for C18 unsaturated acid (103.0 μg/cm^2-hr for linolenic acid 18:2) and alcohol (116.3 μg/cm^2-hr for linolenyl alcohol) adjuvants. Other effective skin penetration enhancers included pelargonic acid (201.9 $\pm$ 65.4 μg/cm^2-hr), capric acid (187.9 $\pm$ 67.5 μg/cm^2-hr), propylene glycol laurate 43.8 $\pm$ 5.5 μg/cm^2-hr) and laureth-4 (34.5 $\pm$ 8.3 μg/cm^2-hr). This excised human skin experiment used infinite dosing (278 μl/cm^2) to compare 64 adjuvants for their ability to increase the *in vitro* flux of naloxone from PG. The control of PG alone (without added adjuvant) had a naloxone flux value of 1.6 $\pm$ 0.4 μg/cm^2-hr.

[00011] In the 44 years since Shen first published that laureth-4 increased the percutaneous absorption of salicylic acid in rabbits, one photodynamic drug/device combination product and three topical drug products have been approved by the FDA that contain laureth-4. None of the three topical drug products use laureth-4 as a skin permeation enhancer. LAC-HYDRIN Cream (1.1% laureth-4) and LAC-HYDRIN Lotion (1.3% laureth-4) treat dry skin (xerosis) and are not designed to promote delivery past the stratum corneum, the target tissue for treating dry skin. The third approved product is VELTIN Gel (3% laureth-4), a dual-active gel that combines clindamycin phosphate and tretinoin for the treatment of acne. Laureth-4 and propylene glycol are used in this product to increase the solubility of tretinoin to 0.025%. Clindamycin phosphate is readily soluble in water without the addition of laureth-4 as a solubilizing agent. A formulator would not add a skin penetration enhancer to a topical clindamycin due to the clear warning in the VELTIN Gel label that systemic absorption of clindamycin could cause severe colitis that may result in death.

SUMMARY

[00012] In accordance with one example of the disclosure, it has surprisingly been discovered that the addition of laureth-4 to a topical formulation of the novel JAK inhibitor SHR0302 significantly increases the skin permeation of SHR0302. In some instances, the

increase is a 5-fold to 30-fold increase in skin permeation as compared to a topical formulation without laureth-4.

[00013] In the present disclosure, a topical pharmaceutical composition comprising a JAK inhibitor, laureth-4, and a solvent is provided. The JAK inhibitor may be SHR0302 (also known as ARQ-250). In one aspect, there is provided a topical pharmaceutical composition comprising a JAK inhibitor, laureth-4, and a solvent, wherein the JAK inhibitor is SHR0302.

[00014] The pharmaceutical composition can comprise a JAK inhibitor in an amount of about 0.1 to about 1.0% w/w. The pharmaceutical composition can comprise laureth-4 in an amount of about 0.5 to about 5% w/w. The pharmaceutical composition can further comprise dimethyl sulfoxide. Additionally, the pharmaceutical composition can comprise an antioxidant, a preservative, an emulsifier, a moisturizer, or a thickener.

[00015] The topical pharmaceutical composition can be selected from the group consisting of an oil-in-water emulsion, a water-in-oil emulsion, a microemulsion, a nanoemulsion, a foam, a spray, a hydrophilic ointment, or a hydrophobic ointment.

[00016] The topical pharmaceutical composition can further comprise a corticosteroid, timolol, methotrexate, or cyclosporine.

[00017] The topical pharmaceutical composition can enhance skin permeation by 5-fold to 30-fold relative to a topical pharmaceutical formulation without laureth-4 as measured by in vitro permeation testing.

[00018] In certain examples of the present disclosure, a method of treating an inflammatory skin disease, disorder, or condition in a subject in need thereof is provided. The method comprises topically administering to the subject a pharmaceutical composition comprising a JAK inhibitor, laureth-4, and a solvent.

[00018a] In another aspect, there is provided use of a pharmaceutical composition comprising a JAK inhibitor, laureth-4, and a solvent, wherein the JAK inhibitor is SHR0302, in the manufacture of a medicament for the treatment of an inflammatory skin disease, disorder, or condition in a subject in need thereof, wherein said pharmaceutical composition is to be topically administered to the subject.

[00018b] In another aspect, there is provided a topical pharmaceutical composition comprising a JAK inhibitor, laureth-4, and a solvent, wherein the JAK inhibitor is SHR0302, for use in therapy.

[00019] The inflammatory skin disease, disorder, or condition can be one of atopic dermatitis, rosacea, psoriasis, seborrheic dermatitis, vitiligo, eczema, or alopecia areata.

[00020] The pharmaceutical compositions can be administered to the subject one or more times per day.

