Summary

Compositions and methods of the disclosure address problems with imatinib-based PAH treatments through the use of specialized formulations and delivery mechanisms. Particularly, the disclosure recognizes that crystalline form and polymorph composition of drugs like imatinib and salts thereof can have significant effects on drug solubility, delivery, absorption, and metabolism. Accordingly, crystal form can be important for determining dosage and predicting patient response. In one aspect, the present disclosure provides an inhalable formulation comprising imatinib or a salt thereof, wherein greater than 80% of the imatinib or salt thereof in the inhalable formulation is present in a single crystal form, with the proviso that the salt is not mesylate. In another aspect, the present disclosure provides an inhalable formulation comprising particles of imatinib, wherein the imatinib retains its crystal structure in the particles and the inhalable formulation comprises less than 5% amorphous imatinib particles.

In certain examples, the disclosure provides a formulation of inhalable imatinib with a higher ratio of API (active pharmaceutical ingredient) than found in conventional formulations. In certain examples, formulations comprising 50% or more imatinib or imatinib salts are provided. Compositions and methods of the disclosure recognize that large volumes may be difficult or dangerous for patients to inhale and that, therefore, minimizing the amount of non-API components in the formulation can improve patient comfort, safety, and compliance by reducing the overall amount of compound that is inhaled while still providing a therapeutically effective API concentration in target tissue.

Furthermore, aerodynamic properties important to inhalable drug uptake can more easily be managed when less of the formulation is required for carriers or other additives. The performance of dry-powder formulations consisting of 50%, 75%, and 90% API was tested via aerodynamic particle size distribution, blend content uniformity, capsule content uniformity, and emitted dose by dosage unit sampling apparatus (DUSA) with favorable results as shown in Example 3 below. By providing functional inhalable formulations with high concentrations of imatinib or salts thereof, compositions and methods of the disclosure can provide the load-reducing benefits discussed above while still delivering therapeutic results and avoiding the severe adverse events associated with other drug delivery routes.

Inhalable compositions of the disclosure offer greater lung exposure than equivalent doses of imatinib or imatinib mesylate administered through conventional oral routes or by IV. While a relatively high oral dose of imatinib or imatinib mesylate would be required to achieve the same target lung exposure as achieved by inhalation of the inventive formulations, significantly lower dosages can be delivered using the inventive compositions and methods.

In various examples, the imatinib or salts thereof used in compositions and methods of the disclosure can consist of entirely or almost entirely a single crystal form (e.g., greater than 80%, 85%, 90%, 95%, 99% or 100% of a single crystal form), thereby allowing for controlled and predictable dosing and patient response. In certain examples, greater than 95% of imatinib or a salt thereof in the inhalable formulation may be present in a single crystal form. Various crystal forms are discussed in detail below and x-ray powder diffraction diagrams are provided.

Additionally, the primary active metabolite of imatinib is N-desmethyl imatinib and has been found to exhibit the same potency as the imatinib parent compound. N-desmethyl imatinib also exhibits an increased half-life relative to the parent imatinib compound. Compounds and methods of the disclosure take advantage of this characteristic by providing inhalable formulations of N-desmethyl imatinib in the absence of the parent compound. Such formulations provide therapeutic benefits in treating PAH and other conditions with more efficient delivery to and longer residence in the effected tissue due to the increased half-life of the metabolite. This combination can allow for fewer doses with lower concentrations of active pharmaceutical ingredient relative to conventional oral or IV administration of imatinib mesylate.

In certain examples inhalable imatinib compounds may be micronized through wet or dry milling (e.g., jet milling) to achieve the desired particle size for dry powder formulations for inhalation. Imatinib or appropriate salts thereof may be micronized to particle sizes of about 0.5 μm to about 5 μm mass median aerodynamic diameter (MMAD) for desired deep lung penetration. Inhaled products can be limited in terms of mass of powder that can be administered and certain imatinib salts will contribute significantly to the molecular weight of the inhaled compound. Accordingly, in certain examples, the imatinib free base may be preferred for efficient delivery of the active moiety to lung tissue. If required, various excipients or carriers can be added to imatinib or salts thereof before or after micronization depending on application while maintaining a relatively high (e.g., 50% or greater) ratio of the API. For example, carriers, excipients, conditioners, and force control agents such as lactose (which when used as a carrier

