Methods for Solid Tumor Treatment

Cross Reference

This application claims priority to U.S. Provisional Patent Application Serial Nos. 62/318014 filed April 4, 2016 and 62/378543 filed August 23, 2016, both incorporated by reference herein in their entirety.

Background

Millions of patients are diagnosed each year world-wide as having cancer, and millions more die from cancer or cancer-related complications each year. The risk of cancer increases significantly with age, many cancers occur more commonly in developed countries, and cancer rates are increasing as life expectancy increases in the developed world. Current therapies include systemic treatments such as intravenous (IV) infusion injection of chemotherapeutic agents. These therapies, however, generally have significant undesired side effects to the patient due to systemic toxicity. Direct injection of chemotherapeutic agents into tumors has been attempted, however, the chemotherapeutic agents tend to "leak" out of the tumor especially when the chemotherapeutic agents are solubilized. Thus, improved methods for treating patients having cancer are needed.

Summary

In one aspect of the invention, there is provided use of a composition comprising chemotherapeutic particles comprising at least 95% paclitaxel, docetaxel, or pharmaceutically acceptable salts thereof, wherein the particles have a specific surface are (SSA) determined by BET analysis of between 10 m^2/g and 50 m^2/g and a bulk density of between 0.050 g/cm^3 and 0.15 g/cm^3, in the manufacture of a medicament for treating a solid tumor in a subject, wherein the medicament is to be administered by direct injection into the tumor or peritumoral injection.

In one example, disclosed is a method for treating a solid tumor, comprising administering to a subject with a solid tumor an amount effective of a composition comprising chemotherapeutic particles to treat the tumor, wherein the composition is directly injected into the tumor.

In one example, disclosed is a method for inhibiting tumor metastasis, comprising administering to a subject with a tumor an amount effective of a composition comprising chemotherapeutic particles to inhibit tumor metastasis.

In another example, disclosed is a suspension comprising chemotherapeutic particles, a pharmaceutically acceptable carrier, and a polysorbate.

In another example, disclosed is a kit comprising a first vial containing chemotherapeutic particles; a second vial containing a polysorbate; and instructions for reconstituting the chemotherapeutic particles into a suspension and for diluting the suspension with a diluent solution prior to administration to a patient.

Also disclosed in the context of the present invention are the following examples 1 to 77:

Example 1 is a method for treating a solid tumor, comprising administering to a subject with a solid tumor an amount effective of a composition comprising chemotherapeutic particles to treat the tumor, wherein the composition is directly injected into the tumor, such as a malignant tumor.

Example 2 is the method of example 1 wherein the composition consists of the chemotherapeutic particles and a pharmaceutically acceptable carrier, such as a liquid carrier.

Example 3 is the method of any one of examples 1-2, wherein the administering results in chemotherapeutic migrating into the lymphatic system of the subject.

Example 4 is a method for inhibiting tumor metastasis, comprising administering to a subject with a malignant tumor an amount effective of a composition comprising chemotherapeutic particles to inhibit tumor metastasis.

Example 5 is the method of example 4, wherein the composition is directly injected into the tumor, or is peritumorally injected.

Example 6 is the method of any one of examples 4-5, wherein the composition consists of the chemotherapeutic particles and a carrier (such as a liquid, semi-solid, or solid carrier).

Example 7 is the method of any one of examples 1-3 and 6, wherein the carrier is an aqueous liquid carrier.

Example 8 is the method of example 7 wherein the aqueous liquid carrier is saline, such as normal saline.

Example 9 is the method of any one of examples 1-8, wherein the composition is a suspension.

Example 10 is the method of any one of examples 1-9 wherein the particles are (i) uncoated; (ii) not embedded, contained, enclosed or encapsulated within a solid excipient; and (iii) not microspheres, liposomes, or microcapsules containing chemotherapeutic and an excipient.

Example 11 is the method of any one of examples 1-10, wherein the chemotherapeutic is selected from the group consisting of paclitaxel; derivatives of paclitaxel, docetaxel, cabazitaxel, taxanes; epithilones, Vinca alkaloids, such as vinblastine, vincristine, vindesine, vinorelbine; camptothecin analogs; epipodophyllotoxins, such as cisplatin, carboplatin, oxaliplatin, etoposide and teniposide; doxorubicin, anthrcyclines, 5-fluorouracil, topotecan, gemcitabine, peroxisome proliferator-activated receptor (PPAR) ligands, and antiangiogenics, or a pharmaceutically acceptable salt thereof.

