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(54) **NEBULIZED IMATINIB FORMULATIONS, MANUFACTURE, AND USES THEREOF**

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(57) **ABSTRACT**

The invention relates to nebulized imatinib formulations, manufacture, and uses thereof.

NEBULIZED IMATINIB FORMULATIONS, MANUFACTURE, AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Nonprovisional application Ser. No. 16/874,168, filed May 14, 2020, which claims the benefit of, and priority to, U.S. Provisional Application Nos. 62/849,054, filed May 16, 2019; 62/849,056, filed May 16, 2019; 62/849,058, filed May 16, 2019; 62/849,059, filed May 16, 2019; 62/877,575, filed Jul. 23, 2019; 62/942,408, filed Dec. 2, 2019; 62/984,037, filed Mar. 2, 2020; and 62/958,481, filed Jan. 8, 2020; the content of each of which is hereby incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0002] The invention relates to inhalable imatinib formulations, manufacture, and uses thereof.

BACKGROUND

[0003] Pulmonary arterial hypertension (PAH) is a condition involving elevated blood pressure in the arteries of the lungs with unknown causes and is differentiated from systemic hypertension. PAH is a progressive disease where resistance to blood flow increases in the lungs causing damage to the lungs, the pulmonary vasculature and the heart that can eventually lead to death. While symptoms are treatable with vasodilators and other medications, there is no known disease modifying therapy or cure and advanced cases can eventually require lung transplants.

[0004] Imatinib, especially the mesylate salt thereof, is a tyrosine kinase inhibitor approved for use in treating certain types of cancer. Imatinib's potential to inhibit the tyrosine kinase platelet-derived growth factor receptor (PDGFR) which is highly upregulated in the pulmonary arteries in cases of PAH, led to interest in its use in treating PAH. See, Olschewski, H, 2015, Imatinib for Pulmonary Arterial Hypertension—Wonder Drug or Killer Drug? Respiration, 89:513-514, incorporated herein by reference. To that end, studies have been conducted to determine the potential of imatinib in treating PAH and patients have been found to respond favorably to such treatment. Unfortunately, an unacceptable amount of severe adverse events including subdural hematoma blunted enthusiasm for the drug. Frost, et al., 2015, Long-term safety and efficacy of imatinib in pulmonary arterial hypertension, J Heart Lung Transplant, 34(11): 1366-75, incorporated herein by reference.

SUMMARY

[0005] Compositions and methods of the invention address problems with imatinib-based PAH treatments through the use of specialized formulations and delivery mechanisms. Particularly, inhalable imatinib solutions and suspensions are provided along with methods of delivery 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 invention provide new means of treating PAH and other diseases without the compromises and risks of prior attempts.

[0006] 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.

[0007] Other types of nebulizers contemplated for use with formulations and methods of the invention include soft mist inhalers and ultrasonic wave nebulizers. Methods and kits of the invention may include dehydration and reconstitution agents for dehydrating and reconstituting liquid formulations of the invention in a sterile manner for nebulization.

[0008] In certain embodiments, formulations may comprise 50% or more imatinib or imatinib salts. Compositions and methods of the invention 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.

[0009] 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. By providing inhalable formulations with high concentrations of imatinib or salts thereof, compositions and methods of the invention 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.

[0010] Nebulizer-ready formulations of the invention may comprise imatinib or salts thereof in solution or suspension form in various embodiments. Imatinib suspensions may comprise imatinib particles 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 embodiments, greater than 95% of imatinib or a salt thereof in the inhalable formulation may be present in a single crystal form.

[0011] In certain embodiments inhalable imatinib compounds may be micronized through wet or dry milling (e.g., jet milling) to achieve the desired particle size for suspensions for nebulization. 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). In certain embodiments, 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, and conditioners such as 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 embodiments of the invention 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.

[0012] In some embodiments, all or most amorphous imatinib may be excluded 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, avoiding amorphous content can also be important to providing predictable and efficient therapy.

