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(54) Title: NANOPARTICULATE SORAFENIB FORMULATIONS

(57) Abstract: The present invention is directed to compositions comprising a nanoparticulate sorafenib, or a salt, such as a sorafenib tosylate, or derivative thereof, having improved bioavailability. The nanoparticulate sorafenib particles of the composition have an effective average particle size of less than about 2000 nm and are useful in the treatment of cancer, renal cancer, and related diseases.



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NANOPARTICULATE SORAFENIB FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of U.S. Provisional Patent Application No. 60/819,367, filed on July 10, 2006, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

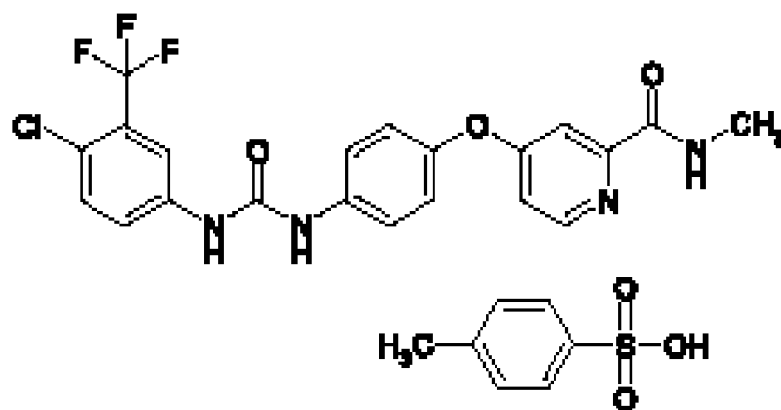
[0002] The invention relates generally to compounds and compositions useful in the treatment of cancer and related diseases or conditions. More specifically, the invention relates to nanoparticulate multi-kinase inhibitors compositions, such as sorafenib tosylate compositions, having an effective average particle size of less than about 2000 nm. The invention also relates to methods of formulating and manufacturing nanoparticulate multi-kinase inhibitor, such as sorafenib tosylate compositions, and to methods of treatment using the compositions.

BACKGROUND OF THE INVENTION

[0003] The following discussion of the background of the invention is merely provided to aid the reader in understanding the invention and is not admitted to describe or constitute prior art to the invention.

A. Background Regarding Sorafenib Tosylate

[0004] Sorafenib tosylate (also known as BAY 43-9006), a multi-kinase inhibitor targeting several serine/threonine and receptor tyrosine kinases, is the tosylate salt of sorafenib. Sorafenib tosylate has the chemical name 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-N 2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate and its structural formula is:



[0005] Sorafenib tosylate is a white to yellowish or brownish solid with a molecular formula of $C_{21}H_{16}ClF_3N_4O_3 \times C_7H_8O_3S$ and a molecular weight of 637.0 g/mole. Sorafenib tosylate is practically insoluble in aqueous media, slightly soluble in ethanol and soluble in PEG 400.

[0006] Sorafenib tosylate is offered under the registered trademark NEXAVAR®. Each red, round NEXAVAR film-coated tablet contains sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib and the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide and ferric oxide red.

[0007] Sorafenib tosylate is a synthetic compound targeting growth signaling and angiogenesis. Sorafenib tosylate acts as a multi-kinase inhibitor, targeting several serine/threonine and receptor tyrosine kinases, and has been shown to both inhibit tumor cell proliferation and tumor angiogenesis. For example, sorafenib blocks the enzyme RAF kinase, a critical component of the RAF/MEK/ERK signaling pathway that controls cell division and proliferation. Sorafenib has also been shown to inhibit CRAF, BRAF, V600E, KIT, FLT-3 and RET. In addition, sorafenib inhibits the VEGFR-2/PDGFR-beta signaling cascade (including VEGFR-2, VEGFR-3, PDGFR- β and RET), thereby blocking tumor angiogenesis. Thus, sorafenib tosylate acts on both the tumor cells and tumor vasculature. Note that RAF kinases are serine/threonine kinases, whereas KIT, FLT-3, VEGFR-2, VEGFR-3 and PDGFR- β are receptor tyrosine kinases. Mutations of BRAF have been associated with melanomas, mutations of KIT have been associated with gastrointestinal stromal tumors, and mutations of FLT-3 have been associated with acute myelogenous leukemia.

[0008] Sorafenib tosylate may be used to alleviate the symptoms of cancers such as kidney cancer (*e.g.*, advanced renal carcinoma, (“RCC”) or metastatic renal cell carcinoma (“mRCC”)).

[0009] Sorafenib tosylate is practically insoluble in water. As such, the dissolution rate and bioavailability of conventional sorafenib tosylate formulations are likely poor. Further, the effectiveness of the drug may be enhanced if taken without food, thus increasing the likelihood of patient compliance problems (*e.g.*, for maximum effect, patients should take the recommended dosage one hour before or two hours after eating). Thus, it would be desirable to increase the dissolution rate and bioavailability for faster drug onset, and to eliminate the need to take the drug without food. The present invention fulfills such needs by providing nanoparticulate sorafenib tosylate compositions which overcome these and other shortcomings of conventional formulations.

B. Background Regarding Nanoparticulate Active Agent Compositions

[0010] Nanoparticulate active agent compositions, first described in U.S. Patent No. 5,145,684 (“the ‘684 patent”), comprise particles of a poorly soluble therapeutic or diagnostic agent having adsorbed onto or associated with the surface thereof a non-crosslinked surface stabilizer. The ‘684 patent also describes method of making such nanoparticulate active agent compositions but does not describe compositions comprising sorafenib in nanoparticulate form. Methods of making nanoparticulate active agent compositions are described in, for example, U.S. Patent Nos. 5,518,187 and 5,862,999, both for “Method of Grinding Pharmaceutical Substances;” U.S. Patent No. 5,718,388, for “Continuous Method of Grinding Pharmaceutical Substances;” and U.S. Patent No. 5,510,118 for “Process of Preparing Therapeutic Compositions Containing Nanoparticles.”

[0011] Nanoparticulate active agent compositions are also described, for example, in U.S. Patent Nos. 5,298,262 for “Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;” 5,302,401 for “Method to Reduce Particle Size Growth During Lyophilization;” 5,318,767 for “X-Ray Contrast Compositions Useful in Medical Imaging;” 5,326,552 for “Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;” 5,328,404 for “Method of X-Ray Imaging Using Iodinated Aromatic

Propanedioates;" 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" 5,399,363 and 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,518,738 for "Nanoparticulate NSAID Formulations;" 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" 5,552,160 for "Surface Modified NSAID Nanoparticles;" 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,573,750 for "Diagnostic Imaging

X-Ray Contrast Agents;" 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" 5,718,919 for "Nanoparticles Containing the R(-)Enantiomer of Ibuprofen;" 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" 6,270,806 for "Use of PEG-Derivatized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form;" 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers;" 6,431,478 for

“Small Scale Mill;” 6,432,381 for “Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract,” U.S. Pat. No. 6,582,285 for "Apparatus for Sanitary Wet Milling;" and U.S. Pat. No. 6,592,903 for "Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate;" 6,656,504 for “Nanoparticulate Compositions Comprising Amorphous Cyclosporine;” 6,742,734 for “System and Method for Milling Materials;” 6,745,962 for “Small Scale Mill and Method Thereof;” 6,811,767 for “Liquid Droplet Aerosols of Nanoparticulate Drugs;” 6,908,626 for “Compositions Having a Combination of Immediate Release and Controlled Release Characteristics;” 6,969,529 for “Nanoparticulate Compositions Comprising Copolymers of Vinyl Pyrrolidone and Vinyl Acetate as Surface Stabilizers;” 6,976,647 for “System and Method for Milling Materials;” 6,991,191 for “Method of Using a Small Scale Mill,” 7,101,576 for “Nanoparticulate Megestrol Formulation,” and 7,198,795 for “In vitro methods for evaluating the in vivo effectiveness of dosage forms of microparticulate of nanoparticulate active agent compositions;” all of which are specifically incorporated by reference.

