an unmet need for novel pharmaceutical compositions and methods of administering drugs via the pilosebaceous unit.

SUMMARY ~~OF THE INVENTION~~

[0007] The present ~~invention~~ disclosure relates to pharmaceutical compositions for the topical administration of a drug to the pilosebaceous unit and methods for administering the same. The inventors of the present disclosure ~~invention~~ have made the surprising discovery that a pharmaceutical composition comprising small particles of an active pharmaceutical ingredient can be delivered to the pilosebaceous unit resulting in deeper penetration into the dermis and improved efficacy. In preferred ~~embodiments~~examples, the pharmaceutical composition comprises SHR0302 or spironolactone as an active pharmaceutical ingredient.

[0008] In certain examples~~embodiments~~ of the present disclosure~~invention~~, a pharmaceutical composition is provided comprising a therapeutically effective amount of an active pharmaceutical ingredient and a silicone selected from the group consisting of dimethicone, cyclomethicone, and combinations thereof. The active pharmaceutical ingredient has a primary particle size distribution that is characterized by a D90 value of less than about 20 µm. In certain examples~~embodiments~~, the pharmaceutical ingredient has a primary particle size distribution that is characterized by a D90 value of less than about 10 µm or more preferably less than about 5 µm. In certain examples~~embodiments~~, the composition comprises about 0.10% w/w to about 7.5% w/w of the active pharmaceutical ingredient. The pharmaceutical compositions of the present disclosure ~~invention~~ can be capable of delivering the active pharmaceutical ingredient to the pilosebaceous unit. In certain examples~~embodiments~~, the active pharmaceutical ingredient is capable of achieving dermal penetration of at least 1 mm in the subject.

[0009] In certain examples ~~embodiments~~ of the present disclosure~~invention~~, a pharmaceutical composition is

provided comprising a therapeutically effective amount of SHR0302 or a pharmaceutically acceptable salt thereof. The SHR0302 can have a primary particle size distribution characterized by a D90 value of less than about 20 µm, less than about 10 µm, or more preferably less than about 5 µm. The SHR0302 can further have a primary particle size distribution characterized by a D50 value of less than about 5 µm, less than about 1 µm, or more preferably less than about 0.7 µm. The SHR0302 can further have a primary particle size distribution characterized by a D10 value of less than about 1 µm, less than about 0.5 µm, or more preferably less than about 0.25 µm.

[00010] The pharmaceutical composition further comprises a silicone selected from the group consisting of dimethicone, cyclomethicone, and combinations thereof. In certain examples ~~embodiments~~ of the present disclosure~~invention~~, the pharmaceutical composition comprises SHR0302 suspended in at least one of dimethicone and cyclomethicone.

[00011] In certain examples~~embodiments~~, the pharmaceutical composition can comprise about 0.10% w/w to about 5% w/w of SHR0302 or a salt thereof. In preferred examples ~~embodiments~~, the pharmaceutical composition can comprise from about 0.1% w/w to about 3% w/w of SHR0302 or a salt thereof.

[00012] In certain examples ~~embodiments~~ of the present disclosure~~invention~~, a method of treating alopecia areata in a subject in need thereof is provided. The method comprises topically administering to the subject the pharmaceutical compositions of SHR0302 described herein. In the methods of the present disclosure~~invention~~, the SHR0302 or salt thereof can be delivered to the pilosebaceous unit. In the methods disclosed herein, administration of the pharmaceutical composition can result in dermal penetration of SHR0302 of at least about 1 mm in the subject, and preferably to the depth of the hair bulb for a terminal hair, about 2 to 3 mm in the subject.

[00013] In certain examples ~~embodiments~~ of the present disclosure~~invention~~, a pharmaceutical composition is provided comprising a therapeutically effective amount of spironolactone or a pharmaceutically acceptable salt thereof. The spironolactone can have a primary particle size distribution characterized by a D90 value of less than about 6 µm, less than about 1 µm, or more preferably less than about 0.25 µm. The spironolactone can further have a primary particle size distribution characterized by a D50 value of less than about 2.7 µm, less than about 0.75 µm, or more preferably less than about 0.15 µm. The spironolactone can further have a primary particle size distribution characterized by a D10 value of less than about 1.2 µm, less than about 0.50 µm, or more preferably less than about 0.10 µm.

[00014] The pharmaceutical composition further comprises a silicone selected from the group consisting of dimethicone and cyclomethicone. In certain examples ~~embodiments~~ of the present disclosure~~invention~~, the pharmaceutical composition of spironolactone is an oil-in-water emulsion.

[00015] Further, the pharmaceutical composition can comprise about 0.10% w/w to about 7.5% w/w of spironolactone or a salt thereof. In certain examples ~~embodiments~~, the pharmaceutical composition can comprise from about 0.5% w/w to about 5% w/w of spironolactone or a salt thereof.