[00021] The method can comprise administration of the JAK inhibitor, SHR0302. The JAK inhibitor can be present in the pharmaceutical composition in an amount of about 0.1 to about 1.0% w/w. Laureth-4 can be present in the pharmaceutical composition in an amount of about 0.5 to about 5% w/w. The method of administration can comprise administering a pharmaceutical composition comprising dimethyl sulfoxide. Further, the pharmaceutical composition further comprising a corticosteroid, timolol, methotrexate, or cyclosporine.

[00022] The method of administration to a subject can result in skin penetration of the topical pharmaceutical composition that is enhanced by 5-fold to 30-fold relative to a topical pharmaceutical formulation without laureth-4 as measured by in vitro permeation testing.

[00023] In certain examples, a method for enhancing the skin penetration in a subject of a topical pharmaceutical formulation is provided. The method comprises preparing a formulation comprising a JAK inhibitor, laureth-4 and a solvent. In the method, the skin penetration of the topical pharmaceutical composition is enhanced by 5-fold to 30-fold relative to a topical pharmaceutical formulation without laureth-4.

[00023a] In another aspect, there is provided a topical pharmaceutical formulation comprising a JAK inhibitor, laureth-4, and a solvent, wherein the JAK inhibitor is SHR0302, for use in for enhancing the skin penetration in a subject, wherein the skin penetration of the topical pharmaceutical formulation is enhanced by 5-fold to 30-fold relative to a topical pharmaceutical formulation without laureth-4.

BRIEF DESCRIPTION OF THE DRAWINGS

[00024] 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.

[00025] FIG. 1 illustrates IVPT results comparing an exemplary SHR0302 formulation with and without laureth-4. The x-axis depicts time (in hours) and the y-axis depicts ng/mL cumulative SHR0302 in receptor solution. The results show that the addition of laureth-4

CLAIMS

What is claimed is:

1. A topical pharmaceutical composition comprising a JAK inhibitor, laureth-4, and a solvent, wherein the JAK inhibitor is SHR0302.

2. The topical pharmaceutical composition of claim 1, wherein the JAK inhibitor is present in an amount of about 0.1 to about 1.0% w/w.

3. The topical pharmaceutical composition of claim 1, wherein the laureth-4 is present in an amount of about 0.5 to about 5% w/w.

4. The topical pharmaceutical composition of claim 1, further comprising dimethyl sulfoxide.

5. The topical pharmaceutical composition of claim 1, further comprising an antioxidant, a preservative, an emulsifier, a moisturizer, or a thickener.

6. The topical pharmaceutical composition of claim 1, wherein said composition is selected from the group consisting of an oil-in-water emulsion, a water-in-oil emulsion, a microemulsion, a nanoemulsion, a foam, a spray, a hydrophilic ointment, or a hydrophobic ointment.

7. The topical pharmaceutical composition of claim 1, further comprising a corticosteroid, timolol, methotrexate, or cyclosporine.

8. The topical pharmaceutical composition of claim 1, wherein skin penetration of the topical pharmaceutical composition is enhanced by 5-fold to 30-fold relative to a topical pharmaceutical formulation without laureth-4 as measured by in vitro permeation testing.

9. Use of a pharmaceutical composition comprising a JAK inhibitor, laureth-4, and a solvent, wherein the JAK inhibitor is SHR0302, in the manufacture of a medicament

for the treatment of an inflammatory skin disease, disorder, or condition in a subject in need thereof, wherein said pharmaceutical composition is to be topically administered to the subject.

10. The use of claim 9, wherein said inflammatory skin disease, disorder, or condition is atopic dermatitis, rosacea, psoriasis, seborrheic dermatitis, vitiligo, eczema, or alopecia areata.

11. The use of claim 9, wherein the pharmaceutical compositions is to be administered to the subject one or more times per day.

12. The use of claim 9, wherein the JAK inhibitor is present in the pharmaceutical composition in an amount of about 0.1 to about 1.0% w/w.

13. The use of claim 9, wherein the laureth-4 is present in the pharmaceutical composition in an amount of about 0.5 to about 5% w/w.

14. The use of claim 9, wherein the pharmaceutical composition further comprising dimethyl sulfoxide.

15. The use of claim 9, wherein the pharmaceutical composition further comprising a corticosteroid, timolol, methotrexate, or cyclosporine.

16. The use of claim 9, wherein skin penetration of the topical pharmaceutical composition is to be enhanced by 5-fold to 30-fold relative to a topical pharmaceutical formulation without laureth-4 as measured by in vitro permeation testing.

17. A topical pharmaceutical composition comprising a JAK inhibitor, laureth-4, and a solvent, wherein the JAK inhibitor is SHR0302, for use in therapy.

18. A topical pharmaceutical formulation comprising a JAK inhibitor, laureth-4, and a solvent, wherein the JAK inhibitor is SHR0302, for use in for enhancing the skin penetration in a subject, wherein the skin penetration of the topical pharmaceutical formulation is enhanced by 5-fold to 30-fold relative to a topical pharmaceutical formulation

without laureth-4.