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(57) Abrégé/Abstract:
The present disclosure relates to compositions and pharmaceutical formulations comprising at least one active pharmaceutical ingredient chosen from nitrocatechol derivatives of formula I as defined herein and salts, esters, hydrates, solvates and other derivatives thereof and methods of making the same.

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(54) Title: PHARMACEUTICAL FORMULATIONS COMPRISING NITROCATECHOL DERIVATIVES AND METHODS OF MAKING THE SAME

(57) Abstract: The present disclosure relates to compositions and pharmaceutical formulations comprising at least one active pharmaceutical ingredient chosen from nitrocatechol derivatives of formula I as defined herein and salts, esters, hydrates, solvates and other derivatives thereof and methods of making the same.

"PHARMACEUTICAL FORMULATIONS COMPRISING NITROCATECHOL DERIVATIVES AND METHODS OF MAKING THE SAME"

FIELD OF THE DISCLOSURE

The present disclosure relates to compositions and pharmaceutical formulations comprising at least one active pharmaceutical ingredient chosen from nitrocatechol derivatives and salts thereof.

BACKGROUND

Levodopa (L-DOPA) has been used in clinical practice for several decades in the symptomatic treatment of various conditions, including Parkinson's disease. L-DOPA is able to cross the blood-brain barrier, where it is then converted to dopamine and increases the levels thereof. However, conversion of L-DOPA to dopamine may also occur in the peripheral tissue, possibly causing adverse effects upon administration of L-DOPA. Therefore, it has become standard clinical practice to co-administer a peripheral amino acid decarboxylase (AADC) inhibitor, such as carbidopa or benserazide, which prevents conversion to dopamine in peripheral tissue.

This has led to an interest in the development of inhibitors of the enzyme catechol-O-methyltransferase (COMT) based on the hypothesis that inhibition of the enzyme may provide clinical improvements in patients afflicted with Parkinson's disease undergoing treatment with L-DOPA, since COMT catalyses the degradation of L-DOPA.

It has been found, as set forth in International Publication Nos. WO 2007/013830 and WO 2007/117165 that compounds of formula I disclosed herein, which are nitrocatechol derivatives, are potent and long-acting COMT inhibitors. Those compounds are both

bioactive and bioavailable. Thus, compounds of formula I have potentially valuable pharmaceutical properties in the treatment of some central and peripheral nervous system disorders where inhibition of O-methylation of catecholamines may be of therapeutical benefit, such as, for example, mood disorders, Parkinson's disease and disorders, restless leg syndrome, gastrointestinal disturbances, oedema formation states, and hypertension. Furthermore, these compounds may also have activity in treating other diseases and disorders, not related to the inhibition of O-methylation of catecholamines.

It has also been found, however, that the compounds of formula I are sensitive to certain excipients, which may cause decomposition of the compounds of formula I and/or lack of stability of the compositions and formulations containing these compounds. The compounds of formula I may also exhibit a low bulk density and/or poor flow characteristics, which may increase the difficulty in formulating and/or manufacturing a stable dosage formulation containing the active compound.

SUMMARY

The inventors have now discovered stable compositions and formulations thereof comprising at least one active pharmaceutical ingredient ("API") chosen from nitrocatechol derivatives of formula I as defined herein and salts, esters, hydrates, solvates and other derivatives thereof. The at least one nitrocatechol derivative is preferably 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide or 5-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol. The at least one nitrocatechol derivative may also be a mixture of 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide and 5-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol.

In at least one embodiment, the API is present in granular form. In some embodiments, the compositions and/or formulations may comprise a further API, for

example the compositions and/or formulations may comprise, in addition to the at least one API chosen from nitrocatechol derivatives of formula 1, further APIs such as L-DOPA, a peripheral amino acid decarboxylase (AADC) inhibitor, such as carbidopa or benserazide. In further embodiments, the compositions and/or formulations may also comprise at least one filler and at least one binder. Preferably, the filler is not a phosphate derivative. Preferably, the binder is not a polyvinylpyrrolidone ("PVP") derivative compound. In various embodiments when the API is present in granular form, the at least one filler and at least one binder may, independently, be intragranular (i.e., granulated with the API and/or contained within the same granules as the API), extragranular (i.e., present outside the granules of API), or part intragranular and part extragranular. In yet further embodiments of the present disclosure, the compositions may exhibit a bulk density that is greater than that of the API alone, and that may, in certain embodiments, be a significantly increased. The compositions may also exhibit improvements in other characteristics such as compressibility. Use of the methods described herein may also result in improvements in the granule properties of the compositions such as improved granule size and uniformity of granule size and/or of granule mass. The compositions and/or formulations are stable over time and under different conditions, and may, in certain embodiments exhibit enhanced stability.

In one composition aspect, the invention relates to a stable composition comprising: at least one active pharmaceutical ingredient (API) which is 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-l,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide, or a salt, an ester, a hydrate, or a solvate thereof; and at least one component which is a filler, wherein the filler is not a phosphate derivative, or a binder, wherein the binder is not a polyvinylpyrrolidone derivative; wherein the at least one active pharmaceutical ingredient is present in the form of granules, and wherein the composition has a bulk density of greater than 0.2 g/mL.

In a further composition aspect, the invention relates to a method of manufacturing a stable pharmaceutical formulation, said method comprising: granulating at least one active pharmaceutical ingredient (API) which is 2,5 dichloro-3-(5-(3;4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide or a salt thereof to form

granules; mixing at least one component which is a filler or a binder with the at least one active pharmaceutical ingredient before, during or after granulation to form a composition; wherein the filler is not a phosphate derivative; or the binder is not a polyvinylpyrrolidone derivative; and preparing a pharmaceutical formulation in the form of a dosage form, wherein the granules and/or composition has a bulk density of greater than 0.2 g/mL.

DETAILED DESCRIPTION

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention as claimed. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein.

In various embodiments, the present disclosure relates to stable compositions and formulations thereof comprising at least one API chosen from nitrocatechol derivatives of

formula I as defined herein and salts, esters, hydrates, solvates and other derivatives thereof, at least one filler, and at least one binder. In a further embodiment, the at least one filler is not a phosphate derivative and/or the at least one binder is not a PVP derivative compound. The API may be present in granular form.