may be conditioned with various solvents to increase separation of imatinib during inhalation), magnesium stearate, leucine, isoleucine, dileucine, trileucine, lecithin, distearylphosphatidylcholine (DSPC) or other lipid-based carriers, or various hydrophilic polymers where they exhibit appropriate physico-chemical properties may be included. The skilled artisan will appreciate that excipients or carriers are optional and that many examples of the disclosure do not require excipients or carriers. In compounds including carriers or excipients, API:carrier ratios may be greater than 50:50, 75:25, or 90:10. Additional ratios are contemplated as discussed below.

In drug delivery and particularly that of inhalable formulations, particle geometry plays an important role in pharmacokinetics. Particle aerodynamics as determined by their size and shape can have significant effects on lung penetration via inhalation. Particle engineering also allows for more efficient deagglomeration, for example as inhalable powder is delivered from a device and as it transits through the oropharynx. Effective PAH treatment with imatinib without unwanted adverse events requires targeted delivery to reach therapeutic concentrations in the lung without systemic concentrations that might result in adverse events such as subdural hematoma. To achieve predictable and consistent levels of target lung concentrations with the desired low levels of systemic absorption, inhalable imatinib formulations should ideally be made up of micro or sub-micron particles of uniform geometry.

In some examples, compositions and methods of the disclosure leverage particle molding technologies to create such imatinib particles specifically for inhalable formulations. Molds are preferably prepared from an elastomeric material and can be created by pouring the material, in liquid form, over a patterned object before curing the material. Mold-based preparation of pharmaceuticals include PRINT technology available from Liquidia Technologies, Inc. (Morrisville, NC) and described in U.S. Pat. Nos. 8,812,393; 9,444,907; 8,685,461, 7,976,759; and 8,944,804, the content of each of which is incorporated herein by reference.

Microfabrication techniques such as etching of a substrate (e.g.,a silicon wafer) are well known in the semiconductor field and can be used to create a pattern consisting of repeated raised features consistent with the desired size and shape of the final imatinib particles for the inhalable formulation. The liquid mold material can then be laid over the patterned substrate and allowed to harden to produce a mold consisting of repeated reliefs that are the negative of the desired size and shape of the final imatinib particles of the inhalable formulation. Liquid

imatinib solutions or suspensions can then be poured into the reliefs in the mold and hardened. The final imatinib particles having the desired size and shape can then be released from the mold for inclusion in the inhalable formulation.

In certain examples, compositions and methods of the disclosure use the advantages afforded by engineered, uniform micro and sub-micron imatinib particles for inhalable formulations (e.g., efficient uptake in the target tissue with lower off-target concentrations, consistent dosing, and predictable modeling of pharmacokinetics), particularly in treating conditions such as PAH, lung transplant rejection, pulmonary veno-occlusive disease (PVOD) and pulmonary hypertension, heart failure with preserved ejection fraction (HFpEF) and schistosomiasis. By combining the specific factors of inhalable imatinib formulations with the unique capabilities of molded pharmaceutical technology, the compositions and methods of the present disclosure provide a new approach for treating the above conditions without the risks associated with systemic imatinib treatments.

Another advantage of the compounds and methods of the disclosure is the ability to exclude all or most amorphous imatinib from the formulation, even after micronization. As noted above, because crystal form can be important to drug pharmacokinetics and dosing, as well as physicochemical stability and avoiding amorphous content can therefore be important to providing predictable and efficient therapy.

Because the inhalable formulations described herein can modulate the uptake of imatinib in the target tissue of the lungs or microvasculature, formulations of the disclosure can be used to treat various conditions of the pulmonary cardiovascular system while avoiding the adverse events associated with higher doses that are administered by other routes of administration that introduce the drug systemically prior to reaching the target tissue. For example, compounds and methods of the disclosure can be used to treat PAH as well as lung transplant rejection, pulmonary veno-occlusive disease (PVOD) and pulmonary hypertension secondary to other diseases like heart failure with preserved ejection fraction (HFpEF) or schistosomiasis. Dose ranges can include between about 10 mg to about 100 mg per dose for inhalation on a twice to four times per day schedule. About 0.1 mg to about 80 mg of the active imatinib compound may then be deposited within the lungs after inhalation. Because compositions of the disclosure can have relatively high concentrations of API (e.g., 50% or greater), the above doses can be

achieved with less overall volume of inhalable compared to conventional formulations having 1% - 3% API.