[0013] Because the inhalable formulations described herein can modulate the uptake of imatinib in the target tissue of the lungs or microvasculature, formulations of the invention 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 invention 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 invention 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.

[0014] In certain embodiments, formulations of the invention can include processing and administration of imatinib in free base form. Free base imatinib formulations of the invention can retain crystallinity after micronization. Accordingly, compounds and methods of the invention include inhalable formulations of free base imatinib.

[0015] Aspects of the invention 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.

[0016] In certain embodiments formulations may further comprise one or more excipients. In some embodiments nebulized formulations may comprise solubilized imatinib or a salt thereof in solution. The subject can be a mammal and, in preferred embodiments, 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 embodiments the formulation may be nebulized using a vibrating mesh nebulizer.

[0017] In certain aspects, the invention 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 embodiments, 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.

[0018] In certain embodiments, the formulation may further include one or more excipients. The nebulizer can be operable to generate droplets of the liquid formulation sized between about 0.5 μm and about 5 μm.

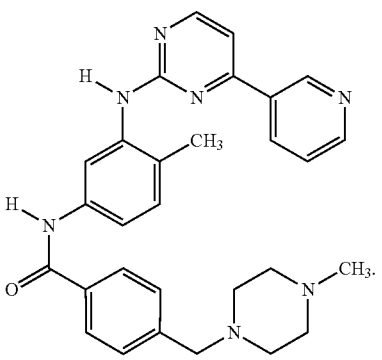
[0019] In various embodiments, the imatinib or a salt thereof may be partitioned into two or more volumes, each of the two or more volumes corresponding to a therapeutically effective individual dose for treating the condition of the pulmonary cardiovascular system. Each volume the imatinib or a salt thereof can be a sterile liquid formulation. Kits of the invention 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.

[0020] Aspects of the invention 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.

[0021] In certain embodiments, 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 embodiments, nebulizing can include transferring the reconstituted solution from the second sealed container to the nebulizer using a needle or a dispensing pin.

DETAILED DESCRIPTION

[0022] The invention relates to inhalable formulations of imatinib and salts thereof. Specifically, inhalable formulations compatible with nebulizers for inhalation as well as methods and kits for nebulized imatinib treatments. Imatinib, as used throughout the application, refers to the free base compound or salts thereof. Imatinib as the free base has the below structure.



[0023] The methods and compositions described herein provide greater concentrations of imatinib in target lung tissue than obtained with equivalent doses administered orally or through IV.

[0024] In various embodiments, imatinib suspensions having the characteristics described herein (e.g., low polymorphism, high API ratios, and amorphous content) can be delivered via inhalation using, for example, a nebulizer. While imatinib or salts thereof may be nebulized in solution, imatinib suspensions may offer advantages over solutions in certain embodiments as discussed below.

[0025] Nebulizers use oxygen, compressed air, or ultrasonic power to break up solutions and suspensions into small aerosol droplets that can be directly inhaled by a user in need of treatment. Formulations and methods of the invention may use any known type of nebulizer including soft mist inhalers, jet nebulizers, ultrasonic wave nebulizers, and vibrating mesh nebulizers. Jet nebulizers and vibrating mesh nebulizers, for example, are commercially available from Vectura Group plc (UK).

[0026] Soft mist inhalers use mechanical energy stored in a spring by user-actuation to pressurize a liquid container, causing the contained-liquid to spray out of a nozzle for inhalation in the form of a soft mist. Soft mist inhalers do not rely on gas propellant or electrical power for operation. The average droplet size in soft mist inhalers is about 5.8 micrometers.

[0027] Jet nebulizers are the most commonly used and may be referred to as atomizers. Jet nebulizers use a compressed gas (e.g., air or oxygen) to aerosolize a liquid medicine when released therethrough at high velocity. The resulting aerosolized droplets of therapeutic solution or suspension are then inhaled by a user for treatment. The compressed gas may be pre-compressed in a storage container or may be compressed on-demand by a compressor in the nebulizer.