Example 12 is the method of any one of examples 1-11, wherein the chemotherapeutic is a taxane, or a pharmaceutically acceptable salt thereof.

Example 13 is the method of any one of examples 1-12, wherein the chemotherapeutic is paclitaxel, or a pharmaceutically acceptable salt thereof.

Example 14 is the method of any one of examples 1-13, wherein the tumor is selected from the group consisting of sarcomas, carcinomas, and lymphomas, breast tumors, prostate tumors, head and neck tumors, glioblastomas, bladder tumors, pancreatic tumors, liver tumors, ovarian tumors, colorectal tumors, cutaneous, lymphoid, and gastrointestinal tumors.

Example 15 is the method of example 13, wherein the tumor is selected from the group consisting of ovarian, bladder, breast, prostate, pulmonary, pancreatic, cutaneous, lymphoid, and gastrointestinal tumors.

Example 16 is the method of example 13, wherein the tumor is selected from the group consisting of ovarian and bladder tumors.

Example 17 is the method of any one of examples 1-12, wherein the chemotherapeutic is docetaxel, or a pharmaceutically acceptable salt thereof.

Example 18 is the method of example 17, wherein the tumor is selected from the group consisting of ovarian, bladder, breast, and prostate tumors.

Example 19 is the method of example 17, wherein the tumor is selected from the group consisting of breast and prostate tumors.

Example 20 is the method of any one of examples 1-19, wherein the chemotherapeutic particles comprise at least 95% chemotherapeutic and wherein the particles have a specific surface area (SSA) of at least 10 m^2/g, or at least 12 m^2/g, 14 m^2/g, 16 m^2/g, 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 32 m^2/g, 34 m^2/g, or 35 m^2/g.

Example 21 is the method of example 20, wherein the chemotherapeutic particles have an SSA of between about 10 m^2/g and about 50 m^2/g.

Example 22 is the method of any one of examples 20-21, wherein the chemotherapeutic particles have an SSA of:

(a) between16 m^2/g and 31 m^2/g or between 32 m^2/g and 50 m^2/g;

(b) between16 m^2/g and 30 m^2/g or between 32 m^2/g and 50 m^2/g;

(c) between16 m^2/g and 29 m^2/g or between 32 m^2/g and 50 m^2/g;

(d) between17 m^2/g and 31 m^2/g or between 32 m^2/g and 50 m^2/g;

(e) between17 m^2/g and 30 m^2/g or between 32 m^2/g and 50 m^2/g;

(f) between17 m^2/g and 29 m^2/g, or between 32 m^2/g and 50 m^2/g;

(g) between16 m^2/g and 31 m^2/g or between 33 m^2/g and 50 m^2/g;

(h) between16 m^2/g and 30 m^2/g or between 33 m^2/g and 50 m^2/g;

(i) between16 m^2/g and 29 m^2/g or between 33 m^2/g and 50 m^2/g;

(j) between17 m^2/g and 31 m^2/g or between 33 m^2/g and 50 m^2/g;

(k) between17 m^2/g and 30 m^2/g or between 33 m^2/g and 50 m^2/g;

(l) between17 m^2/g and 29 m^2/g, or between 33 m^2/g and 50 m^2/g;

(m) between 16 m^2/g and 31 m^2/g, or ≥32 m^2/g;

(h) between17 m^2/g and 31 m^2/g, or ≥ 32 m^2/g;

(i) between16 m^2/g and 30 m^2/g, or ≥ 32 m^2/g;

(j) between17 m^2/g and 30 m^2/g, or ≥ 32 m^2/g;

(k) between16 m^2/g and 29 m^2/g, or ≥ 32 m^2/g;

(l) between17 m^2/g and 29 m^2/g, or ≥ 32 m^2/g;

(m) between 16 m^2/g and 31 m^2/g, or ≥33 m^2/g;

(n) between17 m^2/g and 31 m^2/g, or ≥ 33 m^2/g;

(o) between16 m^2/g and 30 m^2/g, or ≥ 33 m^2/g;

(p) between17 m^2/g and 30 m^2/g, or ≥ 33 m^2/g;

(q) between16 m^2/g and 29 m^2/g, or ≥ 33 m^2/g; or

(r) between17 m^2/g and 29 m^2/g, or ≥ 33 m^2/g.