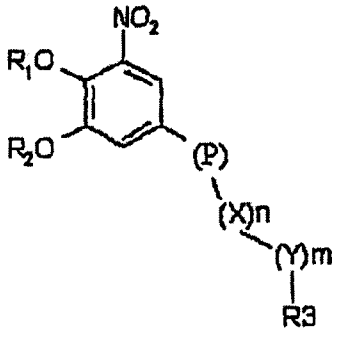
As used herein, the term "granules," "granular form," "API granules" and variations thereof, refer to the particles produced by wet or dry granulation of the API chosen from nitrocatechol derivatives of formula I as defined herein and salts, esters, hydrates, solvates and other derivatives thereof. In various embodiments of the present disclosure, the API may comprise two or more nitrocatechol derivatives of formula I, for example the composition may comprise 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide and 5-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol. The granules may further comprise at least one filler and/or at least one binder.

As used herein, the term "composition," and variations thereof, is intended to mean a composite comprising at least one API chosen from nitrocatechol derivatives of formula I as defined herein and salts, esters, hydrates, solvates and other derivatives thereof, at least one filler, and at least one binder. In certain embodiments, the composition may comprise two or more nitrocatechol derivatives of formula I (i.e. APIs), for example the composition may comprise 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide and 5-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol, at least one phosphate derivative, and at least one PVP derivative compound. The composition may comprise granules of the at least one API, and the at least one filler and at least one binder may independently be intragranular (i.e., granulated with the API and/or contained within the same granules as the API), extragranular (i.e., present outside the granules of API, or part intragranular and part extragranular. For example, the filler may be 10 wt% to 90 wt%, 20 wt% to 80 wt%, 30 wt% to 70 wt%, 40 wt% to 60 wt%, or about 50 wt% intragranular, with the remaining

portion being extragranular. The binder may be 10 wt% to 90 wt%, 20 wt% to 80 wt%, 30 wt% to 70 wt%, 40 wt% to 60 wt%, or about 50 wt% intragranular, with the remaining portion being extragranular. The composition may further comprise at least one excipient, which may be intragranular, extragranular, or part intra- and part extra-granular. The composition is preferably suitable for filling a capsule, making a tablet, and/or for directly administering to patients, for example packaged in sachets.

As used herein, the terms "formulation," "pharmaceutical formulation," and variations thereof, are intended to include compositions described herein that are further processed or formulated into a dosage form. By way of example only, in various exemplary embodiments, the formulations may comprise a composition described herein, typically in the form of granules, in a dosage form suitable for administration to a subject, such as a capsule or compressed dosage form such as a tablet. In a further exemplary embodiment, the formulations may comprise a composition described herein, typically in the form of granules, mixed with at least one excipient in a dosage form suitable for administration to a subject, such as a capsule or compressed dosage form such as a tablet.

As used herein, the nitrocatechol derivatives of formula I are defined as follows:



(I)

wherein:

R_1 and R_2 are independently selected from hydrogen or a group which is hydrolysable under physiological conditions, optionally substituted lower alkanoyl or aroyl;

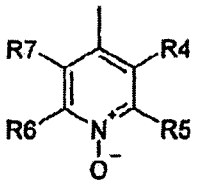
X is a methylene group;

Y is an atom of oxygen, nitrogen, or sulphur,

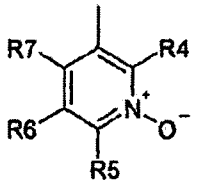
n is selected from 0, 1, 2, and 3;

m is 0 or 1;

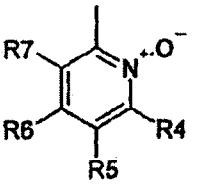
R_3 is a pyridine group chosen from the formulas A, B, C, D, E and F which is connected as indicated by the unmarked bond:



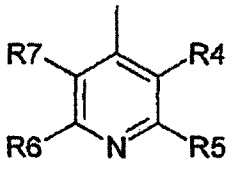
A



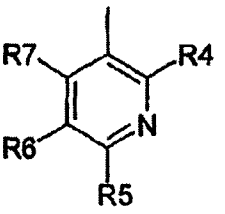
B



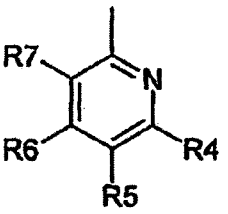
C



D



E



F

wherein:

R_4, R_5, R_6, and R_7 are independently chosen from hydrogen, C_1-C_6-alkyl, C_1-C_6-thioalkyl, C_1-C_6-alkoxy, C_6-C_{12}-aryloxy or a C_6-C_{12}-thioaryl group, C_1-C_6-alkanoyl or C_7-C_{13}-aroyl group, amino, C_1-C_6-alkylamino, C_1-C_6-dialkylamino, C_3-C_{12}-cycloalkylamino, C_3-C_{12}-heterocycloalkylamino, C_1-C_6-alkylsulphonyl, C_6-C_{12}-arylsulphonyl, halogen, C_1-C_6-haloalkyl, e.g., trifluoromethyl, cyano, nitro or a heteroaryl group; or two or more of residues R_4, R_5, R_6 and R_7 taken together represent aliphatic or heteroaliphatic rings or aromatic or heteroaromatic rings; and

P is a central unit, for example a planar unit, such as those selected from the regioisomers of 1,3,4-oxadiazol-2,5-diyl; 1,2,4-oxadiazol-3,5-diyl; 4-methyl-4H-1,2,4-triazol-3,5-diyl; 1,3,5-triazin-2,4-diyl; 1,2,4-triazin-3,5-diyl; 2H-tetrazol-2,5-

diyl; 1,2,3-thiadiazol-4,5-diyl; 1-alkyl-3-(alkoxycarbonyl)-1H-pyrrol-2,5-diyl wherein alkyl is represented by methyl, ethyl, n-propyl and n-butyl and wherein alkoxy is represented by methoxy, ethoxy, n-propoxy and isopropoxy; 1-alkyl-1H-pyrrol-2,5-diyl wherein alkyl is represented by methyl, ethyl, n-propyl and n-butyl; thiazol-2,4-diyl; 1-H-pyrazol-1,5-diyl; pyrimidin-2,4-diyl; oxazol-2,4-diyl; carbonyl; 1H-imidazol-1,5-diyl; isoxazol-3,5-diyl; furan-2,4-diyl; 3-alkoxycarbonylfuran-2,4-diyl wherein alkoxy is represented by methoxy, ethoxy, n-propoxy, and isopropoxy; benzene-1,3-diyl; and (Z)-1-cyanoethen-1,2-diyl. Suitable groups which are hydrolysable under physiological conditions are well known in the art and include groups that form, with the O atom, an ether, ester, carbonic acid or an ester linkage.

Preferably, P is chosen from 1,3,4-oxadiazol-2,5-diyl and 1,2,4-oxadiazol-3,5-diyl.

The at least one nitrocatechol derivative of formula I is preferably 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide or 5-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol.

The at least one nitrocatechol derivative of formula I may also be a mixture of 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide and 5-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol.

