

SOLID DISPERSIONS AND PHARMACEUTICAL COMPOSITIONS COMPRISING A SUBSTITUTED INDANE AND METHODS FOR THE PREPARATION AND USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/752,685, filed October 30, 2018, which is incorporated by reference in the disclosure of this application.

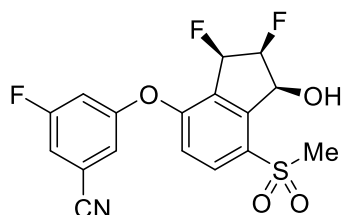
BACKGROUND OF THE INVENTION

[0002] An adequate supply of oxygen to tissues is essential in maintaining mammalian cell function and physiology. A deficiency in oxygen supply to tissues is a characteristic of a number of pathophysiologic conditions in which there is insufficient blood flow to provide adequate oxygenation. The hypoxic (low oxygen) environment of tissues activates a signaling cascade that drives the induction or repression of the transcription of a multitude of genes implicated in events such as angiogenesis (neo-vascularization), glucose metabolism, and cell survival/death. A key to this hypoxic transcriptional response lies in the transcription factors, the hypoxia-inducible factors (HIF). HIFs are dysregulated in a vast array of cancers through hypoxia-dependent and independent mechanisms and expression is associated with poor patient prognosis.

[0003] HIFs consist of an oxygen-sensitive HIF α subunit and a constitutively expressed HIF β subunit. When HIFs are activated, the HIF α and HIF β subunits assemble a functional heterodimer (the α subunit heterodimerizes with the β subunit). Both HIF α and HIF β have two identical structural characteristics, a basic helix-loop-helix (bHLH) and PAS domains (PAS is an acronym referring to the first proteins, PER, ARNT, SIM, in which this motif was identified). There are three human HIF α subunits (HIF-1 α , HIF-2 α , and HIF-3 α) that are oxygen sensitive. Among the three subunits, HIF-1 α is the most ubiquitously expressed and induced by low oxygen concentrations in many cell and tissue types. HIF-2 α is highly similar to HIF-1 α in both structure and function, but exhibits more restricted cell and tissue-specific expression, and might also be differentially regulated by nuclear translocation. HIF-3 α also exhibits conservation with HIF-1 α and HIF-2 α in the HLH and PAS domains. HIF-1 β (also referred to as ARNT - Aryl Hydrocarbon Receptor Nuclear Translocator), the dimerization partner of the HIF α subunits, is constitutively expressed in all cell types and is not regulated by oxygen concentration.

SUMMARY

[0004] The present disclosure provides a solid dispersion comprising a compound of Formula (I):



Formula (I).

In some examples, the solid dispersion further comprises a pharmaceutically acceptable polymer. The polymer may comprise hydrophobic regions and hydrophilic regions. In some examples, the polymer is selected from cellulose esters; cellulose ethers; polyalkylene oxides; polyvinyl chlorides; polyvinyl alcohols; polyacrylates; polymethacrylates; homopolymers and copolymers of N-vinyl lactams, polyacrylamides, and vinyl acetates; graft copolymers of polyethylene glycol, polyvinyl caprolactam, and polyvinyl acetate; oligosaccharides; polysaccharides; and mixtures thereof. In some examples, the polymer is a cellulose ester or a cellulose ether. In some examples, the polymer is selected from methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, cellulose acetate phthalate (CAP), hypromellose (HPMC), hydroxypropyl cellulose, hypromellose phthalate (HPMCP), hypromellose acetate succinate (HPMCAS), poly(ethylene glycol) methyl, poly-ethylene glycol vinyl acetate vinylcaprolactam (Soluplus), polyethylene glycol 6000 (PEG 6000), polyvinylpyrrolidone (PVP), polyvinylpyrrolidone vinyl acetate (PVP-VA), Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1(e.g., Eudragit RS 100), methacrylic acid copolymer type B (e.g., Eudragit S 100), methacrylic acid copolymer type B, polyvinyl acetate phthalate (e.g., Sureteric), polyoxyethylene-polyoxypropylene block copolymer (e.g., Pluronic F-68) and polyoxyethylene (20) sorbitan monooleate (Tween 80). In some examples, the polymer is selected from HPMCAS, CAP and poly-ethylene glycol vinyl acetate vinylcaprolactam (e.g., Soluplus). In some examples, the polymer is selected from HPMCAS-L, HPMCAS-M and HPMCAS-H, such as HPMCAS-H.

