Summary

The ~~invention~~disclosure provides pharmaceutical formulations that contain high concentrations of rifabutin. Preferred compositions of the ~~invention~~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 ~~invention~~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 ~~invention~~disclosure enable rifabutin to be provided parenterally, including intravenously or by inhalation. In addition, formulations of the ~~invention~~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. In another aspect, the present disclosure provides a method of preparing a formulation of rifabutin, 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 a formulation of rifabutin, 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 ~~aspect~~example of the ~~invention~~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 ~~invention~~disclosure preferably comprise rifabutin powder dissolved in an organic solvent.

According to the ~~invention~~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 ~~invention~~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 ~~aspect~~example, the ~~invention~~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 ~~invention~~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 ~~invention~~disclosure are reconstituted solutions that may need to be diluted prior to non-oral administration. A formulation of the ~~invention~~disclosure includes solvent and water in a

defined ratio. The ratio may be a v/v ratio. The solution may include the solvent and distilled water in a ratio of from about 9:1 to about 1:9, from about 9:1 to about 1:4, from about 9:1 to about 1:2, from about 9:1 to about 1:1, from about 4:1 to about 1:9, from about 4:1 to about 1:4, from about 4:1 to about 1:2, from about 4:1 to about 1:1, from about 2:1 to about 1:9, from about 2:1 to about 1:4, from about 2:1 to about 1:2, or from about 2:1 to about 1:1. The solution may include the solvent and distilled water in ratio of about 9:1, about 4:1, about 2:1, about 1:1, about 1:2, about 1:4, or about 1:9.

The solvent may be polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monooleate polyoxyethylene sorbitan monolaurate (Tween 20), polyethylene glycol (PEG), propylene glycol, N-methyl-2-pyrrolidone (NMP), glycerin, ethanol, dimethylacetamide (DMA), diethylene glycol monoethyl ether (transcutol HP), or dimethyl isosorbide (DMI).

The acid may be hydrochloric, methanesulfonic, phosphoric, L-tartaric, D-glucuronic, L-malic, D-gluconic, L-lactic, acetic, or L-aspartic acid.

A reconstituted solution of the ~~invention~~disclosure preferably contains about 250mg/ml (1:1 solvent/water) or about 166.7 mg/ml. (1:2 solvent/water), however concentrations of the reconstituted solution may be as high as about 300 mg/ml. In certain ~~embodiment~~examples, a more dilute solution is required and that is obtained by adding more water to the solvent. For example, rifabutin in a 1:4 solvent/water ratio will result in a solution of about 50mg/ml. However, such a dilution will take additional time to dissolve rifabutin powder. Alternatively, rifabutin can be dissolved in a solvent and reconstituted solutions are then obtained without further modification. In general, for an IV solution, the desire is to keep the rifabutin/solvent ratio as low as possible. Appropriate ranges are provided herein.

Formulations of the ~~invention~~disclosure are effective for treatment of a bacterial infection. The infection may include one or more of *A. baumannii*, *C. jejuni*, *C. trachomatis*, *H. ducreyi*, *H. influenzae*, *H. pylori*, *M. chelonae*, *M. kansasii*, *M. leprae*, *M. tuberculosis*, *Mycobacterium avium*, *Mycobacterium intracellulare*, *N. gonorrhoeae*, *N. meningitidis*, *staphylococci*, *streptococci* (e.g., group A *streptococci*), and *T. gondii* or any other pathogen that is susceptible to rifabutin.

The amount of acid relative to rifabutin may be between 1 and 3 molar equivalents or between 1 and 2 molar equivalents. The amount of acid relative to rifabutin may be 1 molar equivalent.

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 ~~aspect~~example, the ~~invention~~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 ~~aspect~~example, the ~~invention~~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 ~~invention~~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 rifabutin 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 ~~aspect~~example, the ~~invention~~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.*

meningitidis, *staphylococci*, *streptococci* (e.g., group A *streptococci*), and *T. gondii* or any other pathogen that is susceptible to rifabutin.

The formulation may have any of the properties described above in relation to formulations.

The formulation may be provided parenterally, intravenously, or by inhalation.

~~Aspect~~Examples of the disclosure provide a use of rifabutin, an acid, a solvent, and a diluent for making a medicament for treating a bacterial infection.

In certain ~~embodiment~~examples, the diluent is water.

In certain ~~embodiment~~examples, 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 certain ~~embodiment~~examples, the w/v ratio of rifabutin to solvent is about 1:2.