In certain examples, formulations of the disclosure can include processing and administration of imatinib in free base form. Free base imatinib formulations of the disclosure can retain crystallinity after micronization and are less hygroscopic than certain imatinib salts. Accordingly, compounds and methods of the disclosure include inhalable formulations of free base imatinib.

Methods and formulations of the disclosure may include spray-dried imatinib or salts thereof for inhalation. While carriers such as lactose may be used after micronization to aid in delivery via inhalation, those carriers may generally comprise larger diameter particles and complication in the separation of the active imatinib compound may result in lower amounts of the inhaled compound reaching the lungs. Furthermore, the amount of active compound reaching the lungs may be less predictable using such carriers and methods, making dosing more complicated. Accordingly, spray-dried methods may be used wherein imatinib or salts thereof along with various excipients or other additives may be micronized to a desired particle size and suspended or solubilized for spray-drying and inhalation. Using formulations with a higher (e.g., 50% or more) ratio of API can also help achieve more predictable drug concentrations in the target tissue.

In certain examples, the micronized imatinib may be suspended in a feedstock for the purposes of spray-drying to avoid the creation of amorphous or polymorphic imatinib content that may occur if dissolved in a solution (e.g. in an appropriate organic solvent or within an acidified aqueous solution) upon spray-drying. By creating a stable suspension of micronized imatinib for spray-drying, once dried, the inhalable formulation can retain the desired crystal structure, particle size, and low levels of amorphous content obtained before the micronization process.

Stable suspensions for spray-drying may be obtained through manipulation of factors affecting imatinib solubility such as pH, ionic strength, and dispersing agents or surfactants. Excipients that may be used before micronization in the spray-drying methods described above include, for example, leucine, dileucine, trileucine, bulking agents such as trehalose or mannitol, lecithin, DSPC or other lipid-based carriers, citrate, or acetate.

In some examples, inhalable imatinib solutions and suspensions may be provided along with methods of delivering such formulations through inhalation via a nebulizer. Nebulizers are drug delivery devices that aerosolize solutions and suspensions for inhalation using compressed gas. By providing imatinib directly to the lungs through nebulized formula, treatment of pulmonary and cardiovascular diseases become feasible without the high-systemic concentrations of imatinib found to be associated with subdural hematoma or other adverse events. Accordingly, systems and methods of the disclosure provide new means of treating PAH and other diseases without the compromises and risks of prior attempts.

Formulations for nebulization may be provided in solution or suspension form. Imatinib formulations may be used with any type of nebulizer. For example, commercially available nebulizers from Vectura Group plc (UK) including jet nebulizers such as the Akita jet nebulizer and the FOX vibrating mesh nebulizer.

Other types of nebulizers contemplated for use with formulations and methods of the disclosure include soft mist inhalers and ultrasonic wave nebulizers. Methods and kits of the disclosure may include dehydration and reconstitution agents for dehydrating and reconstituting liquid formulations of the disclosure in a sterile manner for nebulization.

Examples of the disclosure include an inhalable formulation comprising imatinib or a salt thereof, wherein greater than 95% of the imatinib or salt thereof in the inhalable formulation is present in a single crystal form, with the proviso that the salt is not mesylate.

The single crystal form may be type A as defined herein. In certain examples, the single crystal form may be type B as defined herein. Inhalable formulations of the disclosure may include greater than 99% of the imatinib in a single crystal form. In various examples, 100% of the imatinib in the inhalable formulation may be present in a single crystal form.

The inhalable formulation may be in a dry powder. In some examples, the inhalable formulation may be a suspension of crystalline imatinib. The imatinib may be present in a therapeutically effective amount to treat a condition of the pulmonary cardiovascular system, such as pulmonary arterial hypertension (PAH). The salt may be at least one selected from the group consisting of glycollate, isethionate, xinafoate, furoate, trifenatate, HCl, sulfate, phosphate, lactate, maleate, malate, fumarate, tartrate, succinate, adipate, citrate, and malonate. In preferred examples, the salt may be glycolate, malate, tartrate, malonate, isethionate, or citrate. The inhalable formulation may further include one or more carrier agents.

