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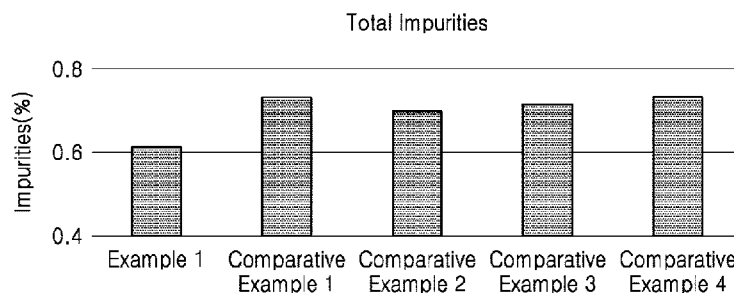
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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING AN AMIDE DERIVATIVE OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF INHIBITING GROWTH OF CANCER CELLS AND A STABILIZER HAVING LOW MELTING POINT



(57) Abstract: The present invention relates to a pharmaceutical composition comprising a thienopyrimidine compound, or a pharmaceutically acceptable salt thereof, or a hydrate of a pharmaceutically acceptable salt thereof and one or more low melting point stabilizer(s) inhibiting generation of impurities, and a pharmaceutical dosage form prepared using and comprising the same.



Description

Title of Invention: PHARMACEUTICAL COMPOSITION COMPRISING AN AMIDE DERIVATIVE OR A PHARMA- CEUTICALLY ACCEPTABLE SALT THEREOF INHIBITING GROWTH OF CANCER CELLS AND A STABILIZER HAVING LOW MELTING POINT

Technical Field

- [1] The present invention relates to a pharmaceutical composition comprising an amide derivative or a pharmaceutically acceptable salt thereof or a hydrate of a pharmaceutically acceptable salt thereof, which effectively inhibits growth of cancer cells, and a stabilizer having a low melting point; and a pharmaceutical dosage form prepared using and comprising the same.

Background Art

- [2] Cells are involved with many signal transduction pathways. Such signal transduction pathways are organically connected to each other, form a complex mechanism and regulate cell proliferation, growth, death and the like (William G. Kaelin *et al.*, *Nature Reviews Cancer*, 2005, 5:689-698). Accordingly, when a regulation function in cells is unbalanced due to genetic or environmental causes, signal transduction is abnormally amplified or destroyed, which may cause diseases such as tumors (Douglas Hanahan *et al.*, *The Hallmarks of Cancer*, 2000, 100:57-70).
- [3] It has been reported that protein tyrosine kinases have an important role in an intracellular signal transduction (Irena Melnikova, *et al.*, *Targeting protein kinases*, 2004, 3:993-994), and abnormal expression or mutations thereof are frequently observed in cancer cells. Protein tyrosine kinases are enzymes that catalyze transfer of phosphate groups from ATP to tyrosine on a protein substrate. Several growth factor receptor proteins perform intracellular signal transduction by such tyrosine kinase activities. An interaction between a growth factor and receptors thereof is essential for normal regulation of cell growth. However, when regulation of signal by the receptor malfunctions due to receptor mutation or overexpression, tumor cells are induced, which may ultimately lead to cancer.
- [4] Several growth factors and receptors thereof are being studied in terms of their roles as protein tyrosine kinases. Among them, research on an epidermal growth factor (EGF) and its receptor (EGFR) tyrosine kinase is being actively conducted (Nancy E. Hynes *et al.*, *Nature Reviews Cancer*, 2005, 5:341-354). The EGFR tyrosine kinase that contains a receptor part and a tyrosine kinase part, is positioned through a cell

membrane, and thus has a role of delivering an extracellular signal into cells.

- [5] Purity of an active substance of a drug is an important factor in providing a safe and effective pharmaceutical formulation. Impurities of drugs can induce various side effects during treatment. Problematic drug impurities include impurities that are not possible to completely remove or that are generated in a process of preparing active substances and/or the final drug formulation/pharmaceutical dosage form and decomposition products during storage that are generated from the final pharmaceutical dosage form due to various environmental factors such as temperature, moisture and light.

Disclosure of Invention

Technical Problem

- [6] An object of the present invention is to provide a pharmaceutical composition allowing for a lower impurity level after manufacturing of the final pharmaceutical dosage form, comprising amide derivatives or pharmaceutically acceptable salts thereof or hydrates of pharmaceutically acceptable salts thereof for inhibiting growth of cancer cells.
- [7] Another object of the present invention is to provide a pharmaceutical dosage form prepared using and comprising the pharmaceutical composition.

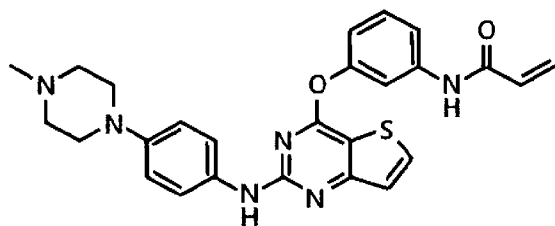
Solution to Problem

- [8] In order to achieve the above objects, the present invention provides a pharmaceutical composition comprising the compound *N* - (3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-*d*]pyrimidine-4-yloxy)phenyl) acrylamide, represented by Formula 1, or a pharmaceutically acceptable salt thereof or a hydrate of a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API); and one or more low melting point stabilizer(s) and, optionally, one or more pharmaceutically acceptable excipient(s).

[9]

[10] [Formula 1]

[11]



- [12] The present invention also provides a pharmaceutical composition comprising a compound represented by Formula 1, or a pharmaceutically acceptable salt thereof, or a hydrate of a pharmaceutically acceptable salt thereof, and one or more low melting point stabilizer(s) for preventing and/or treating cancers, tumors, inflammatory

diseases, autoimmune diseases or immune-mediated diseases.

- [13] In order to achieve the object, the present invention also provides a pharmaceutical dosage form prepared using and comprising the pharmaceutical composition.

Advantageous Effects of Invention

- [14] The pharmaceutical composition of the present invention can provide a lower level of impurities for the active pharmaceutical ingredient generated during the dosage form manufacturing process. A pharmaceutical dosage form prepared using and comprising the same is capable of maintaining quality during long-term storage.

Brief Description of Drawings

- [15] FIG. 1 depicts the results of a stability test comparing the amount of total impurities (in % by weight) produced during manufacturing for the tablet of Example 1 with those of Comparative Examples 1 to 4, which comprise no polyethylene glycol as low melting point stabilizer.
- [16] FIG. 2 depicts the results of a stability test comparing the amount of total impurities (in % by weight) produced during manufacturing for the tablets of Examples 1 and 4 against the formulation of Comparative Example 5, which did not undergo any tableting step.
- [17] FIG. 3 depicts the results of a stability test comparing the amount of total impurities (in % by weight) produced during manufacturing for the tablets of Examples 1 and 5 to 8, all containing polyethylene glycol, but possessing differing tablet hardness.
- [18] FIG. 4 depicts the results of a stability test comparing the amount of total impurities (in % by weight) produced during manufacturing for the tablets of Examples 1 to 3 with Comparative Examples 1 and 10 with differing levels of polyethylene glycol.
- [19] FIG. 5 depicts the results of a stability test comparing the amount of total impurities (in % by weight) produced during manufacturing for the tablet of Examples 1 with those of Examples 9 to 13 in which polyethylene glycol is replaced with other low melting point stabilizers.
- [20] FIG. 6 depicts the results of a stability test comparing the amount of total impurities (in % by weight) produced during manufacturing for the tablet of Example 1 with those of Comparative Examples 6 to 9 in which non-low melting point stabilizer is contained.
- [21] FIG. 7 is the X-ray powder diffraction pattern of solid form **1X** (a dihydrochloride hydrate, preferably monohydrate, of the compound of Formula 1) when irradiated with a Cu-K α light source.
- [22] FIG. 8 is the ^{13}C cross polarization/magic angle spinning total suppression of sidebands solid state nuclear magnetic resonance (CP/MAS TOSS ssNMR) of solid form **1X** (a dihydrochloride hydrate, preferably monohydrate, of the compound of

Formula 1)

Mode for the Invention

[23] The present disclosure will be described with reference to exemplary embodiments.

[24] Unless otherwise defined, all terms including technical and scientific terms used herein have the same meaning as commonly understood within the context by one of ordinary skill in the art to which this invention belongs. However, unless otherwise specified, the term described below will have the meaning indicated below over the entire specification:

[25] As used herein, the term to which this invention belongs. However, unless otherwise specified not explicitly indicated. These terms generally refer to a range of numbers that one of skill in the art would consider equivalent to the recited values (i.e., having the same function or result). In many instances these terms may include numbers that are rounded to the nearest significant figure. Specifically, the term "about" may refer to being within 5% of a particular value or range (*e.g.* range of parts by weight, wt% *etc.*), and preferably within 1% to 2%. For example, "about 10 wt%" refers to 9.5 wt% to 10.5 wt%, and preferably, 9.8 wt% to 10.2 wt%.

[26] Although exemplary methods or materials are listed herein, other similar or equivalent ones are also within the scope of the present invention. All publications disclosed as references herein are incorporated in their entirety by reference.

[27] The inventors have studied to prepare a pharmaceutical composition having improved stability, comprising amide derivatives or pharmaceutically acceptable salts thereof or hydrates of pharmaceutically acceptable salts thereof for inhibiting growth of cancer cells. The inventors have found that use of low melting point stabilizers in the pharmaceutical composition leads to a lower level of certain impurities in the pharmaceutical dosage form comprising them.

[28] In one aspect of the present invention is provided a pharmaceutical composition comprising as the active pharmaceutical ingredient a compound represented by Formula 1 or a pharmaceutically acceptable salt thereof or a hydrate of a pharmaceutically acceptable salt thereof; one or more low melting point stabilizer(s) and, optionally, one or more pharmaceutically acceptable excipient(s).

[29] Characteristics and types of components of the pharmaceutical composition of the present invention will be described below in further detail.

[30]

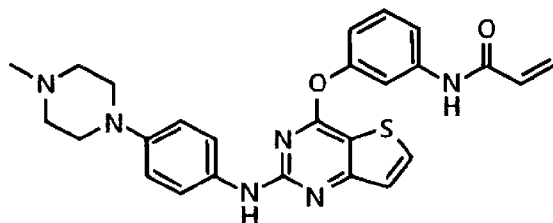
[31] (1) Active pharmaceutical ingredient

[32] In the inventive pharmaceutical composition, a compound represented by the following Formula 1 or a pharmaceutically acceptable salt thereof or a hydrate of a pharmaceutically acceptable salt thereof may be used as the active pharmaceutical in-

gredient (API).

[33] [Formula 1]

[34]



[35] The compound of Formula 1 according to the present invention may be prepared by various methods, for instance, those described in WO 2011/162515.