[0005] In some examples, the compound of Formula (I) is present in an amount from 1% to 50% by weight of the solid dispersion. In some examples, the polymer is present in an amount from 50% to 99% by weight of the solid dispersion. In some examples, the compound of Formula (I) is present in an amount from 15% to 35% by weight of the solid dispersion. In some examples, the polymer is present in an amount from 65% to 85% by weight of the solid dispersion. In some examples, the compound of Formula (I) is present in an amount from 22.5% to 27.5% by weight of the solid dispersion. In some examples, the polymer is present in an amount from 72.5% to 77.5% by weight of the solid dispersion. In some examples, the compound of Formula (I) is present in an amount of about 25% by weight of the solid dispersion. In some examples, the polymer is present in an amount of about 75% by weight of the solid dispersion. In some examples, the weight ratio of the compound of Formula (I) to the polymer is from 1:99 to 1:1, such as from 15:85 to 35:65. In some examples, the weight ratio of the compound of Formula (I) to the polymer is from 22.5:77.5 to 27.5:72.5, such as about 25:75.

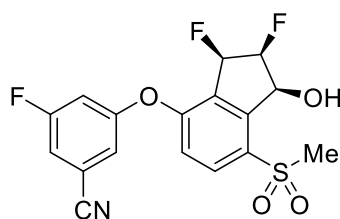
[0006] In some examples, the solid dispersion is substantially non-crystalline. In some examples, the solid dispersion is amorphous. In some examples, the solid dispersion exhibits a glass transition temperature (T_g) between 80 to 100 °C, such as between 82 to 92 °C. In some examples, the solid dispersion exhibits a glass transition temperature (T_g) at about 87 °C, such as 87 ± 3 °C. In some examples, the solid dispersion comprises less than 2% of impurities by weight. In some examples, the solid dispersion comprises less than 2% of impurities by weight after three months of storage at room temperature. In some examples, the solid dispersion comprises less than 2% of water by weight. In some examples, the solid dispersion comprises less than 2% of water after three months of storage at room temperature. In some examples, the solid dispersion comprises less than 5000 ppm of acetone.

In some examples, the enantiomeric excess of the compound of Formula (I) is at least 95%, such as at least 99%.

[0007] In some examples, the particle size distribution of the solid dispersion is characterized by a d_{10} of less than 6 μm . In some examples, the particle size distribution of the solid dispersion is characterized by a d_{50} of less than 18 μm . In some examples, the particle size distribution of the solid dispersion is characterized by a d_{90} of less than 45 μm . In some examples, the solid dispersion is characterized by a bulk density of at least 0.20 g/mL. In some examples, the solid dispersion is characterized by a tapped density of at least 0.35 g/mL. In some examples, the particle size distribution of the solid dispersion is characterized by a d_{10} of less than 15 μm . In some examples, the particle size distribution of the solid dispersion is characterized by a d_{50} of less than 45 μm . In some examples, the particle size distribution of the solid dispersion is characterized by a d_{90} of less than 90 μm . In some examples, the solid dispersion is characterized by a bulk density of at least 0.15 g/mL. In some examples, the solid dispersion is characterized by a tapped density of at least 0.30 g/mL. In some examples, the solid dispersion is characterized by a C_{max} GB of at least 300 $\mu\text{gA/mL}$. In some examples, the solid dispersion is characterized by a C_{max} FaSSIF of at least 400 $\mu\text{gA/mL}$. In some examples, the solid dispersion is characterized by an AUC FaSSIF of at least 40,000 $\mu\text{gA/mL}$. In some examples, the solid dispersion is characterized by an AUC FaSSIF of at least 85,000 $\mu\text{gA/mL}$. In some examples, the solid dispersion is obtained by spray drying. In some examples, the solid dispersion is obtained by melting, solvent evaporation, spray drying, fusion, kneading, co-grinding, lyophilization, hot melt extrusion, melt agglomeration, or supercritical fluid technology.