Example 23 is the method of any one of examples 20-22, wherein the chemotherapeutic is paclitaxel, or a pharmaceutically acceptable salt thereof.

Example 24 is the method of any one of examples 20-22, wherein the chemotherapeutic is docetaxel, or a pharmaceutically acceptable salt thereof.

Example 25 is the method of any one of examples 1-24, wherein the chemotherapeutic particles include at least 95% by weight of a taxane, or a pharmaceutically acceptable salt thereof, wherein the particles have one or both of the following characteristics:

(i) a mean bulk density between about 0.050 g/cm^3 and about 0.15 g/cm^3, and/or

(ii) have a specific surface area (SSA) of at least 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 32 m^2/g, 34 m^2/g, or 35 m^2/g.

Example 26 is the method of example 25, wherein the taxane is selected from the group consisting of paclitaxel, docetaxel, cabazitaxel, taxadiene, baccatin III, taxchinin A, brevifoliol, and taxuspine D, or a pharmaceutically acceptable salt thereof.

Example 27 is the method of example 25, wherein the taxane is selected from the group consisting of paclitaxel, docetaxel, and cabazitaxel, or a pharmaceutically acceptable salt thereof.

Example 28 is the method of example 27, wherein the taxane is paclitaxel or a pharmaceutically acceptable salt thereof, and wherein the particles have a mean bulk density between about 0.050 g/cm^3 and about 0.12 g/cm^3, or between about 0.060 g/cm^3 and about 0.11 g/cm^3.

Example 29 is the method of example 27 or 28, wherein the taxane is paclitaxel or a pharmaceutically acceptable salt thereof , and wherein the paclitaxel particles have a specific surface area (SSA) of at least 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 32 m^2/g, 34 m^2/g, or 35 m^2/g.

Example 30 is the method of any of examples 27-29, wherein the taxane is paclitaxel or a pharmaceutically acceptable salt thereof, and wherein the wherein the paclitaxel particles have a SSA of between about 22 m^2/g and about 40 m^2/g, 25 m^2/g and about 40 m^2/g, 30 m^2/g and about 40 m^2/g, or between about 35 m^2/g and about 40 m^2/g.

Example 31 is the method of any one of examples 28-30, wherein the paclitaxel particles have a bulk density of between about 0.060 g/cm^3 and about 0.11 g/cm^3 and a SSA of between about 22 m^2/g and about 40 m^2/g.

Example 32 is the method of any one of examples 28-31, wherein at least 40% (w/w) of the paclitaxel is dissolved in 30 minutes or less in a solution of 50% methanol /50% water (v/v) at 37°C and pH 7.0 in a USP II paddle apparatus operating at 75 RPM.

Example 33 is the method of example 27, wherein the taxane is docetaxel or a pharmaceutically acceptable salt thereof, and wherein the particles have a mean bulk density

between about 0.050 g/cm^3 and about 0.12 g/cm^3, or between about 0.06 g/cm^3 and about 0.1 g/cm^3.

Example 34 is the method of example 27 or 33, wherein the taxane is docetaxel or a pharmaceutically acceptable salt thereof, and wherein the docetaxel particles have a SSA of at least 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 35 m^2/g, 40 m^2/g, or 42 m^2/g.

Example 35 is the method of example 27 or 33-34, wherein the taxane is docetaxel or a pharmaceutically acceptable salt thereof, and wherein the docetaxel particles have a SSA of between about 40 m^2/g and about 50 m^2/g, or between about 43 m^2/g and about 46 m^2/g.

Example 36 is the method of any one of examples 33-35, wherein the docetaxel particles have a bulk density of between about 0.06 g/cm^3 and about 0.1 g/cm^3 and a SSA of between about 40 m^2/g and about 50 m^2/g.

Example 37 is the method of any one of examples 33-36, wherein at least 20% (w/w) of the docetaxel is dissolved in 30 minutes or less in a solution of 15% methanol /85% water (v/v) at 37°C and pH 7.0 in a USP II paddle apparatus operating at 75 RPM.