[0012] In addition, U.S. Patent Publication No. 20070122486 for “Nanoparticulate insulin;” U.S. Patent Publication No. 20070110776 for “In vitro methods for evaluating the in vivo effectiveness of dosage forms of microparticulate or nanoparticulate active agent compositions;” U.S. Patent Publication No. 20070104792 for “Nanoparticulate tadalafil formulations;” U.S. Patent Publication No. 20070098805 for “Methods of making and using novel griseofulvin compositions;” U.S. Patent Publication No. 20070065374 for “Nanoparticulate leukotriene receptor antagonist/corticosteroid formulations;” U.S. Patent Publication No. 20070059371 for “Nanoparticulate ebastine formulations;” U.S. Patent Publication No. 20070048378 for “Nanoparticulate anticonvulsant and immunosuppressive compositions;” U.S. Patent Publication No. 20070042049 for “Nanoparticulate benidipine compositions;” U.S. Patent Publication No. 20070015719 for “Nanoparticulate clarithromycin formulations;” U.S. Patent Publication No. 20070003628 for “Nanoparticulate clopidogrel formulations;” U.S. Patent Publication No. 20070003615 for “Nanoparticulate clopidogrel and aspirin combination formulations;” U.S. Patent Publication No. 20060292214 for “Nanoparticulate acetaminophen formulations;” U.S. Patent Publication No. 20060275372 for “Nanoparticulate imatinib mesylate

formulations;" U.S. Patent Publication No. 20060246142 for "Nanoparticulate quinazoline derivative formulations," U.S. Patent Publication No. 20060246141 for "Nanoparticulate lipase inhibitor formulations," U.S. Patent Publication No. 20060216353 for "Nanoparticulate corticosteroid and antihistamine formulations," U.S. Patent Publication No. 20060210639 for "Nanoparticulate bisphosphonate compositions," U.S. Patent Publication No. 20060210638 for "Injectable compositions of nanoparticulate immunosuppressive compounds," U.S. Patent Publication No. 20060204588 for "Formulations of a nanoparticulate finasteride, dutasteride or tamsulosin hydrochloride, and mixtures thereof," U.S. Patent Publication No. 20060198896 for "Aerosol and injectable formulations of nanoparticulate benzodiazepine," U.S. Patent Publication No. 20060193920 for "Nanoparticulate Compositions of Mitogen-Activated (MAP) Kinase Inhibitors," U.S. Patent Publication No. 20060188566 for "Nanoparticulate formulations of docetaxel and analogues thereof," U.S. Patent Publication No. 20060165806 for "Nanoparticulate candesartan formulations," "U.S. Patent Publication No. 20060159767 for "Nanoparticulate bicalutamide formulations," U.S. Patent Publication No. 20060159766 for "Nanoparticulate tacrolimus formulations," U.S. Patent Publication No. 20060159628 for "Nanoparticulate benzothiophene formulations," U.S. Patent Publication No. 20060154918 for "Injectable nanoparticulate olanzapine formulations," U.S. Patent Publication No. 20060121112 for "Topiramate pharmaceutical composition," U.S. Patent Publication No. 20020012675 A1, for "Controlled Release Nanoparticulate Compositions," U.S. Patent Publication No. 20040195413 A1, for "Compositions and method for milling materials," U.S. Patent Publication No. 20040173696 A1 for "Milling microgram quantities of nanoparticulate candidate compounds," U.S. Patent Publication No. 20020012675 A1, for "Controlled Release Nanoparticulate Compositions," U.S. Patent Publication No. 20050276974 for "Nanoparticulate Fibrate Formulations," U.S. Patent Publication No. 20050238725 for "Nanoparticulate Compositions Having a Peptide as a Surface Stabilizer," U.S. Patent Publication No. 20050233001 for "Nanoparticulate Megestrol Formulations," U.S. Patent Publication No. 20050147664 for "Compositions Comprising Antibodies and Methods of Using the Same for Targeting Nanoparticulate Active Agent Delivery," U.S. Patent Publication No. 20050063913 for "Novel Metaxalone Compositions," U.S. Patent Publication No.

20050042177 for “Novel Compositions of Sildenafil Free Base;” U.S. Patent Publication No. 20050031691 for “Gel Stabilized Nanoparticulate Active Agent Compositions;” U.S. Patent Publication No. 20050019412 for “Novel Glipizide Compositions;” U.S. Patent Publication No. 20050004049 for “Novel Griseofulvin Compositions;” U.S. Patent Publication No. 20040258758 for “Nanoparticulate Topiramate Formulations;” U.S. Patent Publication No. 20040258757 for “Liquid Dosage Compositions of Stable Nanoparticulate Active Agents;” U.S. Patent Publication No. 20040229038 for “Nanoparticulate Meloxicam Formulations;” U.S. Patent Publication No. 20040208833 for “Novel Fluticasone Formulations;” U.S. Patent Publication No. 20040195413 for “Compositions and Method for Milling Materials;” U.S. Patent Publication No. 20040156895 for “Solid Dosage Forms Comprising Pullulan;” U.S. Patent Publication No. U.S. Patent Publication No. U.S. Patent Publication No. 20040156872 for “Novel Nimesulide Compositions;” U.S. Patent Publication No. 20040141925 for “Novel Triamcinolone Compositions;” U.S. Patent Publication No. 20040115134 for “Novel Nifedipine Compositions;” U.S. Patent Publication No. 20040105889 for “Low Viscosity Liquid Dosage Forms;” U.S. Patent Publication No. 20040105778 for “Gamma Irradiation of Solid Nanoparticulate Active Agents;” U.S. Patent Publication No. 20040101566 for “Novel benzoyl peroxide compositions;” U.S. Patent Publication No. 20040057905 for “Nanoparticulate Beclomethasone Dipropionate Compositions;” U.S. Patent Publication No. 20040033267 for “Nanoparticulate Compositions of Angiogenesis Inhibitors;” U.S. Patent Publication No. 20040033202 for “Nanoparticulate Sterol Formulations and Novel Sterol Combinations;” U.S. Patent Publication No. 20040018242 for “Nanoparticulate nystatin formulations;” U.S. Patent Publication No. 20040015134 for “Drug Delivery Systems and Methods;” U.S. Patent Publication No. 20030232796 for “Nanoparticulate Polycosanol Formulations & Novel Polycosanol Combinations;” U.S. Patent Publication No. 20030215502 for “Fast Dissolving Dosage Forms Having Reduced Friability;” U.S. Patent Publication No. 20030185869 for “Nanoparticulate Compositions Having Lysozyme as a Surface Stabilizer;” U.S. Patent Publication No. 20030181411 for “Nanoparticulate Compositions of Mitogen-Activated Protein (MAP) Kinase Inhibitors;” U.S. Patent Publication No. 20030137067 for “Compositions Having a Combination of Immediate Release and Controlled Release Characteristics;” U.S. Patent Publication

No. 20030108616 for “Nanoparticulate Compositions Comprising Copolymers of Vinyl Pyrrolidone and Vinyl Acetate as Surface Stabilizers;” U.S. Patent Publication No. 20030095928 for “Nanoparticulate Insulin;” U.S. Patent Publication No. 20030087308 for “Method for High Through- put Screening Using a Small Scale Mill or Microfluidics;” U.S. Patent Publication No. 20030023203 for “Drug Delivery Systems & Methods;” U.S. Patent Publication No. 20020179758 for “System and Method for Milling Materials;” and U.S. Patent Publication No. 20010053664 for “Apparatus for Sanitary Wet Milling,” describe nanoparticulate active agent compositions and are specifically incorporated by reference. None of these references describe compositions of nanoparticulate sorafenib.

[0013] Amorphous small particle compositions are described, for example, in U.S. Patent Nos. 4,783,484 for “Particulate Composition and Use Thereof as Antimicrobial Agent;” U.S. Pat. No. 4,826,689 for “Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;” U.S. Pat. No. 4,997,454 for “Method for Making Uniformly-Sized Particles From Insoluble Compounds;” U.S. Pat. No. 5,741,522 for “Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;” and U.S. Pat. No. 5,776,496, for “Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter,” all of which are specifically incorporated herein by reference.

[0014] Sorafenib has high therapeutic value in the treatment of cancer and related diseases. However, because it is practically insoluble in water, the dissolution of conventional microcrystalline sorafenib tablets is poor in aqueous (*e.g.*, physiological) environments. Thus, sorafenib has limited bioavailability, which limits the therapeutic outcome for all treatments requiring sorafenib. Accordingly, there is a need in the art for sorafenib formulations which overcome this and other problems associated with its use in the treatment of cancer and related diseases.

[0015] There is a need for compositions of multi-kinase inhibitors such as sorafenib tosylate, that have enhanced bioavailability, increased dissolution rate, reduced drug dosage, and reduced adverse side effects. The present compositions and methods satisfy these needs.

SUMMARY OF THE INVENTION

[0016] The compositions and methods disclosed herein relate to compositions comprising at least one multi-kinase inhibitor, such as sorafenib or a salt (such as sorafenib tosylate) or derivative thereof (referred to herein collectively as sorafenib), having an effective average particle size of less than about 2000 nm. In one embodiment of the invention, the compositions also comprise at least one surface stabilizer. The compositions may be used to treat diseases or disorders such as, but not limited to cancers, such as advanced renal carcinoma, ("RCC") and metastatic renal cell carcinoma ("mRCC").

[0017] Additionally, the compositions may comprise at least one primary and at least one secondary surface stabilizer. Exemplary surface stabilizers may include one or more of an anionic surface stabilizer, a cationic surface stabilizer, a non-ionic surface stabilizer, a zwitterionic surface stabilizers, and an ionic surface stabilizer.

