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(54) Title: TOUCH-FREE TOPICAL SPRAY OF HALOBETASOL

(57) **Abstract:** The present invention relates to a touch-free topical spray of halobetasol comprising a composition which is delivered through a dispensing system, wherein the composition comprises from about 0.01% w/w to about 0.5% w/w of halobetasol based on 5 the total weight of the composition for the treatment of skin disorders, wherein the dispensing system comprises a metered valve assembly comprising a metered valve having a stem connected to an actuator, wherein the actuator is provided with an insert having an orifice diameter in a range of about 0.2 mm to about 1.5 mm, and wherein no rubbing-in is required when said composition is applied to affected skin. Said topical spray 10 compositions offer ease of application leading to enhanced patient compliance. Further, said compositions are delivered from a dispensing system in metered doses. It also relates to processes for the preparation of the touch-free topical spray compositions.



TOUCH-FREE TOPICAL SPRAY OF HALOBETASOL

Field of the Invention

The present invention relates to a touch-free topical spray of halobetasol comprising a composition which is delivered through a dispensing system, wherein the composition comprises from about 0.01% w/w to about 0.5% w/w of halobetasol based on the total weight of the composition for the treatment of skin disorders, wherein the dispensing system comprises a metered valve assembly comprising a metered valve having a stem connected to an actuator, wherein the actuator is provided with an insert having an orifice diameter in a range of about 0.2 mm to about 1.5 mm, and wherein no rubbing-in is required when said composition is applied to affected skin. Said topical spray compositions offer ease of application leading to enhanced patient compliance. Further, said compositions are delivered from a dispensing system in metered doses. It also relates to processes for the preparation of the touch-free topical spray compositions.

Background of the Invention

Halobetasol is a super-potent corticosteroid widely used for the treatment of dermal ailments. Topical dosage forms of halobetasol such as cream, ointment, and lotion are commercially available under the trade name Ultravate® and have been used for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses.

The available cream, ointment, and lotion dosage forms of halobetasol pose high level of patient non-compliance. The physical application of these dosage forms is not desirable as touching of sore or otherwise adversely affected skin may cause additional discomfort to the patients. Further, high viscosity of these dosage forms makes physical application difficult when intended to apply on large areas of the skin and may also cause clogging of skin pores thus affecting the desired delivery. Also, the available dosage forms are unable to deliver the metered dose of the composition which is highly desirable for a super-potent corticosteroid to avoid adverse side effects. Additionally, the available dosage forms remain prone to contamination during use.

Pharmaceutical sprays provide the best alternative and exhibit numerous advantages such as possibility of controlling the dose and absence of contamination during use over the existing dosage forms of halobetasol. Though sprays lead to improved patient-compliance over creams and ointments, these may always not be easy to apply.

Clobetasol, another super-potent corticosteroid available in the spray dosage form under the trade name Clobex[®] requires a need to gently rub-in upon application to the desired site of action. Clobex[®] shows a tendency to run or drip, and is thus not retained onto the desired site of action for a sufficient time. To overcome this, patients are advised to gently
5 rub-in the composition upon its application. This requirement of rubbing-in results in patient non-compliance as it abolishes the whole purpose of spray as being touch-free. The requirement of rubbing-in may irritate the otherwise adversely affected skin and may also increase the chances of cross-contamination.

There remains a need in the art to develop patient compliant, metered, touch-free
10 topical spray composition of halobetasol in which the physical contact remains completely avoided.

The present invention provides a touch-free topical spray of halobetasol which improves the deposition of the sprayed formulation onto the skin and thus offers ease of application. The composition is delivered as a fine spray which includes jet of droplets
15 which get finely distributed onto the skin. Said composition does not show any running of or dripping upon its application and thus there is no need to rub-in the composition onto the affected skin leading to enhanced patient-compliance. Said composition is touch-free, easy to apply with minimal chances of cross-contamination and further with no need of washing hands after application. The particular design of a dispensing system with specific
20 dimensions of an actuator and an insert determine the droplet characteristics such that the spray upon delivery to the site of action does not require any rubbing-in of the composition. The inventors of the present invention have surprisingly found that the performance of the spray can be significantly improved onto the skin by altering the droplet characteristics such as droplet size of the composition upon its delivery from the
25 dispensing system. The inventors found that a particular droplet size upon delivery from the dispensing system does not lead to any dripping or running of the composition when applied onto the skin. The size of droplets are sufficiently small to form a uniform spray with a characteristic of 'no-running' and yet sufficiently large to ensure that the droplets do not form a fine mist that can be inhaled. Further, evaporation of a propellant gives a
30 soothing and cooling effect to the patients which further enhance the patient compliance. Said topical spray composition is pressurized, non-occlusive, and non-irritant. Also, said topical composition is delivered from a dispensing system in metered doses which is a significant advance over available cream, ointment, and lotion dosage forms of

halobetasol. Further, the inventors have surprisingly found that the spray of present invention shows enhanced permeation into the skin layers as compared to the marketed halobetasol cream formulation.

Summary of the Invention

5 The touch-free topical spray composition of the present invention allows for the application of halobetasol with no physical contact on the area of application, except by the spray itself. The present invention provides a touch-free topical spray composition of halobetasol which quickly dries to form a thin and uniform film and thus deposits onto the skin without any running of or dripping. The present invention thus provides touch-free,
10 easy to use, storage-stable, preservative-free topical spray composition of halobetasol with enhanced patient compliance. Evaporation of the propellant provides a cooling effect which is well received by patients. Further, the composition can be useful for treating skin disorders involving hairy skin or difficult to reach areas such as scalp. Also, said composition is delivered in metered doses which prevent both over-dosing and under-
15 dosing which is highly desirable for a super-potent corticosteroid. The touch-free topical spray composition of the present invention comprises halobetasol, a non-aqueous solvent, and a propellant. It also relates to processes for the preparation of the touch-free topical spray composition. It further relates to a method of treating skin disorders including corticosteroid responsive dermatoses by administering said topical spray composition.