[00016] In certain examples ~~embodiments~~ of the present disclosure~~invention~~, a pharmaceutical composition is provided comprising a therapeutically effective amount of spironolactone or a pharmaceutically acceptable salt thereof and water. The spironolactone can have a primary particle size distribution characterized by a D90 value of less than about 6 µm, less than about 1 µm, or more preferably less than about 0.25 µm. The spironolactone can further have a primary particle size distribution characterized by a D50 value of less than about 2.7 µm, less than about 0.75 µm, or more preferably less than about 0.15 µm. The spironolactone can further have a primary particle

size distribution characterized by a D10 value of less than about 1.2 µm, less than about 0.50 µm, or more preferably less than about 0.10 µm.

[00016a] In one aspect, the present disclosure provides a pharmaceutical composition comprising: a therapeutically effective amount of spironolactone or a pharmaceutically acceptable salt thereof, wherein a primary particle size distribution of the spironolactone is characterized by a D90 value of less than about 6 µm; and water.

[00017] In certain examples ~~embodiments~~, the pharmaceutical composition comprises about 0.10% w/w to about 7.5% w/w of spironolactone or a salt thereof. In certain examples ~~embodiments~~, the pharmaceutical composition can comprise from about 0.5% w/w to about 5% w/w of spironolactone or a salt thereof. In certain examples ~~embodiments~~, the pharmaceutical composition is an aqueous suspension. In certain examples ~~embodiments~~, the pharmaceutical composition further comprises dioctyl sodium sulfosuccinate and/or hydroxyl propyl cellulose. In certain examples ~~embodiments~~, the pharmaceutical composition comprises about 0.01% w/w to about 1% w/w of dioctyl sodium sulfosuccinate and/or about 0.01% to about 1.5% w/w of hydroxyl propyl cellulose.

[00018] In certain examples ~~embodiments~~ of the present disclosure~~invention~~, a pharmaceutical composition is provided consisting essentially of or consisting of a therapeutically effective amount of spironolactone or a pharmaceutically acceptable salt thereof, dioctyl sodium sulfosuccinate, hydroxyl propyl cellulose, and water. The spironolactone can have a primary particle size distribution characterized by a D90 value of less than about 6 µm, less than about 1 µm, or more preferably less than about 0.25 µm. The spironolactone can further have a primary particle size distribution characterized by a D50 value of less than about 2.7 µm, less than about 0.75 µm, or more preferably less than about 0.15 µm. The spironolactone can

further have a primary particle size distribution characterized by a D10 value of less than about 1.2 µm, less than about 0.50 µm, or more preferably less than about 0.10 µm.

[00018a] In another aspect, the present disclosure provides a pharmaceutical composition consisting essentially of: a therapeutically effective amount of spironolactone or a pharmaceutically acceptable salt thereof, wherein a primary particle size distribution of the spironolactone is characterized by a D90 value of less than about 6 µm; a surfactant; a pharmaceutically acceptable cellulose polymer; and water.

[00019] In certain examples ~~embodiments~~, the pharmaceutical composition comprises about 0.10% w/w to about 7.5% w/w of spironolactone or a salt thereof. In certain examples ~~embodiments~~, the pharmaceutical composition can comprise from about 0.5% w/w to about 5% w/w of

spironolactone or a salt thereof. In certain examples ~~embodiments~~, the pharmaceutical composition is an aqueous suspension. In certain examples ~~embodiments~~, the pharmaceutical composition comprises about 0.01% w/w to about 1% w/w of dioctyl sodium sulfosuccinate and about 0.01% to about 1.5% w/w of hydroxyl propyl cellulose.

[00020] In certain examples ~~embodiments~~, the pharmaceutical composition is capable of delivering spironolactone to the pilosebaceous unit of a patient. In certain examples ~~embodiments~~, the pharmaceutical composition is capable of achieving dermal penetration of at least 1 mm in the patient, and preferably about 2 or 3 mm in the subject.

[00021] In certain examples ~~embodiments~~ of the present disclosure~~invention~~, a method of treating acne in a subject in need thereof is provided. In certain examples ~~embodiments~~, the subject is a human male or female. In preferred examples ~~embodiments~~, the subject is a female human. The method comprises topically administering to the subject the pharmaceutical compositions of spironolactone described herein. In the methods of the present disclosure~~invention~~, the spironolactone or salt thereof can be delivered to the pilosebaceous unit. In the methods disclosed herein, administration of the pharmaceutical composition can result in dermal penetration of spironolactone of at least 1 mm in the subject, and preferably about 2 or 3 mm in the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[00022] The accompanying drawings, which are incorporated herein and form part of the disclosure, help illustrate various embodiments of the present invention and, together with the description, further serve to describe the invention to enable a person skilled in the pertinent art to make and use the embodiments disclosed herein.