[0028] Ultrasonic wave nebulizers rely on an electronic oscillator to generate a high frequency ultrasonic wave that, when directed through a reservoir of a therapeutic suspension of solution, aerosolized the medicine for inhalation.

[0029] Vibrating mesh nebulizers use the vibration of a membrane having thousands of holes at the top of the liquid reservoir to aerosolize a fine-droplet mist for inhalation. Vibrating mesh nebulizers avoid some of the drawbacks of ultrasonic wave nebulizers, offering more efficient aerosolization with reduced treatment times and less heating of the liquid being nebulized.

[0030] In various embodiments, nebulizers used in the invention may include pulsed air flow as described in U.S. Pat. No. 7,866,317, mixed flow of aerosol and compressed gas as described in U.S. Pat. No. 8,181,644, or other nebulizer features as described in U.S. Pat. Nos. 7,647,928; 8,910,625; and 7,891,358; and U.S. Pat. Pub. No. 2015/0174343, the content of each of which is incorporated herein by reference. In certain embodiments, concentration of imatinib formulations may be achieved at various areas of the lung through manipulation of delayed release technology such as described in U.S. Pat. No. 8,534,277, incorporated herein by reference.

[0031] In certain embodiments, nebulizer formulations may include particles sized and shaped as described in U.S. Pat. No. 8,101,160, or prepared using methods described in U.S. Pat. Pub. No. 2018/0257084, the content of each of which is incorporated herein by reference. Formulations and methods of the invention may include nebulized imatinib administered using techniques or in combination with other inhalable compounds as described in U.S. Pat. Nos. 7,928,089; 9,486,427; and 8,834,848 as well as U.S. Pat. Pub. Nos. 2017/0014424, 2016/0193434, 2010/0297030, 2013/0034534, and 2017/0304566, the content of each of which is incorporated herein by reference.

[0032] Kits of the invention may include a nebulizer such as those described above along with an effective does of a solution or suspension of imatinib or salts thereof for treating a cardiovascular or pulmonary disease such as PAH. Kits may include additional materials for reconstituting dry ingredients including imatinib formulations for nebulization in a sterile manner. For example, kits may include sealed containers of dry ingredients and sterile solvents (e.g., water) as well as syringes, needles, dispensing pins, mini-spikes, or other means of accessing the solvent within the sealed container and adding it to the dry ingredients. Accordingly, solutions can be reconstituted in a sterile manner and then nebulized by users as described herein.

[0033] Similarly, methods of dehydrating and otherwise preparing ingredients for storage and transportation in a sterile manner are contemplated. Dehydration and lyophilization methods and systems are well known and can be applied herein in a sterile manner to prepare formulations of imatinib or salts thereof for storage and shipment prior to reconstitution and nebulization. See Walters, et al., 2014, Next Generation Drying Technologies for Pharmaceutical Applications, Journal of Pharmaceutical Sciences 103:2673-2695, incorporated herein by reference. Commercial lyophilizers are available, for example, from SP Scientific, Warminster, Pa. Dehydration of formulations of the invention for nebulizing may be performed using any known dehydration methods or agents such as critical point drying with CO2 under pressure, solvent substitution, vacuum, or blow drying (e.g., in a nitrogen atmosphere).

[0034] Nebulized doses in high API ratio formulations can make up a relatively high percentage of the overall formulation, allowing them to be delivered in lower overall volumes than conventional formulations of between 1% and 3% API. Reducing the volume a patient must inhale can increase patient comfort and compliance, thereby improving results. Additionally, a higher percentage of API content can improve the API distribution and blend uniformity. Accordingly, methods and compositions of the invention allow for treatment of conditions of the pulmonary cardiovascular system (e.g., PAH) with lower doses and less inhalable volume than would be required in systemic administration, thereby lowering the risk of adverse events including subdural hematoma (See, Frost et al.). Thus, the invention provides viable treatment methods for life threatening diseases that were heretofore too risky for practical application.

