may extend more than 3 mm below the skin surface into the subcutaneous fatty tissue and vellus hair, which is the fine, often unnoticed body hair that extends less than 1 mm into the dermis. The hair follicle, hair shaft, and sebaceous gland, which secrets a lubricating oil matter into the hair follicles, comprise what is known as a pilosebaceous unit. While the stratum corneum has traditionally been viewed as the primary pathway for the penetration of drugs, it is also the main barrier to percutaneous absorption. In the past, researchers have questioned the significance of the pilosebaceous unit in drug delivery.

[0005] More recently, however, the potential role of the pilosebaceous unit and alternative mechanisms for the transdermal delivery of drugs have been investigated. Amit Verma et al., Transfollicular drug delivery: current perspectives, Research and Reports in Transdermal Drug Delivery (April 20, 2016). The mammalian hair follicle is a complex, dynamic structure in which unique biochemical and immunological reactions occur. While the pilosebaceous unit may be an acceptable target for drug delivery, there are several challenges to drug delivery to the pilosebaceous unit. One of the challenges relating to drug delivery to the pilosebaceous unit is the need to bypass the stratum corneum, which extends approximately 10-20 μm deep and the upper capillary plexus, which extends approximately 80 μm deep.

[0006] There is currently a need for pharmaceutical compositions capable of penetrating deeper into the dermis, approximately 1,000 μm to 2,000 μm to the pilosebaceous unit. There is an unmet need for novel pharmaceutical compositions and methods of administering drugs via the pilosebaceous unit.

SUMMARY

[0007] The present disclosure relates to pharmaceutical compositions of spironolactone for the topical administration of the drug to the pilosebaceous unit and methods for administering the same. The pharmaceutical compositions comprise small

particles of spironolactone suspended in water. The inventors of the present invention have surprisingly determined that aqueous suspensions of spironolactone can be targeted to the pilosebaceous unit after topical administration.

[0008] In certain examples of the present disclosure, 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.

[0008a] In an aspect of the present disclosure, there is provided 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.

[0009] In certain examples, the pharmaceutical composition comprises about 0.10% w/w to about 7.5% w/w of spironolactone or a salt thereof. In certain examples, 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, the pharmaceutical composition is an aqueous suspension. In certain examples, the pharmaceutical composition further comprises dioctyl sodium sulfosuccinate and/or hydroxyl propyl cellulose. In certain examples, 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. In certain examples, the pharmaceutical composition is a topical formulation.

[00010] In certain examples, the pharmaceutical composition is capable of delivering spironolactone to the pilosebaceous unit of a subject. In certain examples, the pharmaceutical composition is capable of achieving dermal penetration of at least 1 mm in the subject, and preferably about 2 or 3 mm in the subject.

[00011] In certain examples of the present disclosure, 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.

[00011a] In another aspect of the present disclosure, there is provided 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; dioctyl sodium sulfosuccinate; hydroxyl propyl cellulose; and water.

[00012] In certain examples, the pharmaceutical composition comprises about 0.10% w/w to about 7.5% w/w of spironolactone or a salt thereof. In certain examples, 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, the pharmaceutical composition is an aqueous suspension. In certain examples, 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.

[00013] In certain examples, the pharmaceutical composition is capable of delivering spironolactone to the pilosebaceous unit of a subject. In certain

examples, the pharmaceutical composition is capable of achieving dermal penetration of at least 1 mm in the subject, and preferably about 2 or 3 mm in the subject.

[00014] In certain examples, the pharmaceutical composition is provided in a package selected from the group consisting of a sachet comprising a towelette or wipe, a pump comprising a spray or foam, a control flow applicator comprising a sponge, a dropper or dropper bottle comprising a suspension.

[0014a] In another aspect of the present disclosure, there is provided a package comprising the pharmaceutical composition as defined herein, wherein the package is selected from the group consisting of a sachet comprising a towelette or wipe, a pump comprising a spray or foam, a control flow applicator comprising a sponge, or a dropper or dropper bottle comprising a suspension.