Certain examples of the disclosure may include methods of treating a condition of the pulmonary cardiovascular system including providing to a subject an inhalable formulation comprising imatinib or a salt thereof, wherein greater than 95% of the imatinib or salt thereof in the inhalable formulation is present in a single crystal form, with the proviso that the salt is not mesylate.

In certain examples, methods of the disclosure may include preparing an inhalable formulation by micronizing imatinib particles, suspending the micronized imatinib particles in a solution, and spray drying the suspended micronized imatinib particles. Under this approach, inhalable micronized particles are modified such that they can be delivered more readily from an inhaler device and show better lung deposition, while retaining the original form of the API to allow for modulation of residence time in the lungs (i.e. slowed dissolution rate relative to amorphous drug).

The micronized particles may comprise a MMAD in the range of 0.5-5um. In certain examples, one or more excipients is included in the suspending step. In various examples, the excipient may be a water soluble excipient, such as leucine, dileucine, trileucine, trehalose, mannitol, citrate, or acetate. In other example, the excipient may be a water insoluble excipient, such as lecithin, DSPC or limonene. Such insoluble excipients may be dissolved in a non-aqueous medium that is miscible or immiscible with water, thereby creating an emulsion. Alternatively, a liposomal dispersion could be created into which the suspended imatinib could be added and homogenized or where it could be spray dried in separate feedstocks. These approaches are further described below.

The inhalable formulation may contain a therapeutically effective amount of imatinib particles for treating a condition of the pulmonary cardiovascular system. The condition of the pulmonary cardiovascular system can be pulmonary arterial hypertension (PAH).

In some examples, the inhalable formulation may comprise less than about 3% amorphous imatinib particles by mass. The inhalable formulation can comprise less than about 1% amorphous imatinib particles. The inhalable formulation may include less than 5% water or, in certain examples, less than 1% water by mass. In certain examples, the disclosure may include an inhalable formulation produced by the above methods.

Examples of the disclosure can include an inhalable formulation comprising micronized particles of imatinib, wherein the imatinib retains its crystal structure in the particles and the

inhalable formulation comprises less than 5% amorphous imatinib particles by mass. The particles can comprise a size of about 0.5 to about 5 μm mass median aerodynamic diameter (MMAD). The inhalable formulation may further comprise one or more carrier agents.

In certain examples, the one or more carrier agents include lactose. Imatinib may be present in a therapeutically effective amount to treat a condition of the pulmonary cardiovascular system. The condition of the pulmonary cardiovascular system can be pulmonary arterial hypertension (PAH). In various examples, the inhalable formulation can comprise less than 3% amorphous imatinib particles. The inhalable formulation may comprise less than 1% amorphous imatinib particles. The inhalable formulation can include less than 5% water. In some examples, the inhalable formulation may comprise less than 1% water.

In certain examples, the disclosure can include methods of treating a condition of the pulmonary cardiovascular system including providing to a subject an inhalable formulation comprising micronized particles of imatinib, wherein the imatinib retains its crystal structure in the particles and the inhalable formulation comprises less than 5% amorphous imatinib particles. In some examples, the subject may be a human.

Aspects of the disclosure include an inhalable formulation consisting of at least about 50% imatinib or a salt thereof. The inhalable formulation may include one or more carrier agents. The imatinib or salt thereof may be about 50% of the formulation and the carrier agents may make up the remainder of the formulation. The one or more carrier agents can comprise lactose. In certain examples, the inhalable formulation may be a dry powder.

In various examples, the imatinib or salt thereof can be present in a therapeutically effective amount to treat a condition of the pulmonary cardiovascular system. The condition of the pulmonary cardiovascular system may be pulmonary arterial hypertension (PAH). Greater than 80% of the imatinib or salt thereof in the inhalable formulation can be present in a single crystal form. The single crystal form can be type A. In certain examples, the salt may be at least one selected from the group consisting of glycolate, malate, tartrate, malonate, isethionate, and citrate.

In certain examples, methods of the disclosure may include treating a condition of the pulmonary cardiovascular system by providing to a subject an inhalable formulation consisting of at least about 50% imatinib or a salt thereof. In various examples, the subject may be a human.

