of claims 1 to 34 having a porosity of 11%.
36. The granulated composition of any of claims 1 to 35 having an average particle size of at least about 250 μm .
37. The granulated composition of any of claims 1 to 36 having an average particle size of at least about 300 μm .
38. A pharmaceutical composition (e.g., tablet) comprising the granulated composition of any of claims 1 to 37.
39. A method of making a granulated composition of any of claims 1 to 34 comprising:

providing a crystalline form of 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile comprising at least 95 wt% of a first chiral crystalline form;

providing a filler;

mixing the crystalline form and the filler in a weight ratio of at least 1:10;

subjecting the mixture to a granulating method selected from fluid bed granulation, high or low shear granulation, and dry granulation to provide a granulated composition;

wherein the granulated composition has no more than 10 wt% of an amorphous form of 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile; and

wherein the granulated composition has no more than 5 wt% of a second chiral form of 2-(4-(4-(aminomethyl)-1-oxo-1,2-dihydrophthalazin-6-yl)-1-methyl-1H-pyrazol-5-yl)-4-chloro-6-cyclopropoxy-3-fluorobenzonitrile.

40. The method of claim 39, wherein the granulating method is fluid bed granulation.
41. The method of claim 39, wherein the granulating method is high shear granulation.
42. The method of claim 39, wherein the granulating method is low shear granulation.