[0008] The present disclosure also provides an amorphous solid dispersion comprising, by weight relative to the total weight of the solid dispersion:

(a) 22.5% to 27.5% of a compound of Formula (I):



Formula (I); and

(b) 72.5% to 77.5% of HPMCAS.

[0009] The present disclosure also provides a pharmaceutical composition comprising a solid dispersion described herein and a pharmaceutically acceptable excipient. In some examples, the pharmaceutical composition is a capsule or a tablet. In some examples, the pharmaceutical composition is formulated for oral delivery. In some examples, the pharmaceutically acceptable excipient comprises a binder, a filler, a disintegrant, a lubricant, a glidant, or a combination thereof. In some examples, the solid dispersion is present in an amount from 15% to 50% by weight of the pharmaceutical composition. In some examples, the pharmaceutical composition comprises, by weight relative to the total weight of the pharmaceutical composition: (a) 15% to 50% of the solid dispersion; (b) 20% to 50% of a binder; (c) 20% to 40% of a filler; (d) 1.0% to 5.0% of a disintegrant; and

(e) 0.25% to 1.25% of a lubricant. In some examples, the binder is microcrystalline cellulose. In some examples, the filler is mannitol. In some examples, the disintegrant is croscarmellose sodium. In some examples, the lubricant is magnesium stearate. In some examples, the pharmaceutical composition further comprises, by weight relative to the total weight of the pharmaceutical composition, 0.1% to 1.25% of a glidant, optionally wherein the glidant is colloidal silicon dioxide. In some examples, the pharmaceutical composition further comprises a coating, optionally wherein the coating is a poly(vinyl) alcohol polymer-based coating. In certain examples, the poly(vinyl) alcohol polymer-based coating in the pharmaceutical composition further comprises polyethylene glycol. In specific examples, the pharmaceutical composition has a coating which is OpaDry II.

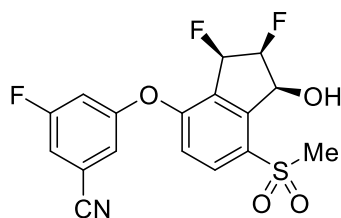
[0010] The present disclosure also provides a packaged solid dispersion comprising a solid dispersion described herein and a desiccant. In some examples, the desiccant is SiO₂. In some examples, the packaging comprises a low moisture vapor transmission container.

[0011] The present disclosure also provides a method of treating von Hippel-Lindau (VHL) disease, comprising administering to a subject in need thereof an effective amount of a solid dispersion or a pharmaceutical composition described herein. In some examples, the subject also suffers from a hemangioblastoma, a pheochromocytoma, a pancreatic neuroendocrine tumor or renal cell carcinoma, such as renal cell carcinoma. The present disclosure also provides a method of treating renal cell carcinoma, comprising administering to a subject in need thereof an effective amount of a solid dispersion or a pharmaceutical composition described herein. In some examples, the renal cell carcinoma is clear cell renal cell carcinoma.

[0012] The present disclosure also provides a method of treating a HIF-2 α -mediated disease or condition, comprising administering to a subject in need thereof a therapeutically effective amount of a solid dispersion or a pharmaceutical composition described herein. In some examples, the disease or condition is cancer. In some examples, the disease or condition is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, and colitis. The present disclosure also provides a method of inhibiting HIF-2 α , comprising contacting HIF-2 α with an effective amount of a solid dispersion or a pharmaceutical composition described herein. The methods described herein may further comprise administering a second therapeutic agent.

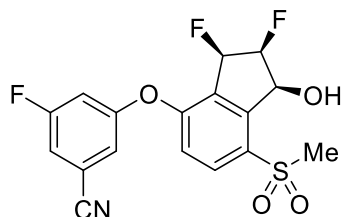
[0013] The present disclosure also provides a process for preparing a solid dispersion described herein, comprising: (a) providing a solution of the compound of Formula (I) and the polymer in a solvent; and (b) removing the solvent to provide the solid dispersion. In some examples, the solvent comprises acetone, methyl ethyl ketone, tetrahydrofuran, water, or a combination thereof. In some examples, the solvent comprises acetone. In some examples, the solvent comprises up to 5% water. In some examples, the solvent is removed by freeze evaporation or spray drying. In some examples, the solvent is removed by spray drying. The process may further comprise drying the solid dispersion in a tray dryer, thereby removing residual solvent. In some examples, the solution comprises 8% to 14% solids by weight.