[0018] In some embodiments, the compositions may additionally include one or more pharmaceutically acceptable excipients, carriers, active agents or combinations thereof. In some embodiments, active agents may includes agents useful for the treatment of cancer or cancer side-effects or cancer treatment side-effects. By way of example, but not by way of limitation, such related condition may include compromised immune system; viral or bacterial infections; nausea; vomiting; pain; non-renal cancer; fatigue; skin irritation; bone marrow depression; and a combination thereof. Such active agents may include one or more of chemotherapeutics, pain relievers, anti-depressants, anti-inflammatories, anti-nausea medications such as ondansetron, and synthetic cannabinoids such as nabilone and dronabinol, antibiotics, and antivirals.

[0019] The nanoparticulate sorafenib compositions described herein may be formulated for dosage or administration in a variety of forms. Although any pharmaceutically acceptable dosage form may be utilized, dosage forms contemplated include, but are not limited to formulations for oral, pulmonary, rectal, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, topical, liquid dispersions, gels, aerosols, ointments, creams, bioadhesives, lyophilized formulations, tablets, capsules, controlled release formulations, fast melt formulations, delayed release formulations, extended release formulations, pulsatile release formulations, mixed immediate release, controlled release formulations and

combinations thereof. In some embodiments, solid dosages, such as an oral tablet, may be preferred. In other embodiments, parenteral formulations, such as for injection, may be preferred.

[0020] The nanoparticulate sorafenib compositions disclosed herein are also contemplated to exhibit improved pharmacokinetic properties as compared to a non-nanoparticulate composition of the same sorafenib.

[0021] In further embodiments, the pharmacokinetic profiles of the nanoparticulate sorafenib compositions may be substantially similar (*e.g.*, are not significantly affected) when administered in the fed or fasted subject; in other embodiments, the nanoparticulate sorafenib compositions may be bioequivalent when administered to a fed or fasted subject; in still other embodiments, the nanoparticulate sorafenib compositions may not produce significantly different absorption levels when administered under fed versus fasted conditions.

[0022] Additionally disclosed are methods related to making nanoparticulate sorafenib compositions having an effective average particle size of less than about 2000 nm. By way of example, but not by way of limitation, methods may include contacting particles of sorafenib with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate sorafenib composition having an effective average particle size of less than about 2000 nm. In some methods, contacting may include grinding, wet grinding, homogenization, freezing, template emulsion, precipitation, supercritical fluid particle generation techniques and combinations thereof.

[0023] Also disclosed are methods of using the nanoparticulate sorafenib formulations, for example, to treat or prevent diseases, disorders, symptoms or conditions in a subject. Exemplary methods may include administering to a subject a stable nanoparticulate sorafenib composition including at least one sorafenib or a salt or derivative thereof having an effective average particle size of less than about 2000 nm, and at least one surface stabilizer. In some embodiments, the subject may have been diagnosed with cancers, such as advanced renal carcinoma, ("RCC") or metastatic renal cell carcinoma ("mRCC"). In other methods, the compositions may be used to treat symptoms indicative of cancer. Some treatment methods may include administering a composition including a nanoparticulate sorafenib, at least one surface stabilizer and one or more active agents useful for the treatment cancer and

related disorders. By way of example, but not by way of limitation, such active agents may include one or more of chemotherapeutics, pain relievers, anti-depressants, anti-inflammatories, anti-nausea medications such as ondansetron, and synthetic cannabinoids such as nabilone and dronabinol, antibiotics, and antivirals. In some methods, the composition is administered in the form of an oral tablet. In other methods, the composition is administered parenterally, such as by injection.

[0024] Both the foregoing summary and the following detailed description are exemplary and explanatory and are intended to provide further details of the compositions and methods as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description.

DETAILED DESCRIPTION

A. Nanoparticulate Sorafenib Compositions

[0025] The compositions of the invention comprise a multi-kinase inhibitor such as sorafenib or a salt (such as sorafenib tosylate) or derivative thereof. The compositions comprise a sorafenib, and preferably at least one surface stabilizer associated with or adsorbed on the surface of the drug. The sorafenib particles may have an effective average particle size of less than about 2000 nm.

[0026] Advantages of the nanoparticulate sorafenib formulation of the invention as compared to non-nanoparticulate sorafenib compositions (*e.g.*, microcrystalline or solubilized dosage forms) include, but are not limited to: (1) smaller tablet or other solid dosage form size; (2) smaller doses of drug required to obtain the same pharmacological effect; (3) improved pharmacokinetic profiles, (4) increased bioavailability; (5) substantially similar pharmacokinetic profiles of the sorafenib compositions when administered in the fed versus the fasted state; (6) bioequivalency of the sorafenib compositions when administered in the fed versus the fasted state; (7) an increased rate of dissolution for the sorafenib compositions; and (8) the sorafenib compositions can be used in conjunction with other active agents useful in the treatment of cancer and related diseases, disorders, symptoms or conditions.

[0027] The present invention also relates to nanoparticulate sorafenib compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or

vehicles, collectively referred to as carriers. The compositions may be formulated for parental injection (*e.g.*, intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, bioadhesive or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments, or drops), buccal, intracisternal, intraperitoneal, or topical administrations, and the like.

[0028] In some embodiments, a preferred dosage form may be a solid dosage form such as a tablet, although any pharmaceutically acceptable dosage form can be utilized. Exemplary solid dosage forms include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, or granules, and the solid dosage form can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof.

[0029] The present invention is described herein using several definitions, as set forth below and throughout the application.

[0030] The term “effective average particle size of less than about 2000 nm,” as used herein, means that at least about 50% of the nanoparticulate sorafenib particles have a size of less than about 2000 nm (by weight or by other suitable measurement technique, such as by number or by volume) when measured by, for example, sedimentation flow fractionation, photon correlation spectroscopy, light scattering, disk centrifugation, and other techniques known to those of skill in the art.

[0031] As used herein, “about” will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, “about” will mean up to plus or minus 10% of the particular term.

[0032] As used herein with reference to stable nanoparticulate sorafenib, “stable” connotes, but is not limited to one or more of the following parameters: (1) the particles do not appreciably flocculate or agglomerate due to interparticle attractive forces or otherwise significantly increase in particle size over time; (2) that the physical structure of the particles is not altered over time, such as by conversion from an amorphous phase to a crystalline phase; (3) that the particles are chemically stable; and/or (4) where the sorafenib has not been subject to a heating step at or above the

melting point of the sorafenib in the preparation of the nanoparticles of the present invention.

[0033] The term “conventional” or “non-nanoparticulate” active agent shall mean an active agent which is solubilized or which has an effective average particle size of greater than about 2000 nm. Nanoparticulate active agents as defined herein have an effective average particle size of less than about 2000 nm.

[0034] The phrase “poorly water soluble drugs” as used herein refers to those drugs that have a solubility in water of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, or less than about 1 mg/ml.

[0035] As used herein, the phrase “therapeutically effective amount” shall mean that drug dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that a therapeutically effective amount of a drug that is administered to a particular subject in a particular instance will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art.

[0036] The term “particulate” as used herein refers to a state of matter which is characterized by the presence of discrete particles, pellets, beads or granules irrespective of their size, shape or morphology. The term “multiparticulate” as used herein means a plurality of discrete or aggregated particles, pellets, beads, granules or mixtures thereof irrespective of their size, shape or morphology.

B. Preferred Characteristics of the Nanoparticulate Sorafenib Compositions

1. Increased Bioavailability

[0037] The compositions of the invention comprising a nanoparticulate sorafenib, or a salt (such as sorafenib tosylate) or derivative thereof, are proposed to exhibit increased bioavailability, and require smaller doses as compared to prior or conventional sorafenib formulations.

[0038] In some embodiments, the nanoparticulate sorafenib compositions, upon administration to a mammal, produce therapeutic results at a dosage which is less than that of a non-nanoparticulate dosage form of the same sorafenib.

2. Improved Pharmacokinetic Profiles

[0039] The sorafenib compositions described herein may also exhibit a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the sorafenib compositions preferably includes, but is not limited to: (1) a $C_{\max}$ for sorafenib or a derivative or salt thereof, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the $C_{\max}$ for a non-nanoparticulate formulation of the same sorafenib, administered at the same dosage; and/or (2) an AUC for sorafenib or a derivative or a salt thereof, when assayed in the plasma of a mammalian subject following administration, that is preferably greater than the AUC for a non-nanoparticulate formulation of the same sorafenib, administered at the same dosage; and/or (3) a $T_{\max}$ for sorafenib or a derivative or a salt thereof, when assayed in the plasma of a mammalian subject following administration, that is preferably less than the $T_{\max}$ for a non-nanoparticulate formulation of the same sorafenib, administered at the same dosage. The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of sorafenib or derivative or a salt thereof.