[36]

[37] In the present invention, the pharmaceutically acceptable salts may be those which can generally be used in the relevant art. For example, salts of inorganic acids such as hydrochloric acid, sulfuric acid, disulfuric acid, nitric acid, phosphoric acid, perchloric acid or bromic acid; salts of organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, succinic acid, benzoic acid, citric acid, maleic acid, malonic acid, malic acid, tartaric acid, gluconic acid, lactic acid, gestisic acid, fumaric acid, lactobionic acid, salicylic acid, phthalic acid, embonic acid, aspartic acid, glutamic acid, camphorsulfonic acid, benzenesulfonic acid, or acetylsalicylic acid (aspirin); and metal salts obtained by a reaction with alkali metals such as calcium, sodium, magnesium, strontium or potassium, may be used, but the present invention is not limited thereto.

[38]

[39] In one embodiment of the present invention, the active pharmaceutical ingredient is a hydrochloride salt of the compound of Formula 1.

[40] In a specific embodiment, the hydrochloride salt of the compound of Formula 1 is amorphous.

[41] In another specific embodiment, the hydrochloride salt of the compound of Formula 1 is crystalline.

[42] In a particular embodiment of the present invention, the crystalline hydrochloride salt is anhydrous.

[43] In another particular embodiment of the present invention, the crystalline hydrochloride salt is a hydrate.

[44] In still another specific embodiment, the crystalline hydrochloride salt is a dihydrochloride.

[45] In a further specific embodiment, this dihydrochloride salt is a hydrate, preferably a monohydrate.

[46] In yet another specific embodiment, the crystalline hydrochloride salt is a monohydrochloride.

- [47] In a still further specific embodiment, this monohydrochloride salt is a hydrate.
- [48]
- [49] Crystalline form of salts of the compound of Formula 1
- [50] The salts of the compound of Formula 1 may be prepared in a crystalline form, an amorphous form, or a mixture thereof, and preferably in a crystalline form. The crystalline form of a hydrochloride salt of Formula 1 compound, in particular the crystalline dihydrochloride monohydrate, has excellent stability and is thus preferable in that it has a physicochemical property which facilitates its formulation.
- [51] In a specific embodiment of the inventive pharmaceutical composition, the crystalline form of a dihydrochloride hydrate, preferably monohydrate, is used as the active pharmaceutical ingredient (API). Most preferably, this dihydrochloride monohydrate has the crystalline form designated as 1X (see PCT/KR2016/015535). This crystalline form 1X is associated with high water solubility, and has excellent non-hygroscopicity/non-humidification and stability
- [52]
- [53] This preferred crystalline form 1X exhibits an X-ray powder diffraction (XRPD) pattern comprising peaks at diffraction angles of $2\theta = 5.6^\circ \pm 0.2^\circ$ and $27.3^\circ \pm 0.2^\circ$ when irradiated with a Cu-K α light source (XRPD1-1).
- [54]
- [55] More specifically, the above crystalline form 1X exhibits an XRPD pattern comprising peaks at diffraction angles of $2\theta = 5.6^\circ \pm 0.2^\circ$, $21.1^\circ \pm 0.2^\circ$ and $27.3^\circ \pm 0.2^\circ$ when irradiated with a Cu-K α light source (XRPD1-2).
- [56] More specifically, the above crystalline form 1X has an XRPD pattern comprising peaks at diffraction angles of $2\theta = 5.6^\circ \pm 0.2^\circ$, $11.1^\circ \pm 0.2^\circ$ and $27.3^\circ \pm 0.2^\circ$ when irradiated with a Cu-K α light source (XRPD1-3).
- [57] More specifically, the above crystalline form 1X has an XRPD pattern comprising peaks at diffraction angles of $2\theta = 5.6^\circ \pm 0.2^\circ$, $11.1^\circ \pm 0.2^\circ$, $21.1^\circ \pm 0.2^\circ$, and $27.3^\circ \pm 0.2^\circ$ when irradiated with a Cu-K α light source (XRPD1-4).
- [58] More specifically, the above crystalline form 1X has an XRPD pattern comprising peaks at diffraction angles of $2\theta = 5.6^\circ \pm 0.2^\circ$, $11.1^\circ \pm 0.2^\circ$, $14.0^\circ \pm 0.2^\circ$ and $27.3^\circ \pm 0.2^\circ$ when irradiated with a Cu-K α light source (XRPD1-5).
- [59] More specifically, the above crystalline form 1X has an XRPD pattern comprising peaks at diffraction angles of $2\theta = 5.6^\circ \pm 0.2^\circ$, $11.1^\circ \pm 0.2^\circ$, $14.0^\circ \pm 0.2^\circ$, $20.8^\circ \pm 0.2^\circ$, $21.1^\circ \pm 0.2^\circ$, and $27.3^\circ \pm 0.2^\circ$ when irradiated with a Cu-K α light source (XRPD1-6).
- [60] More specifically, the above crystalline form 1X has an XRPD pattern comprising peaks at diffraction angles of $2\theta = 5.6^\circ \pm 0.2^\circ$, $10.7^\circ \pm 0.2^\circ$, $11.1^\circ \pm 0.2^\circ$, $14.0^\circ \pm 0.2^\circ$, $20.8^\circ \pm 0.2^\circ$, $21.1^\circ \pm 0.2^\circ$, $22.5^\circ \pm 0.2^\circ$, and $27.3^\circ \pm 0.2^\circ$ when irradiated with a Cu-K α light source (XRPD1-7).

- [61] These peaks may be those having a relative intensity (I/I_0) of about 10% or more.
- [62] Still more specifically, said crystalline form 1X has an XRPD pattern with peaks at diffraction angles as contained in Table A when irradiated with a Cu-K α light source.

[63] [Table A]

[64]

2θ (± 0.2)	d	I/I_0 (%)	2θ (± 0.2)	d	I/I_0 (%)
5.6	15.9	100	22.5	4.0	10.2
8.9	9.9	6.7	23.2	3.8	9.0
10.7	8.3	14.2	24.1	3.7	6.5
11.1	7.9	19.1	24.7	3.6	3.6
11.4	7.7	6.1	25.0	3.6	8.8
12.2	7.3	5.1	26.4	3.4	6.5
14.0	6.3	15.6	26.8	3.3	4.5
14.6	6.1	9.3	27.3	3.3	24.7
15.5	5.7	4.8	27.7	3.2	3.6
15.7	5.6	5.0	28.8	3.1	6.5
16.8	5.3	3.0	29.4	3.0	6.5
18.5	4.8	3.3	29.8	3.0	5.0
18.9	4.7	6.2	30.1	3.0	4.4
19.9	4.5	6.9	30.6	2.9	3.0
20.4	4.3	7.8	31.3	2.9	4.0
20.8	4.3	20.0	32.4	2.8	4.4
21.1	4.2	41.6	34.7	2.6	3.5
21.4	4.1	3.0	37.9	2.4	3.3
21.7	4.1	4.5	39.7	2.3	3.0

[65]

2θ (± 0.2)	d	I/I_0 (%)	2θ (± 0.2)	d	I/I_0 (%)
2θ : diffraction angle, d: distance between crystal faces, I/I_0 (%): relative intensity (I indicates the intensity of each peak; I_0 indicates the intensity of the highest peak.)					

- [66] Even more specifically, said crystalline form 1X is characterised by an X-ray powder diffraction pattern as shown in Figure 7 when irradiated with a Cu-K α light source.
- [67] The above crystalline form 1X may have a ^{13}C CP/MAS TOSS ssNMR spectrum comprising peaks at the following ^{13}C chemical shifts: 44.6 ± 0.2 ppm and 56.6 ± 0.2 ppm (ssNMR1-1).
- [68] More specifically, the above crystalline form 1X may have a ^{13}C CP/MAS TOSS ssNMR spectrum comprising peaks at the following ^{13}C chemical shifts: 44.6 ± 0.2 ppm, 45.4 ± 0.2 ppm, 50.8 ± 0.2 ppm and 56.6 ± 0.2 ppm (ssNMR1-2).
- [69] The above crystalline form 1X may have a ^{13}C CP/MAS TOSS ssNMR spectrum

comprising peaks at the following ^{13}C chemical shifts: 149.6 ± 0.2 ppm, 152.6 ± 0.2 ppm and 164.3 ± 0.2 ppm (ssNMR1-3).

[70] More specifically, the above crystalline form 1X may have a ^{13}C CP/MAS TOSS ssNMR spectrum comprising peaks at the following ^{13}C chemical shifts: 116.5 ± 0.2 ppm, 130.7 ± 0.2 ppm, 146.8 ± 0.2 ppm, 149.6 ± 0.2 ppm, 152.6 ± 0.2 ppm and 164.3 ± 0.2 ppm (ssNMR1-4).

[71] More specifically, the above crystalline form 1X may have a ^{13}C CP/MAS TOSS ssNMR spectrum comprising peaks at the following ^{13}C chemical shifts: 44.6 ± 0.2 ppm, 56.6 ± 0.2 ppm, 149.6 ± 0.2 ppm, 152.6 ± 0.2 ppm and 164.3 ± 0.2 ppm (ssNMR1-5).

[72] Still more specifically, said crystalline form 1X has a ^{13}C CP/MAS TOSS ssNMR spectrum comprising peaks at the ^{13}C chemical shifts collected in Table B below (expressed in ppm ± 0.2 ppm):

[73] [Table B]

[74]

Peak #	Chemical Shift (ppm)	Peak #	Chemical Shift (ppm)	Peak #	Chemical Shift (ppm)
1	44.6	8	116.5	15	144.2
2	45.4	9	119.1	16	146.8
3	50.8	10	120.8	17	149.6
4	56.6	11	128.1	18	152.6
5	108.4	12	130.7	19	164.3
6	112.5	13	134.8	20	165.9
7	114.4	14	140.4	-	-

[75] Even more specifically, said crystalline form 1X is characterised by a ^{13}C CP/MAS TOSS ssNMR spectrum as shown in Figure 8 when irradiated with a Cu-K α light source.

[76] The above crystalline form 1X may have

[77] (a) an X-ray powder diffraction (XRPD) pattern comprising peaks at diffraction angle 2θ values of $5.6^\circ \pm 0.2^\circ$ and $27.3^\circ \pm 0.2^\circ$ when irradiated with a Cu-K α light source; and

[78] (b) a ^{13}C CP/MAS TOSS ssNMR spectrum comprising peaks at the following ^{13}C chemical shifts: 44.6 ± 0.2 ppm and 56.6 ± 0.2 ppm.

[79] The above crystalline form 1X may have

[80] (a) an X-ray powder diffraction (XRPD) pattern comprising peaks at diffraction angle 2θ values of $5.6^\circ \pm 0.2^\circ$ and $27.3^\circ \pm 0.2^\circ$ when irradiated with a Cu-K α light source; and

[81] (b) a ^{13}C CP/MAS TOSS ssNMR spectrum comprising peaks at the following ^{13}C chemical shifts: 149.6 ± 0.2 ppm, 152.6 ± 0.2 ppm and 164.3 ± 0.2 ppm.