Example 38 is the method of any one of examples 1-22, wherein the chemotherapeutic particles include at least 95% by weight of paclitaxel, or a pharmaceutically acceptable salt thereof, wherein the particles have a specific surface area (SSA) of at least 12 m^2/g.

Example 39 is the method of example 38, wherein the paclitaxel particles have a SSA of at least 12 m^2/g, 15 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 32 m^2/g, 34 m^2/g, or 35 m^2/g.

Example 40 is the method of any one of examples 38-39, wherein at least 40% (w/w) of the paclitaxel is dissolved in 30 minutes or less in a solution of 50% methanol /50% water (v/v) at 37°C and pH 7.0 in a USP II paddle apparatus operating at 75 RPM.

Example 41 is the method of any one of examples 1-22, wherein the chemotherapeutic particles include at least 95% by weight of paclitaxel, wherein at least 40% (w/w) of the paclitaxel is dissolved in 30 minutes or less in a solution of 50% methanol /50% water (v/v) at 37°C and pH 7.0 in a USP II paddle apparatus operating at 75 RPM.

Example 42 is the method of any one of examples 1-22, wherein the chemotherapeutic particles include at least 95% by weight of docetaxel, wherein at least 20% (w/w) of the docetaxel is dissolved in 30 minutes or less in a solution of 15% methanol /85% water (v/v) at 37°C and pH 7.0 in a USP II paddle apparatus operating at 75 RPM.

Example 43 is the method of any one of examples 1-42, wherein the particles have a mean particle size number of between about 0.4 μm and about 1.2 μm, or between about 0.6 μm and about 1.0 μm.

Example 44 is the method of any one of examples 1-43, wherein the particles are uncoated and the composition excludes polymers, proteins, polyethoxylated castor oil, and/or polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol.

Example 45 is the method of any one of examples 1-42, wherein the chemotherapeutic particle is present in a suspension further comprising a pharmaceutically acceptable aqueous carrier.

Example 46 is the method of any one of examples 1-45, wherein the particles comprise at least 96%, 97%, 98%, 99%, or 100% of the compound.

Example 47 is the method of any one of examples 1-46, wherein the chemotherapeutic particle is present in a suspension further comprising a polysorbate, such as polysorbate 80, wherein the polysorbate is present in the suspension at a concentration of between about 0.01% v/v and about 1.5% v/v, or between about 0.01% v/v and about 1% v/v, about 0.01% v/v and about 0.5% v/v, about 0.01% v/v and about 0.4% v/v, about 0.01% v/v and about 0.25% v/v, about 0.05% v/v and about 0.5% v/v, about 0.05% v/v and about 0.25% v/v, about 0.1% v/v and about 0.5% v/v, about 0.1% v/v and about 0.25% v/v, about 0.1% v/v, about 0.16 v/v, or about 0.25% v/v.

Example 48 is the method of example 47, wherein the chemotherapeutic is present in the suspension at a concentration between about 1 mg/ml and about 40 mg/ml, or about 6 mg/ml and about 20 mg/ml.

Example 49 is the method of example 48 wherein the chemotherapeutic particle comprises paclitaxel, or a pharmaceutically acceptable salt thereof, wherein the paclitaxel is present in the suspension at a concentration of between about 1 mg/ml and about 40 mg/ml, or about 6 mg/ml and about 20 mg/ml.

Example 50 is the method of example 48 wherein the chemotherapeutic particle comprises docetaxel, or a pharmaceutically acceptable salt thereof, wherein the paclitaxel is present in the suspension at a concentration of between about 1 mg/ml and about 40 mg/ml, or about 6 mg/ml and about 20 mg/ml.

Example 51 is a suspension, comprising:

(a) chemotherapeutic particles;

(b) a pharmaceutically acceptable carrier; and

(c) a polysorbate, wherein the polysorbate is present in the suspension at a concentration of between about 0.01% v/v and about 1.5% v/v, or between about 0.01% v/v and about 1% v/v, about 0.01% v/v and about 0.5% v/v, about 0.01% v/v and about 0.4% v/v,

about 0.01% v/v and about 0.25% v/v, about 0.05% v/v and about 0.5% v/v, about 0.05% v/v and about 0.25% v/v, about 0.1% v/v and about 0.5% v/v, about 0.1% v/v and about 0.25% v/v, about 0.1% v/v, about 0.16 v/v, or about 0.25% v/v.