Brief Description of the Drawings

- 20 **Figure 1:** Schematic diagram of a partial cut-away view of a dispensing system of the present invention
- Figure 2:** Schematic diagram of a metered valve of a dispensing system of the present invention
- 25 **Figure 3:** Spray pattern of (a) halobetasol spray as per Example 1 of the present invention and (b) Clobex[®] Spray illustrating the running off
- Figure 4:** Plume of (a) halobetasol spray as per Example 1 of the present invention and (b) Clobex[®] Spray

Detailed Description of the Invention

30 A first aspect of the present invention provides a touch-free topical spray for the treatment of skin disorders, wherein the spray is formed from a composition delivered

through a dispensing system, wherein the composition comprises from about 0.01% w/w to about 0.5% w/w of halobetasol based on the total weight of the composition, wherein the dispensing system comprises a metered valve assembly comprising a metered valve having a stem connected to an actuator, wherein the actuator is provided with an insert
5 having an orifice diameter in a range of about 0.2 mm to about 1.5 mm, wherein the topical spray is in the form of droplets, and wherein no rubbing-in is required when said composition is applied to affected skin.

According to one embodiment of the above aspect, the touch-free topical spray does not require further topical application by hand.

10 A second aspect of the present invention provides a touch-free topical spray composition comprising from about 0.01% w/w to about 0.5% w/w of halobetasol based on the total weight of the composition for the treatment of skin disorders, wherein no rubbing-in is required when said composition is applied to affected skin. For example, provided herein is a touch-free topical spray for the treatment of skin disorders, wherein
15 the spray is formed from a composition delivered through a dispensing system, wherein the composition comprises about 0.01% w/w to about 0.5% w/w of halobetasol, based on the total weight of the composition, and wherein the dispensing system comprises a metered valve assembly comprising a metered valve having a stem connected to an actuator, wherein the actuator is provided with an insert having an orifice diameter in a
20 range of about 0.2 mm to about 1.5 mm, wherein the topical spray is in the form of droplets and wherein no rubbing-in is required when said spray is applied to affected skin. Also contemplated herein is a touch-free topical spray kit for the treatment of skin disorders comprising a solution composition of halobetasol and a dispensing system comprising a metered valve assembly comprising a metered valve, wherein the actuator
25 has an insert having an orifice diameter in a range of about 0.2 mm to about 1.5 mm and produces a topical spray in the form of droplets, and wherein no rubbing-in is required when said spray is applied to affected skin.

According to another embodiment of the above aspects, the composition comprises about 0.05% w/w of halobetasol based on the total weight of the composition.

30 According to another embodiment of the above aspects, the composition comprises halobetasol propionate.

According to another embodiment of the above aspects, the composition is a solution.

According to another embodiment of the above aspects, the composition is delivered through a dispensing system in the form of droplets.

5 According to another embodiment of the above aspects, the droplets are having a D_{90} of less than 150 μm . In a particular embodiment, the droplets have a D_{90} of less than 100 μm . In a more particular embodiment, the droplets have a D_{90} of less than 50 μm . In an even more particular embodiment, the droplets have a D_{90} from about 20 μm to about 50 μm .

10 According to another embodiment of the above aspects, the droplets are having a D_{50} of less than 80 μm . In a particular embodiment, the droplets have a D_{50} of less than 50 μm . In a more particular embodiment, the droplets have a D_{50} of less than 30 μm . In an even more particular embodiment, the droplets have a D_{50} from about 5 μm to about 50 μm .

15 According to another embodiment of the above aspects, the droplets are having a D_{10} of less than 40 μm . In a particular embodiment, the droplets have a D_{10} of less than 30 μm . In a more particular embodiment, the droplets have a D_{10} of less than 20 μm . In an even more particular embodiment, the droplets have a D_{10} from about 7 μm to about 12 μm .

20 According to another embodiment of the above aspects, the droplets are having a droplet size distribution of a D_{90} of less than 150 μm , a D_{50} of less than 80 μm , a D_{10} of less than 40 μm .

 According to another embodiment of the above aspects, the composition is delivered through a dispensing system in the form of droplets, wherein more than 10% of
25 the droplets are smaller than 10 μm in size.

 According to another embodiment of the above aspects, the droplets are having a droplet span in a range of about 1.10 to about 1.40.

 According to another embodiment of the above aspects, the droplets form a plume with a plume angle in a range of about 5° to about 40°. In a preferred embodiment, the
30 plume angle is in a range of about 10° to about 30°. In a more preferred embodiment, the plume angle is in a range of about 10° to about 25°.

According to another embodiment of the above aspects, the droplets form a plume with a plume width in a range of about 10 mm to about 65 mm. In a preferred embodiment, the plume width is in a range of about 15 mm to about 50 mm. In a more preferred embodiment, the plume width is in a range of about 20 mm to about 40 mm.

- 5 According to another embodiment of the above aspects, the composition is characterized by having a specific gravity of about 0.5 g/mL to about 0.8 g/mL. In a particular embodiment, the composition is characterized by having a specific gravity of about 0.6 g/mL to about 0.8 g/mL.