[0014] The present disclosure also provides a pharmaceutical solid dosage form for oral delivery of a compound of Formula (I),



Formula (I),

wherein the solid dosage form comprises (a) a solid dispersion comprising a compound of Formula (I); and (b) one or more pharmaceutically acceptable excipients. In one aspect, the present disclosure provides a pharmaceutical solid dosage form for oral delivery of a compound of Formula (I),



Formula (I),

wherein the solid dosage form comprises a solid dispersion comprising the compound of Formula (I) and one or more pharmaceutically acceptable excipients, and the solid dosage form is a capsule or a tablet. In some examples, the solid dosage form is a capsule or a tablet. In some examples, the solid dosage form is a tablet. In some examples, the one or more pharmaceutically acceptable excipients comprise a binder, a filler, a disintegrant and a lubricant. In some examples, the solid dispersion is present in an amount from 15% to 50% by weight of the solid dosage form. In some examples, the solid dispersion comprises a pharmaceutically acceptable polymer. In some examples, the pharmaceutically acceptable polymer is HPMCAS. In some examples, the polymer is present in an amount from 15% to 35% by weight of the solid dosage form. In some examples, the compound of Formula (I) is present in an amount from 1% to 15% by weight of the solid dosage form. The solid dosage form may comprise 5 mg to 100 mg of the compound of Formula (I), such as about 10 mg of the compound of Formula (I) or about 40 mg of the compound of Formula (I).

[0015] A solid dosage form of the present disclosure may comprise a binder in an amount from 20% to 50% by weight of the solid dosage form, optionally wherein the binder is microcrystalline cellulose. The solid dosage form may comprise a filler in an amount from 20% to 40% by weight of the solid dosage form. In some examples, the solid dosage form comprises an intragranular filler and an extragranular filler, wherein the intragranular filler is present in an amount from 12% to 22% by weight of the solid dosage form, and wherein the extragranular filler is present in an amount from 8% to 18% of the solid dosage form. In some examples, the filler is mannitol. The solid dosage form may comprise a disintegrant in an amount from 1.0% to 5.0% by weight of the solid dosage form. In some examples, the solid dosage form comprises an intragranular disintegrant and an extragranular disintegrant, wherein the intragranular disintegrant is present in an amount from 0.9% to 3.0% by weight of the solid dosage form, and wherein the extragranular disintegrant is present in an amount from 0.1% to

2.0% of the solid dosage form. In some examples, the disintegrant is croscarmellose sodium. The solid dosage form may comprise a lubricant in an amount from 0.25% to 1.25% by weight of the solid dosage form. In some examples, the solid dosage form comprises an intragranular lubricant and an extragranular lubricant, wherein the intragranular lubricant is present in an amount from 0.15% to 0.75% by weight of the solid dosage form, and wherein the extragranular lubricant is present in an amount from 0.10% to 0.50% of the solid dosage form. In some examples, the lubricant is magnesium stearate. In some examples, the solid dosage form comprises a glidant in an amount from 0.10% to 1.25% by weight of the solid dosage form. In some examples, the glidant is colloidal silicon dioxide, such as CabOSil. In some examples, the solid dosage form comprises a coating. In some examples, the coating is PVA-based, such as OpaDry II.

[0016] A solid dosage form of the present disclosure may exhibit a hardness of between 5 and 25 KP. In some examples, the weight of the solid dosage form is between 50 and 750 mg, such as about 125 mg or about 500 mg. In some examples, the solid dosage form comprises less than 2% of impurities by weight. In some examples, the solid dosage form comprises less than 2% of impurities by weight after six months of storage at room temperature. In some examples, the solid dosage form comprises less than 3% of water by weight. In some examples, the solid dosage form comprises less than 3% of water by weight after six months of storage at room temperature. In some examples, the solid dosage form is characterized by a disintegration time between 1 and 5 minutes.

[0017] The present disclosure also provides a packaged solid dosage form comprising a solid dosage form described herein and a desiccant. In some examples, the desiccant is SiO₂. In some examples, the packaging comprises a low moisture vapor transmission container. The packaged dosage form may further comprise a cotton, rayon or polyester coil. The present disclosure also provides a kit comprising a solid dosage form described herein and instructions for administering the solid dosage form to a subject in need thereof.