Example 52 is a kit, comprising:

(a) a first vial containing chemotherapeutic particles;

(b) a second vial containing a polysorbate and a pharmaceutically acceptable carrier;

(c) instructions for reconstituting the chemotherapeutic particles into a suspension by combining the contents of the first vial and the second vial, and for diluting the suspension with a diluent solution, such as 0.9% saline solution, prior to administration to a patient.

Example 53 is the suspension of example 51 or the kit of example 52, wherein the chemotherapeutic particles are selected from the group consisting of paclitaxel; derivatives of paclitaxel, docetaxel, cabazitaxel, taxanes; epithilones, Vinca alkaloids, such as vinblastine, vincristine, vindesine, vinorelbine; camptothecin analogs; epipodophyllotoxins, such as cisplatin, carboplatin, oxaliplatin, etoposide and teniposide; doxorubicin, anthrcyclines, 5-fluorouracil, topotecan, gemcitabine, peroxisome proliferator-activated receptor (PPAR) ligands, and antiangiogenics, or a pharmaceutically acceptable salt thereof.

Example 54 is the suspension or kit of any one of examples 51-53, wherein the chemotherapeutic is a taxane, or a pharmaceutically acceptable salt thereof.

Example 55 is the suspension or kit of any one of examples 51-54, wherein the chemotherapeutic is paclitaxel, or a pharmaceutically acceptable salt thereof.

Example 56 is the suspension or kit of any one of examples 51-54, wherein the chemotherapeutic is docetaxel, or a pharmaceutically acceptable salt thereof.

Example 57 is the suspension of any one of examples 51 and 53-56, wherein the chemotherapeutic is present in the suspension at a concentration between about 1 mg/ml and about 40 mg/ml, or about 6 mg/ml and about 20 mg/ml.

Example 58 is the suspension or kit of any one of examples 51-57, wherein the chemotherapeutic particles comprise at least 95% chemotherapeutic and wherein the particles have a specific surface area (SSA) of at least 10 m^2/g, or at least 12 m^2/g, 14 m^2/g, 16 m^2/g, 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 32 m^2/g, 34 m^2/g, or 35 m^2/g.

Example 59 is the suspension or kit of any one of examples 51-58, wherein the chemotherapeutic particles have an SSA of between about 10 m^2/g and about 50 m^2/g.

Example 60 is the suspension or kit of any one of examples 51-59, wherein the chemotherapeutic particles have an SSA of:

(a) between16 m^2/g and 31 m^2/g or between 32 m^2/g and 50 m^2/g;

(b) between16 m^2/g and 30 m^2/g or between 32 m^2/g and 50 m^2/g;

(c) between16 m^2/g and 29 m^2/g or between 32 m^2/g and 50 m^2/g;

(d) between17 m^2/g and 31 m^2/g or between 32 m^2/g and 50 m^2/g;

(e) between17 m^2/g and 30 m^2/g or between 32 m^2/g and 50 m^2/g;

(f) between17 m^2/g and 29 m^2/g, or between 32 m^2/g and 50 m^2/g;

(g) between16 m^2/g and 31 m^2/g or between 33 m^2/g and 50 m^2/g;

(h) between16 m^2/g and 30 m^2/g or between 33 m^2/g and 50 m^2/g;

(i) between16 m^2/g and 29 m^2/g or between 33 m^2/g and 50 m^2/g;

(j) between17 m^2/g and 31 m^2/g or between 33 m^2/g and 50 m^2/g;

(k) between17 m^2/g and 30 m^2/g or between 33 m^2/g and 50 m^2/g;

(l) between17 m^2/g and 29 m^2/g, or between 33 m^2/g and 50 m^2/g;

(m) between 16 m^2/g and 31 m^2/g, or ≥32 m^2/g;

(h) between17 m^2/g and 31 m^2/g, or ≥ 32 m^2/g;

(i) between16 m^2/g and 30 m^2/g, or ≥ 32 m^2/g;

(j) between17 m^2/g and 30 m^2/g, or ≥ 32 m^2/g;

(k) between16 m^2/g and 29 m^2/g, or ≥ 32 m^2/g;

(l) between17 m^2/g and 29 m^2/g, or ≥ 32 m^2/g;

(m) between 16 m^2/g and 31 m^2/g, or ≥33 m^2/g;

(n) between17 m^2/g and 31 m^2/g, or ≥ 33 m^2/g;

(o) between16 m^2/g and 30 m^2/g, or ≥ 33 m^2/g;

(p) between17 m^2/g and 30 m^2/g, or ≥ 33 m^2/g;

(q) between16 m^2/g and 29 m^2/g, or ≥ 33 m^2/g; or

(r) between17 m^2/g and 29 m^2/g, or ≥ 33 m^2/g.