- 10 According to another embodiment of the above aspects, the skin disorder is selected from the group consisting of corticosteroid responsive dermatoses including psoriasis, atopic dermatitis, sebopsoriasis, palmoplantaris, pustulosis, ichthyosis, dermatoses, eczema, rosacea, acne vulgaris, pruritis, seborrhea, skin cancers, inflammation, and combinations thereof.

- 15 According to another embodiment of the above aspects, the skin disorder is corticosteroid responsive dermatoses including psoriasis and atopic dermatitis.

According to another embodiment of the above aspects, the treatment of the skin disorders comprises co-administration of at least one additional drug used to treat topical skin conditions.

- 20 According to another embodiment of the above aspect, the additional drugs are selected from the group comprising Vitamin D analogues such as calcipotriene and calcitriol, retinoids such as tazarotene, calcineurin inhibitors such as tacrolimus and pimecrolimus, salicylic acid, coal tar, anthralin, antimicrobials, or combinations thereof. The co-administration includes simultaneous or sequential administration of additional drugs. Alternatively, the additional drugs can be administered together in a single
25 composition.

- 30 According to another embodiment of the above aspect, the dispensing system comprises a pressurized container and a metered valve assembly further comprising a mounting cup attached to the pressurized container by crimping, a housing, a spring, a dip tube, and a gasket. The metered valve assembly is described in Figure 2. Alternatively, the metered valve assembly may comprise a metering chamber.

According to another embodiment of the above aspect, the pressurized container may have a capacity ranging from about 5 g to about 200 g. In particular, the pressurized container may have a capacity of 15 g, 50 g, or 100 g.

5 According to another embodiment of the above aspect, the metered valve may have a capacity ranging from about 50 μ L to about 200 μ L. In particular, the metered valve may have a capacity ranging from about 120 μ L to about 180 μ L, more particularly about 150 μ L.

According to another embodiment of the above aspect, the actuator is having a diameter ranging from about 5.0 mm to about 20.0 mm. In particular, the actuator
10 diameter is in a range of about 10.0 mm to about 16.0 mm. More particularly, the actuator diameter is in a range of about 13.0 mm to about 15.0 mm.

According to another embodiment of the above aspect, the actuator is having a height ranging from about 5.0 mm to about 20.0 mm. In particular, the actuator height is in a range of about 10.0 mm to about 16.0 mm. More particularly, the actuator height is in a
15 range of about 13.0 mm to about 15.0 mm.

According to another embodiment of the above aspect, the actuator is provided with an insert having an orifice diameter in a range of about 0.2 mm to about 1.5 mm. In particular, the insert is having an orifice diameter in a range of about 0.2 mm to about 0.7 mm. More particularly, the insert is having an orifice diameter of about 0.5 mm.

20 According to another embodiment of the above aspect, the dip tube length ranges from about 50 mm to about 150 mm. For the pressurized container with a capacity of 15 g, the dip tube length ranges from about 50 mm to about 85 mm, for the pressurized container with a capacity of 50 g, the dip tube length ranges from about 90 mm to about 120 mm, and for the pressurized container with a capacity of 100 g, the dip tube length
25 ranges from about 110 mm to about 150 mm.

The dimensions of the actuator, insert used in the present invention are designed in a way to deliver the composition with a focused plume. The focused plume avoids the escape of droplets which may cause inhalation into the lungs leading to systemic side effects.

30 The components of the dispensing system used in the present invention are made of materials which are compatible with the composition contained inside and prevents degradation of the composition.

According to another embodiment of the above aspect, the pressurized container body is composed of a material selected from the group consisting of a metal such as aluminium or its alloy, stainless steel, or, tinplate; glass; polyester; ceramic; polyethylene terephthalate; or the like. In particular, the container body is composed of aluminium.

- 5 Further, the container body is lined with an inert material to avoid any degradation of the composition due to interaction between the container body and the composition. The inert materials are selected from group consisting of resins such as acrylic, phenolic, epoxyphenolic, polyester, epoxy, or vinyl resins, fluoropolymers, such as perfluoroethylenepropylene copolymer fluororubber (FPM), perfluoroalkoxyalkanes, 10 perfluoroalkoxyalkylenes, ethylene tetrafluoroethylene copolymer (EFTE), polytetrafluoroethylene (PTFE); ethylene-propylene diene monomer rubber (EPDM), polyamides, polyimides, polypropylene, polyethylene, or the like, in particular epoxyphenolic. The dip tube, the actuator, and the housing is composed of polyethylene or polypropylene or their copolymers. The stem is made up of a resin such as 15 polyoxymethylene. The mounting cup made up of metals such as aluminum alloy. The dispensing system may further comprise gaskets or seals of materials composed of compatible materials fluoroelastomers, rubber such as nitrile rubber, fluororubber, ethylene-propylene diene monomer rubber, fluorinated ethylene-propylene copolymer.

- A third aspect of the present invention provides a touch-free topical spray 20 composition of halobetasol delivered in the form of droplets from a dispensing system in up to 4 actuations given one after another on the same surface, wherein the droplets form a spray pattern when dispensed from a distance of 3.5 inches onto the surface, wherein the spray pattern does not substantially change, and a single actuation delivers an average shot weight ranges from about 90 mg to about 110 mg of the composition.