[0035] In certain embodiments, compounds of the invention include formulations of imatinib or salts thereof. In preferred embodiments, the free base imatinib is used in a formulation for inhalation to treat a condition of the pulmonary cardiovascular system such as PAH. Certain salt forms are also contemplated. In various embodiments, imatinib salts that were found to exhibit suitable thermal stability and few or single polymorphic forms include glycollate, isethionate, malonate, tartrate, and malate. Other salt forms contemplated herein are xinafoate, furoate, trifenatate, HCl, sulfate, phosphate, lactate, maleate, fumarate, succinate, adipate, mesylate, and citrate.

[0036] When the compounds of the present invention are administered as pharmaceuticals, to humans and mammals, they can be given alone or as a pharmaceutical composition containing, for example, 0.1 to 99.5% of active ingredient (e.g., imatinib or a salt thereof) in combination with a pharmaceutically acceptable carrier. In preferred embodiments, to reduce inhaled volumes for patients and improve patient outcomes, formulations can comprise at least 50% imatinib or a salt thereof.

[0037] In certain embodiments, imatinib formulations of the invention may include one or more excipients. For example, lecithin phospholipids such as DSPC may be used as an excipient for nebulized inhalation. In certain embodiments, excipients may include various hydrophilic polymers. See, for example, Karolewicz, B., 2016, A review of polymers as multifunctional excipients in drug dosage form technology, Saudi Pharm J., 24(5):525-536, incorporated herein by reference.

[0038] In the high-API-ratio formulations contemplated herein, carriers or excipients may make up the remainder of the formulation in amounts of 50% or less of the overall composition. In certain embodiments, inhalable formulations may have API:carrier ratios of 50:50, 55:45, 60:40, 65:35, 70:30, 75:25, 80:20, 85:15, 90:10, or 95:5. Certain inhalable formulations may be pure API with no additional components. In various embodiments, formulations may include imatinib or salts thereof as the API in amounts greater than 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, or 45%. As used herein, API ratios refer to % w/w.

[0039] In various embodiments, micronized imatinib and salts thereof retain crystallinity, even after micronization and suspension for nebulization. For example, imatinib formulations of the invention can include less than 50%, less than 25%, less than 20%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1% amorphous imatinib by mass. In preferred embodiments, formulations of the invention include no observable amorphous imatinib content. Of particular note is, by suspending micronized imatinib particles in a solution as opposed to solubilizing, the desired crystalline form and low amorphous content obtained during micronization is carried through to nebulization because the imatinib crystals are not dissolved in the solution to a significant degree.

[0040] As discussed above, in order to accurately and consistently model pharmacokinetics of the imatinib formulations for proper dosing, low polymorphism is desired. To that end, inhalable formulations of the invention include imatinib or a salt thereof present in a single crystal form. In various embodiments, imatinib or a salt thereof may be present at greater than 75%, 80%, 85%, 90%, 95%, or, in preferred embodiments, greater than 99% in a single crystal form by mass. The single crystal form may be, for example, type A or type B in various embodiments.

[0041] For nebulized suspensions, micronization and particle diameter may be of particular importance for efficient delivery and imatinib may be preferably micronized to a mass median diameter of 2 μm or less. The suspension solution for nebulizer inhalation can be aqueous and doses may be divided into individual containers or compartments for sterile storage prior to use.

[0042] Micronized imatinib particle size can range from about 0.5 μm to about 5 μm depending on application. In preferred embodiments the size range is about 1 μm to about 3 μm to achieve deep lung penetration.

[0043] In various embodiments, the imatinib formulations of the invention may be pharmaceutical compositions for use in treating various conditions of the pulmonary cardiovascular system, such as PAH. For example, imatinib is a potent inhibitor of the platelet-derived growth factor receptor (PDGFR) and other signaling kinases. Accordingly, the compositions of the invention may be used to treat any disease or disorder that involves inhibition of PDGFR or other kinases sensitive to imatinib.