In embodiments where the at least one nitrocatechol derivative is a mixture of two nitrocatechol derivatives, such as 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide and 5-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol, the ratio of the two components may be approximately 50:50 or any variation thereof, such as approximately 60:40, 70:30, 80:20, 90:10, 95:5, 97:3, or 99:1, or the proportion of one of the nitrocatechol derivatives may be present in an amount up to and including 5%, up to an including 3 % or up to and including

1% of the amount of the other nitrocatechol, for example 5-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol may be present in an amount of up to and including 5%, up to and including 3% or up to and including 1% of the amount of 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide.

The at least one API chosen from nitrocatechol derivatives of formula I as disclosed herein, and salts, esters, hydrates, solvates and other derivatives thereof, may exhibit low bulk density, thereby making it difficult to formulate and manufacture a dosage form. For example, 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide, a nitrocatechol of formula I, exhibits a bulk density of less than 0.1 g/ml prior to granulation and/or formulation, and 5-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol may exhibit a bulk density of around 0.2 g/ml prior to granulation and/or formulation, as determined by the method described hereinbelow.

Formulating APIs of low bulk density can often give rise to many problems. For example poor content uniformity, particle segregation, little or no flowability, high average weight variability, capping and lamination of tablets and high friability of tablets.

In at least one exemplary embodiment, the amount (or dosage) of the at least one API present in the compositions and/or formulations is preferably a therapeutically effective amount. As used herein, "therapeutically effective amount" means an amount of a therapeutic agent sufficient to treat, alleviate, and/or prevent any condition treatable and/or preventable by administration of a composition of the disclosure, in any degree. That amount can, for example, be an amount sufficient to exhibit a detectable therapeutic or preventative or ameliorative effect. The effect may include, for example, treatment, alleviation, and/or prevention of the conditions listed herein. The actual amount required, e.g. for treatment of any particular patient, will depend upon a variety of factors including

the disorder being treated and/or prevented; its severity; the specific pharmaceutical composition employed; the age, body weight, general health, gender, and diet of the patient; the mode of administration; the time of administration; the route of administration; the rate of excretion of the therapeutic agent; the duration of the treatment; any drugs used in combination or coincidental with the therapeutic agent; and other such factors well known to those skilled in the art. In various embodiments, for example, a formulation, i.e, a capsule or tablet dosage form, may contain 1 mg or more of API, for example 2.5 mg or more, 5 mg or more, 10 mg or more, 20 mg or more, 40 mg or more, 50 mg or more, or 100 mg or more of API. The API content in the formulation can vary from 0.02 wt% to 90 wt%, for example from 0.1 wt% to 70 wt%, from 0.2 wt% to 50 wt%, or from 0.3 wt% to 45 wt%.

The at least one filler of the present disclosure includes calcium carbonate, cellulose powder, silicified microcrystalline cellulose, cellulose acetate, compressible sugar, confectioner's sugar, dextrane, dextrin, dextrose, fructose, kaolin, lactitol, lactose, magnesium carbonate, magnesium oxide, maltodextrin, maltose, mannitol, microcrystalline cellulose, polydextrose, simethicone, sodium alginate, sodium chloride, sorbitol, starches, pregelatinized starch, sucrose, trehalose, and xylitol.

Preferably, the at least one filler is not a phosphate derivative. As used herein, the term "phosphate derivative," and variations thereof, is intended to mean substances comprising calcium phosphate, including, but not limited to: calcium phosphate, dibasic anhydrous (for example, A-TAB ™, Di-Cafos A-N ™, Emcompress ™ Anhydrous, and Fujicalin ™); calcium phosphate, dibasic dihydrate (for example, Cafos ™, Calipharm ™, Calstar ™, Di-Cafos ™, Emcompress ™); and calcium phosphate tribasic (for example, Tri-Cafos ™, TRI-CAL ™ WG, TRI-TAB ™). In a further embodiment, the at least one filler may be chosen from starches, lactose, and cellulose. In at least one embodiment, at least two fillers may be present, for example a combination of starch, lactose, and/or cellulose.

In various embodiments, for example, the at least one filler may constitute 0.5 wt% to 99.5 wt% of the composition and/or formulation, for example, 20 wt% to 95 wt%, 40 wt % to 95 wt%, 40 wt % to 85 wt%, 40 wt % to 70 wt%, 60 wt% to 95 wt%, or 80 wt% to 95 wt% of the total weight of the composition and/or formulation. The filler may be intragranular, extragranular or part intragranular and part extragranular. By way of example, a composition and/or formulation may comprise 85 wt% filler. The amount of the at least one filler will vary depending, in part, upon the desired dosage, bulk density, and stability of the composition and/or formulation.

The at least one binder of the present disclosure may be selected from acacia, alginic acid, carbomer, carboxymethylcellulose sodium, ceratonia, cottonseed oil, dextrin, dextrose, gelatin, guar gum, hydrogenated vegetable oil type I, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, hypromellose, magnesium aluminium silicate, maltodextrin, maltose, methylcellulose, ethylcellulose, microcrystalline cellulose, polydextrose, polyethylene oxide, polymethacrylates, sodium alginate, starch, pregelatinised starch, stearic acid, sucrose and zein.

In various embodiments of the present disclosure, the at least one binder is not a PVP derivative compound. As used herein, the term "PVP derivative compound" and variations thereof, is intended to mean substances comprising polyvinyl pyrrolidone (PVP) and substituted versions thereof, including, but not limited to: povidone (for example, plasdone and kollidon); copovidone (for example, plasdone S-630 ™ and kollidon VA-64 ™); and cross-linked PVP (for example crospovidone). In a further embodiment, the at least one binder may be chosen from starches, and in at least one embodiment, it may be starch 1500™.

In various embodiments, the at least one binder may constitute 0.5 wt% to 40 wt% of

the composition and/or formulation, for example, 1 wt% to 25 wt%, 5 wt% to 20 wt%, 8 wt % to 15 wt%, or 10 wt% to 15 wt% of the total weight of the composition and/or formulation. The binder may be intragranular, extragranular or part intragranular and part extragranular. By way of example only, a composition and/or formulation may comprise between 6 wt% and 8 wt% binder, such as 7 wt% or 6.3 wt% binder. The amount of the at least one binder will vary depending, in part, upon the desired dosage, bulk density, and stability of the resulting composition and/or formulation.