- 25 A fourth aspect of the present invention provides a method for treating skin disorders comprising: topically spraying a touch-free topical spray composition comprising halobetasol to a surface, wherein the composition is delivered in the form of droplets from a dispensing system in up to 4 actuations one after another on to the same surface, wherein the droplets form a spray pattern when dispensed from a distance of 3.5 30 inches onto the surface, wherein the spray pattern does not substantially change, and a single actuation of the dispensing system delivers an average shot weight of about 90 mg to about 110 mg of the composition.

A fifth aspect of the present invention provides a touch-free topical spray composition of halobetasol delivered in the form of droplets from a dispensing system in up to 5 actuations given one after another on the same surface, wherein the droplets form a spray pattern when dispensed from a distance of 3.5 inches onto the surface, wherein the spray pattern does not substantially change, and a single actuation delivers an average shot weight of about 65 mg to about 95 mg of the composition.

A sixth aspect of the present invention provides a method for treating skin disorders comprising: topically spraying a touch-free topical spray composition comprising halobetasol to a surface, wherein the composition is delivered in the form of droplets from a dispensing system in up to 5 actuations one after another on to the same surface, wherein the droplets form a spray pattern when dispensed from a distance of 3.5 inches onto the surface, wherein the spray pattern does not substantially change, and a single actuation of the dispensing system delivers an average shot weight of about 65 mg to about 95 mg of the composition.

In an embodiment of the above aspects, the spray pattern is characterized by having a $D_{\max}$ in a range of about 4 mm to about 100 mm, a $D_{\min}$ in a range of about 4 mm to 100 mm, and an ovality in a range of about 1.00 to about 3.00. In a particular embodiment of the above aspects, the spray pattern is characterized by having a $D_{\max}$ in a range of about 10 mm to about 60 mm, a $D_{\min}$ in a range of about 10 mm to 60 mm, and an ovality in a range of about 1.00 to about 2.00.

A seventh aspect of the present invention provides a touch-free topical spray composition of halobetasol delivered in the form of droplets from a dispensing system in up to 4 actuations given one after another on the same surface, wherein the droplets are characterized by a droplet size such that the composition does not require any rubbing-in when delivered from a distance of 3.5 inches onto the surface and a single actuation delivers an average shot weight ranges from about 90 mg to about 110 mg of the composition.

An eighth aspect of the present invention provides a touch-free topical spray composition of halobetasol delivered in the form of droplets from a dispensing system in up to 5 actuations given one after another on the same surface, wherein the droplets are characterized by a droplet size such that the composition does not require any rubbing-in

when delivered from a distance of 3.5 inches onto the surface and a single actuation delivers an average shot weight of about 65 mg to about 95 mg of the composition.

A ninth aspect of the present invention provides a touch-free topical spray composition of halobetasol delivered in the form of droplets from a dispensing system in
5 up to 4 actuations given one after another on the same surface, wherein the droplets form a spray pattern when dispensed from a distance of 3.5 inches onto the surface, wherein the droplets are characterized by having a droplet size such that the spray pattern does not substantially change, and a single actuation delivers an average shot weight ranges from about 90 mg to about 110 of the composition.

10 A tenth aspect of the present invention provides a method for treating skin disorders comprising: topically spraying a touch-free topical spray composition comprising halobetasol to a surface, wherein the composition is delivered in the form of droplets from a dispensing system in up to 4 actuations one after another on to the same surface, wherein the droplets form a spray pattern when dispensed from a distance of 3.5
15 inches onto the surface, wherein the droplets are characterized by having an droplet size such that the spray pattern does not substantially change and a single actuation of the dispensing system delivers an average shot weight of about 90 mg to about 110 mg of the composition.

An eleventh aspect of the present invention provides a touch-free topical spray
20 composition of halobetasol delivered in the form of droplets from a dispensing system in up to 5 actuations given one after another on the same surface, wherein the droplets form a spray pattern when dispensed from a distance of 3.5 inches onto the surface, wherein the droplets are characterized by having a droplet size such that the spray pattern does not substantially change, and a single actuation delivers an average shot weight of about 65
25 mg to about 95 mg of the composition.

A twelfth aspect of the present invention provides a method for treating skin disorders comprising: topically spraying a touch-free topical spray composition comprising halobetasol to a surface, wherein the composition is delivered in the form of droplets from a dispensing system in up to 5 actuations one after another on to the same
30 surface, wherein the droplets form a spray pattern when dispensed from a distance of 3.5 inches onto the surface, wherein the droplets are characterized by having an droplet size such that the spray pattern does not substantially change and a single actuation of the

dispensing system delivers an average shot weight of about 65 mg to about 95 mg of the composition.

In an embodiment of the above aspects, the spray pattern is characterized by having a $D_{\max}$ in a range of about 4 mm to about 100 mm, a $D_{\min}$ in a range of about 4 mm to 100 mm, and an ovality in a range of about 1.00 to about 3.00. In a particular embodiment of the above aspects, the spray pattern is characterized by having a $D_{\max}$ in a range of about 10 mm to about 60 mm, a $D_{\min}$ in a range of about 10 mm to 60 mm, and an ovality in a range of about 1.00 to about 2.00.

A thirteenth aspect of the present invention provides a touch-free topical spray composition of halobetasol delivered in the form of droplets from a dispensing system in up to 4 actuations given one after another on the same surface, wherein the composition is characterized by a specific gravity such that the composition does not require any rubbing-in when delivered from a distance of 3.5 inches onto the surface and a single actuation delivers an average shot weight ranges from about 90 mg to about 110 mg of the composition.