- [82] The above crystalline form (ex.1) may also be characterized by any other combination of lists of XRPD peaks (XRPD1-1 to XRPD1-7) and ^{13}C chemical shifts (ssNMR1-1 to ssNMR1-5) as listed above.
- [83] X-ray powder diffraction (XRPD) analyses of samples were performed in the range from $3^\circ 2\theta$ to $40^\circ 2\theta$ using a D8 Advance (Bruker ASX, Germany) analyzer. When the amount of a given sample was less than 100 mg, about 5 mg to 10 mg of the sample was gently compressed on a glass slide which was fit into a sample holder. When the amount of a given sample was greater than 100 mg, about 100 mg of the sample was gently compressed in a plastic sample holder so that the sample surface becomes flat and positioned immediately on top of the sample holder level.
- [84] The measurement was performed as follows:
- [85] Anode material ($K\alpha$): Cu $K\alpha$ (1.54056 Å)
- [86] Scan range: 3° to 40°
- [87] Generator settings: 100 mA, 40.0 kV
- [88] Scan speed: 1 sec/step
- [89] Diver slit: 0.3°
- [90] Anti-scatter slit: 0.3°
- [91] Temperature: 20°C
- [92] Step size: $0.02^\circ 2\theta$
- [93] Rotation: use
- [94] Goniometer radius: 435 mm.
- [95]
- [96] Solid State Nuclear Magnetic Resonance Spectroscopy (ssNMR) was performed in the solid state, for example, as follows. A sample in an amount of 100 mg was weighed and added into a 4 mm sample tube. ^{13}C NMR spectra (^{13}C CP/MAS TOSS ssNMR) were recorded at room temperature using a Bruker Avance II 500 MHz Solid NMR system (Bruker, Germany) analyzer with 4 mm probe type CP/MAS BB-1H under the following conditions:
- [97] Frequency: 125.76 MHz,
- [98] Spectral width: 20 kHz,
- [99] Rotational speed of the sample at the magic angle: 5 kHz,
- [100] Pulse Sequence: CP (Cross Polarization) SPINAL64 with decoupling (decoupling power of 80 kHz),
- [101] Delay repeats: 5 s
- [102] Contact time: 2 ms
- [103] Number of scans: 4096.
- [104] External standard: adamantane
- [105] Said crystalline form 1X may have a water content of about 3.1% (theoretical water

content value of 3.11% for monohydrate) measured using a Karl Fischer titrator (795KFT Titrino (Metrohm, Switzerland)) and a melting point of about 202°C to 225°C measured by differential scanning calorimetry (STA-1000 from Scinco, Korea).

[106]

[107] In one embodiment, a pharmaceutical composition according to the present invention comprises a hydrochloride salt of the compound of formula 1 as the active pharmaceutical ingredient, wherein at least 50 % by weight of the active pharmaceutical ingredient is in the form of the crystalline form 1X as defined hereinbefore. Preferably in said pharmaceutical composition at least 80 % by weight, more preferably at least 90 % by weight, most preferably at least 95 % by weight of the active pharmaceutical ingredient is in the form of the crystalline form 1X as defined hereinbefore.

[108] The active pharmaceutical ingredient may be contained in an amount that is generally effective for exhibiting pharmacological activity, and may be contained in a range of 1 mg to 1000 mg per unit pharmaceutical dosage form in the present invention, e.g. 50 mg or 75 mg or 150 mg or 200 mg or 400 mg or 600 mg or 800 mg in the form of the compound of Formula 1 or their corresponding amount in the form of a pharmaceutically acceptable salt or a hydrate of a pharmaceutically acceptable salt. In one embodiment the content of the dihydrochloride monohydrate per unit pharmaceutical dosage form is in an amount corresponding to 200 mg of the free base (Formula 1). In another embodiment the content of the dihydrochloride monohydrate per unit pharmaceutical dosage form is in an amount corresponding to 400 mg of the free base (Formula 1). The amount of active pharmaceutical ingredient (in wt%) in the pharmaceutical composition is in the range of about 1% to 65%, preferably about 55% to 65%.

[109]

[110] (2) Low melting point stabilizer

[111] The pharmaceutical composition of the present invention comprises one or more low melting point stabilizer(s) defined by certain characteristics.

[112] A low melting point stabilizer suitable to be used in a pharmaceutical composition according to the invention inhibits the generation of certain impurities during a dosage form manufacturing process and has a melting point of 80 °C or below. For example, the low melting point stabilizer may be selected from the group consisting of polyethylene glycols (for example, PEG 1000, 1500, 1540, 2000, 3000, 4000, 6000, 8000, 20000 and 35000), glyceryl behenate, glyceryl monostearate, sorbitan fatty acid esters such as sorbitan monopalmitate or sorbitan monostearate, a polyoxyethylene-polyoxypropylene block copolymer such as Polyoxyl 150 distearate, and Poloxamer (e.g., 188 and 407), ethylene glycol stearate, fatty acids with melting points of 80 °C or less such as lauric acid, palmitic acid, or stearic acid, and any mixtures of the foregoing.

- [113] The level of the low melting point stabilizer may be about 0.15 to 0.6 parts by weight based on 1 part by weight of the active pharmaceutical ingredient. The low melting point stabilizer used at this range provides reduction in the impurities produced during a dosage form manufacture, such as tablet manufacture without compromising processability and drug release characteristics.
- [114] In one embodiment of the inventive pharmaceutical composition, the low melting point stabilizer is polyethylene glycol. In a specific embodiment, polyethylene glycol with a molecular weight range from 1000 to 35000 is used. In an even more specific embodiment, polyethylene glycol with a molecular weight in a range from 1000 to 8000 is used. For example, a molecular weight range from 2000 to 8000 may be preferably used in a solid formulation. Properties such as melting point vary with the grade. For example, PEG 8000, also known as Macrogol 8000 (Ph. Eur.), is most preferred and has a low melting point of 55 to 63 °C.
- [115] In another embodiment, the low melting point stabilizer is polyethylene glycol having a content of, based on 1 part by weight of the API, about 0.15 to 0.6 parts by weight, more specifically about 0.2 to 0.5 parts by weight, even more specifically about 0.2 to 0.3 parts by weight, and still more specifically about 0.21 to 0.26 parts by weight of polyethylene glycol. Preferably, the polyethylene glycol used is PEG 8000.
- [116]
- [117] Although not wishing to be bound by any particular theory for the working principles of the present invention, but only to help better understand the present invention, the low melting point stabilizer is thought to provide protection against friction:
- [118] During dry granulation and compression, pressure is applied to the pharmaceutical composition. The particles in the powder mixture are relocated and the mixture is densified. The particle movement causes friction between the particles which may be the reason for an increase of certain impurities in the core tablet formulation. Low melting point stabilizers, such as e.g. polyethylene glycol 8000 (PEG 8000), may act as stabilizer as they may protect the active pharmaceutical ingredient from mechanical stress during dry granulation and compression.
- [119] When the low melting point stabilizer is used at a content of less than about 0.15 parts by weight, it may fail to inhibit generation of impurities. When the low melting point stabilizer is used at a content of greater than about 0.6 parts by weight, it may cause problems in drug release.
- [120]
- [121] (3) Pharmaceutically acceptable excipients
- [122] The pharmaceutical composition according to the present invention may further comprise one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients may be those generally used in the field. For example, the phar-

maceutically acceptable excipients may be selected from the group consisting of diluents, binders, disintegrants, lubricants, colorants, glidants, sorbents, and any mixtures thereof, and any excipient generally used in the pharmaceutical field.

- [123] **Diluents** (also referred to as fillers) increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the pharmaceutical composition easier for the patient and care giver to handle. Diluents which may be used in the pharmaceutical composition include diluents commonly used in solid pharmaceutical compositions. In one embodiment of the present invention, diluent(s) is/are selected from the group consisting of solid organics, as
- [124] - sugars
- [125] (e.g. monosaccharides like glucose; oligosaccharides like sucrose, or disaccharides, as lactose in various crystalline modifications, as precipitated, spray-dried, drum-dried, or co-processed with further excipients as microcrystalline cellulose, or sorbitol, mannitol, xylitol, lactitol, erythritol, dulcitol, ribitol, erythritol);
- [126] - cellulose and its derivatives (e.g. powdered cellulose or microcrystalline cellulose);
- [127] - starch or modified starches (e.g. pre-gelatinized, or partially hydrolysed);
- [128] or solid inorganics, as
- [129] - calcium phosphate, dibasic calcium phosphate, hydroxyl apatite, calcium sulphate, calcium carbonate;
- [130] or semisolids as
- [131] -lipids or paraffin;
- [132] and mixtures thereof, but the present invention is not limited thereto. Preferred diluent(s) is/are mannitol and microcrystalline cellulose or mixtures thereof.
- [133] The diluent(s) may be contained in an amount of about 2 to 50 wt%, specifically about 5 to 40 wt%, more specifically about 8 to 30 wt%, and preferably about 10 to 25 wt% based on the total weight of the pharmaceutical composition.
- [134] **Binders** help to bind the active pharmaceutical ingredient and other excipients together. Binders which may be used in the pharmaceutical composition include binders commonly used in solid pharmaceutical compositions. In one embodiment of the present invention, binder(s) is/are selected from the group consisting of
- [135] - cellulose and/or its derivatives as ethylcellulose, carboxymethylcellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose;
- [136] - starch or modified starches (e.g. pre-gelatinized or partially hydrolysed);
- [137] - polyvinylpyrrolidones (e.g. Kollidon® K30), polyvinylacetates, polyvinylalcohols or co-polymerisates thereof (e.g. Copovidone);
- [138] and mixtures thereof but the present invention is not limited thereto. Preferred binder is hydroxypropyl cellulose.
- [139] The binder may be contained in an amount of about 1 to 25 wt%, specifically about 1

to 10 wt%, and more specifically about 1 to 5 wt%, and preferably about 3 wt% based on the total weight of the pharmaceutical composition.

[140] **Disintegrants** increase the dissolution rate of a solid pharmaceutical composition in the patient's body. Disintegrants which may be used in the pharmaceutical composition include disintegrants commonly used in solid pharmaceutical compositions. In one embodiment of the present invention, disintegrant(s) is/are selected from the group consisting of sodium starch glycolate, croscopovidone, croscarmellose, sodium carboxymethylcellulose and dried corn starch, and any mixtures thereof, but the present invention is not limited thereto. A preferred disintegrant is croscopovidone.

[141] The disintegrant may be contained in an amount of about 1 to 30 wt%, and more specifically about 2 to 6 wt%, and preferably about 3 wt% based on the total weight of the pharmaceutical composition.

[142] **Lubricants** are added to a pharmaceutical composition for ease in processing, to prevent adhesion to the equipment used during processing. Lubricants which may be used in the pharmaceutical composition include lubricants commonly used in solid pharmaceutical compositions. In one embodiment of the present invention, lubricant(s) is/are selected from the group consisting of stearic acid, magnesium stearate, calcium stearate, sodium stearyl fumarate, glycerol tribehenate, polyethylene glycol, and any mixtures thereof, but the present invention is not limited thereto. A preferred lubricant is magnesium stearate.