In one exemplary embodiment, the composition and/or formulation comprises 0.2 to 50 wt% API, 5 to 10 wt% binder, and 33 to 85 wt% filler, such as the following compositions and/or formulations:

API	0.2 – 50 wt%
Filler	35.0 - 85.0 wt%
Binder	1.0 - 15.0 wt%
Lubricants	1.0 - 15.0 wt%
Disintegrant	1.0 - 15.0 wt %

API	30.0-50.0 wt%
Filler	35.0-60.0 wt%
Binder	3.0-10.0 wt%
Lubricants	1.0-10.0 wt%
Disintegrant	3.0-10.0 wt%

API	0.2 – 35 wt%
Filler	50.0-85.0 wt%
Binder	3.0-10.0 wt%
Lubricants	1.0 – 10.0 wt%
Disintegrant	3.0-10.0 wt%

The invention also relates to formulations comprising a composition of the invention. Such formulations may be in the form of a dosage form such as a capsule or a compressed form such as a tablet.

The invention also includes a method of making a composition or formulation of the invention comprising the steps of:

- granulating at least one active pharmaceutical ingredient chosen from 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide and 5-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol and salts thereof to form granules;
- mixing at least one filler with the at least one active pharmaceutical ingredient before, during or after granulation;
- mixing at least one binder with the at least one active pharmaceutical ingredient before, during or after granulation; and
- preparing a pharmaceutical formulation in the form of a dosage form.

Preferably the filler is not a phosphate derivative. Preferably, the binder is not a polyvinylpyrrolidone ("PVP") derivative compound.

The at least one API, at least one filler, and at least one binder may be combined by mixing (also referred to herein as blending). The appropriate apparatus and mixing time and rate may easily be determined by those of skill in the art based on, for example, the amount of material present, the type of mixing process used, and other parameters known to those of skill in the art. For example, in various embodiments, the components may be mixed manually, using a V-blender, a high shear mixer, or any other mixing apparatus and/or process known to those of skill in the art. As a further example, the components may be mixed for any appropriate period of time, such as 1 to 20 minutes or 2 to 10 minutes.

In various exemplary embodiments, the mixture may be dry or wet granulated. Preferably, the granules are wet-granulated using at least one granulation liquid. By way of example, the at least one granulation liquid may be chosen from water, ethanol, isopropanol, and/or acetone. The granulation liquid is preferably water. The appropriate apparatus and mixing time and rate for granulation may be determined by those of skill in the art based on, for example, the amount of material and the amount of granulation liquid, if present. For example, in various embodiments, the components may be granulated manually, using a high shear mixer, planetary mixer or any other granulator apparatus and/or process known to those of skill in the art. As a further example, in various embodiments, the components may be granulated for any appropriate period of time, such as 1 to 60 minutes or 2 to 30 minutes. Determination of the endpoint of granulation is within the capability of the skilled person but can be determined by observance of stabilization of granule size and particle cohesion resulting in a decrease in air trapped inside the granule, or by attainment of steady state of rheological or correlated determination of voltage, conductivity torque, power consumption or near IR techniques. Granulation speeds may vary from 5% to 100% of the granulator mixing speed, such as from 25% to 100%.

After the wet-granulation process is complete, the granules may then be dried. Granules may be dried to loss on drying (LOD) values below 6%, preferably below 5% and even more preferably between 1-3%. A suitable method for calculating LOD is described hereinbelow. The appropriate drying apparatus and drying time and temperature may be determined by those of skill in the art based on, for example, the amount of material present, moisture content of the material, and the granulation liquid. As non-limiting examples, a fluid bed dryer or tray dryer may be used, for example at a temperature of 25°C or higher, 40°C or higher, or 70°C or higher, to dry the granules. For example, the granules may be dried at a temperature of 66°C.

The granules may be sieved. Sieving the granules separates out granules of a

particular particle size, and may be used to select particles of an advantageous size for formulating a dosage form or manufacturing a dosage form. In various embodiments, the granules may be sieved over a screen or sieve of 0.5 mm or larger, for example a 0.6 mm, 0.8 mm, 1.0 mm and 1.6 mm screen.

The composition may further include at least one additional excipient which may be blended with the at least one API, at least one filler and at least one binder before, during or after granulation. For example, in at least one embodiment, the at least one additional excipient may be chosen from excipients such as disintegrants, glidants, and lubricants.

Suitable disintegrants of the present disclosure include agar, calcium carbonate, alginic acid, calcium phosphate (tribasic), carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, docusate sodium, guar gum, low substituted hydroxypropyl cellulose, magnesium aluminium silicate, methylcellulose, microcrystalline cellulose, sodium alginate, sodium starch glycolate, polacrilin potassium, silicified microcrystalline cellulose, starch and pre- gelatinized starch, and mixtures thereof. The disintegrant may be a combination of disintegrants and/or at least two disintegrants are present, for example a combination of sodium starch glycolate and sodium carboxymethyl starch, such as that sold under the trade name Explotab™.

The disintegrant may constitute 0.5 wt% to 40 wt% of the composition and/or formulation, for example, 1 wt% to 25 wt%, 5 wt% to 20 wt%, 10 wt % to 15 wt%, or 5 wt% to 15 wt%. By way of example, a composition and/or formulation may comprise between 6 wt% and 9 wt% disintegrant, such as 6.8 wt% disintegrant. The amount of the at least one disintegrant will vary depending, in part, upon the desired dosage, bulk density, and stability of the resulting composition and/or formulation.

Suitable glidants of the present disclosure include calcium silicate, cellulose,

powdered, colloidal silicon dioxide, magnesium silicate, magnesium trisilicate, starch, and talc, and mixtures thereof.

The glidant may constitute 0.1 wt% to 15 wt% of the composition and/or formulation, for example, 0.5 wt% to 15 wt%, 1 wt % to 10 wt%, or 2 wt% to 6 wt%. The amount of glidant will vary depending, in part, upon the desired dosage, bulk density, and stability of the resulting composition and/or formulation.

Lubricants of the present disclosure include calcium stearate, glycerine monostearate, glyceryl behenate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil type I, magnesium lauryl sulphate, magnesium stearate, medium-chain triglycerides, poloxamer, polyethylene glycol, sodium benzoate, sodium chloride, sodium lauryl sulphate, sodium stearyl fumarate, stearic acid, talc, sucrose stearate, and zinc stearate, and mixtures thereof.

Lubricants may constitute 0.1 wt% to 15 wt% of the composition and/or formulation, for example, 0.5 wt% to 15 wt%, 1 wt % to 10 wt%, 1 wt % to 2 wt%, or 2 wt% to 8 wt%. The amount of lubricant will vary depending, in part, upon the desired dosage, bulk density, and stability of the resulting composition and/or formulation.

The at least one excipient may be added before, during or after mixing of the at least one API and before (prior to) or during granulation and, thus may be an intragranular excipient. Alternatively, the at least one excipient may be added to the composition after granulation, for example by blending with the granules, and thus may be present as an extragranular excipient. In various embodiments, at least one first excipient may be added prior to or during granulation and at least one second excipient and/or more of the at least one first excipient may be added to the composition after granulation. For example, disintegrants may be added prior to or during granulation, whereas lubricants and glidants may be added after granulation.