[0044] In certain embodiments, the compositions of the invention may be used to treat PAH. For treatment of PAH or other disorders, a therapeutically effective amount of a pharmaceutical composition of imatinib according to the various embodiments described herein can be delivered, via inhalation to deliver the desired amount of imatinib compound to the target lung tissue.

[0045] Dosages for treating PAH and other conditions of the pulmonary cardiovascular system may be in the range of between about 1 mg to about 100 mg per dose for inhalation on once, twice or three times per day schedule. About 0.1 mg to about 80 mg of the imatinib or salt thereof may then be deposited within the lung after inhalation. In certain embodiments, about 0.1 to about 1 mg/kg in a dose and may be administered one to four times a day to obtain the desired therapeutic results.

[0046] In certain embodiments, imatinib formulations of the invention may be used to treat pulmonary hypertension as a result of schistosomiasis. See, for example, Li, et al., 2019, The ABL kinase inhibitor imatinib causes phenotypic changes and lethality in adult *Schistosoma japonicum*, Parasitol Res., 118(3):881-890; Graham, et al., 2010, Schistosomiasis-associated pulmonary hypertension: pulmonary vascular disease: the global perspective, Chest, 137(6 Suppl): 20S-29S, the content of each of which is incorporated herein by reference.

[0047] Imatinib pharmaceutical compositions of the invention may be used to treat lung transplant recipients to prevent organ rejection. See, Keil, et al., 2019, Synergism of imatinib, vatalanib and everolimus in the prevention of chronic lung allograft rejection after lung transplantation (LTx) in rats, Histol Histopathol, 1:18088, incorporated herein by reference.

[0048] In certain embodiments, pharmaceutical compositions described herein can be used to treat pulmonary veno-occlusive disease (PVOD). See Sato, et al., 2019, Beneficial Effects of Imatinib in a Patient with Suspected Pulmonary Veno-Occlusive Disease, Tohoku J Exp Med. 2019 February; 247(2):69-73, incorporated herein by reference.

[0049] For treatment of any conditions of the pulmonary cardiovascular system for which imatinib may produce a therapeutic effect, compounds and methods of the invention may be used to provide greater concentration at the target lung tissue through inhalation along with consistent, predictable pharmacokinetics afforded by low polymorphism and amorphous content. The efficient localization of therapeutic compound at the target tissue allows for lower systemic exposure and avoidance of the adverse events associated with prolonged oral administration of imatinib mesylate.

[0050] Methods of the invention can include preparation of imatinib formulations. As noted above, imatinib or salts

thereof may be administered via inhalation of nebulized suspensions. Imatinib particles for suspension may be obtained via any known method including, in preferred embodiments, jet milling. Jet milling can be used to grind imatinib and, potentially, various additives (e.g., excipients) using a jet (or jets) of compressed air or gas to force collisions between the particles as they transit at near sonic velocity around the perimeter of a toroidal chamber. The size reduction is the result of the high-velocity collisions between particles of the process material. Outputs of the jet mill may allow particles to exit the apparatus once a desired size has been reached. As noted herein, desired particle size may be in the range of about 0.5 μm to about 5 μm.

[0051] In certain embodiments, bulk imatinib may be micronized to the desired size for inhalation via wet milling wherein the imatinib particles are suspended in a slurry and reduced through shearing or impact with a grinding media.

[0052] An unexpected finding of the invention is that micronized imatinib obtained using methods of the invention has been found to exhibit no apparent polymorphs other than the designated Type A and very low levels of amorphous content. Accordingly, this can result in improved stability of the drug substance and any drug product upon storage. Single crystal forms such as described may allow for more predictable in vivo behavior and appropriate dosing can be determined.