A fourteenth aspect of the present invention provides a touch-free topical spray composition of halobetasol delivered in the form of droplets from a dispensing system in up to 5 actuations given one after another on the same surface, wherein the composition is characterized by a specific gravity such that the composition does not require any rubbing-in when delivered from a distance of 3.5 inches onto the surface and a single actuation delivers an average shot weight of about 65 mg to about 95 mg of the composition.

A fifteenth aspect of the present invention provides a touch-free topical spray composition of halobetasol delivered in the form of droplets from a dispensing system in up to 4 actuations given one after another on the same surface, wherein the droplets form a spray pattern when dispensed from a distance of 3.5 inches onto the surface, wherein the composition is characterized by having a specific gravity such that the spray pattern does not substantially change, and a single actuation delivers an average shot weight ranges from about 90 mg to about 110 of the composition.

A sixteenth aspect of the present invention provides a method of treating skin disorders, comprising: topically spraying a touch-free topical spray composition comprising halobetasol to a surface, wherein the composition is delivered in the form of droplets from a dispensing system, in up to 4 actuations one after another on to the same

surface, wherein the droplets form a spray pattern when dispensed from a distance of 3.5 inches from the surface, wherein the composition has a specific gravity such that the spray pattern does not substantially change, and wherein a single actuation of the dispensing system delivers an average shot weight ranges from about 90 mg to about 110 of the composition.

A seventeenth aspect of the present invention provides a touch-free topical spray composition of halobetasol delivered in the form of droplets from a dispensing system in up to 5 actuations given one after another on the same surface, wherein the droplets form a spray pattern when dispensed from a distance of 3.5 inches onto the surface, wherein the composition is characterized by having a specific gravity such that the spray pattern does not substantially change, and a single actuation delivers an average shot weight of about 65 mg to about 95 mg of the composition.

An eighteenth aspect of the present invention provides a method of treating skin disorders, comprising: topically spraying a touch-free topical spray composition comprising halobetasol to a surface, wherein the composition is delivered in the form of droplets from a dispensing system, in up to 5 actuations one after another on to the same surface, wherein the droplets form a spray pattern when dispensed from a distance of 3.5 inches from the surface, wherein the composition has a specific gravity such that the spray pattern does not substantially change, and wherein a single actuation of the dispensing system delivers an average shot weight ranges from about 65 mg to about 95 of the composition.

In an embodiment of the above aspects, the spray pattern is characterized by having a $D_{\max}$ in a range of about 4 mm to about 100 mm, a $D_{\min}$ in a range of about 4 mm to 100 mm, and an ovality in a range of about 1.00 to about 3.00. In a particular embodiment of the above aspects, the spray pattern is characterized by having a $D_{\max}$ in a range of about 10 mm to about 60 mm, a $D_{\min}$ in a range of about 10 mm to 60 mm, and an ovality in a range of about 1.00 to about 2.00.

According to another embodiment of the above aspects, the composition is applied onto the affected skin twice daily for two consecutive weeks for treating skin disorders. In particular, the skin disorder is corticosteroid responsive dermatoses, more particularly corticosteroid responsive dermatoses is psoriasis and atopic dermatitis. For moderate to severe plaque psoriasis, treatment may be extended for an additional two weeks for

localized lesions that have not sufficiently improved after the initial two weeks treatment. The topical spray composition is applied onto the affected skin twice daily for not more than four weeks for treating skin disorders.

According to another embodiment of the above aspects, the composition is applied
5 onto the affected skin for not more than 75 sprays per application for treating corticosteroid responsive dermatoses. Particularly, the composition is applied onto the affected skin for not more than about 35 sprays per application for treating corticosteroid responsive dermatoses when the average shot weight ranges from about 90 mg to about 110 mg. Alternatively, the composition is applied onto the affected skin for not more than
10 about 44 sprays per application for treating corticosteroid responsive dermatoses when the average shot weight ranges from about 90 mg to about 110 mg.

According to another embodiment of the above aspects, the composition is applied onto the affected skin for not more than 150 sprays per day for treating corticosteroid responsive dermatoses. Particularly, the composition is applied onto the affected skin for
15 not more than about 70 sprays per day for treating corticosteroid responsive dermatoses when the average shot weight ranges from about 90 mg to about 110 mg. Alternatively, the composition is applied onto the affected skin for not more than about 88 sprays per day for treating corticosteroid responsive dermatoses when the average shot weight ranges from about 65 mg to about 95 mg.

According to another embodiment of the above aspects, the composition of
20 halobetasol is applied onto the affected skin for not more than 50 g per week for treating corticosteroid responsive dermatoses.

According to another embodiment of the above aspects, the dispensing system upon each actuation delivers an average shot weight in a range of from about 50 mg to
25 about 150 mg. In a preferred embodiment, the average shot weight ranges from about 75 mg to about 125 mg. In a more preferred embodiment, the average shot weight ranges from about 90 mg to about 110 mg. Alternatively, the average shot weight may also range from about 65 mg to about 95 mg of the composition.

The composition of the present invention has an internal pressure ranging from
30 about 40 to about 150 psig, in particular from about 60 psig to about 100 psig.

The specific gravity of the composition of the present invention ranges from about 0.5 g/mL to about 0.8 g/mL. Particularly, the specific gravity of the composition ranges

from about 0.6 g/mL to about 0.8 g/mL. The specific gravity of bulk solution ranges from about 0.6 g/mL to about 1.0 g/mL. Particularly, the specific gravity of bulk solution ranges from about 0.7 g/mL to about 0.9 g/mL.

According to another embodiment of the above aspects, the composition of
5 halobetasol is stable.

According to another embodiment of the above aspects, the composition is non-foaming.

