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 type A, wherein the imatinib type A 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 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.

Examples of the disclosure include an inhalable formulation consisting of at least about 50% imatinib or a salt thereof. In another aspect, the present disclosure provides an inhalable formulation comprising at least about 50% 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. 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.

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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).

Examples of the disclosure include an inhalable formulation comprising molded particles of imatinib or a salt thereof. In one aspect, the present disclosure provides an inhalable formulation comprising molded particles of imatinib, wherein the molded particles comprise a mass median aerodynamic diameter in the range of 0.5-5µm. 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

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 type A, wherein the imatinib type A 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 0.5 to 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, wherein the molded particles comprise a mass median aerodynamic diameter in the range of 0.5-5μm.

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

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 imatinib is present in a crystal form.

32. An inhalable formulation comprising at least about 50% 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.

33. The inhalable formulation of claim 32, wherein the inhalable formulation further comprises one or more carrier agents.

34. The inhalable formulation of claim 33, 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.

35. The inhalable formulation of claim 33, wherein the one or more carrier agents comprise lactose.

36. The inhalable formulation of claim 32, wherein the inhalable formulation is a dry powder.

37. The inhalable formulation of claim 32, wherein the imatinib or salt thereof is present in a therapeutically effective amount to treat a condition of the pulmonary cardiovascular system.

38. The inhalable formulation of claim 37, wherein the condition of the pulmonary cardiovascular system is pulmonary arterial hypertension (PAH).

39. The inhalable formulation of claim 32, wherein the single crystal form is type A.

40. The inhalable formulation of claim 32, wherein the salt is at least one selected from the group consisting of glycolate, malate, tartrate, malonate, isethionate, and citrate.