[143] The lubricant may be contained in an amount of about 0.5 to 5 wt%, and more specifically 0.5 to 2 wt%, and preferably about 1 wt% based on the total weight of the pharmaceutical composition.

[144] **Glidants** improve the flowability of a non-compacted solid pharmaceutical composition and improve the accuracy of dosing. Glidants which may be used in the pharmaceutical composition include glidants commonly used in solid pharmaceutical compositions. Glidants which may be used in the pharmaceutical composition include, but are not limited to, colloidal silicon dioxide, magnesium trisilicate, starch, talc, tribasic calcium phosphate, and any combinations thereof.

[145] If there should exist any ambiguity in respect of the naming of stabilizers or any of the excipients as herein disclosed (i.e. due to differences in regional pharmacopeia) then it is the European Pharmacopoeia which is decisive.

[146] Thus, in one aspect, the present invention also provides a pharmaceutical dosage form prepared using and comprising the pharmaceutical composition described above.

[147] In one embodiment, the pharmaceutical dosage form is a solid one. In another embodiment, the pharmaceutical dosage form is a liquid one, for example a syrup. In a specific embodiment, the solid pharmaceutical dosage form is a tablet. Such tablets may be formulated using art-known compression and tableting methods, for instance,

dry granulation or wet granulation using process aids such as solvents.

- [148] A tablet as an example of the pharmaceutical dosage form according to the present invention, may have a hardness of 6 to 22 kp. When the tablet of the present invention has a hardness of less than 6 kp, friability may increase, and when the tablet has a hardness of greater than 22 kp, a dissolution rate may decrease.
- [149] In order to prevent the solid pharmaceutical dosage form according to the present invention from coming in contact with a user's hand or skin during handling, the pharmaceutical composition may comprise a coating, i.e. be coated with a coating agent selected from the group consisting of an immediate release film former, an enteric coating agent, a sustained release coating agent and any mixtures thereof. In a more specific embodiment of the pharmaceutical composition and the pharmaceutical dosage form, such coating may additionally comprise colorants/pigments such as iron oxide or titanium dioxide, or plasticizers.
- [150] Exemplary coating agents used for the present invention may include hydroxy propyl cellulose, hydroxy propylmethyl cellulose, a polyvinyl alcohol and a polyvinyl alcohol-polyethylene glycol graft polymer (Kollicoat IR, BASF) as the immediate release film former; a (meth)acrylic acid copolymer (EUDRAGIT, Evonik Industries), phthalic acid hydroxy propylmethyl cellulose and phthalic acid cellulose acetate as the enteric coating agent; and cellulose acetate, ethyl cellulose and a polyvinyl acetate as the sustained release coating agent.
- [151] The coating agent may be used in an amount of 1 to 10 wt%, preferably 1 to 5 wt%, more preferably 2 to 4 wt% based on the total weight of the pharmaceutical composition before coating.
- [152] Further embodiments of the pharmaceutical compositions according to the invention are as follows:

[153]

Ingredients	amount (wt%)
active pharmaceutical ingredient of Formula 1, or a pharmaceutically acceptable salt thereof, or a hydrate of a pharmaceutically acceptable salt thereof	55-65
one or more low melting point stabilizer(s) having a melting point of 80°C or less	10-20
one or more diluent(s)	10-20
one or more binder(s)	1-5
one or more disintegrant(s)	1-5
one or more lubricant(s)	0.5-5
optionally one or more additional excipient(s)	ad 100%

[154]

Ingredients	amount (wt%)
active pharmaceutical ingredient of Formula 1, or a pharmaceutically acceptable salt thereof, or a hydrate of a pharmaceutically acceptable salt thereof	55-65
PEG 8000	10-20
mixture of mannitol and microcrystalline cellulose	10-20
hydroxypropyl cellulose	1-5
crospovidone	1-5
Magnesium stearate	0.5-5
one or more coating agent(s)	ad 100%

[155] General description of the manufacturing process of the tablet cores:

[156] Step 1.1 Pre-mixing: Polyethylene glycol, active pharmaceutical ingredient (i.e. compound of Formula 1 in any form as herein described, preferably as a dihydrochloride monohydrate), a part of magnesium stearate, hydroxypropyl cellulose, microcrystalline cellulose and mannitol are mixed.

- [157] Step 1.2 Dry granulating: The pre-mix from step 1.1 is dry granulated using a dry granulator to obtain granules.
- [158] Step 2 Mixing: Crospovidone and the rest of magnesium stearate is added in one step or in subsequent steps to the granules from step 1.2 and mixed to obtain the final blend.
- [159] Step 3 Tablet cores: The final blend from the previous step is compressed into tablet cores using a tablet press.
- [160] General description of the manufacturing process of the film coated tablets (starting from the tablet cores obtained in steps 1 to 3):
- [161] Step 4.1 Dispersion: The ready-to-use coating mixture is suspended in a mixture of purified water and alcohol at room temperature to obtain the film-coating suspension.
- [162] Step 4.2 Film-coating: The tablet cores from step 3 are coated with the film-coating suspension from step 4.1.
- [163]
- [164] The pharmaceutical composition of the present invention and the pharmaceutical dosage form prepared using the same comprise the compound of Formula 1 (or salts, hydrates, hydrates of salts as described hereinbefore), and effectively inhibit growth of cancer cells or tumors that are caused by the epidermal growth factor receptor tyrosine kinase or variants thereof.
- [165]
- [166] The pharmaceutical composition of the present invention and the pharmaceutical dosage form prepared using and comprising the same can be used for preventing and/or treating cancers, tumors, inflammatory diseases, autoimmune diseases or immune-mediated diseases.
- [167] The cancers or the tumors may be cancer cells or tumors induced by an epidermal growth factor receptor tyrosine kinase or a variant thereof, where a variant includes any EGFR kinases that differ from the wild type EGFR kinase sequence by means of one or more mutations, for example, substitution, addition and deletion. The EGFR tyrosine kinase-induced cancers or tumors may include, for example, liver cancer, hepatocellular carcinoma, thyroid cancer, colon cancer, testicular cancer, bone cancer, oral cancer, basal cell carcinoma, ovarian cancer, a brain tumor, a gallbladder carcinoma, biliary tract cancer, head and neck cancer, colorectal cancer, a vesical carcinoma, tongue cancer, esophageal cancer, a glioma, a glioblastoma, renal cancer, a malignant melanoma, gastric cancer, breast cancer, a sarcoma, a pharynx carcinoma, uterine cancer, cervical cancer, prostate cancer, rectal cancer, pancreatic cancer, lung cancer, skin cancer, and other solid cancers, but not limited thereto.
- [168] In one embodiment this EGFR tyrosine kinase-induced cancer is lung cancer. In a more specific embodiment, this lung cancer is non-small cell lung cancer (NSCLC) (including for example locally advanced or metastatic NSCLC (stage IIIB/IV), NSCLC

adenocarcinoma, NSCLC with squamous histology, NSCLC with non-squamous histology), in particular NSCLC adenocarcinoma.

- [169] In one embodiment this EGFR tyrosine kinase-induced cancer harbors an EGFR exon 20 insertion or an EGFR exon 19 deletion (Del19) or an EGFR L858R mutation or an EGFR T790M mutation, or any combination thereof.
- [170] In one embodiment this EGFR tyrosine kinase-induced cancer harbors one or more EGFR mutations wherein at least one EGFR mutation is selected from Del19 (deletion in exon 19), L858R and T790M, and any combination thereof.
- [171] In one embodiment this EGFR tyrosine kinase-induced cancer harbors the EGFR mutation Del19.
- [172] In one embodiment this EGFR tyrosine kinase-induced cancer harbors the EGFR mutation L858R.
- [173] In one embodiment this EGFR tyrosine kinase-induced cancer harbors the EGFR mutation T790M.
- [174] In one embodiment this EGFR tyrosine kinase-induced cancer harbors at least two EGFR mutations selected from the group consisting of Del19/T790M and L858R/T790M.
- [175] In one embodiment this EGFR tyrosine kinase-induced cancer is non-small cell lung cancer (NSCLC), in particular NSCLC adenocarcinoma, harboring an EGFR exon 20 insertion or an EGFR exon 19 deletion (Del19) or an EGFR L858R mutation or an EGFR T790M mutation, or any combination thereof.
- [176] In one embodiment this EGFR tyrosine kinase-induced cancer is non-small cell lung cancer (NSCLC), in particular NSCLC adenocarcinoma, harboring one or more EGFR mutations wherein at least one EGFR mutation is selected from Del19 (deletion in exon 19), L858R and T790M, and any combination thereof..
- [177] In one embodiment this EGFR tyrosine kinase-induced cancer is non-small cell lung cancer (NSCLC), in particular NSCLC adenocarcinoma, harboring at least two EGFR mutations selected from the group consisting of Del19/T790M and L858R/T790M.
- [178] In one embodiment this EGFR tyrosine kinase-induced cancer is non-small cell lung cancer (NSCLC), in particular NSCLC adenocarcinoma, harboring the EGFR mutation Del19.
- [179] In one embodiment this EGFR tyrosine kinase-induced cancer is non-small cell lung cancer (NSCLC) harboring the EGFR mutation L858R.
- [180] In one embodiment this EGFR tyrosine kinase-induced cancer is non-small cell lung cancer (NSCLC), in particular NSCLC adenocarcinoma, harboring the EGFR mutation T790M.
- [181] Examples of the inflammatory diseases, the autoimmune diseases and the immune-mediated diseases may include arthritis, rheumatoid arthritis, spondyloarthropathy,

gouty arthritis, osteoarthritis, juvenile arthritis, other arthritic conditions, lupus, systemic lupus erythematosus (SLE), skin-related diseases, psoriasis, eczema, dermatitis, atopic dermatitis, pain, pulmonary disorders, lung inflammation, adult respiratory distress syndrome (ARDS), pulmonary sarcoidosis, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease (COPD), cardiovascular disease, atherosclerosis, myocardial infarction, congestive heart failure, cardiac reperfusion injury, inflammatory bowel disease, Crohn's disease, ulcerative colitis, irritable bowel syndrome, asthma, Sjogren syndrome, autoimmune thyroid disorders, urticaria, multiple sclerosis, scleroderma, organ transplant rejection, xenograft, chronic idiopathic thrombocytopenic purpura (ITP), Parkinson's disease, Alzheimer's disease, diabetic associated disease, inflammation, pelvic inflammatory disease, allergic rhinitis, allergic bronchitis, allergic sinusitis, leukemia, lymphoma, B-cell lymphoma, T-cell lymphoma, myeloma, acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), hairy cell leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, myelodysplastic syndrome (MDS), myeloproliferative neoplasms (MPN), diffuse large B-cell lymphoma, and follicular lymphoma, but not limited thereto.