According to another embodiment of the above aspects, the composition is preservative-free.

10 According to another embodiment of the above aspects, the composition is stabilizer-free.

According to another embodiment of the above aspects, the composition is substantially anhydrous.

According to another embodiment of the above aspects, the composition further
15 comprises a non-aqueous solvent and a propellant.

According to another embodiment of the above aspects, the topical spray composition has a non-aqueous solvent to propellant ratio ranging from about 1:0.1 to about 1:15. In particular, the ratio ranges from about 1:0.2 to about 1:10, more particularly, the ratio ranges from about 1:0.4 to about 1:3.

20 According to another embodiment of the above aspects, the composition has an emollient to non-aqueous solvent ratio ranging from about 1: 1 to about 1:20, in particular from about 1:1 to about 1:10.

According to another embodiment of the above aspects, the topical spray composition has an emollient to propellant ratio ranging from about 1:2 to about 1:10.

25 A nineteenth aspect of the present invention provides a process for the preparation of a composition of halobetasol, wherein the process comprises the steps of:

(a) dissolving halobetasol in one portion of a non-aqueous solvent;

(b) optionally mixing an emollient and another portion of the non-aqueous solvent into the solution of step (a) to form a solution;

30 (c) dispensing the solution of step (b) in a pressurized container;

(d) crimping the container of step (c) with a metered valve assembly;

(e) charging the propellant in the container of step (d); and

(f) fitting an actuator on the container of step (e).

A twentieth aspect of the present invention provides a touch-free topical spray
5 composition of halobetasol delivered in the form of plurality of droplets, wherein the
droplets have a size distribution of D_{90} of less than 150 μm , and wherein the composition
comprises (a) about 0.05% w/w of halobetasol based on the total weight of the
composition; (b) a non-aqueous solvent and; and (c) a propellant; wherein when
administering topically to a patient, the topical spray composition does not require further
10 application by hand.

A twenty first aspect of the present invention provides a touch-free topical spray
composition of halobetasol delivered in the form of plurality of droplets, wherein the
droplets have a size distribution of D_{50} of less than 80 μm , and wherein the composition
comprises (a) about 0.05% w/w of halobetasol based on the total weight of the
15 composition; (b) a non-aqueous solvent and; and (c) a propellant; wherein when
administering topically to a patient, the topical spray composition does not require further
application by hand.

A twenty second aspect of the present invention provides a touch-free topical spray
composition of halobetasol delivered in the form of plurality of droplets, wherein the
20 droplets have a size distribution of D_{10} of less than 40 μm , and wherein the composition
comprises (a) about 0.05% w/w of halobetasol based on the total weight of the
composition; (b) a non-aqueous solvent and; and (c) a propellant; wherein when
administering topically to a patient, the topical spray composition does not require further
application by hand.

A twenty third aspect of the present invention provides a touch-free topical spray
composition of halobetasol delivered in the form of plurality of droplets, wherein the
droplets have a droplet size distribution of D_{90} of less than 150 μm , a D_{50} of less than 80
 μm , a D_{10} of less than 40 μm ; and wherein the composition comprises (a) about 0.05%
25 w/w of halobetasol based on the total weight of the composition; (b) a non-aqueous
solvent and; and (c) a propellant; wherein when administering topically to a patient, the
30 topical spray composition does not require further application by hand.

According to one embodiment of the above aspects, the droplet size is measured by Spraytec[®] instrument.

According to another embodiment of the above aspects, the non-aqueous solvent is ethyl alcohol.

5 According to another embodiment of the above aspects, the composition further comprises an emollient.

A twenty fourth aspect of the present invention provides a method of treating a patient having a corticosteroid responsive dermatoses comprising topically administering by spray an effective amount of a touch-free topical spray composition of halobetasol
10 delivered in the form of plurality of droplets, wherein the droplets have a size distribution of D_{90} of less than 150 μm , and wherein the composition comprises (a) about 0.05% w/w of halobetasol based on the total weight of the composition; (b) a non-aqueous solvent and; (c) a propellant; wherein when administering topically to the patient, the topical spray composition does not require further application by hand.

15 A twenty fifth aspect of the present invention provides a method of treating a patient having a corticosteroid responsive dermatoses comprising topically administering by spray an effective amount of a touch-free topical spray composition of halobetasol delivered in the form of plurality of droplets, wherein the droplets have a size distribution of D_{50} of less than 80 μm , and wherein the composition comprises (a) about 0.05% w/w of
20 halobetasol based on the total weight of the composition; (b) a non-aqueous solvent and; (c) a propellant; wherein when administering topically to the patient, the topical spray composition does not require further application by hand.

A twenty sixth aspect of the present invention provides a method of treating a patient having a corticosteroid responsive dermatoses comprising topically administering
25 by spray an effective amount of a touch-free topical spray composition of halobetasol delivered in the form of plurality of droplets, wherein the droplets have a size distribution of D_{10} of less than 40 μm , and wherein the composition comprises (a) about 0.05% w/w of halobetasol based on the total weight of the composition; (b) a non-aqueous solvent and; (c) a propellant; wherein when administering topically to the patient, the topical spray
30 composition does not require further application by hand.

A twenty seventh aspect of the present invention provides a method of treating a patient having a corticosteroid responsive dermatoses comprising topically administering

by spray an effective amount of a touch-free topical spray composition of halobetasol delivered in the form of plurality of droplets, wherein the droplets have a size distribution of D_{90} of less than 150 μm , a D_{50} of less than 80 μm , a D_{10} of less than 40 μm ; and wherein the composition comprises (a) about 0.05% w/w of halobetasol based on the total weight of the composition; (b) a non-aqueous solvent and; (c) a propellant; wherein when
5 administering topically to the patient, the topical spray composition does not require further application by hand.