[0053] In some embodiments an imatinib suspension can be formed. The suspension may result from dry micronization followed by suspension of the resulting dry powder or can be obtained as the outcome of a wet milling procedure. Imatinib suspensions of micronized crystal forms may be used in nebulized inhalation treatments.

[0054] As maintaining a stable solution of crystalline imatinib is important to many features of the formulations and methods of the invention, formulation methods include manipulation of the suspension to prevent dissolution of the imatinib. Aqueous solution factors such as pH, ionic strength and dispersing agents may be used to obtain a stable suspension for nebulized inhalation. For example, the pH of the aqueous solution may be adjusted to prevent dissolution.

[0055] Additionally, the presence of ions in aqueous solution may tend to 'salt out' the imatinib. The solubility of the both imatinib and its mesylate salt may decrease with salinity. Accordingly, salt in the aqueous solution may be used to reduce solubility of the imatinib crystals in certain embodiments.

[0056] To promote dispersion and thoroughly deagglomerate the imatinib particles, a dispersing agent or surfactant (e.g., Tween 20 or Tween 80) may be added but should not cause dissolution of the imatinib in suspension.

[0057] In certain embodiments, excipients can be added to the suspension before nebulization. In various embodiments, the excipient may be a water-soluble excipient, such as leucine, dileucine, trileucine, trehalose, mannitol, citrate or acetate. In other embodiment, the excipient may be a water insoluble excipient, such as lecithin, distearylphosphatidylcholine (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.

[0058] The effective dosage of each agent can readily be determined by the skilled person, having regard to typical factors such as the age, weight, sex and clinical history of the patient. In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce the desired therapeutic effect. Such an effective dose will generally depend upon the factors described above.

[0059] If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

[0060] The pharmaceutical compositions of the invention include a "therapeutically effective amount" or a "prophylactically effective amount" of one or more of the compounds of the present invention, or functional derivatives thereof. An "effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result, e.g., a diminishment or prevention of effects associated with PAH. A therapeutically effective amount of a compound of the present invention or functional derivatives thereof may vary according to factors such as the disease state, age, sex, and weight of the subject, and the ability of the therapeutic compound to elicit a desired response in the subject. A therapeutically effective amount is also one in which any toxic or detrimental effects of the therapeutic agent are outweighed by the therapeutically beneficial effects.

[0061] A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to, or at an earlier stage of disease, the prophylactically effective amount may be less than the therapeutically effective amount. A prophylactically or therapeutically effective amount is also one in which any toxic or detrimental effects of the compound are outweighed by the beneficial effects.

[0062] Dosage regimens may be adjusted to provide the optimum desired response (e.g. a therapeutic or prophylactic response). For example, a single inhalable bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigency of the therapeutic situation. Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular subject, composition, and mode of administration, without being toxic to the patient.

[0063] The term "dosage unit" as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the compound, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

[0064] In some embodiments, therapeutically effective amount can be estimated initially either in cell culture assays or in animal models, usually rats, non-human primates, mice, rabbits, dogs, or pigs. The animal model is also used to achieve a desirable concentration range and route of administration. Such information can then be used to deter-

mine useful doses and routes for administration in other subjects. Generally, the therapeutically effective amount is sufficient to reduce PAH symptoms in a subject. In some embodiments, the therapeutically effective amount is sufficient to eliminate PAH symptoms in a subject.

[0065] Dosages for a particular patient can be determined by one of ordinary skill in the art using conventional considerations, (e.g. by means of an appropriate, conventional pharmacological protocol). A physician may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. The dose administered to a patient is sufficient to effect a beneficial therapeutic response in the patient over time, or, e.g., to reduce symptoms, or other appropriate activity, depending on the application. The dose is determined by the efficacy of the particular formulation, and the activity, stability, or half-life of the compounds of the invention or functional derivatives thereof, and the condition of the patient, as well as the body weight or surface area of the patient to be treated. The size of the dose is also determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular vector, formulation, or the like in a particular subject. Therapeutic compositions comprising one or more compounds of the invention or functional derivatives thereof are optionally tested in one or more appropriate in vitro and/or in vivo animal models of disease, such as models of PAH, to confirm efficacy, tissue metabolism, and to estimate dosages, according to methods well known in the art. In particular, dosages can be initially determined by activity, stability or other suitable measures of treatment vs. non-treatment (e.g., comparison of treated vs. untreated cells or animal models), in a relevant assay. Administration can be accomplished via single or divided doses.