[182] Therefore, the present invention provides pharmaceutical compositions and pharmaceutical dosage forms as described herein for preventing and/or treating cancers, tumors, inflammatory diseases, autoimmune diseases or immune-mediated diseases as described herein.

[183] Also, the present invention provides a method of preventing and/or treating cancers, tumors, inflammatory diseases, autoimmune diseases or immune-mediated diseases in a subject in need thereof. The method comprises administering a pharmaceutical composition or a pharmaceutical dosage form of the present invention, to a subject in need thereof. The subject may be, for example, a mammal, and more specifically, a human.

[184] The pharmaceutical composition of the present invention may be administered through several routes including oral, percutaneous, subcutaneous, intravenous or intramuscular injection. The pharmaceutical composition of the present invention may be administered once or multiple times at an effective dose generally used. However, an actual dose of the active pharmaceutical ingredient should be determined according to several related factors such as an administration route, patient's age, sex, and body weight, and severity of disease. Therefore, the dose does not limit the scope of the present invention in any respect.

[185] The pharmaceutical composition of the present invention is formulated into a conventional formulation in the field of pharmaceuticals, and may be administered through oral, oromucosal, sublingual, intrarectal, intravaginal, intranasal, local or parenteral administration. The oral administration is preferable. For example, the pharmaceutical

composition according to the present invention may be provided and (orally) administered in a pharmaceutical dosage form like, e.g., in a tablet form, e.g. containing a starch or lactose, a capsule form which may contain an excipient, or an elixir or syrup form containing a chemical agent for flavor or a colorant through oral, oromucosal, or sublingual administration. Also, the pharmaceutical composition may be parenterally injected through, for example, intravenous, intracavernous, intramuscular, subcutaneous and intraductal administration.

[186] The present invention will be described below in further detail with reference to the following examples. However, the following examples are only examples of the present invention, and the scope of the present invention is not limited thereto.

[187]

[188] **Examples 1 to 3:** Preparation of tablets containing polyethylene glycol

[189] For the active pharmaceutical ingredient (API), powdered dihydrochloride monohydrate salt of the compound of Formula 1 (Hanmi Fine Chemical Co., Ltd.) was used. The API, mannitol (ROQUETTE), microcrystalline cellulose (MINGTAI), hydroxypropyl cellulose (L-Type, NISSO), and polyethylene glycol 8000 (Ph. Eur) (JP: Macrogol 6000, SANYO) were mixed according to pharmaceutical compositions described in the following Table 1, and the resulting mixture was subjected to dry granulation using a Roll Compactor (TFC-LAB, FREUND).

[190] Crospovidone (BASF) was added to and mixed with the granules prepared above, and then magnesium stearate (PETER GREVEN) was added thereto to obtain a final mixture. A tablet having hardness of 14 kp was prepared from the obtained final mixture using a tablet machine (GRC-18, Sejong Pharmatech Co., Ltd.). The above prepared tablet was coated with a coating agent, Opadry Y-1-7000 (COLORCON), using an automatic coating system (SFC-30, Sejong Pharmatech Co., Ltd.) in an amount of 2 wt% with respect to a total weight of the tablet.

[191] [Table 1]

[192]

		Ex. 1	Ex. 2	Ex. 3
Dry granules	API	475	475	475
	Mannitol	65	65	65
	Microcrystalline cellulose	40	40	40
	Hydroxypropyl cellulose	20	20	20
	Polyethylene glycol 8000 (Ph. Eur) (parts by weight against the API)	120 (0.25)	106 (0.22)	240 (0.51)
Mixing	Crospovidone	20	20	20
Final mixing	Magnesium stearate	10	10	10
Total weight (mg)		750	736	870
Tablet hardness (kp)		14	14	14

[193] **Examples 4 to 8:** Preparation of tablets containing polyethylene glycol

[194] Tablets sharing the same pharmaceutical composition as Example 1 shown in Table 2 were prepared except that the hardness of the tablet was adjusted to 7, 9, 11 or 18 kp. Example 4 was prepared after final mixing without tableting process.

[195] [Table 2]

[196]

		Ex. 4	Ex. 5	Ex. 6	Ex. 7	Ex. 8
Dry granules	API	475	475	475	475	475
	Mannitol	65	65	65	65	65
	Microcrystalline cellulose	40	40	40	40	40
	Hydroxypropyl cellulose	20	20	20	20	20
	Polyethylene glycol 8000 (parts by weight against the API)	120 (0.25)	120 (0.25)	120 (0.25)	120 (0.25)	120 (0.25)
Mixing	Crospovidone	20	20	20	20	20
Final mixing	Magnesium stearate	10	10	10	10	10
Total weight (mg)		750	750	750	750	750
Tablet hardness (kp)		0	7	9	11	18

[197] **Examples 9 to 18:** Preparation of tablets containing low melting point stabilizers

other than polyethylene glycol

[198] Tablets were prepared in the same manner as in Example 1 except that sorbitan monopalmitate, sorbitan monostearate, Poloxamer 188, Poloxamer 407, ethylene glycol stearate, glyceryl behenate, glyceryl monostearate, lauric acid, palmitic acid, or stearic acid were used in place of polyethylene glycol 8000 (Ph. Eur).

[199] [Table 3]

[200]

		Ex. 9	Ex. 10	Ex. 11	Ex. 12	Ex. 13
Dry granules	API	475	475	475	475	475
	Mannitol	65	65	65	65	65
	Microcrystalline cellulose	40	40	40	40	40
	Hydroxypropyl cellulose	20	20	20	20	20
	Sorbitan monopalmitate	120	-	-	-	-
	Sorbitan monostearate	-	120	-	-	-
	Poloxamer 188	-	-	120	-	-
	Poloxamer 407	-	-	-	120	-
	Ethylene glycol stearate	-	-	-	-	120
Mixing	Crospovidone	20	20	20	20	20
Final mixing	Magnesium stearate	10	10	10	10	10
Total weight (mg)		750	750	750	750	750
Tablet hardness (kp)		14	14	14	14	14

[201] [Table 4]

[202]

		Ex. 14	Ex. 15	Ex. 16	Ex. 17	Ex. 18
Dry granules	API	475	475	475	475	475
	Mannitol	65	65	65	65	65
	Microcrystalline cellulose	40	40	40	40	40
	Hydroxypropyl cellulose	20	20	20	20	20
	Glyceryl behenate	120	-	-	-	-
	Glyceryl monostearate	-	120	-	-	-
	Lauric acid	-	-	120	-	-
	Palmitic acid	-	-	-	120	-
	Stearic acid	-	-	-	-	120
Mixing	Crospovidone	20	20	20	20	20
Final mixing	Magnesium stearate	10	10	10	10	10
Total weight (mg)		750	750	750	750	750
Tablet hardness (kp)		14	14	14	14	14

[203] **Comparative Examples 1 to 5:** Preparation of tablets with no polyethylene glycol.

[204] The tablets of Comparative Examples 1 to 4 were prepared in the same manner as in Example 1 with hardness values ranging from 9 to 18 kp, except that no polyethylene glycol was added. Comparative Example 5 was prepared after final mixing without tableting process.

[205] [Table 6]

[206]

		Comp. Ex. 1	Comp. Ex. 2	Comp. Ex. 3	Comp. Ex. 4	Comp. Ex. 5
Dry granules	API	475	475	475	475	475
	Mannitol	65	65	65	65	65
	Microcrystalline cellulose	40	40	40	40	40
	Hydroxypropyl cellulose	20	20	20	20	20
Mixing	Crospovidone	20	20	20	20	20
Final mixing	Magnesium stearate	10	10	10	10	10
Total weight (mg)		630	630	630	630	630
Tablet hardness (kp)		14	9	11	18	0

[207] **Comparative Examples 6 to 10:** Preparation of tablets containing non-low melting point stabilizers

[208] Tablets were prepared in the same manner as in Example 1 except that citric acid, ascorbic acid, magnesium carbonate, or magnesium oxide were used in place of polyethylene glycol 8000 (Ph. Eur.) according to the pharmaceutical compositions described in the following Table 7.

[209]

[210] [Table 7]

[211]

		Comp. Ex. 6	Comp. Ex. 7	Comp. Ex. 8	Comp. Ex. 9	Comp. Ex. 10
Dry granules	API	475	475	475	475	475
	Mannitol	65	65	65	65	65
	Microcrystalline cellulose	40	40	40	40	40
	Hydroxypropyl cellulose	20	20	20	20	20
	Polyethylene glycol 8000 (Ph. Eur.)	-	-	-	-	60 (0.13 pbw)
	Citric acid	120	-	-	-	-
	Ascorbic acid	-	120	-	-	-
	Magnesium carbonate	-	-	120	-	-
	Magnesium oxide	-	-	-	120	-
Mixing	Crospovidone	20	20	20	20	20
Final mixing	Magnesium stearate	10	10	10	10	10
Total weight (mg)		750	750	750	750	690
Tablet hardness (kp)		14	14	14	14	14

[212] **Test Example 1:** Measurement of content of impurities

[213] In order to evaluate manufacturing of the formulations prepared in Examples and Comparative Examples above, the amount of total impurities was measured. The measurement and quantification of impurities were conducted as follows.

[214] **<Test method>**

[215] Device used: HPLC (Hitachi 2000 series, Japan)

[216] Detector: UV absorptiometer (measurement wavelength: 254 nm)

[217] Column: Inertsil ODS-2 (4.6x150 mm, 5 μ m) or a column equivalent thereto

[218] Flow rate : 1.0 mL/min

[219] Column temperature : 30 °C

[220] Mobile phase

[221]

Time (min)	Phosphate buffer solution (pH 2.5)(%)	Acetonitrile
0	65	35
5	65	35
25	30	70
27	65	35
35	65	35

[222]

[223]

<Calculation method>

[224]

The content of each impurity was determined by calculating the area under the corresponding peak in the chromatogram of high performance liquid chromatography (HPLC) determined under ultraviolet irradiation at 254 nm. The ratio of peak areas between the corresponding impurity and the API was calculated for all impurity species to yield total impurities content.

[225]

[226]

As shown in Tables 8-13 below and Figures 1-6, the inventive pharmaceutical compositions comprising the low melting point stabilizers were capable of significantly suppressing total impurities during tablet manufacture. Such enhancement in manufacturing stability was more impressive for certain impurities, for example those having relative retention time (RRT) of 1.4 or 1.8 in HPLC runs according to above test method (data not shown).

[227]

[228]

[Table 8]

[229]

	Ex. 1	Comp. Ex. 1	Comp. Ex. 2	Comp. Ex. 3	Comp. Ex. 4
Total impurities	0.615	0.733	0.702	0.718	0.735

[230]

As shown in Table 8, and FIG. 1, in the formulations of Comparative Examples 1 to 4 in which no low melting point stabilizer was included, the initial amount of total impurities directly after manufacturing was higher, compared to the formulation of Example 1 which contained polyethylene glycol as low melting point stabilizer. In other words, more impurities were observable in the Comparative Examples tablets tested after tableting, during which the hardness of the tablet increases.