A twenty eighth aspect of the present invention provides a method of treating a patient having a corticosteroid responsive dermatoses consisting essentially of topically
10 administering by spray an effective amount of a touch-free topical spray composition of halobetasol delivered in the form of plurality of droplets, wherein the droplets have a size distribution of D_{90} of less than 150 μm , and wherein the composition comprises (a) about 0.05% w/w of halobetasol based on the total weight of the composition; (b) a non-aqueous solvent and; (c) a propellant wherein when administering topically to the patient, the
15 topical spray composition does not require further application by hand.

A twenty ninth aspect of the present invention provides a method of treating a patient having a corticosteroid responsive dermatoses consisting essentially of topically administering by spray an effective amount of a touch-free topical spray composition of halobetasol delivered in the form of plurality of droplets, wherein the droplets have a size
20 distribution of D_{50} of less than 80 μm , and wherein the composition comprises (a) about 0.05% w/w of halobetasol based on the total weight of the composition; (b) a non-aqueous solvent and; (c) a propellant wherein when administering topically to the patient, the topical spray composition does not require further application by hand.

A thirtieth aspect of the present invention provides a method of treating a patient
25 having a corticosteroid responsive dermatoses consisting essentially of topically administering by spray an effective amount of a touch-free topical spray composition of halobetasol delivered in the form of plurality of droplets, wherein the droplets have a size distribution of D_{10} of less than 40 μm , and wherein the composition comprises (a) about 0.05% w/w of halobetasol based on the total weight of the composition; (b) a non-aqueous
30 solvent and; (c) a propellant wherein when administering topically to the patient, the topical spray composition does not require further application by hand.

A thirty first aspect of the present invention provides a method of treating a patient having a corticosteroid responsive dermatoses consisting essentially of topically administering by spray an effective amount of a touch-free topical spray composition of halobetasol delivered in the form of plurality of droplets, wherein the droplets have a size distribution of D_{90} of less than 150 μm , a D_{50} of less than 80 μm , a D_{10} of less than 40 μm ; and wherein the composition comprises (a) about 0.05% w/w of halobetasol based on the total weight of the composition; (b) a non-aqueous solvent and; (c) a propellant wherein when administering topically to the patient, the topical spray composition does not require further application by hand.

10 According to another embodiment of the above aspects, the droplet size is measured by Spraytec[®] instrument.

According to another embodiment of the above aspects, the non-aqueous solvent is ethyl alcohol.

15 According to another embodiment of the above aspects, the composition further comprises an emollient.

A thirty second aspect of the present invention provides a touch-free topical spray composition of halobetasol in which the composition is delivered through a dispensing system in the form of plurality of droplets, wherein the composition comprises about 0.05% w/w of halobetasol, a non-aqueous solvent, and a propellant, wherein when administering topically to a patient, the touch-free topical spray composition does not require rubbing in of the composition onto the skin.

According to one embodiment of the above aspect, the composition further comprises an emollient.

25 According to another embodiment of the above aspect, there is provided a method of treating a patient having a corticosteroid responsive dermatoses, comprising topically administering by spray an effective amount of the touch-free composition of halobetasol in which the composition is delivered through a dispensing system in the form of plurality of droplets, wherein the composition comprises about 0.05% w/w of halobetasol, a non-aqueous solvent, and a propellant, wherein when administering topically to a patient, the touch-free topical spray composition does not require rubbing in of the composition onto the skin.

According to another embodiment of the above aspect, there is provided a method of treating a patient having a corticosteroid responsive dermatoses consisting essentially of topically administering by spray an effective amount of the touch-free composition of in which the composition is delivered through a dispensing system in the form of plurality of droplets, wherein the composition comprises about 0.05% w/w of halobetasol, a non-
5 aqueous solvent, and a propellant, wherein when administering topically to a patient, the touch-free topical spray composition does not require rubbing in of the composition onto the skin.

A thirty third aspect of the present invention provides a method of treating a
10 patient suffering from a corticosteroid responsive dermatoses, comprising: topically spraying a spray of a plurality of droplets, wherein the composition comprises about 0.05 %w/w halobetasol, and wherein when the spray is initiated about 3.5 inches from a surface, the spray has a plume angle of about 5° to about 40°.

One of the embodiment of the present invention provides a topical spray system of
15 halobetasol for topical administration to a subject having a corticosteroid responsive dermatosis comprising i) a composition comprising about 0.05% w/w of halobetasol, based on the total weight of the composition and (ii) a dispensing system, wherein the dispensing system delivers the composition to the skin of the subject, and wherein the topical spray system is effective in penetration of the halobetasol into the epidermis or
20 dermis of the skin of the subject where the halobetasol has its effect on the corticosteroid responsive dermatosis.

Another embodiment of the present invention provides a topical spray system of halobetasol for topical administration to a subject having a corticosteroid responsive dermatosis comprising i) a composition comprising about 0.05% w/w of halobetasol,
25 based on the total weight of the composition and (ii) a dispensing system, wherein the dispensing system delivers the composition to the skin of the subject, such that topical spray system exhibits a high level of penetration into the epidermis and/or the dermis of the skin of the subject.