Examples of the disclosure include an inhalable formulation comprising N-desmethyl imatinib or a salt thereof, wherein the formulation does not include imatinib. The N-desmethyl imatinib may be present in a therapeutically effective amount to treat a condition of the pulmonary cardiovascular system which may be pulmonary arterial hypertension (PAH).. The inhalable formulation can be a dry powder and can include micronized particles comprising a mass median aerodynamic diameter in the range of 0.5-5µm.

In salt formulations, the salt may be selected from mesylate, glycollate, isethionate, xinafoate, furoate, trifenatate, HCl, sulfate, phosphate, lactate, maleate, malate, fumarate. In certain examples, the inhalable formulation can include one or more carrier agents. The carrier agent can be selected from lactose, magnesium stearate, leucine, isoleucine, dileucine, trileucine, lecithin, and distearylphosphatidylcholine (DSPC).

In certain examples, the disclosure can include methods of treating a condition of the pulmonary cardiovascular system by providing to a subject an inhalable formulation comprising N-desmethyl imatinib or a salt thereof, wherein the formulation does not include imatinib. In various examples, the subject may be a human and the condition of the pulmonary cardiovascular system can be pulmonary arterial hypertension (PAH).

Aspects of the disclosure include an inhalable formulation comprising molded particles of imatinib or a salt thereof. The molded particles can be hardened in a mold from a liquid composition. The molded particles can have a mass median aerodynamic diameter in the range of 0.5-5µm. The molded particles can further comprise one or more excipients. The excipient may be a water soluble excipient selected from the group consisting of leucine, dileucine, trileucine, trehalose, mannitol, citrate, and acetate. In certain examples, the excipient can be a water insoluble excipient selected from the group consisting of lecithin, distearylphosphatidylcholine (DSPC) and limonene.

Inhalable formulations of the disclosure can include one or more carrier agents. The inhalable formulation can be a dry powder or a suspension of the molded particles. The imatinib of salt thereof may be present in a therapeutically effective amount to treating a condition of the pulmonary cardiovascular system.

In various examples, the salt can be at least one selected from the group consisting of glycollate, isethionate, mesylate, xinafoate, furoate, trifenatate, HCl, sulfate, phosphate, lactate, maleate, malate, fumarate, tartrate, succinate, adipate, citrate, and malonate. In preferred

examples, the salt may be glycolate, malate, tartrate, malonate, isethionate, or citrate. The imatinib may be present in a crystal form.

Examples of the disclosure include methods of preparing an inhalable formulation of imatinib or a salt thereof including applying a liquid composition comprising imatinib or a salt thereof to a mold, hardening the liquid composition within cavities in the mold to form particles within the cavities, and releasing the particles from the cavities in the mold, thereby preparing an inhalable formulation of imatinib or a salt thereof.

Examples of the disclosure include methods of treating a condition of the pulmonary cardiovascular system. Methods may include providing to a subject a nebulized formulation of imatinib or a salt thereof. The formulation can include droplets that comprise imatinib or a salt thereof. The droplets may be sized between about 0.5 to about 5 μm.

In certain examples formulations may further comprise one or more excipients. In some examples nebulized formulations may comprise solubilized imatinib or a salt thereof in solution. The subject can be a mammal and, in preferred examples, a human. The condition of the pulmonary cardiovascular system may be pulmonary arterial hypertension (PAH). The formulation may be nebulized using a jet nebulizer. In some examples the formulation may be nebulized using a vibrating mesh nebulizer.

In certain examples, the disclosure may include a kit for treating a condition of the pulmonary cardiovascular system, comprising a liquid formulation of imatinib or a salt thereof and a nebulizer. The liquid formulation may be a sterile liquid formulation. The imatinib or a salt thereof may be a dry composition or a salt thereof and the kit may comprise one or more liquids for reconstituting the imatinib or salt thereof. In various examples, the nebulizer may be a jet nebulizer, a vibrating mesh nebulizer, a soft mist inhaler, or an ultrasonic wave nebulizer. The dry composition of the imatinib or a salt thereof may include particles of imatinib or a salt thereof. The particles of imatinib or a salt thereof may have been micronized. The micronized particles may be sized about 0.5 to about 5 μm.