[0040] In one embodiment, a composition comprising at least one nanoparticulate sorafenib or a derivative or salt thereof exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same sorafenib (*e.g.*, NEXAVAR®), administered at the same dosage, a $T_{\max}$ not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, or not greater than about 5% of the $T_{\max}$ exhibited by the non-nanoparticulate sorafenib formulation.

[0041] In another embodiment, the composition comprising at least one nanoparticulate sorafenib or a derivative or salt thereof, exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same sorafenib (*e.g.*, NEXAVAR), administered at the same dosage, a $C_{\max}$ which is at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least

about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the C_{max} exhibited by the non-nanoparticulate sorafenib formulation.

[0042] In yet another embodiment, the composition comprising at least one nanoparticulate sorafenib or a derivative or salt thereof, exhibits in comparative pharmacokinetic testing with a non-nanoparticulate formulation of the same sorafenib (*e.g.*, NEXAVAR), administered at the same dosage, an AUC which is at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the AUC exhibited by the non-nanoparticulate sorafenib formulation.

3. The Pharmacokinetic Profiles of the Sorafenib Compositions are Not Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

[0043] In one embodiment of the invention, the pharmacokinetic profile of the nanoparticulate sorafenib compositions are not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there would be little or no appreciable difference in the quantity of drug absorbed or the rate of drug absorption when the nanoparticulate sorafenib compositions are administered in the fed or fasted state.

[0044] For conventional sorafenib formulations, *i.e.*, NEXAVAR®, the absorption of sorafenib may be increased if administered without food. This difference in absorption observed with conventional sorafenib formulations is undesirable. The nanoparticulate sorafenib formulations described herein are proposed to overcome this problem, as the sorafenib formulations are likely to reduce or preferably substantially eliminate significantly different absorption levels when administered under fed as compared to fasting conditions.

[0045] Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as

the subject does not need to ensure that they are taking a dose either with or without food. This is significant, as with poor subject compliance an increase in the medical condition for which the drug is being prescribed may be observed.

4. Bioequivalency of Sorafenib Compositions When Administered in the Fed Versus the Fasted State

[0046] In one embodiment of the invention, administration of a nanoparticulate sorafenib composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state. The difference in absorption of the nanoparticulate sorafenib compositions, when administered in the fed versus the fasted state, preferably is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 55%, less than about 50%, less than about 45%, less than about 40%, less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%.

[0047] In some embodiments, the invention encompasses compositions comprising at least one nanoparticulate sorafenib, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, in particular as defined by $C_{\max}$ and AUC guidelines given by the U.S. Food and Drug Administration and the corresponding European regulatory agency (EMA). Under U.S. FDA guidelines, two products or methods are bioequivalent if the 90% Confidence Intervals (CI) for AUC and $C_{\max}$ are between 0.80 to 1.25 ($T_{\max}$ measurements are not relevant to bioequivalence for regulatory purposes). To show bioequivalency between two compounds or administration conditions pursuant to Europe's EMA guidelines, the 90% CI for AUC must be between 0.80 to 1.25 and the 90% CI for $C_{\max}$ must be between 0.70 to 1.43.

5. Dissolution Profiles of the Sorafenib Compositions

[0048] The nanoparticulate sorafenib compositions are proposed to have unexpectedly dramatic dissolution profiles. Rapid dissolution of an administered active agent is preferable, as faster dissolution generally leads to faster onset of action and greater bioavailability. Additionally, a faster dissolution rate would allow for a larger dose of the drug to be absorbed, which would increase drug efficacy. To

improve the dissolution profile and bioavailability of the sorafenib, it would be useful to increase the drug's dissolution so that it could attain a level close to 100%.

[0049] The sorafenib compositions of the invention preferably have a dissolution profile in which within about 5 minutes at least about 20% of the composition is dissolved. In other embodiments, at least about 30% or at least about 40% of the sorafenib composition is dissolved within about 5 minutes. In yet other embodiments, preferably at least about 40%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of the sorafenib composition is dissolved within about 10 minutes. In further embodiments, preferably at least about 70%, at least about 80%, at least about 90%, or at least about 100% of the sorafenib composition is dissolved within 20 minutes.

[0050] In some embodiments, dissolution is preferably measured in a medium which is discriminating. Such a dissolution medium will produce two very different dissolution curves for two products having very different dissolution profiles in gastric juices; *i.e.*, the dissolution medium is predictive of *in vivo* dissolution of a composition. An exemplary dissolution medium is an aqueous medium containing the surfactant sodium lauryl sulfate at 0.025 M. Determination of the amount dissolved can be carried out by spectrophotometry. The rotating blade method (European Pharmacopoeia) can be used to measure dissolution.

6. Redispersibility of the Sorafenib Compositions of the Invention

[0051] An additional feature of the sorafenib compositions described herein may include redispersion such that the effective average particle size of the redispersed sorafenib particles is less than about 2 microns. This is significant, as if upon administration the sorafenib compositions of the invention did not redisperse to a substantially nanoparticulate size, then the dosage form may lose the benefits afforded by formulating the sorafenib into a nanoparticulate size.

[0052] Not wishing to be bound by any theory, it is proposed that nanoparticulate active agent compositions benefit from the small particle size of the active agent; if the active agent does not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated active agent particles are formed, owing to the extremely high surface free energy of the nanoparticulate system and the thermodynamic driving force to achieve an overall reduction in free energy. With the

formation of such agglomerated particles, the bioavailability of the dosage form may fall.

[0053] Moreover, the nanoparticulate sorafenib compositions of the invention exhibit dramatic redispersion of the nanoparticulate sorafenib particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution/redispersion in a biorelevant aqueous media such that the effective average particle size of the redispersed sorafenib particles is less than about 2 microns. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, water, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength. Such redispersion in a biorelevant media is predictive of in vivo efficacy of the sorafenib dosage form.

[0054] Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1M while fasted state intestinal fluid has an ionic strength of about 0.14. See *e.g.*, Lindahl *et al.*, "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," *Pharm. Res.*, 14 (4): 497-502 (1997).

[0055] It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (*i.e.*, weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, etc.

[0056] Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 N, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 N HCl or less, about 0.01 N HCl or less, about 0.001 N HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof.

Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

[0057] Electrolyte concentrations of 0.001 N HCl, 0.01 N HCl, and 0.1 N HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 N HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

[0058] Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts + sodium, potassium and calcium salts of chloride, acetic acid/acetate salts + sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts + sodium, potassium and calcium salts of chloride, and citric acid/citrate salts + sodium, potassium and calcium salts of chloride.

[0059] In other embodiments of the invention, the redispersed sorafenib particles of the invention (redispersed in water, a biorelevant medium, or any other suitable dispersion medium) have an effective average particle size of less than about less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than about 640 nm, less than about 630 nm, less than about 620 nm, less than about 610

nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than about 470 nm, less than about 460 nm, less than about 450 nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than about 380 nm, less than about 370 nm, less than about 360 nm, less than about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about 300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

[0060] In still other embodiments, the redispersed sorafenib particles (redispersed *in vivo*, in a biorelevant media, or in any other suitable media), redisperse such that the particles have an effective average particle size of less than about 2000 nm, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than

about 640 nm, less than about 630 nm, less than about 620 nm, less than about 610 nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than about 470 nm, less than about 460 nm, less than about 450 nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than about 380 nm, less than about 370 nm, less than about 360 nm, less than about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about 300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

[0061] Redispersibility can be tested using any suitable means known in the art. *See e.g.*, the example sections of U.S. Patent No. 6,375,986 for “Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate.”

7. Sorafenib Compositions Used in Conjunction with Other Active Agents

[0062] The compositions comprising a nanoparticulate sorafenib, or a salt (such as sorafenib tosylate) or derivative thereof, can additionally comprise one or more compounds useful in the treatment of cancers, such as advanced renal carcinoma, (“RCC”) or metastatic renal cell carcinoma (“mRCC”), symptoms indicative of cancer, or symptoms related to cancer treatment. Examples of such compounds include, but are not limited to one or more of chemotherapeutics, pain relievers, anti-depressants, anti-inflammatories, anti-nausea medications such as ondansetron, and synthetic cannabinoids such as nabilone and dronabinol, antibiotics, and antivirals.

C. Nanoparticulate Sorafenib Compositions

[0063] The invention provides compositions comprising sorafenib particles and at least one surface stabilizer. The surface stabilizers preferably are adsorbed on, or associated with, the surface of the sorafenib particles. In some embodiments, surface stabilizers preferably physically adhere on, or associate with, the surface of the nanoparticulate sorafenib particles, but do not chemically react with the sorafenib particles or itself. Individually adsorbed molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

[0064] The present invention also includes sorafenib compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (*e.g.*, intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracisternal, intraperitoneal, or topical administration, and the like.