Example 61 is the suspension or kit of any one of examples 51-60, wherein the chemotherapeutic particles include at least 95% by weight of a taxane, or a pharmaceutically acceptable salt thereof, wherein the particles have one or both of the following characteristics:

(i) a mean bulk density between about 0.050 g/cm^3 and about 0.15 g/cm^3, and/or

(ii) have a specific surface area (SSA) of at least 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 32 m^2/g, 34 m^2/g, or 35 m^2/g.

Example 62 is the suspension or kit of any one of examples 51-55 and 57-61, wherein the taxane is paclitaxel or a pharmaceutically acceptable salt thereof, and wherein the

particles have a mean bulk density between about 0.050 g/cm^3 and about 0.12 g/cm^3, or between about 0.060 g/cm^3 and about 0.11 g/cm^3.

Example 63 is the suspension or kit of any one of examples 51-55 and 57-62, wherein the taxane is paclitaxel or a pharmaceutically acceptable salt thereof, and wherein the paclitaxel particles have a specific surface area (SSA) of at least 12 m^2/g, 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 32 m^2/g, 34 m^2/g, or 35 m^2/g.

Example 64 is the suspension or kit of any one of examples 51-55 and 57-63, wherein the taxane is paclitaxel or a pharmaceutically acceptable salt thereof, and wherein the wherein the paclitaxel particles have a SSA of between about 22 m^2/g and about 40 m^2/g, 25 m^2/g and about 40 m^2/g, 30 m^2/g and about 40 m^2/g, or between about 35 m^2/g and about 40 m^2/g.

Example 65 is the suspension or kit of any one of examples 51-55 and 57-64, wherein the paclitaxel particles have a bulk density of between about 0.060 g/cm^3 and about 0.11 g/cm^3 and a SSA of between about 22 m^2/g and about 40 m^2/g.

Example 66 is the suspension or kit of any one of examples 51-55 and 57-65, wherein at least 40% (w/w) of the paclitaxel is dissolved in 30 minutes or less in a solution of 50% methanol /50% water (v/v) at 37°C and pH 7.0 in a USP II paddle apparatus operating at 75 RPM.

Example 67 is the suspension or kit of any one of examples 51-54 and 56-61, wherein the taxane is docetaxel or a pharmaceutically acceptable salt thereof, and wherein the particles have a mean bulk density between about 0.050 g/cm^3 and about 0.12 g/cm^3, or between about 0.06 g/cm^3 and about 0.1 g/cm^3.

Example 68 is the suspension or kit of any one of examples 51-54, 56-61, and 67 wherein the taxane is docetaxel or a pharmaceutically acceptable salt thereof, and wherein the docetaxel particles have a SSA of at least 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 35 m^2/g, 40 m^2/g, or 42 m^2/g.

Example 69 is the suspension or kit of any one of examples 51-54, 56-61, and 67-68, wherein the taxane is docetaxel or a pharmaceutically acceptable salt thereof, and wherein the docetaxel particles have a SSA of between about 40 m^2/g and about 50 m^2/g, or between about 43 m^2/g and about 46 m^2/g.

Example 70 is the suspension or kit of any one of examples 51-54, 56-61, and 67-69, wherein the docetaxel particles have a bulk density of between about 0.06 g/cm^3 and about 0.1 g/cm^3 and a SSA of between about 40 m^2/g and about 50 m^2/g.

Example 71 is the suspension or kit of any one of examples 51-54, 56-61, and 67-70, wherein at least 20% (w/w) of the docetaxel is dissolved in 30 minutes or less in a solution of

15% methanol /85% water (v/v) at 37°C and pH 7.0 in a USP II paddle apparatus operating at 75 RPM.