In certain examples, the formulation may further include one or more excipients. The nebulizer can be operable to generate droplets of the liquid formulation sized between about 0.5μm and about 5 μm.

In various examples, the imatinib or a salt thereof may be partitioned into two or more volumes, each of the two or more volumes corresponding to a therapeutically effective individual

dose for treating the condition of the pulmonary cardiovascular system. Each volume the imatinib or a salt thereof can be a sterile liquid formulation. Kits of the disclosure may further include a first set of one or more agents to dehydrate the liquid formulation to produce a dried composition of the imatinib or a salt thereof and a second set of one or more agents to reconstitute the dried composition as a sterile liquid formulation of the imatinib or a salt thereof.

Examples of the disclosure may include methods of treating a condition of the pulmonary cardiovascular system. Such methods may include providing imatinib or a salt thereof, reconstituting the imatinib or a salt thereof in a sterile solvent to prepare a reconstituted solution of imatinib or salt thereof, and nebulizing the reconstituted solution. The reconstituted solution may include one or more excipients. The imatinib or a salt thereof may be a liquid formulation of the imatinib or a salt thereof, and the method can first include dehydrating the liquid formulation to produce a dried composition of the imatinib or a salt thereof. Dehydrating may be accomplished using one or more dehydrating agents.

In certain examples, the reconstituting step can include transferring the sterile solvent from a first to sealed container to a second sealed container comprising the imatinib or salt thereof using a needle or dispensing pin. Nebulizing may include coupling the second sealed container to a nebulizer. In some examples, nebulizing can include transferring the reconstituted solution from the second sealed container to the nebulizer using a needle or a dispensing pin.

Brief Description of the Drawings

FIG. 1 shows an x-ray powder diffraction diagram of the type A crystal form of imatinib.

FIG. 2 shows an x-ray powder diffraction diagram of the type B crystal form of imatinib.

FIG. 3 diagrams steps of an exemplary method of preparing an inhalable formulation of imatinib.

FIG. 4 shows imatinib lung levels over time for various doses of imatinib solutions and suspensions delivered via various administration routes.

FIG. 5 shows an imatinib lung concentration comparison between 1 mg/kg of imatinib suspension or solution delivered by intratracheal instillation and 1 mg/kg of imatinib delivered by IV.

FIG. 6 diagrams exemplary processing steps for inhalable imatinib preparations.

FIG. 7 shows particle size distribution (PSD) analysis of unmicronized imatinib.

FIG. 8 shows PSD analysis of micronized imatinib at 1 bar.

FIG. 9 shows PSD analysis of micronized imatinib at 2 bar.

FIG. 10 shows PSD analysis of micronized imatinib at 3 bar.

FIG. 11 shows thermalgravimetric analysis (TGA) of imatinib Free Base, pre-micronization.

FIG. 12 shows a differential scanning calorimeter (DSC) thermogram of un-micronized imatinib

FIG. 13 shows a DSC thermogram of micronized imatinib.

FIG. 14 shows a DSC thermogram of co-spray-dried imatinib with leucine.

FIG. 15 shows PSD analysis of various carrier-based imatinib samples discussed in Example 2.

FIG. 16 shows an exemplary manufacturing scheme for a 50:50 Imatinib:Lactose blend.

FIG. 17 shows an exemplary sampling strategy for BCU testing.

FIG. 18 shows an APSD profile for batch NP-106-18104-002 in Example 3.

FIG. 19 shows Metrics Results for batch NP-106-18104-002 in Example 3.

FIG. 20 shows an APSD profile for a 75:25 Imatinib:Lactose Spray-Dried formulation.

FIG. 21 shows Metrics Results for a 75:25 Imatinib:Lactose Spray-Dried formulation.

FIG. 22 shows an APSD profile for a 90:10 Imatinib:Lactose Spray-Dried formulation.

FIG. 23 shows Metrics Results for a 90:10 Imatinib:Lactose Spray-Dried formulation.

FIG. 24 shows an APSD profile for a 50:50 Imatinib:Lactose Spray-Dried formulation.

FIG. 25 shows Metrics Results for a 50:50 Imatinib:Lactose Spray-Dried formulation.