1. Sorafenib Particles

[0065] The compositions of the invention comprise particles of sorafenib or a salt (such as sorafenib tosylate) or derivative thereof. The particles can be in crystalline phase, semi-crystalline phase, amorphous phase, semi-amorphous phase, or a combination thereof.

2. Surface Stabilizers

[0066] The choice of a surface stabilizer for an sorafenib is non-trivial and required extensive experimentation to realize a desirable formulation. Accordingly, the present invention is directed to the surprising discovery that nanoparticulate sorafenib compositions can be made.

[0067] Combinations of more than one surface stabilizers can be used in the invention. Suitable surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Surface stabilizers include nonionic, anionic, cationic, ionic, and zwitterionic surfactants or compounds.

[0068] Representative examples of surface stabilizers include human serum albumin and bovine albumin, hydroxypropyl methylcellulose (now known as hypromellose), hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate (also known as docusate sodium and DOSS), gelatin, casein, cetyl pyridinium chloride, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (*e.g.*, macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (*e.g.*, the commercially available Tweens[®] such as *e.g.*, Tween[®] 20 and Tween[®] 80 (ICI Speciality Chemicals)); polyethylene glycols (*e.g.*, Carbowaxes[®] 3550 and 934 (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (*e.g.*, Plurionics[®] F68 and F108, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (*e.g.*, Tetronic[®] 908, also known as Poloxamine[™] 908, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic[®] 1508 (T-1508) (BASF Wyandotte Corporation), Tritons[®] X-200, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas[™] F-110, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin[®]-LOG or Surfactant[™] 10-G (Olin Chemicals, Stamford, CT); Crodestas[™] SL-40 (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol

derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

[0069] Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, celluloses, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryl pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide (PMMTMABr), hexyldeyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

[0070] Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride or bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂, C₁₅, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyl dimethylammonium halogenides, tricetyl methyl ammonium chloride,

decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearylalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

[0071] Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry* (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry*, (Marcel Dekker, 1990).

[0072] Nonpolymeric surface stabilizers are any nonpolymeric compound, such as benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quaternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quaternary ammonium compounds of the formula $\text{NR}_1\text{R}_2\text{R}_3\text{R}_4^{(+)}$. For compounds of the formula $\text{NR}_1\text{R}_2\text{R}_3\text{R}_4^{(+)}$:

[0073] (i) none of $\text{R}_1\text{-R}_4$ are CH_3 ;

[0074] (ii) one of $\text{R}_1\text{-R}_4$ is CH_3 ;

[0075] (iii) three of $\text{R}_1\text{-R}_4$ are CH_3 ;

[0076] (iv) all of $\text{R}_1\text{-R}_4$ are CH_3 ;

[0077] (v) two of $\text{R}_1\text{-R}_4$ are CH_3 , one of $\text{R}_1\text{-R}_4$ is $\text{C}_6\text{H}_5\text{CH}_2$, and one of $\text{R}_1\text{-R}_4$ is an alkyl chain of seven carbon atoms or less;

[0078] (vi) two of R₁-R₄ are CH₃, one of R₁-R₄ is C₆H₅CH₂, and one of R₁-R₄ is an alkyl chain of nineteen carbon atoms or more;

[0079] (vii) two of R₁-R₄ are CH₃ and one of R₁-R₄ is the group C₆H₅(CH₂)_n, where n>1;

[0080] (viii) two of R₁-R₄ are CH₃, one of R₁-R₄ is C₆H₅CH₂, and one of R₁-R₄ comprises at least one heteroatom;

[0081] (ix) two of R₁-R₄ are CH₃, one of R₁-R₄ is C₆H₅CH₂, and one of R₁-R₄ comprises at least one halogen;

[0082] (x) two of R₁-R₄ are CH₃, one of R₁-R₄ is C₆H₅CH₂, and one of R₁-R₄ comprises at least one cyclic fragment;

[0083] (xi) two of R₁-R₄ are CH₃ and one of R₁-R₄ is a phenyl ring; or

[0084] (xii) two of R₁-R₄ are CH₃ and two of R₁-R₄ are purely aliphatic fragments.

[0085] Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oleyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

[0086] In some embodiments, the surface stabilizers are copovidone (*e.g.*, Plasdone S630, which is random copolymer of vinyl acetate and vinyl pyrrolidone) and docusate sodium.

[0087] The surface stabilizers are commercially available and/or can be prepared by techniques known in the art. *See e.g., Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference.

3. Other Pharmaceutical Excipients

[0088] Pharmaceutical compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art.

[0089] Examples of filling agents include lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel[®] PH101 and Avicel[®] PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC[™]).

[0090] Suitable lubricants, including agents that act on the flowability of the powder to be compressed, include colloidal silicon dioxide, such as Aerosil[®] 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

[0091] Examples of sweeteners include any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acesulfame. Examples of flavoring agents include Magnasweet[®] (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

[0092] Examples of preservatives include potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

[0093] Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel[®] PH101 and Avicel[®] PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose[®] DCL21; dibasic calcium phosphate such as Emcompress[®]; mannitol; starch; sorbitol; sucrose; and glucose.

[0094] Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

[0095] Examples of buffers include phosphate buffer, citrate buffers and buffers made from other organic acids.

[0096] Examples of wetting or dispersing agents include a naturally-occurring phosphatide, for example, lecithin or condensation products of n-alkylene oxide with fatty acids, for example, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxyctanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyethylene sorbitan monooleate.

[0097] Examples of effervescent agents include effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

4. Nanoparticulate Sorafenib Particle Size

[0098] The compositions of the invention comprise nanoparticulate sorafenib, such as nanoparticulate sorafenib tosylate particles which have an effective average particle size of less than about 2000 nm (*i.e.*, 2 microns), less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than

about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than about 640 nm, less than about 630 nm, less than about 620 nm, less than about 610 nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than about 470 nm, less than about 460 nm, less than about 450 nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than about 380 nm, less than about 370 nm, less than about 360 nm, less than about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about 300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

[0099] By “an effective average particle size of less than about 2000 nm” it is meant that at least 50% of the sorafenib particles have a particle size of less than the effective average, by weight (or by another suitable measurement technique, such as by volume, number, *etc.*), *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, *etc.*, when measured by the above-noted techniques. Preferably, at least about 70%, about 90%, or about 95% of the sorafenib particles have a particle size of less than the effective average, *i.e.*, less than about 2000 nm, 1900 nm, 1800 nm, 1700 nm, *etc.*

[0100] In the present invention, the value for D50 of a nanoparticulate sorafenib composition is the particle size below which 50% of the sorafenib particles fall, by weight (or by other suitable measurement technique, such as by volume, number,

etc.). Similarly, D90 is the particle size below which 90% of the sorafenib particles fall, by weight (or by other suitable measurement technique, such as by volume, number, *etc.*).

5. Concentration of Sorafenib and Surface Stabilizers

[0101] The relative amounts of sorafenib, or a salt (such as sorafenib tosylate) or derivative thereof, and one or more surface stabilizers may vary. The optimal amount of the individual components can depend, for example, upon the particular sorafenib selected, the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer, *etc.*

[0102] In some embodiments, the concentration of the sorafenib may vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight, based on the total combined dry weight of the sorafenib and at least one surface stabilizer, not including other excipients.

[0103] In other embodiments, the concentration of the at least one surface stabilizer may vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the sorafenib and at least one surface stabilizer, not including other excipients.

6. Exemplary Nanoparticulate Sorafenib Tablet Formulations

[0104] Several exemplary sorafenib tablet formulations are given below. These examples are not intended to limit the claims in any respect, but rather to provide exemplary tablet formulations of sorafenib which can be utilized in the methods of the invention. Such exemplary tablets can also comprise a coating agent.