The composition comprising at least one API, at least one filler, and at least one binder may be used to make a formulation, such as, for example, to fill capsules or to form tablets.

Capsules for use in the present disclosure include, but are not limited to, gelatin capsules and hydroxypropylmethyl cellulose (hypromellose) capsules. Suitable methods for filling such capsules with a composition according to an embodiment of the disclosure are well-known to those of skill in the art.

Tablets of the present disclosure may be formed by any method known to those of skill in the art such as compression. In at least one embodiment of the present disclosure, the tablets may be coated, for example with aqueous based film-coatings, solvent based film-coatings and/or sugar coatings.

The formulations of the invention may also be coloured, for example by inclusion of a colouring in the composition of the invention and/or by coating the composition and/or formulation.

In at least one embodiment of the present disclosure, the formulation is a capsule comprising at least one API, at least one filler, and at least one binder, optionally in granular form, and may further comprise at least one glidant and/or at least one disintegrant. In at least one embodiment of the present disclosure, the formulation is a tablet comprising at least one API, at least one filler, and at least one binder, optionally in granular form, and may further comprise at least one glidant, at least one lubricant, and/or at least one disintegrant.

The compositions may exhibit improved bulk density and/or flow properties relative to those of the API alone. As used herein, the terms "improved bulk density," "significantly improved bulk density," and variations thereof mean that the bulk density of

the composition is approximately at least double, least three times, at least four times, or at least five times that of the API alone. It is within the ability of one of skill in the art to determine the bulk density of a compound or composition using methods generally accepted in the art. However, suitable methods include, for example, the European Pharmacopeia edition 6, Test 2.9.15 "apparent volume," pages 285-286, EDQM, 2007, and USP 31, vol. 1, test <616> page 231-232, The United States Pharmacopeia Convention, 2008. A suitable method is described below:

Apparatus:

- settling apparatus capable of producing in 1 minute 250 $\pm$ 15 taps from a height of 3 $\pm$ 0.2 mm. The support for the graduated cylinder with its holder, has a mass of 450 $\pm$ 5 g
- a 250 ml graduated cylinder (2 ml intervals) with a mass of 220 $\pm$ 40 g

Method: Into a dry cylinder, introduce without compacting, 100.0 g (*m* g) of the test substance. Secure the cylinder in its holder. Read the unsettled apparent volume (V_0) to the nearest milliliter. Carry out 10, 500 and 1250 taps and read the corresponding volumes V_{10}, V_{500}, V_{1250}, to the nearest milliliter. If the difference between V_{500} and V_{1250} is greater than 2 ml, carry out another 1250 taps.

Alternatively, if it is not possible to select 100.0 g, select a test sample of any mass but with a volume between 50 ml and 250 ml, measure its apparent volume, V_0 as described above, and weigh the sample and specify the mass in the expression of results. Bulk/apparent density may then be determined in g/ml using the following formula:

$$m/V_0$$

where *m* is the mass in grams and V_0 the unsettled apparent volume.

Tapped apparent density may then be determined in g/ml using the following formula:

$$M/V_{1250}$$

where m is the mass in grams and V_{1250} the apparent volume after 1250 hubs.

For example, as set forth above, 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide, a nitrocatecol of formula I, exhibits a bulk density of less than 0.1 g/ml prior to granulating. Compositions according to the present disclosure comprising 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide exhibit bulk densities of 0.2 g/ml or greater, for example 0.4 g/ml or greater, or 0.5 g/ml or greater. Compositions of the present disclosure for use as final blends for capsule filling or tabletting comprising 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide may also exhibit bulk densities of 0.2 g/ml or greater, for example 0.4 g/ml or greater, 0.5 g/ml or greater, and 0.6 /ml or greater.

In certain embodiments of the disclosure, compressed formulations of the disclosure, such as tablets, exhibit apparent density of 0.5 g/mL to 1.5 g/mL, such as 0.6 g/mL to 1.4 g/mL, 0.7 g/mL to 1.3 g/mL, or 0.8 g/mL to 1.2 g/mL.

The apparent density of a compressed formulation is measured in terms of mass and volume of the formulation and is well within the capabilities of the skilled person.

It is also within the ability of one of skill in the art to determine the flowability/flow rate of a compound or composition using methods generally accepted in the art. However, suitable methods include, for example, testing the flow rate through an orifice described in

USP 31, vol. 1, test <1174>, The United States Pharmacopeia Convention, 2008. The flowability may be measured as the mass per time flowing through the 10 mm diameter opening of a glass funnel. A flow rate of value greater than 10 g/second is considered good whereas a value of less than 10 g/second is considered poor.

The compressibility index and Hausner ratio are also suitable methods to assess the compound or compositions. For example, the compressibility index and Hausner ratio may be assessed using USP 31, vol. 1, test <1174>, The United States Pharmacopeia Convention, 2008, and measuring both the bulk volume (V_0) and the tapped volume (V_f) of the granules. The compressibility index (CI) may then be calculated using the following formula:

$$CI\ (\%) = 100 \times [(V_0 - V_f)/V_0]$$

The Hausner ratio (HR) can be calculated by using the following formula:

$$HR = V_0/V_f$$

A compressibility index is considered good when a value of less than 15% is calculated. A Hausner ratio value (a measure of flowability) is considered good when a value of less than 1.25 is calculated.

The compositions and/or formulations are stable and/or exhibit enhanced stability over other compositions and/or formulations. As used herein, the terms "stability," "stable," and variations thereof, is intended to mean that less than 15 wt% of the at least one API in the composition and/or formulation decomposes over 6 months at test conditions of 40°C and 75% relative humidity, or over 3 years at test conditions of 25°C or 30°C and 60% relative humidity or over 15-30 days at test conditions of 70°C and uncontrolled humidity. In various embodiments, for example, less than 10 wt%, less than 8 wt%, less

than 6 wt%, less than 5 wt%, less than 4 wt%, less than 3 wt%, less than 2 wt%, or less than 1 wt% of the at least one API may decompose under these conditions. It is within the ability of one of skill in the art to determine the stability of a compound, composition, or formulation using methods generally accepted in the art. For example, the amount of the at least one API may be measured by any suitable method, e.g., HPLC. For example, in various embodiments, the assay (i.e. the amount of API) of a stable composition or formulation may indicate 85-115% of API after testing conditions, such as 95-105% of API.