Example 72 is the suspension or kit of any one of examples 51-71, wherein the particles have a mean particle size number of between about 0.4 μm and about 1.2 μm, or between about 0.6 μm and about 1.0 μm.

Example 73 is the suspension or kit of any one of examples 51-72, wherein the particles are uncoated and the suspension or kit excludes polymers, proteins, polyethoxylated castor oil, and/or polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol.

Example 74 is the suspension or kit of any one of examples 51-73, wherein the pharmaceutically acceptable carrier is saline, such as 0.9% sodium chloride solution.

Example 75 is the suspension or kit of any one of examples 51-74, wherein the polysorbate is polysorbate 80.

Example 76 is the kit of any one of examples 52-75, wherein the contents of the first and second vial are sterile.

Example 77 is the method, suspension, or kit of any one of examples 1-76, wherein the chemotherapeutic particles are non-agglomerated individual particles.

Description of the Figures

Figure 1. Median tumor volume of PC3 human prostate carcinoma in mice treated by direct tumor injection (ITU) with vehicle and paclitaxel particles (Study P-PPr-01-2015).

Figure 2. Median tumor volume for mouse PC-3 prostate tumor xenografts treated IT with vehicle, NanoDoce™, NanoPac™ and treated IV with docetaxel (Study PD-PPr-02-2016).

Figure 3. Mean tumor volume for mouse MDA-MB-231 xenografts treated IT with vehicle, NanoDoce™, NanoPac™ and treated IV with docetaxel or paclitaxel (Study PD-PB-04-2016).

Figure 4. Mean tumor volume for mouse MX-1 xenografts treated IT with vehicle, NanoDoce™, NanoPac™ and treated IV with docetaxel or paclitaxel (Study P-PB-03-2016).

Detailed Description of the Invention

We claim:

1. Use of a composition comprising chemotherapeutic particles comprising at least 95% paclitaxel, docetaxel, or pharmaceutically acceptable salts thereof, wherein the particles have a specific surface are (SSA) determined by BET analysis of between 10 m^2/g and 50 m^2/g and a bulk density of between 0.050 g/cm^3 and 0.15 g/cm^3, in the manufacture of a medicament for treating a solid tumor in a subject, wherein the medicament is to be administered by direct injection into the tumor or peritumoral injection.

2. The use of claim 1 wherein the composition consists of the chemotherapeutic particles and a pharmaceutically acceptable carrier.

3. The use of any one of claims 1-2, wherein the direct injection results in chemotherapeutic migrating into the lymphatic system of the subject.

4. The use of any one of claims 1-3, wherein the composition is for direct injection into the tumor.

5. The use of any one of claims 2-3, wherein the carrier is an aqueous liquid carrier.

6. The use of claim 5 wherein the aqueous liquid carrier is saline, such as normal saline.

7. The use of any one of claims 1-6, wherein the composition is a suspension.

8. The use of any one of claims 1-7 wherein the particles are (i) uncoated; (ii) not embedded, contained, enclosed or encapsulated within a solid excipient; and (iii) not microspheres, liposomes, or microcapsules containing chemotherapeutic and an excipient.

9. The use of any one of claims 1-8, wherein the chemotherapeutic is paclitaxel, or a pharmaceutically acceptable salt thereof.

10. The use of any one of claims 1-9, wherein the tumor is selected from the group consisting of sarcomas, carcinomas, and lymphomas, breast tumors, prostate tumors, head and neck tumors, glioblastomas, bladder tumors, pancreatic tumors, liver tumors, ovarian tumors, colorectal tumors, cutaneous, lymphoid, and gastrointestinal tumors.

11. The use of claim 9, wherein the tumor is selected from the group consisting of ovarian, bladder, breast, prostate, pulmonary, pancreatic, cutaneous, lymphoid, and gastrointestinal tumors.

12. The use of claim 9, wherein the tumor is selected from the group consisting of ovarian and bladder tumors.

13. The use of any one of claims 1-8, wherein the chemotherapeutic is docetaxel, or a pharmaceutically acceptable salt thereof.

14. The use of claim 13, wherein the tumor is selected from the group consisting of ovarian, bladder, breast, and prostate tumors.

15. The use of claim 13, wherein the tumor is selected from the group consisting of breast and prostate tumors.

16. The use of any one of claims 1-15, wherein the particles have a SSA of at least 12 m^2/g, 14 m^2/g, 16 m^2/g, 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 32 m^2/g, 34 m^2/g, or 35 m^2/g.