Exemplary Nanoparticulate Sorafenib Tablet Formulation #1	
Component	g/Kg
Sorafenib	about 50 to about 500
Hypromellose, USP	about 10 to about 70
Docusate Sodium, USP	about 1 to about 10
Sucrose, NF	about 100 to about 500
Sodium Lauryl Sulfate, NF	about 1 to about 40
Lactose Monohydrate, NF	about 50 to about 400
Silicified Microcrystalline Cellulose	about 50 to about 300
Crospovidone, NF	about 20 to about 300
Magnesium Stearate, NF	about 0.5 to about 5

Exemplary Nanoparticulate Sorafenib Tablet Formulation #2	
Component	g/Kg
Sorafenib	about 100 to about 300
Hypromellose, USP	about 30 to about 50
Docusate Sodium, USP	about 0.5 to about 10
Sucrose, NF	about 100 to about 300
Sodium Lauryl Sulfate, NF	about 1 to about 30
Lactose Monohydrate, NF	about 100 to about 300
Silicified Microcrystalline Cellulose	about 50 to about 200
Crospovidone, NF	about 50 to about 200
Magnesium Stearate, NF	about 0.5 to about 5

Exemplary Nanoparticulate Sorafenib Tablet Formulation #3	
Component	g/Kg
Sorafenib	about 200 to about 225
Hypromellose, USP	about 42 to about 46
Docusate Sodium, USP	about 2 to about 6
Sucrose, NF	about 200 to about 225
Sodium Lauryl Sulfate, NF	about 12 to about 18
Lactose Monohydrate, NF	about 200 to about 205
Silicified Microcrystalline Cellulose	about 130 to about 135
Crospovidone, NF	about 112 to about 118
Magnesium Stearate, NF	about 0.5 to about 3

Exemplary Nanoparticulate Sorafenib Tablet Formulation #4	
Component	g/Kg
Sorafenib	about 119 to about 224
Hypromellose, USP	about 42 to about 46
Docusate Sodium, USP	about 2 to about 6
Sucrose, NF	about 119 to about 224
Sodium Lauryl Sulfate, NF	about 12 to about 18
Lactose Monohydrate, NF	about 119 to about 224
Silicified Microcrystalline Cellulose	about 129 to about 134
Crospovidone, NF	about 112 to about 118
Magnesium Stearate, NF	about 0.5 to about 3

D. Methods of Making Nanoparticulate Sorafenib Compositions

[0105] The nanoparticulate sorafenib compositions can be made using, for example, milling or attrition (including but not limited to wet milling), homogenization, precipitation, freezing, supercritical particle generation, template emulsion techniques, nano-electrospray techniques, or any combination thereof. Exemplary methods of making nanoparticulate compositions are described in the '684 patent. Methods of making nanoparticulate active agent compositions are also described in

U.S. Patent No. 5,518,187 for “Method of Grinding Pharmaceutical Substances;” U.S. Patent No. 5,718,388 for “Continuous Method of Grinding Pharmaceutical Substances;” U.S. Patent No. 5,862,999 for “Method of Grinding Pharmaceutical Substances;” U.S. Patent No. 5,665,331 for “Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;” U.S. Patent No. 5,662,883 for “Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;” U.S. Patent No. 5,560,932 for “Microprecipitation of Nanoparticulate Pharmaceutical Agents;” U.S. Patent No. 5,543,133 for “Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;” U.S. Patent No. 5,534,270 for “Method of Preparing Stable Drug Nanoparticles;” U.S. Patent No. 5,510,118 for “Process of Preparing Therapeutic Compositions Containing Nanoparticles;” and U.S. Patent No. 5,470,583 for “Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation,” all of which are specifically incorporated by reference.

[0106] The resultant nanoparticulate sorafenib compositions or dispersions can be utilized in solid or liquid dosage formulations, such as liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, mixed immediate release and controlled release formulations, *etc.*

1. Milling to Obtain Nanoparticulate Sorafenib Dispersions

[0107] Milling a sorafenib, or a salt or derivative thereof, to obtain a nanoparticulate dispersion comprises dispersing the sorafenib particles in a liquid dispersion medium in which the sorafenib is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of the sorafenib to the desired effective average particle size. The dispersion medium can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol. In some embodiments, a preferred dispersion medium is water.

[0108] The sorafenib particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, sorafenib particles can be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be

added to the sorafenib/surface stabilizer composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

[0109] The grinding media can comprise particles that are preferably substantially spherical in shape, *e.g.*, beads, consisting essentially of polymeric or copolymeric resin. Alternatively, the grinding media can comprise a core having a coating of a polymeric or copolymeric resin adhered thereon.

[0110] In general, suitable polymeric or copolymeric resins are chemically and physically inert, substantially free of metals, solvent, and monomers, and of sufficient hardness and friability to enable them to avoid being chipped or crushed during grinding. Suitable polymeric or copolymeric resins include crosslinked polystyrenes, such as polystyrene crosslinked with divinylbenzene; styrene copolymers; polycarbonates; polyacetals, such as Delrin™ (E.I. du Pont de Nemours and Co.); vinyl chloride polymers and copolymers; polyurethanes; polyamides; poly(tetrafluoroethylenes), *e.g.*, Teflon® (E.I. du Pont de Nemours and Co.), and other fluoropolymers; high density polyethylenes; polypropylenes; cellulose ethers and esters such as cellulose acetate; polyhydroxymethacrylate; polyhydroxyethyl acrylate; and silicone-containing polymers such as polysiloxanes and the like. The polymer can be biodegradable. Exemplary biodegradable polymers or copolymers include poly(lactides), poly(glycolide) copolymers of lactides and glycolide, polyanhydrides, poly(hydroxyethyl methacrylate), poly(imino carbonates), poly(N-acylhydroxyproline)esters, poly(N-palmitoyl hydroxyproline) esters, ethylene-vinyl acetate copolymers, poly(orthoesters), poly(caprolactones), and poly(phosphazenes). For biodegradable polymers or copolymers, contamination from the media itself advantageously can metabolize *in vivo* into biologically acceptable products that can be eliminated from the body.

[0111] The grinding media preferably ranges in size from about 0.01 to about 3 mm. For fine grinding, the grinding media is preferably from about 0.02 to about 2 mm, and more preferably from about 0.03 to about 1 mm in size.

[0112] The polymeric or copolymeric resin can have a density from about 0.8 to about 3.0 g/cm³.

[0113] In a preferred grinding process the sorafenib particles are made continuously. Such a method comprises continuously introducing a sorafenib composition according to the invention into a milling chamber, contacting the

sorafenib composition according to the invention with grinding media while in the chamber to reduce the sorafenib particle size of the composition according to the invention, and continuously removing the nanoparticulate sorafenib composition according to the invention from the milling chamber.

[0114] The grinding media is separated from the milled nanoparticulate sorafenib composition using conventional separation techniques, in a secondary process such as by simple filtration, sieving through a mesh filter or screen, and the like. Other separation techniques such as centrifugation may also be employed.

2. Precipitation to Obtain Nanoparticulate Sorafenib Compositions

[0115] Another method of forming the desired nanoparticulate sorafenib compositions is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving the sorafenib in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one surface stabilizer; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means.

3. Homogenization to Obtain Nanoparticulate Sorafenib Compositions

[0116] Exemplary homogenization methods of preparing active agent nanoparticulate compositions are described in U.S. Patent No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles." Such a method comprises dispersing particles of an sorafenib, or a salt (such as sorafenib tosylate) or derivative thereof, in a liquid dispersion medium, followed by subjecting the dispersion to homogenization to reduce the particle size of an sorafenib to the desired effective average particle size. The sorafenib particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the sorafenib particles can be contacted with one or more surface stabilizers either before or after attrition. Other

compounds, such as a diluent, can be added to the sorafenib/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

4. Cryogenic Methodologies to Obtain Nanoparticulate Sorafenib Compositions

[0117] Another method of forming the desired nanoparticulate sorafenib compositions is by spray freezing into liquid (SFL). This technology comprises an organic or organoaqueous solution of sorafenib with stabilizers, which is injected into a cryogenic liquid, such as liquid nitrogen. The droplets of the sorafenib solution freeze at a rate sufficient to minimize crystallization and particle growth, thus formulating nanostructured sorafenib particles. Depending on the choice of solvent system and processing conditions, the nanoparticulate sorafenib particles can have varying particle morphology. In the isolation step, the nitrogen and solvent are removed under conditions that avoid agglomeration or ripening of the sorafenib particles.

[0118] As a complementary technology to SFL, ultra rapid freezing (URF) may also be used to create equivalent nanostructured sorafenib particles with greatly enhanced surface area.

[0119] URF comprises an organic or organoaqueous solution of sorafenib with stabilizers onto a cryogenic substrate.

5. Emulsion Methodologies to Obtain Nanoparticulate Sorafenib Compositions

[0120] Another method of forming the desired nanoparticulate sorafenib, or a salt or derivative thereof, composition is by template emulsion. Template emulsion creates nanostructured sorafenib particles with controlled particle size distribution and rapid dissolution performance. The method comprises an oil-in-water emulsion that is prepared, then swelled with a non-aqueous solution comprising the sorafenib and stabilizers. The particle size distribution of the sorafenib particles is a direct result of the size of the emulsion droplets prior to loading with the sorafenib a property which can be controlled and optimized in this process. Furthermore, through selected use of solvents and stabilizers, emulsion stability is achieved with no or suppressed Ostwald

ripening. Subsequently, the solvent and water are removed, and the stabilized nanostructured sorafenib particles are recovered. Various sorafenib particles morphologies can be achieved by appropriate control of processing conditions.

6. Supercritical Fluid Techniques Used to Obtain Nanoparticulate Sorafenib Compositions

[0121] Published International Patent Application No. WO 97/144407 to Pace *et al.*, published April 24, 1997, discloses particles of water insoluble biologically active compounds with an average size of 100 nm to 300 nm that are prepared by dissolving the compound in a solution and then spraying the solution into compressed gas, liquid or supercritical fluid in the presence of appropriate surface modifiers.