[231]

[232]

To look into the stabilizing effects during manufacturing in more detail, the following tableted formulations (Example 1 and Comparative Example 1, both of

hardness 14) and untabletted formulations (Example 5 and Comparative Example 5) were tested.

[233]

[234] [Table 9]

[235]

	Ex. 1	Ex. 4	Comp. Ex 1	Comp. Ex 5
Total impurities	0.615	0.402	0.733	0.497

[236]

As shown in Table 9 and FIG. 2, this is consistent with the friction of the tableting step promoting the generation of impurities during which the tablet is prepared under elevated pressure in a tablet machine.

[237]

[238] [Table 10]

[239]

	Ex. 1	Ex. 5	Ex. 6	Ex. 7	Ex. 8
Total impurities	0.615	0.627	0.610	0.611	0.621

[240]

As shown in Table 10 and FIG. 3, it can be seen that, when polyethylene glycol 8000 (Ph. Eur.) was added to the formulation as low melting point stabilizer, despite differences in the tablet hardness caused by variation in the compression force of the tableting step, each formulation of Examples 1, 5, 6, 7 and 8 showed acceptable level of total impurities after manufacturing.

[241]

[242] [Table 11]

[242]

	Comp. Ex 1	Comp. Ex. 10	Ex. 2	Ex. 1	Ex. 3
Total impurities	0.733	0.789	0.583	0.615	0.634

[243]

As shown in Table 11 and FIG. 4, Comparative Example 1 had high initial total impurities after tableting. However, inclusion of more than 0.15 parts by weight of polyethylene glycol based on 1 part by weight of the API afforded significant impurity suppression to an acceptable level.

[244]

[245] [Table 12]

[246]

	Ex. 1	Ex. 9	Ex. 10	Ex. 11	Ex. 12	Ex. 13
Total impurities	0.615	0.610	0.612	0.620	0.625	0.632

[247]

Polyethylene glycol functions as a stabilizer and is characterized by having a low melting point. Therefore, in case when a tablet is prepared by employing a low melting point stabilizer having properties similar to those of polyethylene glycol, as shown in Table 12 and FIG. 5, the stabilizer can alleviate friction to which the tablet is exposed

when a pressure increases in the tablet machine, thereby effectively inhibiting the generation of specific impurities from the API.

[248]

[249] [Table 13]

[250]

	Ex. 1	Comp. Ex. 6	Comp. Ex. 7	Comp. Ex. 8	Comp. Ex. 9
Total impurities	0.615	0.742	0.749	0.738	0.754

[251] On the other hand, when a tablet was prepared using a stabilizer with a melting point higher than 80°C, the resultant formulation displayed an impurity profile similar to Comp. Ex. 1, which lacks a stabilizer, as shown in Table 13, and FIG. 6. It can be concluded that with N-(3-(2-(4-(4-methylpiperazin-1-yl)phenylamino)thieno[3,2-d]pyrimidin-4-yloxy)phenyl)acrylamide hydrochloride as an active pharmaceutical ingredient, addition of a low melting stabilizer is important to guarantee a low level of impurities after manufacturing of tablets.

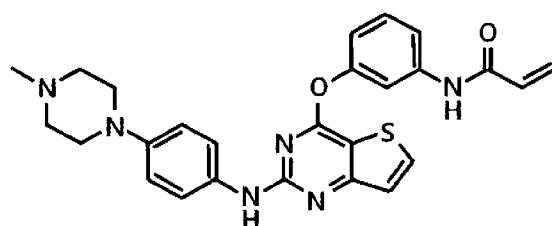
Claims

[Claim 1]

A pharmaceutical composition comprising:

· a compound represented by Formula 1

[Formula 1]



, or a pharmaceutically ac-

ceptable salt thereof, or a hydrate of a pharmaceutically acceptable salt thereof as an active pharmaceutical ingredient, and

· one or more low melting point stabilizer(s) having a melting point of 80°C or less, and

· optionally, one or more pharmaceutically acceptable excipient(s).

[Claim 2]

The pharmaceutical composition according to claim 1, wherein the active pharmaceutical ingredient is a hydrochloride salt of the compound of Formula 1.

[Claim 3]

The pharmaceutical composition according to claim 2, wherein the active pharmaceutical ingredient is a crystalline hydrochloride salt of the compound of Formula 1.

[Claim 4]

The pharmaceutical composition according to claim 3, wherein the active pharmaceutical ingredient is a hydrate of a crystalline hydrochloride salt of the compound of Formula 1.

[Claim 5]

The pharmaceutical composition according to claim 3, wherein the active pharmaceutical ingredient is a crystalline dihydrochloride salt of the compound of Formula 1.

[Claim 6]

The pharmaceutical composition according to claim 5, wherein the active pharmaceutical ingredient is a hydrate, preferably monohydrate, of a crystalline dihydrochloride salt of the compound of Formula 1.

[Claim 7]

The pharmaceutical composition according to claim 5, wherein the active pharmaceutical ingredient is a crystalline dihydrochloride salt of the compound of Formula 1 comprising crystalline form **1X** exhibiting an X-ray powder diffraction (XRPD) pattern comprising peaks at diffraction angles of $2\theta = 5.6^\circ \pm 0.2^\circ$ and $27.3^\circ \pm 0.2^\circ$ when irradiated with a Cu-K α light source.

[Claim 8]

The pharmaceutical composition according to claim 5, wherein the active pharmaceutical ingredient is a crystalline dihydrochloride salt of

- the compound of Formula 1 comprising crystalline form **1X** having a ^{13}C solid state NMR spectrum comprising peaks at the following ^{13}C chemical shifts: 44.6 ± 0.2 ppm and 56.6 ± 0.2 ppm.
- [Claim 9] The pharmaceutical composition according to claim 5, wherein the active pharmaceutical ingredient is a crystalline dihydrochloride salt of the compound of Formula 1 comprising crystalline form **1X** having a ^{13}C solid state NMR spectrum comprising peaks at the following ^{13}C chemical shifts: 149.6 ± 0.2 ppm, 152.6 ± 0.2 ppm and 164.3 ± 0.2 ppm.
- [Claim 10] The pharmaceutical composition according to claim 5, wherein the active pharmaceutical ingredient is a crystalline dihydrochloride salt of the compound of Formula 1 comprising crystalline form **1X** having:
- (a) an X-ray powder diffraction (XRPD) pattern comprising peaks at diffraction angle 2θ values of $5.6^\circ \pm 0.2^\circ$ and $27.3^\circ \pm 0.2^\circ$ when irradiated with a Cu-K α light source; and
 - (b) a ^{13}C solid state NMR spectrum comprising peaks at the following ^{13}C chemical shifts: 44.6 ± 0.2 ppm and 56.6 ± 0.2 ppm.
- [Claim 11] The pharmaceutical composition according to claim 5, wherein the active pharmaceutical ingredient is a crystalline dihydrochloride salt of the compound of Formula 1 comprising crystalline form **1X** having:
- (a) an X-ray powder diffraction (XRPD) pattern comprising peaks at diffraction angle 2θ values of $5.6^\circ \pm 0.2^\circ$ and $27.3^\circ \pm 0.2^\circ$ when irradiated with a Cu-K α light source; and
 - (b) a ^{13}C solid state NMR spectrum comprising peaks at the following ^{13}C chemical shifts: 149.6 ± 0.2 ppm, 152.6 ± 0.2 ppm and 164.3 ± 0.2 ppm.
- [Claim 12] The pharmaceutical composition according to any one of claims 7 to 11, wherein at least 90 wt%, preferably at least 95 wt% of the active pharmaceutical ingredient has crystalline form **1X**.
- [Claim 13] The pharmaceutical composition according to any one of the preceding claims, wherein the active pharmaceutical ingredient represents about 1 to 65 wt% based on the total weight of said composition.
- [Claim 14] The pharmaceutical composition according to any one of the preceding claims, wherein the one or more low melting point stabilizer(s) having a melting point of 80°C or less is/are selected from the group consisting of polyethylene glycols, glyceryl behenate, glyceryl monostearate, sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, ethylene glycol stearate, fatty acids, and any mixtures of

the foregoing.

- [Claim 15] The pharmaceutical composition according to claim 14, wherein the one or more low melting point stabilizer(s) having a melting point of 80°C or less is/are polyethylene glycol(s), preferably with a molecular weight in a range from 1000 to 8000.
- [Claim 16] The pharmaceutical composition according to claim 14, wherein the low melting point stabilizer having a melting point of 80°C or less is PEG 8000.
- [Claim 17] The pharmaceutical composition according to any one of claims 14 to 16, wherein the one or more low melting point stabilizer(s) having a melting point of 80°C or less has/together have a content of about 0.15 to 0.6 parts by weight based on 1 part by weight of the active pharmaceutical ingredient.
- [Claim 18] The pharmaceutical composition according to any one of claims 1 to 17, further comprising one or more diluent(s).
- [Claim 19] The pharmaceutical composition according to claim 18, wherein the one or more diluent(s) is/are selected from mannitol, microcrystalline cellulose, and any mixtures thereof.
- [Claim 20] The pharmaceutical composition according to any one of claims 18 and 19, wherein the one or more diluent(s) represents about 2 to 50 wt% based on the total weight of said composition.
- [Claim 21] The pharmaceutical composition according to any one of claims 1 to 20, further comprising one or more binder(s).
- [Claim 22] The pharmaceutical composition according to claim 21, wherein the binder is hydroxypropyl cellulose.
- [Claim 23] The pharmaceutical composition according to claim 21 or 22, wherein the one or more binder(s) represents about 1 to 25 wt% based on the total weight of said composition.
- [Claim 24] The pharmaceutical composition according to any one of claims 1 to 23, further comprising one or more disintegrant(s).
- [Claim 25] The pharmaceutical composition according to claim 24, wherein the disintegrant is crospovidone.
- [Claim 26] The pharmaceutical composition according to any one of claim 24 or 25, wherein the one or more disintegrant(s) represents about 1 to 30 wt% based on the total weight of said composition.
- [Claim 27] The pharmaceutical composition according to any one of claims 1 to 26, further comprising one or more lubricant(s).
- [Claim 28] The pharmaceutical composition according to claim 27, wherein the

lubricant is magnesium stearate.

[Claim 29] The pharmaceutical composition according to claim 27 or 28, wherein the one or more lubricant(s) represents about 0.5 to 5 wt% based on the total weight of said composition.

[Claim 30] The pharmaceutical composition according to any one of claims 1 to 29, further comprising one or more coating agent(s).

[Claim 31] The pharmaceutical composition according to claim 30, wherein the one or more coating agent(s) represents about 1 to 10 wt% based on the total weight of said composition.