[0066] In certain embodiments, in which an aqueous suspension is part of the manufacturing process, the aqueous suspension may contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents dispersing or wetting agents such as a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such a polyoxyethylene with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, mannitol, or trehalose.

[0067] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives.

[0068] The term "pharmaceutical composition" means a composition comprising a compound as described herein and at least one component comprising pharmaceutically acceptable carriers, diluents, adjuvants, excipients, or vehicles, such as preserving agents, taste-masking agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. The term "pharmaceutically acceptable carrier" is used to mean any carrier, diluent, adjuvant, excipient, or vehicle, as described herein.

[0069] The term "pharmaceutically acceptable" means it is, within the scope of sound medical judgment, suitable for use in contact with the cells of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio.

INCORPORATION BY REFERENCE

[0070] References and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web content, have been made throughout this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes.

EQUIVALENTS

[0071] Various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full content of this document, including references to the scientific and patent literature cited herein. The subject matter herein contains important information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

What is claimed is:

1. A method of treating pulmonary hypertension, the method comprising: providing to a subject a nebulized formulation using a vibrating mesh nebulizer, wherein the nebulized formulation comprises at least 1 mg of imatinib or a salt thereof per dose.

2. The method of claim **1** wherein the formulation comprises between about 1 mg and about 100 mg of imatinib or a salt thereof per dose.

3. The method of claim **1**, wherein the nebulized formulation comprises droplets that comprise imatinib or a salt thereof.

4. The method of claim **3**, wherein the droplets comprise a size of about 0.5 μm to about 5 μm.

5. The method of claim **1**, wherein the formulation further comprises one or more excipients.

6. The method of claim **1**, wherein the formulation comprises imatinib or a salt thereof in solution.

7. The method of claim **1**, wherein the formulation comprises imatinib or a salt thereof in a suspension.

8. The method of claim **1**, wherein the subject is a human.

9. The method of claim **1**, wherein the pulmonary hypertension being treated is pulmonary arterial hypertension (PAH).

10. A kit for treating pulmonary hypertension comprising: one or more doses, each of the one or more doses comprising at least 1 mg of imatinib or a salt thereof; and a vibrating mesh nebulizer.

11. The kit of claim **10**, wherein the imatinib or a salt thereof is a liquid formulation of imatinib or a salt thereof.

12. The kit of claim **11**, wherein the liquid formulation is a sterile liquid formulation.

13. The kit of claim **10**, wherein the one or more doses comprise between about 1 mg and about 100 mg of imatinib or a sale thereof.

14. The kit of claim **10**, wherein the imatinib or a salt thereof is a dry composition of the imatinib or a salt thereof and the kit further comprises one or more liquids to reconstitute the imatinib or a salt thereof into a liquid formulation of the imatinib or a salt thereof.

15. The kit of claim **14**, wherein the dry composition of the imatinib or a salt thereof comprises particles of imatinib or a salt thereof.

16. The kit of claim **15** wherein the particles of imatinib or a salt thereof have been micronized.

17. The kit of claim **16**, wherein the particles comprise a size of about 0.5 to about 5 μm.

18. The kit of claim **11**, wherein the formulation further comprises one or more excipients.

19. The kit of claim **11**, wherein the nebulizer is operable to generate droplets of the liquid formulation sized between about 0.5 μm and about 5 μm.

20. The kit of claim **11**, wherein the pulmonary hypertension being treated is pulmonary arterial hypertension (PAH).

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