7. Nano-Electrospray Techniques Used to Obtain Nanoparticulate Sorafenib Compositions

[0122] In electrospray ionization a liquid is pushed through a very small charged, usually metal, capillary. This liquid contains the desired substance, e.g., sorafenib or a derivative thereof (or “analyte”), dissolved in a large amount of solvent, which is usually much more volatile than the analyte. Volatile acids, bases or buffers are often added to this solution as well. The analyte exists as an ion in solution either in a protonated form or as an anion. As like charges repel, the liquid pushes itself out of the capillary and forms a mist or an aerosol of small droplets about 10 μm across. This jet of aerosol droplets is at least partially produced by a process involving the formation of a Taylor cone and a jet from the tip of this cone. A neutral carrier gas, such as nitrogen gas, is sometimes used to help nebulize the liquid and to help evaporate the neutral solvent in the small droplets. As the small droplets evaporate, suspended in the air, the charged analyte molecules are forced closer together. The drops become unstable as the similarly charged molecules come closer together and the droplets once again break up. This is referred to as Coulombic fission because it is the repulsive Coulombic forces between charged analyte molecules that drive it. This process repeats itself until the analyte is free of solvent and is a lone ion.

[0123] In nanotechnology the electrospray method may be employed to deposit single particles on surfaces, e.g., particles of sorafenib or a derivative thereof. This is accomplished by spraying colloids and making sure that on average there is not more

than one particle per droplet. Consequent drying of the surrounding solvent results in an aerosol stream of single particles of the desired type. Here the ionizing property of the process is not crucial for the application but may be put to use in electrostatic precipitation of the particles.

E. Methods of Using the Nanoparticulate Sorafenib Compositions of the Invention

[0124] The invention provides a method of rapidly increasing the bioavailability (*e.g.*, plasma levels) of sorafenib in a subject. Such a method comprises orally administering to a subject an effective amount of a composition comprising an sorafenib. In some embodiments, the sorafenib compositions, in accordance with standard pharmacokinetic practice, have a bioavailability that is about 50% greater, about 40% greater, about 30% greater, about 20% greater, or about 10% greater than a conventional dosage form. Additionally, when tested in fasting subjects in accordance with standard pharmacokinetic practice, the nanoparticulate sorafenib compositions produce a maximum blood plasma concentration profile in less than about 6 hours, less than about 5 hours, less than about 4 hours, less than about 3 hours, less than about 2 hours, less than about 1 hour, or less than about 30 minutes after the initial dose of the compositions.

[0125] The compositions of the invention may be useful in the treatment of cancer and related diseases, symptoms or conditions. Cancers such as renal cancer (*e.g.*, renal cell carcinoma) are contemplated. Other diseases, symptoms or conditions may include complications associated with compromised immune system (*e.g.*, due to chemotherapy or radiation treatment) such as viral or bacterial infections; nausea; vomiting; pain; other types of cancers (*e.g.*, non-renal cancer); fatigue; skin irritation; bone marrow depression (resulting in *e.g.*, low blood cell count).

[0126] The sorafenib compounds of the invention can be administered to a subject via any conventional means including, but not limited to, orally, rectally, ocularly, parenterally (*e.g.*, intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (*e.g.*, powders, ointments or drops), as a bioadhesive, or as a buccal or nasal spray. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

[0127] The sorafenib compositions may be formulated for parenteral administration; the nanoparticulate formulations would eliminate the need for toxic co-solvents and enhance the efficacy of sorafenib tosylate in the treatment of various types of cancer, including but not limited to advanced renal cell carcinoma. Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethylene-glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0128] The nanoparticulate sorafenib, or a salt or derivative thereof, compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[0129] Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid

polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0130] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to an sorafenib, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

[0131] Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0132] ‘Therapeutically effective amount’ as used herein with respect to an sorafenib, dosage shall mean that dosage that provides the specific pharmacological response for which an sorafenib is administered in a significant number of subjects in need of such treatment. It is emphasized that ‘therapeutically effective amount,’ administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a ‘therapeutically effective amount’ by those skilled in the art. It is to be further understood that sorafenib dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

[0133] One of ordinary skill will appreciate that effective amounts of an sorafenib can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of an sorafenib in the nanoparticulate compositions of the invention may be varied to obtain an amount of an sorafenib that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, the route of administration, the potency of the administered sorafenib, the desired duration of treatment, and other factors.

[0134] Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

F. Examples

[0135] The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples. Throughout the specification, any and all references to a publicly available document, including a U.S. patent, are specifically incorporated by reference.

Example 1

[0136] The purpose of this example is to demonstrate the preparation of compositions comprising nanoparticulate sorafenib or a salt or derivative thereof.

[0137] Exemplary sorafenib formulations, detailed below in Table 1, Column 2, may be synthesized and evaluated as follows. The formulations comprising sorafenib may be milled in the 10 ml chamber of a NanoMill® 0.01 (NanoMill Systems, King of Prussia, PA; see *e.g.*, U.S. patent No. 6,431,478) along with 500 micron PolyMill® attrition media (Dow Chemical Co.), at an exemplary media load of about 89%. Each different formulation may be milled at a speed of 2500 for 60 minutes. Mill speed and milling time may be varied (*e.g.*, 3000 RPM for 90 minutes) to determine optimal milling conditions for a particular formulation or formulations (*e.g.*, empirically determined).

[0138] Following milling, the sorafenib particles may be evaluated using a Lecia DM5000B microscope and Lecia CTR 5000 light source (Laboratory Instruments & Supplies (I) Ltd. Ashbourne CO MEATH ROI). Additionally or alternatively, the particle size of the milled sorafenib particles may be measured, using deionized,

distilled water and a Horiba LA 910 particle size analyzer. After particle size analysis, a “successful composition,” may define formulations in which the initial mean and/or D50 milled sorafenib particle size is less than about 2000 nm. Particles may additionally be analyzed before and after a 60 second sonication.

[0139]

Sample	Exemplary Sorafenib Tosylate Formulations
1	Sorafenib, 5% w/w HPC-SL, 2% w/w Deionised Water, 93% w/w
2	Sorafenib, 5%w/w Plasdone S-630, 1.25%w/w Sodium Lauryl Sulfate, 0.05%w/w Deionised Water, 93.7%w/w
3	Sorafenib, 5%w/w Pharmacoat 603, 1.25%w/w Docusate sodium, 0.05%w/w Deionised Water, 93.7%w/w
4	Sorafenib, 5%w/w Tyloxapol, 1.25%w/w Deionised Water, 93.75%w/w
5	Sorafenib, 5%w/w Tween 80, 1.25%w/w Deionised Water, 93.75%w/w
6	Sorafenib, 5%w/w Lutrol F108, 1.5%w/w Deionised Water, 93.5%w/w
7	Sorafenib, 5%w/w Lutrol F68, 1.25%w/w Docusate sodium, 0.05%w/w Deionised Water, 93.7%w/w
8	Sorafenib, 5%w/w Plasdone K-17, 1.25%w/w Benzalkonium HCl , 0.05%w/w Deionised Water, 93.7%w/w

[0140] It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present inventions without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modification and variations of the invention provided they come within the scope of the appended claims and their equivalents.

[0141] The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or

portions thereof, but it is recognized that various modifications are possible within the scope of the invention. Thus, it should be understood that although the present invention has been illustrated by specific embodiments and optional features, modification and/or variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

[0142] In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

[0143] Also, unless indicated to the contrary, where various numerical values are provided for embodiments, additional embodiments are described by taking any 2 different values as the endpoints of a range. Such ranges are also within the scope of the described invention.

[0144] All references, patents, and/or applications cited in the specification are incorporated by reference in their entirety, including any tables and figures, to the same extent as if each reference had been incorporated by reference in its entirety individually.

WHAT IS CLAIMED IS:

1. A stable nanoparticulate sorafenib composition comprising:
 - (a) particles of an sorafenib or a salt or derivative thereof having an average effective particle size of less than about 2000 nm; and
 - (b) at least one surface stabilizer.
2. The composition of claim 1, wherein sorafenib is in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi amorphous phase, and mixtures thereof.
3. The composition of claim 1 or claim 2, wherein the effective average particle size of the sorafenib particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than about 640 nm, less than about 630 nm, less than about 620 nm, less than about 610 nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than

about 470 nm, less than about 460 nm, less than about 450 nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than about 380 nm, less than about 370 nm, less than about 360 nm, less than about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about 300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, and less than about 50 nm.

4. The composition of any one of claims 1 to 3, wherein the composition is formulated:

(a) for administration selected from the group consisting of oral, pulmonary, intravenous, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, ocular, otic, local, buccal, nasal, and topical administration;

(b) into a dosage form selected from the group consisting of liquid dispersions, gels, aerosols, ointments, creams, lyophilized formulations, tablets, capsules;

(c) into a dosage form selected from the group consisting of controlled release formulations, fast melt formulations, delayed release formulations, extended release formulations, pulsatile release formulations, mixed immediate release formulations, controlled release formulations; or

(d) any combination of (a), (b), and (c).