[Claim 32] The pharmaceutical composition according to claim 1, wherein said composition comprises

Ingredients	amount (wt%)
active pharmaceutical ingredient of Formula 1, or a pharmaceutically acceptable salt thereof, or a hydrate of a pharmaceutically acceptable salt thereof	55-65
one or more low melting point stabilizer(s) having a melting point of 80°C or less	10-20
one or more diluent(s)	10-20
one or more binder(s)	1-5
one or more disintegrant(s)	1-5
one or more lubricant(s)	0.5-5
optionally one or more additional excipient(s)	ad 100%

[Claim 33] The pharmaceutical composition according to claim 1, wherein said composition comprises

Ingredients	amount (wt%)
active pharmaceutical ingredient of Formula 1, or a pharmaceutically acceptable salt thereof, or a hydrate of a pharmaceutically acceptable salt thereof	55-65
PEG 8000	10-20
mixture of mannitol and microcrystalline cellulose	10-20
hydroxypropyl cellulose	1-5
crospovidone	1-5
Magnesium stearate	0.5-5
one or more coating agent(s)	ad 100%

- [Claim 34] A pharmaceutical dosage form comprising a pharmaceutical composition according to any one of claims 1 to 33.
- [Claim 35] A pharmaceutical dosage form according to claim 34, wherein said dosage form is a tablet.
- [Claim 36] A method of preventing and/or treating cancers, tumors, inflammatory diseases, autoimmune diseases or immune-mediated diseases in a subject, preferably a human, in need thereof comprising administering a pharmaceutical composition according to any one of claims 1 to 33 or a pharmaceutical dosage form according to claim 34 or 35 to a subject, preferably a human, in need thereof.
- [Claim 37] A pharmaceutical composition according to any one of claims 1 to 33 or a pharmaceutical dosage form according to claim 34 or 35 for preventing and/or treating cancers, tumors, inflammatory diseases, autoimmune diseases or immune-mediated diseases.
- [Claim 38] The method of preventing and/or treating cancers according to claim 36 or the pharmaceutical composition for preventing and/or treating cancers according to claim 37 or the pharmaceutical dosage form for preventing and/or treating cancers according to claim 37, wherein the cancer is induced by an epidermal growth factor receptor (EGFR) tyrosine kinase or a variant thereof.
- [Claim 39] The method of preventing and/or treating cancers according to claim 38 or the pharmaceutical composition for preventing and/or treating cancers according to claim 38 or the pharmaceutical dosage form for preventing and/or treating cancers according to claim 38, wherein the cancer is induced by an epidermal growth factor receptor (EGFR)

tyrosine kinase harboring an EGFR exon 20 insertion or an EGFR exon 19 deletion (Del19) or an EGFR L858R mutation or an EGFR T790M mutation, or any combinations thereof.

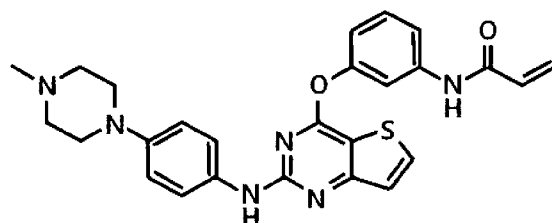
[Claim 40]

The method of preventing and/or treating cancers according to any one of claims 36, 38 and 39 or the pharmaceutical composition for preventing and/or treating cancers according to any one of claims 37 to 39 or the pharmaceutical dosage form for preventing and/or treating cancers according to anyone of claims 37 to 39, wherein the cancer is lung cancer, preferably non-small cell lung cancer (NSCLC), in particular NSCLC adenocarcinoma.

[Claim 41]

A dry granulation process for making a pharmaceutical dosage form comprising as an active pharmaceutical ingredient a compound of formula 1

[Formula 1]



, or a pharmaceutically ac-

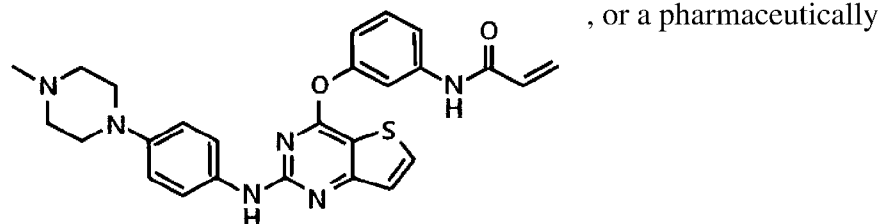
ceptable salt thereof, or a hydrate of a pharmaceutically acceptable salt thereof, and one or more excipients, wherein said process comprises the steps of:

- 1.1 pre-mixing the one or more low melting point stabilizer(s), the active pharmaceutical ingredient, part of the one or more lubricant(s), the one or more binder(s) and the one or more diluent(s);
- 1.2 dry granulating the pre-mix from step 1.1 using a dry granulator to obtain granules;
2. adding the one or more disintegrant(s) and the rest of the one or more lubricant(s) in one step or in subsequent steps to the granules from step 1.2 and mixing to obtain the final blend;
3. compressing the final blend from the previous step into tablet cores using a tablet press;
- 4.1 optionally, suspending a ready-to-use coating mixture in a mixture of purified water and alcohol at room temperature to obtain a film-coating suspension; and
- 4.2 optionally, coating the tablet cores from step 3 with the film-coating suspension from step 4.1.

[Claim 42]

A dry granulation process for making a pharmaceutical dosage form comprising as an active pharmaceutical ingredient a compound of formula 1

[Formula 1]



acceptable salt thereof, or a hydrate of a pharmaceutically acceptable salt thereof, and one or more excipients, wherein said process comprises the steps of:

1.1 pre-mixing PEG 8000, the active pharmaceutical ingredient, part of magnesium stearate, hydroxypropyl cellulose, microcrystalline cellulose and mannitol;

1.2 dry granulating the pre-mix from step 1.1 using a dry granulator to obtain granules;

2. adding crospovidone and the rest of magnesium stearate in one step or in subsequent steps to the granules from step 1.2 and mixing to obtain the final blend;

3. compressing the final blend from the previous step into tablet cores using a tablet press;

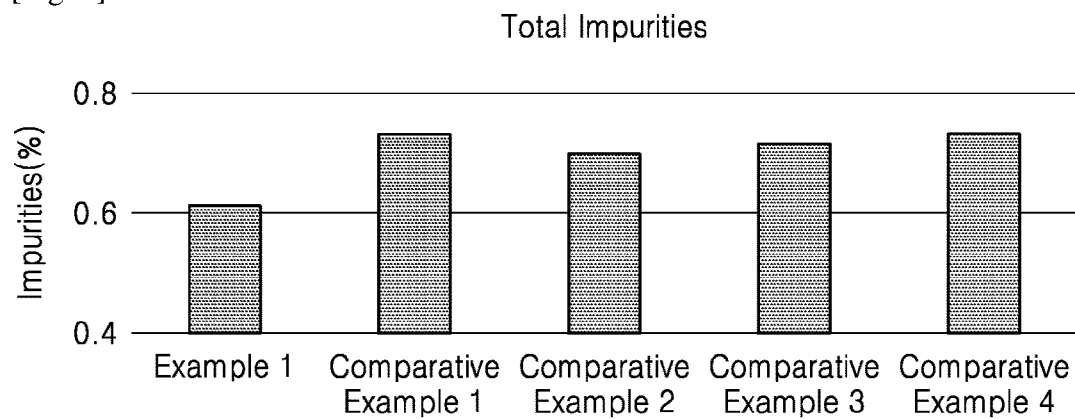
4.1 optionally, suspending a ready-to-use coating mixture in a mixture of purified water and alcohol at room temperature to obtain a film-coating suspension; and

4.2 optionally, coating the tablet cores from step 3 with the film-coating suspension from step 4.1.

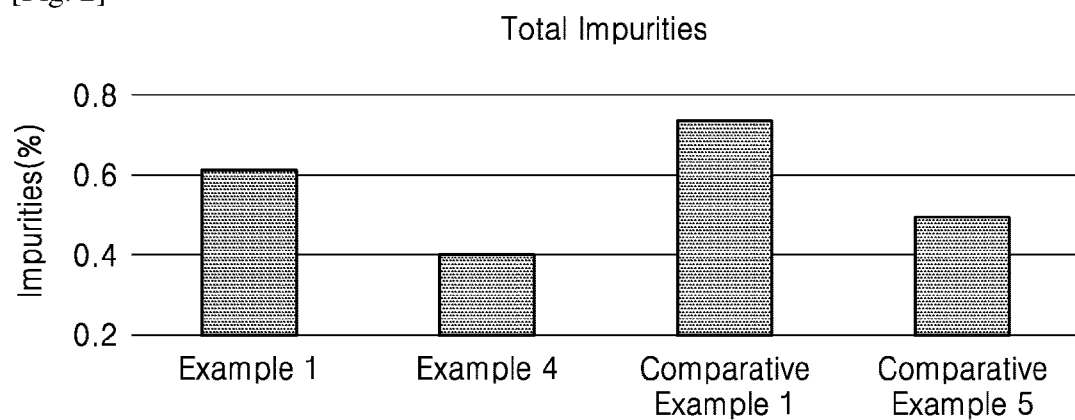
[Claim 43]

A pharmaceutical dosage form obtainable by the process according to claim 40 or 41.

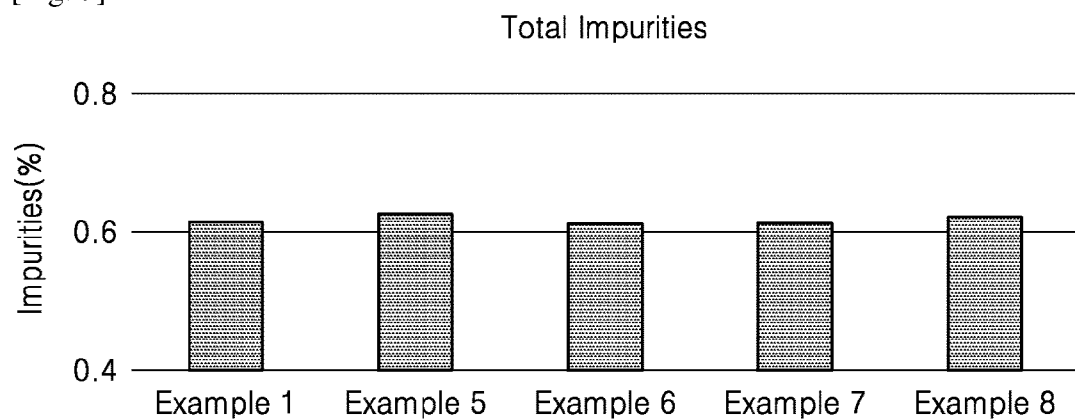
[Fig. 1]



