Summary

The disclosure provides pharmaceutical formulations that contain high concentrations of rifabutin. Preferred compositions of the disclosure comprise a rifabutin powder formulated in water, a solvent and an acid. The inventive combination allows dissolution of rifabutin at high concentration. The formulated solution may be diluted without restriction in order to render a composition suitable for a desired route of administration.

Formulations of the disclosure allow delivery of effective amounts of rifabutin by routes of administration that are not possible with prior rifabutin-containing compositions. For example, formulations of the disclosure enable rifabutin to be provided parenterally, including intravenously or by inhalation. In addition, formulations of the disclosure obviate the need to lyophilize rifabutin prior to reconstituting it for administration, a rather costly process.

In one aspect, the present disclosure provides a rifabutin formulation produced from a rifabutin powder in the presence of an acid, water, and a solvent suitable to promote dissolution of the rifabutin, wherein the formulation has a rifabutin concentration between 50 mg/mL and 250 mg/mL at room temperature. In another aspect, the present disclosure provides a method of preparing the formulation as described herein, the method comprising: preparing a solution comprising a solvent, water and an acid; and adding said solution to rifabutin powder, thereby causing the rifabutin to dissolve in the solution. In yet another aspect, the present disclosure provides a method of preparing the formulation as described herein, the method comprising: preparing a solution comprising water and an acid; and adding said solution to a rifabutin solution in a solvent, thereby producing an aqueous rifabutin formulation.

In another example of the disclosure, rifabutin is prepared as a powder with a shelf-life equivalent to that of the rifabutin active pharmaceutical ingredient (API). As detailed below, rifabutin formulations of the disclosure preferably comprise rifabutin powder dissolved in an organic solvent.

According to the disclosure, highly concentrated rifabutin formulations are rapidly obtained from any rifabutin API and used as such or further diluted ad libitum with sterile water or pharmaceutically-acceptable solutions. Formulations of the disclosure are useful for treating a variety of conditions caused by or associated with bacterial infections, such as, but not limited to,

bacteremia, meningitis, Ventilator-Associated Bacterial Pneumonia (VABP), Hospital-Acquired Bacterial Pneumonia (HABP) and Periprosthetic Joint Infections (PJI).

In one example, the disclosure provides non-oral formulations of rifabutin manufactured by preparing a solution in the presence of an acid suitable to promote dissolution of rifabutin. The solution preferably includes a solvent and water in a ratio appropriate for the intended use of the formulation.

A formulation of the disclosure is suitable for any non-oral route of administration. The formulation is suitable for parenteral, intravenous, intraarterial administration, or pulmonary delivery. The formulation is also suitable for administration by inhalation or by injection.

Formulations of the disclosure are reconstituted solutions that may need to be diluted prior to non-oral administration. A formulation of the disclosure includes solvent and water in a

The w/v ratio of rifabutin to solvent may be from about 4:1 to about 1:4, from about 2:1 to about 1:3, or from about 1:1 to about 1:2. The w/v ratio of rifabutin to solvent may be about 4:1, about 3:1, about 2:1, about 1:1, about 1:2, about 1:3, or about 1:4.

In another example, the disclosure provides methods of preparing a non-oral formulation of rifabutin by preparing a solution including a solvent and distilled water, adding an acid to the solution, and introducing this solution to rifabutin powder, causing the rifabutin to dissolve in the solution.

In another example, the disclosure provides methods of preparing a non-oral formulation of rifabutin by preparing a solution of rifabutin in solvent and a solution of the acid in water and then mixing the two solutions.

The formulation may have any of the properties described above in relation to formulations. The acid and solvent may be any of those described above. The water and solvent may be combined at any ratio described above.

Methods of the disclosure include diluting a formulated rifabutin solution without restriction in order to render a composition suitable for a desired route of administration into a pharmaceutically acceptable diluent such as, but not limited to, sterile water, sodium chloride (i.e., saline) solution, dextrose water, Ringer lactate solution.

The step of dissolving the rifabutin may include swirling, stirring, or agitation of the solution. The step of dissolving the rifabutin may be performed for a defined period. The step of dissolving the rifabutin may be performed for about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, or about 60 minutes.

The rifabutin may be provided as a solid powder.

The rifabutin may be provided as a solution in solvent.

In a further aspect, the present disclosure provides a use of the formulation as described herein in the manufacture of a medicament for treating a bacterial infection in a subject, wherein the rifabutin is to be administered in an injectable formulation or by inhalation. In another example, the disclosure provides methods of treating a bacterial infection in a subject by administering a therapeutically effective amount of a non-oral formulation of rifabutin.

The bacterial infection may include one or more of *A. baumannii*, *C. jejuni*, *C. trachomatis*, *H. ducreyi*, *H. injluenzae*, *H. pylori*, *M. chelonae*, *M. kansasii*, *M. leprae*, *M. tuberculosis* *Mycobacterium avium*, *Mycobacterium intracellulare*, *N. gonorrhoeae*, *N.*

Claims

What is claimed is:

1. A rifabutin formulation produced from a rifabutin powder in the presence of an acid, water, and a solvent suitable to promote dissolution of the rifabutin, wherein the formulation has a rifabutin concentration between 50 mg/mL and 250 mg/mL at room temperature.

2. The formulation of claim 1, wherein the ratio of rifabutin to solvent w/v is about 1:2.

3. The formulation of claim 1, wherein the solvent is selected from the group consisting of: dimethylacetamide (DMA), diethylene glycol monoethyl ether (transcutol HP), and dimethyl isosorbide (DMI).

4. The formulation of claim 3, wherein the solvent is DMI or transcutol HP.

5. The formulation of claim 1, wherein the solvent to water ratio v/v is from 1:1 to 1:2.

6. The formulation of claim 1, wherein the acid is selected from the group consisting of: hydrochloric, methanesulfonic, phosphoric, L-tartaric, D-glucuronic, L-malic, D-gluconic, L-lactic, and acetic.

7. The formulation of claim 6, wherein the acid is acetic acid or D-glucuronic acid.

8. The formulation of claim 1, wherein the rifabutin to acid molar ratio is about 1:1.

9. The formulation of claim 1, further comprising sterile water or pharmaceutically-acceptable solutions to dilute the formulation in order to produce a composition suitable for a desired route of administration.

10. A method of preparing the formulation of claim 1, the method comprising:
preparing a solution comprising a solvent, water and an acid; and

adding said solution to rifabutin powder, thereby causing the rifabutin to dissolve in the solution.

11. The method of claim 10, wherein the solvent is selected from dimethyl isosorbide (DMI) and diethylene glycol monoethyl ether (transcutol HP).

12. The method of claim 10, wherein the acid is selected from acetic acid and D-glucuronic acid.

13. A method of preparing the formulation of claim 1, the method comprising:

preparing a solution comprising water and an acid; and

adding said solution to a rifabutin solution in a solvent, thereby producing an aqueous rifabutin formulation.

14. The method of claim 13, wherein the solvent is selected from dimethyl isosorbide (DMI) and diethylene glycol monoethyl ether (transcutol HP).

15. The method of claim 13, wherein the acid is selected from acetic acid or D-glucuronic acid.

16. Use of the formulation of claim 1 in the manufacture of a medicament for treating a bacterial infection in a subject, wherein the rifabutin is to be administered in an injectable formulation or by inhalation.

17. The formulation of claim 9, wherein the desired route of administration is by injection.

18. The formulation of claim 9, wherein the desired route of administration is by inhalation.