FIG. 26 shows an APSD Comparison profile for various Spray-Dried and Carrier Based DPI (Dry Powder Inhaler) Formulations.

FIG. 27 shows an APSD Comparison profile for batch NP-106-18104-002 at Time Zero and Time 1 Month under two storage conditions as detailed in Example 3.

FIG. 28 shows an APSD Comparison profile for a 75:25 Imatinib:Lactose Spray-Dried formulation at Time Zero and Time 1 Month under two storage conditions as detailed in Example 3.

FIG. 29 shows an APSD Comparison profile for a 90:10 Imatinib:Lactose Spray-Dried formulation at Time Zero and Time 1 Month under two storage conditions as detailed in Example 3.

FIG. 30 shows an APSD Comparison profile for a 50:50 Imatinib:Lactose Spray-Dried formulation at Time Zero and Time 1 Month under two storage conditions as detailed in Example 3.

FIG. 31 shows a DSC thermogram of un-micronized material (Lot. 1Kg) from Example 4.

FIG. 32 shows a DSC thermogram of the micronized sub-lot #1 material (50g) from Example 4.

FIG. 33 shows a DSC thermogram of the micronized bulk material (463.38g) from Example 4.

FIG. 34 shows a DVS isotherm plot of the unmicronized Lot. 1Kg from Example 4.

FIG. 35 shows a DVS isotherm plot of the micronized sub-lot #1 material (50g) from Example 4.

FIG. 36 shows a DVS isotherm plot of the micronized sub-lot #2 material (50g)from Example 4.

FIG. 37 shows a DVS isotherm plot of the micronized material (463.38g) from Example 4.

FIG. 38 shows an XRPD overlay of Imatinib Free Base pre and post micronization from Example 4.

FIG. 39 shows an XRPD isotherm plot of the micronized material (463.38g) from Example 4.

FIG. 40 shows a TGA thermogram of Carrier Based Formulation NP-106-18104-002 from Example 4.

FIG. 41shows a TGA thermogram of Spray-Dried formulation 119#008C (50:50 Imatinib: leucine) from Example 4.

FIG. 42 shows a TGA thermogram of Spray-Dried formulation 119#008A (75:25 Imatinib: leucine) from Example 4.

FIG. 43shows a TGA thermogram of Spray-Dried formulation 119#008B (90:10 Imatinib: leucine) from Example 4.

FIG. 44 shows a sorption/desorption trace of batch 119#008A from Example 4.

FIG. 45 shows a sorption/desorption trace of batch 119#008B from Example 4.

FIG. 46 shows a sorption/desorption trace of batch 119#008C from Example 4.

FIG. 47 shows a sorption/desorption trace of batch NP-106-18104-002 from Example 4.

FIG. 48 shows a background subtracted XRPD trace of batch 119#008A from Example 4.

FIG. 49 shows a background subtracted XRPD trace of batch 119#008B from Example 4.

FIG. 50 shows a background subtracted XRPD trace of batch 119#008C from Example 4.

FIG. 51 shows a background trace of Leucine.

Claims

What is claimed is:

1. An inhalable formulation comprising imatinib or a salt thereof, wherein greater than 80% of the imatinib or salt thereof in the inhalable formulation is present in a single crystal form, with the proviso that the salt is not mesylate.

2. The inhalable formulation of claim 1, wherein the single crystal form is type A.

3. The inhalable formulation of claim 1, wherein greater than 90% of the imatinib in the inhalable formulation is present in a single crystal form.

4. The inhalable formulation of claim 3, wherein 100% of the imatinib in the inhalable formulation is present in a single crystal form.

5. The inhalable formulation of claim 1, wherein the inhalable formulation is a dry powder.

6. The inhalable formulation of claim 1, wherein the imatinib is present in a therapeutically effective amount to treat a condition of the pulmonary cardiovascular system.

7. The inhalable formulation of claim 6, wherein the condition of the pulmonary cardiovascular system is pulmonary arterial hypertension (PAH).

8. The inhalable formulation of claim 1, wherein the salt is at least one selected from the group consisting of glycollate, isethionate, xinafoate, furoate, trifenatate, HCl, sulfate, phosphate, lactate, maleate, malate, fumarate, tartrate, succinate, adipate, citrate, and malonate.