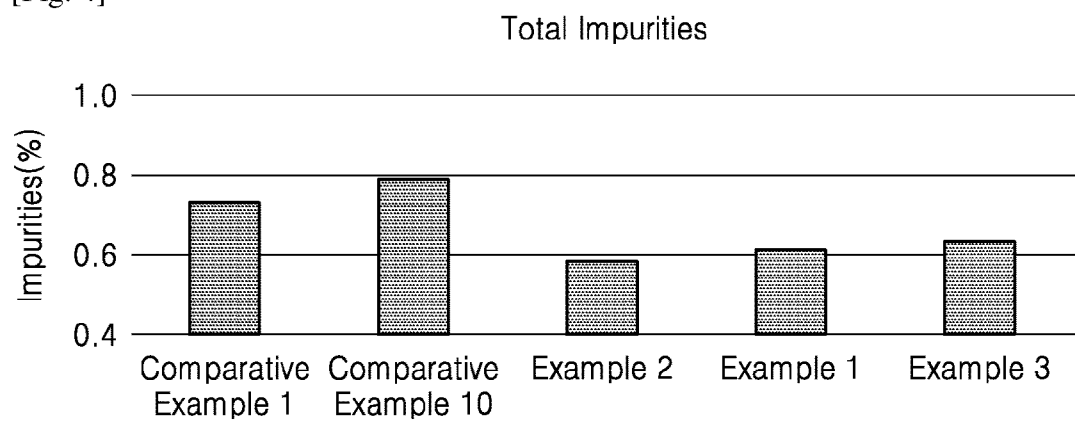
[Fig. 2]



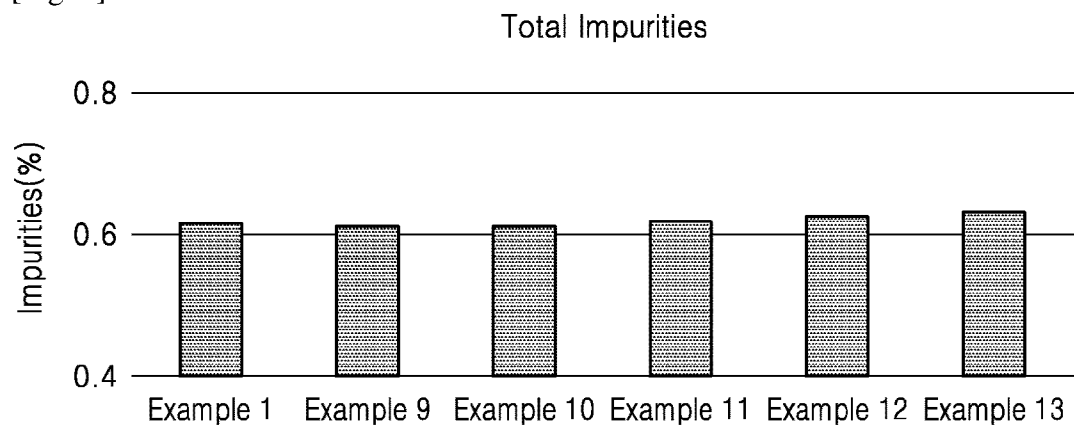
[Fig. 3]



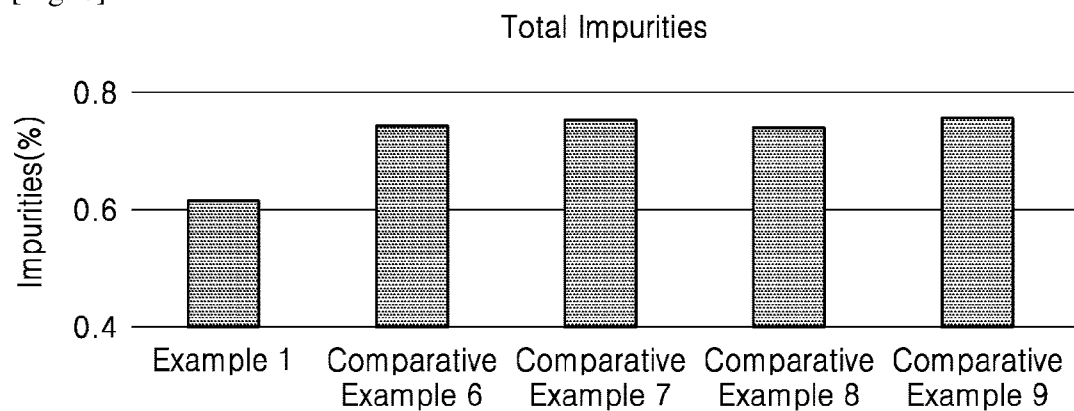
[Fig. 4]



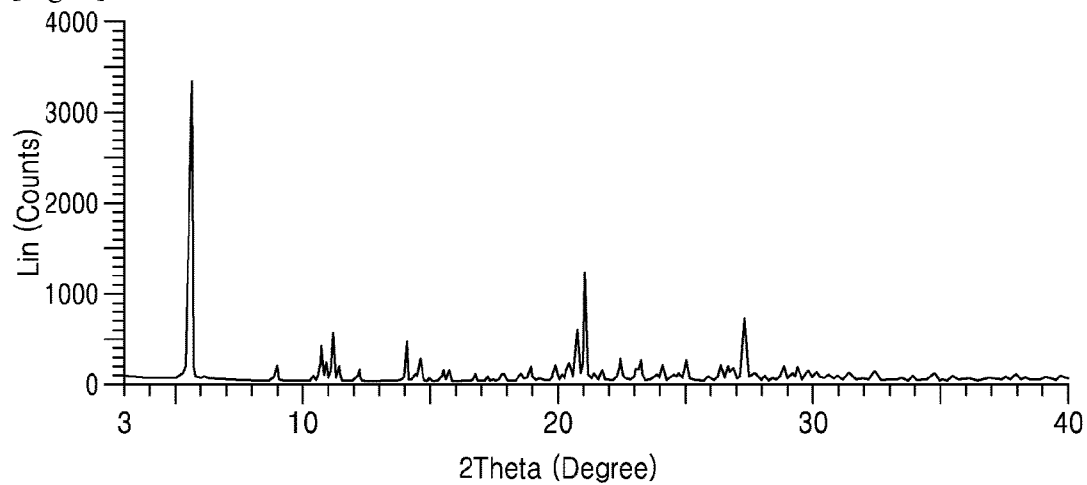
[Fig. 5]



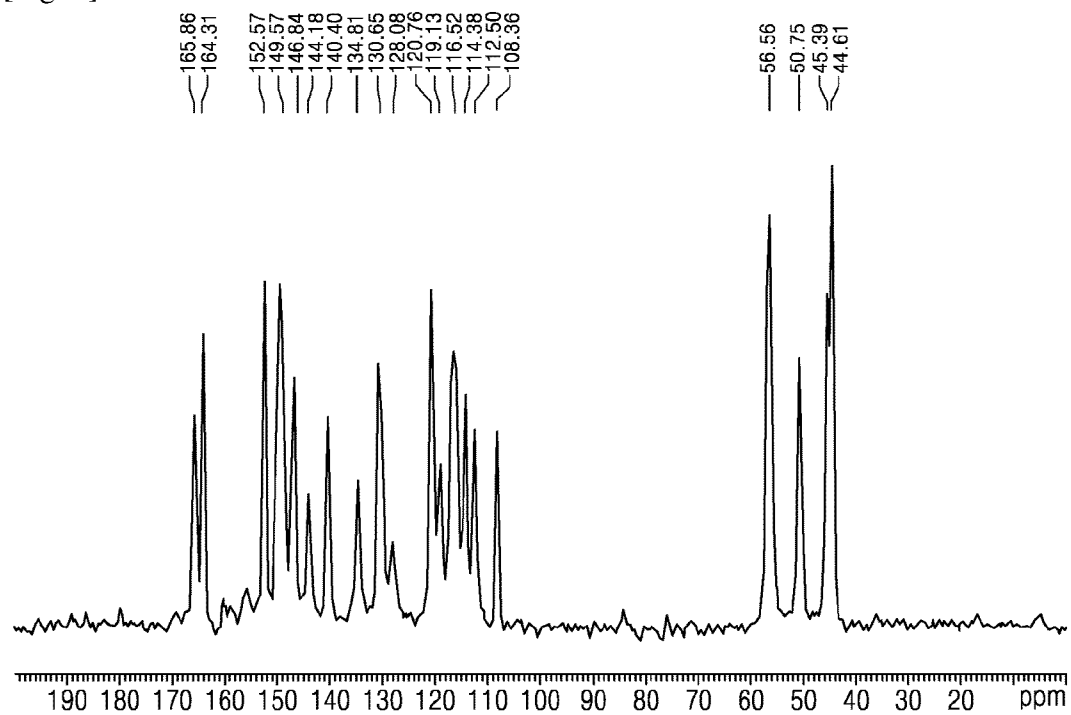
[Fig. 6]



[Fig. 7]



[Fig. 8]



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2017/005480**A. CLASSIFICATION OF SUBJECT MATTER****A61K 31/519(2006.01)i, A61K 31/496(2006.01)i, A61K 47/10(2006.01)i, A61K 47/38(2006.01)i, C07D 495/04(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 31/519; C07D 409/12; A61P 43/00; A61K 31/195; A61K 31/496; C07D 403/14; A61K 31/4743; A61K 9/20; C07D 495/04; C07D 473/16; A61K 47/10; A61K 47/38

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: stabilizer, low melting point, PEG 8000, dry granulation, impurity

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011-162515 A2 (HANMI HOLDINGS CO., LTD.) 29 December 2011 See page 33 and claims 1, 3, 11.	1-12, 32, 33, 41, 42
Y	US 2008-0194687 A1 (RAMPOLDI, L. et al.) 14 August 2008 See claims 1, 5, 7, 8.	1-12, 32, 33, 41, 42
Y	US 2007-0154545 A1 (HRAKOVSKY, J. et al.) 05 July 2007 See claims 1, 2, 8, 12, 15, 18, 23.	32, 33, 41, 42
A	WO 2008-001201 A2 (WOCKHARDT LTD.) 03 January 2008 See the whole document.	1-12, 32, 33, 41, 42
A	WO 2010-129053 A2 (DANA FARBER CANCER INSTITUTE et al.) 11 November 2010 See the whole document.	1-12, 32, 33, 41, 42



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

08 August 2017 (08.08.2017)

Date of mailing of the international search report

08 August 2017 (08.08.2017)

Name and mailing address of the ISA/KR

International Application Division

Korean Intellectual Property Office

189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea



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INTERNATIONAL SEARCH REPORTInternational application No.
PCT/KR2017/005480**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 36, 38-40
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 36 and 38-40 pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv), to search.
2. ☒ Claims Nos.: 15, 16, 19, 22, 25, 28, 31, 35, 39
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 15, 16, 19, 22, 25, 28, 31, 35 and 39 each refer to one of claims which are not drafted in accordance with PCT Rule 6.4(a).
3. ☒ Claims Nos.: 13, 14, 17, 18, 20, 21, 23, 24, 26, 27, 29, 30, 34, 36-38, 40, 43
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2017/005480

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2017/005480

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