[00023] FIG. 1 shows a particle size distribution plot of SHR0302 in an exemplary pharmaceutical composition.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising:

a therapeutically effective amount of spironolactone or a pharmaceutically acceptable salt thereof, wherein a primary particle size distribution of the spironolactone is characterized by a D90 value of less than about 6 µm; and

~~a silicone selected from the group consisting of dimethicone and cyclomethicone~~water.

2. The pharmaceutical composition of claim 1, wherein the composition is an ~~oil-in-water emulsion~~aqueous suspension.

3. The pharmaceutical composition of claim ~~1~~2, wherein the composition comprises about 0.10% w/w to about 7.5% w/w of spironolactone or a salt thereof.

4. The pharmaceutical composition of claim 3, wherein the composition further comprises dioctyl sodium sulfosuccinate.

5. The pharmaceutical composition of claim 4, wherein the composition further comprises hydroxyl propyl cellulose.

~~4.~~6. The pharmaceutical composition of claim ~~1~~3, wherein a primary particle size distribution of the spironolactone is characterized by a D90 value of less than about 1 µm.

~~5.~~7. The pharmaceutical composition of claim 1, wherein a primary particle size distribution of the spironolactone is characterized by a D90 value of less than about 0.25 µm.

~~6.~~8. The pharmaceutical composition of claim 1, wherein a primary particle size distribution of the spironolactone is characterized by a D50 value of less than about 2.7 µm.

~~7.~~9. The pharmaceutical composition of claim 1, wherein a primary particle size distribution of the spironolactone is characterized by a D10 value of less than about 1.2 µm.

10. The pharmaceutical composition of claim 1, wherein the composition is a topical formulation.

11. A pharmaceutical composition consisting essentially of:

a therapeutically effective amount of spironolactone or a pharmaceutically acceptable salt thereof, wherein a primary particle size distribution of the spironolactone is characterized by a D90 value of less than about 6 µm;

a surfactant;

a pharmaceutically acceptable cellulose polymer; and

water.

12. The pharmaceutical composition of claim 11, wherein the surfactant is diocytl sodium sulfosuccinate.

13. The pharmaceutical composition of claim 12, wherein the pharmaceutically acceptable cellulose polymer is hydroxyl propyl cellulose.

14. The pharmaceutical composition of claim 13, wherein the composition is an aqueous suspension.

15. The pharmaceutical composition of claim 13, wherein the composition comprises about 0.10% w/w to about 7.5% w/w of spironolactone or a salt thereof, about 0.01% w/w to about 1% w/w of dioctyl sodium sulfosuccinate; and about 0.01% to about 1.5% w/w of hydroxyl propyl cellulose.

16. The pharmaceutical composition of claim 11, wherein a primary particle size distribution of the spironolactone is characterized by a D90 value of less than about 1 µm.

17. The pharmaceutical composition of claim 11, wherein a primary particle size distribution of the spironolactone is characterized by a D90 value of less than about 0.25 µm.

18. The pharmaceutical composition of claim 11, wherein a primary particle size distribution of the spironolactone is characterized by a D50 value of less than about 2.7 µm.

19. The pharmaceutical composition of claim 11, wherein a primary particle size distribution of the spironolactone is characterized by a D10 value of less than about 1.2 µm.

20. The pharmaceutical composition of claim 15, wherein the composition is capable of achieving dermal penetration of spironolactone of at least 1 mm in a patient.

~~8. A method of treating acne in a subject in need thereof comprising:~~

~~topically administering to the subject a pharmaceutical composition comprising: (a) a therapeutically effective amount of spironolactone or a pharmaceutically acceptable salt thereof, wherein a primary particle size distribution of the spironolactone is characterized by a D90 value of less than about 6 µm; and (b) a silicone selected from the group consisting of dimethicone and cyclomethicone.~~

~~9. The method of claim 8, wherein the spironolactone is delivered to the pilosebaceous unit.~~

~~10. The method of claim 8, wherein the spironolactone achieves dermal penetration of at least 1 mm in the subject.~~

~~11. The method of claim 8, wherein the pharmaceutical composition is an oil-in-water emulsion.~~

~~12. The method of claim 8, wherein the composition comprises about 0.10% w/w to about 7.5% w/w of spironolactone or a salt thereof.~~

~~13. The method of claim 8, wherein a primary particle size distribution of the spironolactone is characterized by a D90 value of less than about 1 µm.~~

~~14. The method of claim 8, wherein a primary particle size distribution of the spironolactone is characterized by a D90 value of less than about 0.25 µm.~~

~~15. The method of claim 8, wherein a primary particle size distribution of the spironolactone is characterized by a D50 value of less than about 2.7 µm.~~

~~16. The method of claim 8, wherein a primary particle size distribution of the spironolactone is characterized by a D10 value of less than about 1.2 µm.~~