[0018] The present disclosure also provides a method of treating von Hippel-Lindau (VHL) disease, comprising administering to a subject in need thereof a solid dosage form described herein. In another aspect, the present disclosure provides a solid dosage form of the present disclosure for use in treating von Hippel-Lindau (VHL) disease in a subject. In another aspect, the present disclosure provides use of a solid dosage form of the present disclosure in the manufacture of a medicament for the treatment of von Hippel-Lindau (VHL) disease in a subject. In some examples, the subject also suffers from a hemangioblastoma, a pheochromocytoma, a pancreatic neuroendocrine tumor or renal cell carcinoma, such as renal cell carcinoma. The present disclosure also provides a method of treating renal cell carcinoma, comprising administering to a subject in need thereof a solid dosage form described herein. In another aspect, the present disclosure provides a solid dosage form of the present disclosure for use in treating renal cell carcinoma in a subject. In another aspect, the present disclosure provides use of a solid dosage form of the present disclosure in the manufacture of a medicament for the treatment of renal cell carcinoma. In some examples, the renal cell carcinoma is clear cell renal cell carcinoma.

[0019] The present disclosure also provides a method of treating a HIF-2 α -mediated disease or condition, comprising administering to a subject in need thereof a solid dosage form described herein. In some examples, the disease or condition is cancer. In some examples, the disease or condition is selected from renal cell carcinoma, von Hippel-Lindau disease, pulmonary arterial hypertension, glioblastoma, and colitis. The present disclosure also provides a method of inhibiting HIF-2 α , comprising contacting HIF-2 α with a solid dosage form described herein. Any of the subject methods may further comprise administering a second therapeutic agent.

[0020] The present disclosure also provides a process for preparing a solid dosage form described herein, comprising: (a) mixing the compound of Formula (I) and the one or more pharmaceutically acceptable excipients to form milled granules; and (b) compressing the granules by applying a compression force of 5 kN to 20 kN. The present disclosure also provides a process for preparing a solid dosage form described herein, comprising: (a) blending a compound of Formula (I), a binder, a filler, a disintegrant and a lubricant, thereby forming a blended mixture; (b) granulating the blended mixture, optionally using a roller compactor, thereby forming a granulated mixture; (c) mixing a second filler, a second disintegrant and a second lubricant with the granulated mixture, thereby forming a tableting mixture; and (d) compressing the tableting mixture into a tablet, wherein the filler and the second filler are the same or different; the disintegrant and the second disintegrant are the same or different; and the lubricant and the second lubricant are the same or different. In some examples, the

process further comprises mixing a glidant with the granulated mixture of (c). In some examples, the process further comprises coating the tablet with a coating, such as OpaDry II.

INCORPORATION BY REFERENCE

[0021] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] **FIG. 1** depicts an XRPD pattern of crystalline compound of Formula (I).

[0023] **FIG. 2** depicts an overlay of diffractograms of seven solid dispersions of a compound of Formula (I), crystalline compound of Formula (I), and spray dried compound of Formula (I). The latter two diffractograms are characterized by sharp, distinct peaks.

[0024] **FIG. 3** depicts an overlay of diffractograms of three solid dispersions of a compound of Formula (I) and crystalline compound of Formula (I).

[0025] **FIG. 4** provides SEM images of solid dispersions of the compound of Formula (I) and HPMCAS-H (left), CAP (middle) or SOLUPLUS (right) at 5,000x magnification.

[0026] **FIG. 5** depicts three sets of overlays of XRPD patterns of solid dispersions of the compound of Formula (I) and crystalline compound of Formula (I). In each set, the top broad curve represents a solid dispersion stored open for 4 weeks at 40 °C and 75% RH, the middle broad curve represents a solid dispersion stored closed for 4 weeks at the same conditions, and the bottom broad curve represents a solid dispersion prior to storage (t=0). The curve containing sharp, distinct peaks represents crystalline compound of Formula (I).

[0027] **FIG. 6** depicts an XRPD pattern of a 1:3 compound of Formula (I):HPMCAS-H solid dispersion.