In certain ~~embodiment~~examples, the solvent is polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monooleate polyoxyethylene sorbitan monolaurate (Tween 20), polyethylene glycol (PEG), propylene glycol, N-methyl-2-pyrrolidone (NMP), glycerin, ethanol, dimethylacetamide (DMA), diethylene glycol monoethyl ether (transcutol HP), or dimethyl isosorbide (DMI).

In certain ~~embodiment~~examples, the solvent is DMI or transcutol HP.

In certain ~~embodiment~~examples, the solvent and water are present in a ratio of from about 9:1 to about 1:9, from about 9:1 to about 1:4, from about 9:1 to about 1:2, from about 9:1 to about 1:1, from about 4:1 to about 1:9, from about 4:1 to about 1:4, from about 4:1 to about 1:2, from about 4:1 to about 1:1, from about 2:1 to about 1:9, from about 2:1 to about 1:4, from about 2:1 to about 1:2, or from about 2:1 to about 1:1.

In certain ~~embodiment~~examples, the solvent and water are present in a ratio of from about 1:1 to about 1:2.

In certain ~~embodiment~~examples, the acid is hydrochloric, methanesulfonic, phosphoric, L-tartaric, D-glucuronic, L-malic, D-gluconic, L-lactic, acetic, or L-aspartic acid.

In certain ~~embodiment~~examples, the acid may be D-glucoronic acid.

In certain ~~embodiment~~examples, the acid may be acetic acid.

In certain ~~embodiment~~examples, the amount of acid relative to rifabutin is between 1 and 3 molar equivalents or between 1 and 2 molar equivalents.

In certain ~~embodiment~~examples, the amount of acid relative to rifabutin may is 1 molar equivalent.

In certain ~~embodiment~~examples, the rifabutin to acid molar ratio is about 1:1.

In certain ~~embodiment~~examples, 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.

In certain ~~embodiment~~examples, the bacterial infection is *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. meningitidis*, *staphylococci*, *streptococci* (e.g., group A *streptococci*), or *T. gondii.*

In another ~~aspect~~example, the ~~invention~~disclosure provides formulations comprising rifabutin, an acid, water, and a solvent suitable to promote dissolution of the rifabutin.

The formulations may contain any ratio of rifabutin to solvent, any ratio of solvent to water, or any ratio of rifabutin to acid described above.

The formulations may contain any solvent or any acid described above.

The formulation may contain any concentration of rifabutin, such as about 250 mg/ml, about 200 mg/ml, about 150 mg/ml, about 100 mg/ml, about 50 mg/ml, about 20 mg/ml, about 10 mg/ml, about 5 mg/ml, about 2.5 mg/ml, about 1 mg/ml, at least about 250 mg/ml, at least about 200 mg/ml, at least about 150 mg/ml, at least about 100 mg/ml, at least about 50 mg/ml, at least about 20 mg/ml, at least about 10 mg/ml, at least about 5 mg/ml, at least about 2.5 mg/ml, at least about 1 mg/ml, from about 1 mg/ml to about 250 mg/ml, from about 2.5 mg/ml to about 250 mg/ml, from about 5 mg/ml to about 250 mg/ml, from about 10 mg/ml to about 250 mg/ml, from about 20 mg/ml to about 250 mg/ml, from about 50 mg/ml to about 250 mg/ml, from about 100 mg/ml to about 250 mg/ml, from about 1 mg/ml to about 200 mg/ml, from about 2.5 mg/ml to about 200 mg/ml, from about 5 mg/ml to about 200 mg/ml, from about 10 mg/ml to about 200 mg/ml, from about 20 mg/ml to about 200 mg/ml, from about 50 mg/ml to about 200 mg/ml, or from about 100 mg/ml to about 200 mg/ml.

Brief Description of the Drawings

FIG. 1. is a schematic illustration of a method for preparing an injectable rifabutin solution or rifabutin for inhalation according to embodiments of the invention.

FIG. 2 is a schematic illustration of methods of analysis of rifabutin formulations.

FIG. 3 is a graph showing rifabutin solubility in formulations.

FIG. 4 is a graph showing rifabutin solubility in formulations.

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.

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: PEG, propylene glycol, NMP, ethanol, DMA, transcutol HP, and dimethyl isosorbide (DMI).

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

5. The formulation of claim 1, wherein the solvent to water ratio v/v is from about 1:1 to about 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, acetic and L-aspartic.

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, wherein the formulation is diluted in order to produce a composition suitable for a desired route of administration.

10. A method of preparing a formulation of rifabutin, 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 DMI and tanscutol HP.

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

13. A method of preparing a formulation of rifabutin, 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 DMI and tanscutol HP.

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

16. ~~A method of treating a bacterial infection in a subject, the method comprising administering a therapeutically effective amount~~ Use of rifabutin 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.