Decomposition is a chemical process made up of at least one reaction, such as oxidation, reduction or hydrolysis, that results in a chemical change in the decomposing substance resulting in the generation of one or more new chemical compounds. These new compounds (or impurities) may result in reduced and/or variable amount of the API in a given composition and/or formulation, reducing its efficacy, and may have unwanted and/or harmful side effects on the patients. As used herein the term "impurity" means any such new compound that is present in the composition and/or formulation in an amount less than 10 wt% of the API, for example less than 5 wt%, less than 3 wt%, less than 1wt %, or less than 0.5 wt% of the API. Thus, the change in total impurities in the composition and/or formulation under the conditions and time periods set forth herein may also be indicative of a stable composition or formulation and may be measures by a suitable method, e.g., HPLC. In various embodiments, for example, the total impurities relative to the API in a stable composition and/or formulation after testing conditions may increase by less than 5 wt%, less than 2 wt%, less than 1 wt% or less than 0.5 wt%,

Stability may also be tested under the influence of a variety of other test conditions, including, for example:

- 40°C at 75% relative humidity for 6 months;
- 25°C or 30°C at 60% relative humidity after 3-5 years (long-term conditions); and
- 70°C at uncontrolled humidity after 15-30 days (stress conditions).

Stability may also be determined by appearance. As used herein, the term "visual stability," and variations thereof, is intended to mean insubstantial changes in the color, integrity of a compressed formulation (for example, not breaking up), shape, and/or size of the granules, composition and/or formulation.

As used herein, the term "enhanced stability," "improved stability" and variations thereof, means that the amount of decomposition of the at least one API in a given composition and/or formulation, and/or the increase in impurities in a given composition and/or formulation is less than that of a comparative composition and/or formulation that has been subject to the test conditions.

Unless otherwise indicated, all numbers used in the specification and claims are to be understood as being modified in all instances by the term "about," whether or not so stated. It should also be understood that the precise numerical values used in the specification and claims form additional embodiments of the disclosure. Efforts have been made to ensure the accuracy of the numerical values disclosed in the Examples. Any measured numerical value, however, can inherently contain certain errors resulting from the standard deviation found in its respective measuring technique.

As used herein the use of "the," "a," or "an" means "at least one," and should not be limited to "only one" unless explicitly indicated to the contrary. Thus, for example, the use of "the formulation" or "a formulation" is intended to mean at least one formulation.

Other embodiments of the disclosure will be apparent to those skilled in the art from consideration of the specification and practice of the present disclosure. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the claims.

EXAMPLES

The following examples are not intended to be limiting of the invention as claimed.

Example 1

Four low dosage capsules were made on a pilot batch scale by first mixing the API, starches, and lactose in the amounts set forth in Table 1 below (batches A-D). The API used in these examples was 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide. Purified water was then added to each mixture, and the mixtures were granulated by mixing.

The granules were then dried using a fluid bed dryer until a loss on drying value of the granule was below 6%. The dried granules were sieved and then blended with the remaining ingredients set forth in Table 1. Gelatin capsules were filled with the formulation using an InCAP HS capsule filling machine.

The granules and final compositions were evaluated for bulk and tapped density using the methods described above. Flowability/flow rate was also assessed by testing the flow rate through an orifice described in USP 31, vol. 1, test <1174>, The United States Pharmacopeia Convention, 2008. The flowability was measured as the mass per time flowing through the 10 mm diameter opening of a glass funnel. A flow rate of value greater than 10 g/second is considered good whereas a value of less than 10 g/second is considered poor.

The compressibility index and Hausner ratio were assessed using USP 31, vol. 1, test <1174>, The United States Pharmacopeia Convention, 2008, and measuring both the bulk volume (V_o) and the tapped volume (V_f) of the granules. The compressibility index (CI) was then calculated using the following formula:

$$CI\ (\%) = 100 \times [(V_0 - V_f)/V_0]$$

The Hausner ratio (HR) can be calculated by using the following formula:

$$HR = V_0/V_f$$

A compressibility index is considered good when a value of less than 15% is calculated. A Hausner ratio value (a measure of flowability) is considered good when a value of less than 1.25 is calculated.

Moisture or dryness was determined by loss on drying as described in USP 31, vol. 1, test <731>, The United States Pharmacopeia Convention, 2008. The test involves accurately weighing the substance to be tested (m_0), (e.g. using a sample amount of 1 to 2 g). The test specimen is then dried at 105°C until a constant weight (m_f) is achieved. The moisture can be calculated by using the following expression:

$$LOD\ (\%) = [(m_0 - m_f)/m_0] * 100$$

Capsules were evaluated for uniformity of mass and impurities. Uniformity of mass was assessed by the individual weight of 20 capsules; average mass and standard deviation were then calculated. Amount of total impurities was obtained using HPLC method with a limit of quantification of below 0.05%.

The results are set forth in Table 2 below. All batches presented good granule and capsule properties.

Example 2

Four high dosage capsules were made on a laboratory scale by first mixing the API, starches, and lactose in the amounts set forth in Table 1 below (batches E-H) in a V-blender. The API used in these examples was 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide. Purified water was added to each mixture and mixed manually. The wet mass thus obtained was then granulated in an oscillation granulator laboratory.

The granules were then dried in a tray dryer until a loss on drying of the granule was below 6%. The dried granules were sieved. The granules were then blended with the remaining ingredients set forth in Table 1 in a V- blender. Gelatin capsules were filled with the formulation using an InCAP HS capsule filling machine.

Each of Batch E-H was evaluated as set forth in Example 1 above and the results are set forth in Table 3 below. All batches presented good granule and capsule properties.

Table 1: Batch Formulations

Ingredient (%/capsule)	BATCH							
	A	B	C	D	E	F	G	H
API 9-1067	0.4	0.4	0.4	0.4	40	40	40	40
Maize starch	0	82.0	40.8	26.0	0	42.4	21.2	14.0
Lactose 200	82.0	0	41.2	56.0	42.4	0	21.2	28.4
Starch 1500™	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8
Explotab™	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8
Purified water	q.ad	q.ad	q.ad	q.ad	q.ad	q.ad	q.ad	q.ad
Silica colloidal hydrated (Syloid™)	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Talc	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
capsule size 1	1 un	1 un	1 un	1 un	1 un	1 un	1 un	1 un

Table 2: Analytical Results for Batches A-D

BATCH	**A**	**B**	**C**	**D**
Granule results				
Bulk density (g/ml)	0.62	0.59	0.60	0.64
Tapped density 1250 (g/ml)	0.75	0.73	0.70	0.74
Compressibility index	Good	Good	Good	Good
Hausner ratio	Good	Good	Good	Good
Flow rate	Good	Good	Good	Good