9. The inhalable formulation of claim 1, wherein the salt is at least one selected from the group consisting of glycolate, malate, tartrate, malonate, isethionate, and citrate.

10. The inhalable formulation of claim 1, wherein the inhalable formulation further comprises one or more carrier agents.

11. An inhalable formulation comprising particles of imatinib, wherein the imatinib retains its crystal structure in the particles and the inhalable formulation comprises less than 5% amorphous imatinib particles.

12. The inhalable formulation of claim 11, wherein the particles of imatinib are micronized.

13. The inhalable formulation of claim 11, wherein the particles comprise mass median aerodynamic diameter in the range of about 0.5 to about 5 μm.

14. The inhalable formulation of claim 11, wherein the inhalable formulation further comprises one or more carrier agents.

15. The inhalable formulation of claim 14, wherein one or more carrier agents is lactose.

16. The inhalable formulation of claim 11, wherein the imatinib is present in a therapeutically effective amount to treat a condition of the pulmonary cardiovascular system.

17. The inhalable formulation of claim 16, wherein the condition of the pulmonary cardiovascular system is pulmonary arterial hypertension (PAH).

18. The inhalable formulation of claim 11, wherein inhalable formulation comprises less than 3% amorphous imatinib particles.

19. The inhalable formulation of claim 11, wherein inhalable formulation comprises less than 1% amorphous imatinib particles.

20. The inhalable formulation of claim 11, wherein the inhalable formulation comprises less than 5% water.

21. The inhalable formulation of claim 11, wherein the inhalable formulation comprises less than 1% water.

22. An inhalable formulation comprising molded particles of imatinib or a salt thereof.

23. The inhalable formulation of claim 22 wherein the molded particles are hardened in a mold from a liquid composition.

23. The inhalable formulation of claim 22 wherein the molded particles comprise a mass median aerodynamic diameter in the range of 0.5-5μm.

24. The inhalable formulation of claim 22 wherein the molded particles further comprise one or more excipients.

25. The inhalable formulation of claim 24 wherein the excipient is a water soluble excipient selected from the group consisting of leucine, dileucine, trileucine, trehalose, mannitol, citrate, and acetate.

26. The inhalable formulation of claim 24 wherein the excipient is a water insoluble excipient selected from the group consisting of lecithin, distearylphosphatidylcholine (DSPC) or limonene.

27. The inhalable formulation of claim 22 further comprising one or more carrier agents.

28. The inhalable formulation of claim 22 wherein the inhalable formulation is a dry powder or a suspension of the molded particles.

29. The inhalable formulation of claim 22 wherein the imatinib or salt thereof is present in a therapeutically effective amount to treating a condition of the pulmonary cardiovascular system.

30. The inhalable formulation of claim 29 wherein the condition of the pulmonary cardiovascular system is pulmonary arterial hypertension (PAH).

31. The inhalable formulation of claim 22 wherein the salt is at least one selected from the group consisting of glycolate, malate, tartrate, malonate, isethionate, or citrate.

32. The inhalable formulation of claim 22 wherein the imatinib is present in a crystal form.

33. An inhalable formulation consisting of at least about 50% imatinib or a salt thereof.

34. The inhalable formulation of claim 33, wherein the inhalable formulation further comprises one or more carrier agents.

35. The inhalable formulation of claim 34, wherein the imatinib or salt thereof makes up about 50% of the formulation and the one or more carrier agents makes up about 50% of the formulation.

36. The inhalable formulation of claim 34, wherein the one or more carrier agents comprise lactose.

37. The inhalable formulation of claim 33, wherein the inhalable formulation is a dry powder.

38. The inhalable formulation of claim 33, wherein the imatinib or salt thereof is present in a therapeutically effective amount to treat a condition of the pulmonary cardiovascular system.

39. The inhalable formulation of claim 38, wherein the condition of the pulmonary cardiovascular system is pulmonary arterial hypertension (PAH).

40. The inhalable formulation of claim 33, wherein greater than 80% of the imatinib or salt thereof in the inhalable formulation is present in a single crystal form.

41. The inhalable formulation of claim 40, wherein the single crystal form is type A.

42. The inhalable formulation of claim 33, wherein the salt is at least one selected from the group consisting of glycolate, malate, tartrate, malonate, isethionate, and citrate.