17. The use of claim 16, wherein the chemotherapeutic particles have an SSA of between 10 m^2/g and 50 m^2/g.

18. The use of any one of claims 1-8, wherein the chemotherapeutic is paclitaxel or a pharmaceutically acceptable salt thereof, and wherein the particles have a mean bulk density between 0.060 g/cm^3 and 0.11 g/cm^3.

19. The use of any one of claims 1-8 and 18, wherein the chemotherapeutic is paclitaxel or a pharmaceutically acceptable salt thereof , and wherein the paclitaxel particles have a SSA of at least 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 32 m^2/g, 34 m^2/g, or 35 m^2/g.

20 The use of any of claims 1-8 and 18-19, wherein the chemotherapeutic is paclitaxel or a pharmaceutically acceptable salt thereof, and wherein the paclitaxel particles have a SSA of between 18 m^2/g and 50 m^2/g.

21. The use of any one of claims 1-8 and 18-20, wherein the paclitaxel particles have a bulk density of between 0.060 g/cm^3 and 0.11 g/cm^3 and a SSA of between 18 m^2/g and 50 m^2/g.

22. The use of any one of claims 1-8, wherein the chemotherapeutic is docetaxel or a pharmaceutically acceptable salt thereof, and wherein the particles have a mean bulk density between 0.06 g/cm^3 and 0.1 g/cm^3.

23. The use of any one of claims 1-8 and 22, wherein the taxane is docetaxel or a pharmaceutically acceptable salt thereof, and wherein the docetaxel particles have a SSA of at least 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 35 m^2/g, 40 m^2/g, or 42 m^2/g.

24. The use of any one of claims 1-8 and 22-23, wherein the chemotherapeutic is docetaxel or a pharmaceutically acceptable salt thereof, and wherein the docetaxel particles have a SSA of between 18 m^2/g and 50 m^2/g.

25. The use of any one of claims 1-8 and 23-24, wherein the docetaxel particles have a bulk density of between 0.06 g/cm^3 and 0.1 g/cm^3 and a SSA of between 18 m^2/g and 50 m^2/g.

26. The use of any one of claims 1-25, wherein the particles have a mean particle size number of between 0.4 μm and 1.2 μm, or between 0.6 μm and 1.0 μm.

27. The use of any one of claims 1-26, wherein the particles are uncoated and the composition excludes polymers, proteins, polyethoxylated castor oil, and/or polyethylene

glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol.

28. The use of any one of claims 1-27, wherein the chemotherapeutic particle is present in a suspension further comprising a pharmaceutically acceptable aqueous carrier.

29. The use of any one of claims 1-28, wherein the particles comprise at least 96%, 97%, 98%, 99%, or 100% of the compound.

30. The use of any one of claims 1-29, wherein the chemotherapeutic particle is present in a suspension further comprising a polysorbate, such as polysorbate 80, wherein the polysorbate is present in the suspension at a concentration of between 0.01% v/v and 1.5% v/v, or between 0.01% v/v and 1% v/v, 0.01% v/v and 0.5% v/v, 0.01% v/v and 0.4% v/v, 0.01% v/v and 0.25% v/v, 0.05% v/v and 0.5% v/v, 0.05% v/v and 0.25% v/v, 0.1% v/v and 0.5% v/v, 0.1% v/v and 0.25% v/v, 0.1% v/v, 0.16 v/v, or 0.25% v/v.

31. The use of claim 30, wherein the chemotherapeutic is present in the suspension at a concentration between 1 mg/ml and 40 mg/ml, or 6 mg/ml and 20 mg/ml.

32. The use of claim 31 wherein the chemotherapeutic particle comprises paclitaxel, or a pharmaceutically acceptable salt thereof, wherein the paclitaxel is present in the suspension at a concentration of between 1 mg/ml and 40 mg/ml, or 6 mg/ml and 20 mg/ml.

33. The use of claim 31 wherein the chemotherapeutic particle comprises docetaxel, or a pharmaceutically acceptable salt thereof, wherein the paclitaxel is present in the suspension at a concentration of between 1 mg/ml and 40 mg/ml, or between 6 mg/ml and 20 mg/ml.