Capsule results				
Uniformity mass (RSD %)	2.39	1.77	1.26	1.14
Impurities (%)	3.34	3.30	3.23	3.38

Table 3: Analytical Results for Batches E-H

BATCH	E	F	G	H
Granule results				
Bulk density (g/ml)	0.60	0.57	0.55	0.56
Tapped density 1250 (g/ml)	0.68	0.62	0.60	0.64
Compressibility index	Good	Good	Good	Good
Hausner Ratio	Good	Good	Good	Good
Flow rate	Good	Poor	Poor	Poor
Capsule results				
Uniformity mass (RSD %)	2.86	2.34	2.08	2.89
Impurities (%)	2.95	3.07	2.98	2.97

Example 3

All batches from Examples 1 and 2 were put on stress studies to determine their stability. Each of the eight batches was stored for 15 days at room temperature as well as under stress conditions (70°C without relative humidity control). All batches were tested for impurities content for both storage conditions, the results of which are set forth in Tables 4 and 5. Impurities values were obtained using HPLC method with a limit of quantification of below 0.05%.

API used in these batches contained around 3% of impurities prior to formulation (composed of impurity 8).

Table 4: Results from Stability Testing on Batches A-D

	A		B		C		D	
Dosage	Low		Low		Low		Low	
Storage	RT	SC	RT	SC	RT	SC	RT	SC
Total Impurities (%)	**3.34**	**3.89**	**3.30**	**5.04**	**3.23**	**5.36**	**3.39**	**4.03**
Impurity 8	3.34	3.03	3.30	2.90	3.23	3.29	3.39	3.17
Impurity 1	< 0.05	0.76	< 0.05	1.37	NP	1.38	NP	0.68
Impurity 2	NP	0.06	NP	0.05	NP	0.19	NP	0.11
Impurity 3	NP	NP	NP	0.07	NP	0.14	NP	NP
Impurity 4	NP	NP	NP	0.20	NP	0.10	<0.05	<0.05
Impurity 5	NP	NP	NP	0.18	NP	0.15	NP	NP
Impurity 6	NP	0.07	NP	0.14	NP	0.14	NP	0.07
Impurity 7	NP	< 0.05	NP	0.12	NP	0.13	NP	NP

RT - room temperature

SC - Stress conditions

NP- not present (below detection limit)

Table 5: Results from Stability Testing on Batches E-H

	E		F		G		H	
Dosage	High		High		High		High	
Storage	RT	SC	RT	SC	RT	SC	RT	SC
Total Impurities (%)	**2.96**	**2.86**	**3.07**	**3.03**	**2.98**	**2.78**	**2.97**	**2.78**
Impurity 8	2.96	2.78	3.07	2.94	2.98	2.71	2.97	2.75
Impurity 1	0.06	0.08	NP	0.10	NP	0.07	NP	0.06
Impurity 2	NP	<0.05	NP	< 0.05	NP	NP	NP	NP
Impurity 3	NP	NP	NP	NP	NP	NP	NP	NP
Impurity 4	<0.05	<0.05	<0.05	<0.05	NP	NP	NP	NP
Impurity 5	NP	NP	NP	NP	NP	NP	NP	NP
Impurity 6	NP	NP	NP	NP	NP	NP	NP	NP
Impurity 7	NP	NP	NP	NP	NP	NP	NP	NP

RT - room temperature

SC - Stress conditions

NP- not present (below detection limit)

Example 4

Batch E from Example 2 was put on long term stability studies to determine its stability. In one study, the batch was stored for 6 months at 25°C and 60% relative humidity, and in a second study, the batch was stored for 6 months at 40°C and 75% relative humidity. After each test, the batch was tested for assay and impurities content, the results of which are set forth in Table 6. Assay and impurities values were obtained using HPLC method with a limit of quantification of below 0.05%.

Table 6: Stability Data for Batch E

Batch	E		
Time	0	6 months	6 months
Storage		25°C / 60% RH	40°C / 75% RH
Assay (%)	96	99	98
Change in Total Impurities Content(%)	<0.05	<0.05	<0.05

Comparative Example

Three intermediate dosage capsules were made by first mixing the API, the filler(s) the binder and the disintegrant (smaller portion in comparative example and the total amount in batches I and J) in the amounts set forth in Table 7 below for 3 minutes in a high shear mixer. The API used in these examples was 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide. Purified water was added to each mixture over a 3 minute period, and the mixtures were granulated by mixing for an additional 3 minutes.

The granules were then dried in a fluid bed dryer until a loss on drying value of the granule was below 6%. The dried granules were sieved and then blended with the remaining ingredients set forth in Table 7 in a biconic blender. Gelatin capsules were filled with the formulation using an InCAP HS capsule filling machine.

Table 7: Formulations for Comparative Example 1

BATCH	Comp.	I	J
Ingredient (%/capsule)			
API	2	2	2
Di-Calcium-Phosphate (filler)	33		
Lactose(filler)		80	54
Microcrystalline Cellulose(filler)	46		
Croscarmellose-Sodium (disintegrant)	2		
Maize starch (filler)			27
Povidone (binder)	7		
Purified Water	q.s.	q.ad	q. ad
Modified starch (Binder)		7	7
Sodium amidoglycolate (Disintegrant)		7	7
Croscarmellose-Sodium (disintegrant)	4		
Silica Colloidal Hydrate (lubricant)	4	2	2
Talc (lubricant)	2	2	2
Magnesium-Stearate (lubricant)	2		

The granules and capsules were evaluated and results are shown in Table 8 below. After two stability studies, one under 25°C and 60% RH and the other under 40°C and 75% RH for 6 months each, it was observed that batches I and J exhibit enhanced stability when

compared with the comparative composition.

Table 8: Stability of Formulae after 6 Months at 40°C at 75% RH

Batch	Comparative (Comp.)			I			J		
Time (months)	0	6	6	0	6	6	0	6	6
Storage		25°C / 60% RH	40°C / 75% RH		25°C / 60% RH	40°C / 75% RH		25°C / 60% RH	40°C / 75% RH
Assay (%)	99	99	92	98	100	102	97	98	100
Change in Total Impurities Content		0.07	2.34		None detected	0.15		None detected	0.15

CLAIMS:

1. A stable composition comprising:

at least one active pharmaceutical ingredient (API) which is 2,5-dichloro-3-(5-(3,4-dihydroxy-5-nitrophenyl)-l,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide, or a salt, an ester, a hydrate, or a solvate thereof; and

at least one component which is a filler, wherein the filler is not a phosphate derivative, or a binder, wherein the binder is not a polyvinylpyrrolidone derivative;

wherein the at least one active pharmaceutical ingredient is present in the form of granules, and

wherein the composition has a bulk density of greater than 0.2 g/mL.