5. The composition of any one of claims 1 to 4, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

6. The composition of any one of claims 1 to 5, additionally comprising one or more active agents useful for the treatment of cancer and related diseases.

7. The composition of claim 6, wherein the cancer is selected from the group consisting of renal cancer, renal cell carcinoma, metastatic renal cell carcinoma and combinations thereof.

8. The composition of claim 6, wherein the one or more active agents is selected from the group consisting of chemotherapeutics, pain relievers, anti-depressants, anti-inflammatories, ondansetron, nabilone, dronabinol, antibiotics, and antivirals.

9. The composition of any one of claims 1 to 8, wherein

(a) the amount of sorafenib is selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of sorafenib and at least one surface stabilizer, not including other excipients;

(b) at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of sorafenib and at least one surface stabilizer, not including other excipients; or

(c) a combination of (a) and (b).

10. The composition of any one of claims 1 to 9, further comprising at least one primary surface stabilizer and at least one secondary surface stabilizer.

11. The composition of any one of claims 1 to 10, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, a non-ionic surface stabilizer, and an ionic surface stabilizer.

12. The composition of any one of claims 1 to 11, wherein at least one surface stabilizer is selected from the group consisting of albumin, human serum

albumin, bovine serum albumin, hypromellose, hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate (dioctyl sodium sulfosuccinate), dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl acetate and vinyl pyrrolidone, a cationic polymer, a cationic biopolymer, a cationic polysaccharide, a cationic cellulosic, a cationic alginate, a cationic nonpolymeric compound, cationic phospholipids, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut

trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™, ALKAQUAT™, alkyl pyridinium salts;

amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

13. The composition of any one of claims 1 to 12, wherein:

- (a) the pharmacokinetic profile of said composition is not significantly affected by the fed or fasted state of a subject ingesting said composition;
- (b) the composition does not produce significantly different absorption levels when administered under fed as compared to fasting conditions; or
- (c) a combination of (a) and (b).

14. The composition of claim 13, wherein the difference in absorption of the active agent composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

15. The composition of any one of claims 1 to 14, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of said composition to a subject in a fed state.

16. The composition of claim 15, wherein "bioequivalency" is established by:

- (a) a 90% Confidence Interval of between 0.80 and 1.25 for both $C_{\max}$ and AUC; or
- (b) a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for $C_{\max}$.

17. The composition of any one of claims 1 to 16, wherein:

(a) the $T_{\max}$ of the sorafenib, when assayed in the plasma of a mammalian subject following administration, is less than the $T_{\max}$ for a non-nanoparticulate composition of the same sorafenib, administered at the same dosage;

(b) the $C_{\max}$ of the sorafenib, when assayed in the plasma of a mammalian subject following administration, is greater than the $C_{\max}$ for a non-nanoparticulate composition of the same sorafenib, administered at the same dosage;

(c) the AUC of the sorafenib, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a non-nanoparticulate composition of the same sorafenib, administered at the same dosage;

or

(d) any combination of (a), (b), and (c).

18. The composition of claim 17, wherein:

(a) the $T_{\max}$ is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, not greater than about 10%, and not greater than about 5% of the $T_{\max}$ exhibited by a non-nanoparticulate composition of the same sorafenib, administered at the same dosage;

(b) the $C_{\max}$ is selected from the group consisting of at least about 50%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 600%, at least about 700%, at least about 800%, at least about 900%, at least about 1000%, at least about 1100%, at least about 1200%, at least about 1300%, at least about 1400%, at least about 1500%, at least about 1600%, at least about 1700%, at least about 1800%, or at least about 1900% greater than the $C_{\max}$ exhibited by a non-nanoparticulate composition of the same sorafenib, administered at the same dosage;

(c) the AUC is selected from the group consisting of at least about 25%, at least about 50%, at least about 75%, at least about 100%, at least about 125%, at least about 150%, at least about 175%, at least about 200%, at least about 225%, at least about 250%, at least about 275%, at least about 300%, at least about 350%, at least about 400%, at least about 450%, at least about 500%, at least about 550%, at

least about 600%, at least about 750%, at least about 700%, at least about 750%, at least about 800%, at least about 850%, at least about 900%, at least about 950%, at least about 1000%, at least about 1050%, at least about 1100%, at least about 1150%, or at least about 1200% greater than the AUC exhibited by the non-nanoparticulate formulation of the same sorafenib, administered at the same dosage; or

(d) any combination of (a), (b), and (c).

19. The composition any one of claims 1 to 18, wherein:

(a) upon administration to a mammal the sorafenib particles redisperse such that the particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than about 640 nm, less than about 630 nm, less than about 620 nm, less than about 610 nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than about 470 nm, less than about 460 nm, less than about 450 nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than about 380 nm, less than about 370 nm, less than about 360 nm, less than

about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about 300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, and less than about 50 nm;

(b) the composition redisperses in a biorelevant media such that the sorafenib particles have an effective average particle size selected from the group consisting of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 990 nm, less than about 980 nm, less than about 970 nm, less than about 960 nm, less than about 950 nm, less than about 940 nm, less than about 930 nm, less than about 920 nm, less than about 910 nm, less than about 900 nm, less than about 890 nm, less than about 880 nm, less than about 870 nm, less than about 860 nm, less than about 850 nm, less than about 840 nm, less than about 830 nm, less than about 820 nm, less than about 810 nm, less than about 800 nm, less than about 790 nm, less than about 780 nm, less than about 770 nm, less than about 760 nm, less than about 750 nm, less than about 740 nm, less than about 730 nm, less than about 720 nm, less than about 710 nm, less than about 700 nm, less than about 690 nm, less than about 680 nm, less than about 670 nm, less than about 660 nm, less than about 650 nm, less than about 640 nm, less than about 630 nm, less than about 620 nm, less than about 610 nm, less than about 600 nm, less than about 590 nm, less than about 580 nm, less than about 570 nm, less than about 560 nm, less than about 550 nm, less than about 540 nm, less than about 530 nm, less than about 520 nm, less than about 510 nm, less than about 500 nm, less than about 490 nm, less than about 480 nm, less than about 470 nm, less than about 460 nm, less than about 450 nm, less than about 440 nm, less than about 430 nm, less than about 420 nm, less than about 410 nm, less than about 400 nm, less than about 390 nm, less than

about 380 nm, less than about 370 nm, less than about 360 nm, less than about 350 nm, less than about 340 nm, less than about 330 nm, less than about 320 nm, less than about 310 nm, less than about 300 nm, less than about 290 nm, less than about 280 nm, less than about 270 nm, less than about 260 nm, less than about 250 nm, less than about 240 nm, less than about 230 nm, less than about 220 nm, less than about 210 nm, less than about 200 nm, less than about 190 nm, less than about 180 nm, less than about 170 nm, less than about 160 nm, less than about 150 nm, less than about 140 nm, less than about 130 nm, less than about 120 nm, less than about 110 nm, less than about 100, less than about 75 nm, and less than about 50 nm; or

(c) a combination of (a) and (b).

20. The composition of claim 19, wherein the biorelevant media is selected from the group consisting of water, aqueous electrolyte solutions, aqueous solutions of a salt, aqueous solutions of an acid, aqueous solutions of a base, and combinations thereof.

21. A method of preparing a nanoparticulate sorafenib, or a salt or derivative thereof, comprising contacting particles of sorafenib with at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate sorafenib composition having an effective average particle size of less than about 2000 nm.

22. The method of claim 21, wherein the contacting comprises grinding, wet grinding, homogenization, freezing, emulsion techniques, supercritical fluid particle generation techniques, precipitation, or a combination thereof.

23. A method for the treatment of renal cancer and related conditions in a subject comprising administering to a subject of an effective amount of a composition comprising:

- (a) particles of sorafenib or salt or derivative thereof having an average effective particle size of less than about 2000 nm; and
- (b) at least one surface stabilizer.

24. The method of claim 23, further comprising one or more active agents useful for the treatment of renal cancer and related condition.

25. The method of claim 23 or claim 24, wherein the related condition is selected from the group consisting of compromised immune system; viral or bacterial infections; nausea; vomiting; pain; non-renal cancer; fatigue; skin irritation; bone marrow depression; and a combination thereof.

26. The method of claim 25, wherein the one or more active agents is selected from the group consisting of chemotherapeutics, pain relievers, anti-depressants, anti-inflammatories, ondansetron, nabilone, dronabinol, antibiotics, and antivirals.

27. The method of any one of claims 23 to 26, wherein the composition is in the form of an oral tablet.

28. The method of any one of claims 23 to 26, wherein the composition is a parenteral formulation for injection.