[00015] In certain examples of the present disclosure, a method of treating a skin or hair disorder in a subject in need thereof is provided. In certain examples, the skin or hair disorder is acne, alopecia areata, or male pattern baldness. In certain examples, the subject is a human male or female. In certain examples for treating acne, 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, 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.

[00015a] In another aspect of the present disclosure, there is provided use of 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) water, in the manufacture of a medicament for treating a hair or skin condition, wherein the hair or skin condition is selected from the group consisting of acne, alopecia areata, or male pattern baldness and wherein the medicament is to be topically administered to a subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[00016] 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.

[00017] FIG. 1 shows a particle size distribution of spironolactone in a suspension of 5.0% spironolactone nano-milled in water with 0.05% dioctyl sulfosuccinate (DOSS) and 1.0% hydroxyl propyl cellulose.

[00018] FIG. 2 is a micrograph taken two weeks after storage past completion of milling for a 5% spironolactone suspension in cyclomethicone that was roller milled to form a suspension having a D90 of less than about 5 μm.

[00019] FIG. 3 is a micrograph taken two weeks after storage past completion of milling for a 5% spironolactone suspension in a 94.5:0.5 wt:wt blend of cyclomethicone and dioctyl sodium sulfosuccinate that was roller milled to form a suspension having a D90 of less than about 5 μm.

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

water.

2. The pharmaceutical composition of claim 1, wherein the composition is an aqueous suspension.

3. The pharmaceutical composition of claim 1, 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 1, wherein the composition further comprises dioctyl sodium sulfosuccinate.

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

6. 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 1 μm.

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.

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.

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 package comprising the pharmaceutical composition of claim 1, wherein the package is selected from the group consisting of a sachet comprising a towelette or wipe, a pump comprising a spray or foam, a control flow applicator comprising a sponge, or a dropper or dropper bottle comprising a suspension.

12. 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;

dioctyl sodium sulfosuccinate;

hydroxyl propyl cellulose; and

water.

13. The pharmaceutical composition of claim 12, wherein the composition is an aqueous suspension.

14. The pharmaceutical composition of claim 12, 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.

15. The pharmaceutical composition of claim 12, wherein a primary particle size distribution of the spironolactone is characterized by a D90 value of less than about 1 μm.

16. The pharmaceutical composition of claim 12, wherein a primary particle size distribution of the spironolactone is characterized by a D90 value of less than about 0.25 μm.

17. The pharmaceutical composition of claim 12, wherein a primary particle size distribution of the spironolactone is characterized by a D50 value of less than about 2.7 μm.

18. The pharmaceutical composition of claim 12, wherein a primary particle size distribution of the spironolactone is characterized by a D10 value of less than about 1.2 μm.

19. A package comprising the pharmaceutical composition of claim 12, wherein the package is selected from the group consisting of a sachet comprising a towelette or wipe, a pump comprising a spray or foam, a control flow applicator comprising a sponge, or a dropper or dropper bottle comprising a suspension.

20. The pharmaceutical composition of claim 12, wherein the composition is a topical formulation.

21. Use of 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) water, in the manufacture of a medicament for treating a hair or skin condition,

wherein the hair or skin condition is selected from the group consisting of acne, alopecia areata, or male pattern baldness and wherein the medicament is to be topically administered to a subject.

22. The use of claim 21, wherein the spironolactone is to be delivered to the pilosebaceous unit.

23. The use of claim 21, wherein the spironolactone achieves dermal penetration of at least 1 mm in the subject.

24. The use of claim 21, wherein the pharmaceutical composition is an aqueous suspension.

25. The use of claim 21, wherein the composition comprises about 0.10% w/w to about 7.5% w/w of spironolactone or a salt thereof.

26. The use of claim 21, wherein the composition further comprises dioctyl sodium sulfosuccinate.

27. The use of claim 21, wherein the composition further comprises hydroxyl propyl cellulose.