[0028] **FIG. 7** provides SEM images of a 1:3 compound of Formula (I):HPMCAS-H solid dispersion at 500x (left) and 5,000x (right) magnification.

[0029] **FIG. 8** shows the particle size distribution of a solid dispersion.

[0030] **FIG. 9** depicts HPLC traces of a blank (bottom trace), compound of Formula (I) (middle trace), and a solid dispersion of a compound of Formula (I) and HPMCAS-H (top trace).

[0031] **FIG. 10** depicts mDSC profiles of a 1:3 compound of Formula (I):HPMCAS-H solid dispersion after 24 hours of exposure to 33% humidity (top curve), 50% humidity (middle curve) or 75% humidity (bottom curve).

[0032] **FIG. 11** provides XRPD patterns of wet solid dispersions held at room temperature for 1 day, 3 days, 5 days, or 7 days (top to bottom curves, respectively).

[0033] **FIG. 12** provides an XRPD pattern of a 1:3 compound of Formula (I):HPMCAS-H solid dispersion.

[0034] **FIG. 13** shows the particle size distribution of a solid dispersion.

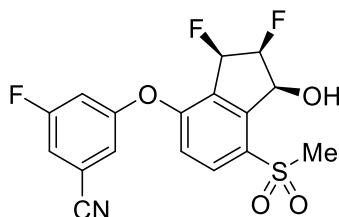
[0035] **FIG. 14** depicts a process flow chart for preparing a solid dosage form.

[0036] **FIG. 15** shows the dissolution profile of 10 and 40 mg tablets.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical solid dosage form for oral delivery of a compound of Formula (I),



Formula (I),

wherein the solid dosage form comprises a solid dispersion comprising the compound of Formula (I) and one or more pharmaceutically acceptable excipients, and the solid dosage form is a capsule or a tablet.

2. The solid dosage form of claim 1, wherein the solid dosage form is a tablet.
3. The solid dosage form of claim 1 or 2, wherein the one or more pharmaceutically acceptable excipients comprise a binder, a filler, a disintegrant and a lubricant.
4. The solid dosage form of claim 3, wherein the one or more pharmaceutically acceptable excipients further comprise a glidant.
5. The solid dosage form of any one of claims 1 to 4, wherein the solid dispersion is present in an amount from 15% to 50% by weight of the solid dosage form.
6. The solid dosage form of any one of claims 1 to 5, wherein the solid dispersion comprises a pharmaceutically acceptable polymer.
7. The solid dosage form of claim 6, wherein the pharmaceutically acceptable polymer is HPMCAS.
8. The solid dosage form of claim 6 or 7, wherein the pharmaceutically acceptable polymer is present in an amount from 15% to 35% by weight of the solid dosage form.
9. The solid dosage form of any one of claims 1 to 8, wherein the compound of Formula (I) is present in an amount from 1% to 15% by weight of the solid dosage form.
10. The solid dosage form of any one of claims 1 to 8, comprising 5 mg to 100 mg of the compound of Formula (I).
11. The solid dosage form of any one of claims 1 to 10, comprising about 10 mg of the compound of Formula (I).
12. The solid dosage form of any one of claims 1 to 10, comprising about 40 mg of the compound of Formula (I).
13. A solid dosage form of any one of claims 1 to 12 for use in treating von Hippel-Lindau (VHL) disease in a subject.
14. Use of a solid dosage form of any one of claims 1 to 12 in the manufacture of a medicament for the treatment of von Hippel-Lindau (VHL) disease in a subject.

15. The solid dosage form for use of claim 13 or the use of claim 14, wherein the subject also suffers from a hemangioblastoma, a pheochromocytoma, a pancreatic neuroendocrine tumor or renal cell carcinoma.

16. The solid dosage form for use of claim 13 or the use of claim 14, wherein the subject suffers from renal cell carcinoma.

17. A solid dosage form of any one of claims 1 to 12 for use in treating renal cell carcinoma in a subject.

18. Use of a solid dosage form of any one of claims 1 to 12 in the manufacture of a medicament for the treatment of renal cell carcinoma.

19. The solid dosage form for use of claim 16 or 17 or the use of claim 16 or 17, wherein the renal cell carcinoma is clear cell renal cell carcinoma.