2. The stable composition of claim 1, wherein the at least one API further comprises 5-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-[1,2,4]oxadiazol-5-yl]-3-nitrobenzene-1,2-diol.

3. The stable composition of claim 1 or 2, wherein less than 10% of the API decomposes over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

4. The stable composition of claim 3, wherein less than 5% of the API decomposes over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

5. The stable composition of claim 4, wherein less than 3% of the API decomposes over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

6. The stable composition of claim 5, wherein less than 1% of the API decomposes over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

7. The stable composition of any one of claims 1 to 6, wherein the increase in total impurities is less than 5% over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

8. The stable composition of claim 7, wherein the increase in total impurities is less than 2% over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

9. The stable composition of claim 8, wherein the increase in total impurities is less than 1% over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

10. The stable composition of claim 9, wherein the increase in total impurities is less than 0.5% over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

11. The stable composition of any one of claims 1 to 10, wherein the at least one component comprises at least one filler which is lactose, maize starch or microcrystalline cellulose.

12. The stable composition of any one of claims 1 to 11, wherein the at least one component comprises at least one binder which is hypromellose, hydroxypropyl cellulose, methyl- or ethyl-cellulose, pregelatinized maize starch or gelatin.

13. The stable composition of any one of claims 1 to 12, wherein the at least one filler or at least one binder is intragranular, extragranular or both.

14. The stable composition of any one of claims 1 to 13, further comprising at least one additional excipient which is a disintegrant, a glidant, or a lubricant.

15. The stable composition of claim 14, wherein the lubricant is selected from calcium stearate, glycerine monostearate, glyceryl behenate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil type I, magnesium lauryl slphate., magnesium stearate, medium-chain triglycerides, sodium lauryl sulphate, sodium stearyl fumarate, stearic acid and zinc stearate.

16. The stable composition of claim 15, wherein the lubricant is magnesium stearate.

17. The stable composition of claim 1, wherein the composition exhibits a bulk density of greater than 0.3 g/mL.

18. The stable composition of claim 17, wherein the composition exhibits a bulk density of greater than 0.5 g/mL.

19. The stable composition of claim 18, wherein the composition exhibits a bulk density of greater than 0.6 g/mL.

20. The pharmaceutical composition of any one of claims 1 to 19, wherein the active pharmaceutical ingredient is present in a therapeutically effective amount.

21. The pharmaceutical composition of any one of claims 1 to 20, wherein the composition comprises an additional API.

22. A pharmaceutical formulation comprising the stable composition of any one of claims 1 to 21.

23. The pharmaceutical formulation of claim 22, wherein the formulation is in the dosage form of a tablet or capsule.

24. The pharmaceutical formulation of claims 22 or 23, wherein the pharmaceutical formulation is stable.

25. The pharmaceutical formulation of any one of claims 22 to 24, further comprising L-DOPA and/or a peripheral AADC inhibitor.

26. A pharmaceutical formulation according to claim 25, wherein the peripheral AADC inhibitor is carbidopa or benserazide.

27. A method of manufacturing a stable pharmaceutical formulation, said method comprising:

granulating at least one active pharmaceutical ingredient (API) which is 2,5 dichloro-3-(5-(3;4-dihydroxy-5-nitrophenyl)-1,2,4-oxadiazol-3-yl)-4,6-dimethylpyridine 1-oxide or a salt thereof to form granules;

mixing at least one component which is a filler or a binder with the at least one active pharmaceutical ingredient before, during or after granulation to form a composition;

wherein the filler is not a phosphate derivative; or the binder is not a polyvinylpyrrolidone derivative; and

preparing a pharmaceutical formulation in the form of a dosage form,

wherein the granules and/or composition has a bulk density of greater than 0.2 g/mL.

28. The method of claim 27, wherein the at least one API further comprises 5-[3-(2,5-dichloro-4,6-dimethylpyridin-3-yl)-[l,2,4]oxadiazol-5-yl]-3- nitrobenzene-l,2-diol.

29. The method of claim 27 or 28, wherein the at least one filler is lactose, maize starch or microcrystalline cellulose.

30. The method of any one of claims 27 to 29, wherein the at least one binder is hypromellose, hydroxypropyl cellulose, methyl- or ethyl-cellulose, pregelatinized maize starch or gelatin.

31. The method of any one of claims 27 to 30, wherein in the pharmaceutical formulation obtained, less than 10% of the API in the dosage form decomposes over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

32. The method of claim 31, wherein in the pharmaceutical formulation obtained, less than 5% of the API in the dosage form decomposes over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

33. The method of claim 32, wherein in the pharmaceutical formulation obtained, less than 3% of the API in the dosage form decomposes over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

34. The method of claim 33, wherein in the pharmaceutical formulation obtained, less than 1% of the API in the dosage form decomposes over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

35. The method of any one of claims 27 to 34, wherein in the pharmaceutical formulation obtained, the increase in total impurities is less than 5% over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

36. The method of claim 35, wherein in the pharmaceutical formulation obtained, the increase in total impurities is less than 2% over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

37. The method of claim 36, wherein in the pharmaceutical formulation obtained, the increase in total impurities is less than 1% over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

38. The method of claim 37, wherein in the pharmaceutical formulation obtained, the increase in total impurities is less than 0.5% over 15 days of storage at 70°C and uncontrolled humidity, over 6 months at 40°C and 75% relative humidity, and/or over 3 years at 60% relative humidity and 30°C or 25°C.

39. The method of any one of claims 27 to 38, wherein the granulation is conducted in a high shear mixer or in a fluid bed dryer.

40. The method of any one of claims 27 to 39, wherein the granulation occurs by a wet granulation process.

41. The method of claim 40, further comprising drying the granules.

42. The method of claim 41, wherein the drying is conducted on a fluid bed drier or in a tray dryer.

43. The method of any one of claims 27 to 42, further comprising sieving the granules.

44. The method of any one of claims 27 to 43, further comprising adding at least one additional excipient before, during or after granulation.

45. The method of claim 27, wherein the granules and/or composition exhibit a bulk density greater than 0.3 g/mL.

46. The method of claim 45, wherein the granules and/or composition exhibit a bulk density greater than 0.4 g/mL.

47. The method of claim 46, wherein the granules and/or composition exhibit a bulk density greater than 0.5 g/mL.

48. The method of claim 47, wherein the granules and/or composition exhibit a bulk density greater than 0.6 g/mL.

49. The method of any one of claims 27 to 48, wherein the dosage form is a tablet, and the step of preparing the formulation comprises compression.

50. The method of any one of claims 27 to 48, wherein the dosage form is a capsule, and the step of preparing the formulation comprises filling a capsule.