Another embodiment of the present invention provides a topical spray system of
30 halobetasol for topical application to a subject having a corticosteroid responsive dermatosis comprising i) a composition comprising about 0.05% w/w of halobetasol, based on the total weight of the composition (ii) a dispensing system, wherein the

dispensing system delivers the composition to the skin of the subject, and wherein 24 hours after administration to the subject with the topical spray system, more than 10% w/w of halobetasol has penetrated into the epidermis and the dermis based on the total weight of the applied dose. Preferably, more than 15% w/w of halobetasol has penetrated into the epidermis and the dermis based on the total weight of the applied dose. More preferably, more than 20% w/w of halobetasol has penetrated into the epidermis and the dermis based on the total weight of the applied dose. Even more preferably, more than 25% w/w of halobetasol has penetrated into the epidermis and the dermis based on the total weight of the applied dose. Even much more preferably, more than 30% w/w of halobetasol has penetrated into the epidermis and the dermis based on the total weight of the applied dose.

Another embodiment of the present invention provides a method of treating corticosteroid responsive dermatoses in a subject in need thereof comprising topically spraying a composition onto the subject's skin using a dispensing system comprising the composition, wherein the method provides an effective amount of halobetasol at a target site for the corticosteroid responsive dermatoses, wherein the target site is selected from an epidermis layer, a dermis layer, or combination thereof. Preferably, the effective amount of halobetasol in epidermis and dermis is at a concentration of at least 10 times higher than the marketed halobetasol cream formulation.

Another embodiment of the present invention provides a method of penetrating halobetasol into the dermis and/or epidermis of a patient in need thereof, comprising: spraying a composition of halobetasol from a dispensing system onto the skin of the patient, wherein the spraying provides droplets of the composition having a D_{90} of less than 150 μm .

Another embodiment of the present invention provides a method of penetrating halobetasol into skin layers of patient, comprising topically administering to the patient a composition comprising halobetasol using a dispensing system, and wherein the composition comprises about 0.05% w/w of halobetasol based on the total weight of the composition.

Another embodiment of the present invention provides a method of treating skin disorders in a patient in need thereof comprising topically spraying a composition using a dispensing system, wherein upon topically spraying the ratio of amount of halobetasol

retained into the skin layers to the amount of halobetasol remained unabsorbed onto the skin is at least 0.5. The skin layers include stratus corneum, epidermis and dermis.

Another embodiment of the present invention provides a method of treating skin disorders in a patient in need thereof comprising topically spraying a composition using a dispensing system, wherein upon topically spraying the amount of halobetasol retained
5 into the skin layers is at least 10 times higher than the marketed halobetasol cream formulation. The skin layers include stratus corneum, epidermis and dermis.

According to another embodiment of the above aspects, the corticosteroid responsive dermatoses is selected from the group consisting of atopic dermatitis, psoriasis,
10 or both.

A thirty fourth aspect of the present invention provides a touch-free topical spray comprising a pharmaceutical composition which is delivered through a dispensing system, wherein the dispensing system comprises a metered valve assembly comprising a metered valve having a stem connected to an actuator, wherein the actuator is provided with an
15 insert having an orifice diameter in a range of about 0.2 mm to about 1.5 mm.

According to an embodiment of the above aspect, the composition comprises one or more propellants.

According to another embodiment of the above aspect, the composition further comprises one or more emollients and a non-aqueous solvent.

According to another embodiment of the above aspect, the composition comprises
20 halobetasol propionate.

The term “topical,” as used herein, refers to a composition meant for application to the skin, scalp, nail, or mucosal tissue.

The term “spray,” as used herein, means to dispense the composition as a mass or
25 jet of droplets from a dispensing system.

The term “stable,” as used herein, means chemical stability of halobetasol in a dispensing system in both upright and inverted positions, wherein not more than 5% w/w of total related substances are formed on storage at 40°C and 75% relative humidity or at 25°C and 60% relative humidity for a period of at least one month to the extent necessary
30 for sale and use of composition. More particularly, the compositions remain stable for at

least three months. Even more particularly, the compositions remain stable for at least six months.

The term “halobetasol,” as used herein, includes halobetasol and its salts, esters, polymorphs, hydrates, solvates, prodrugs, chelates, and complexes. The preferred ester of halobetasol is halobetasol propionate. The composition of the present invention comprises halobetasol in an amount from about 0.01% w/w to about 0.5% w/w based on the total weight of the composition. In particular, the composition of the present invention comprises halobetasol in an amount of about 0.05% w/w based on the total weight of the composition.

The term “bulk solution,” as used herein, means a solution without a propellant. The solution comprises halobetasol, non-aqueous solvent and optionally an emollient.

In the present invention, the ratio of the bulk solution to the propellant ranges from about 1:20 to about 20:1, particularly from about 1:10 to about 10:1, more particularly about 1:1.

The term “substantially anhydrous,” as used herein means that the content of free water in the composition is not more than 40% w/w, particularly not more than 30% w/w, more particularly not more than 15% w/w, based on the total weight of the composition.

The composition of the present invention is microbiologically stable.

The term “microbiologically stable,” as used herein means not more than 200 of the total aerobic microbial count (cfu/g), not more than 20 of the total combined yeast/moulds count (cfu/g), and absence of *Staphylococcus aureus* (per g) and *Pseudomonas aeruginosa* (per g), for at least one month to the extent necessary for sale and use of composition on storage at 40°C and 75% relative humidity or at 25°C and 60% relative humidity. More particularly, the compositions remain microbiologically stable for at least three months. Even more particularly, the compositions remain microbiologically stable for at least six months.

The term “D₅₀,” as used herein refers to the diameter of droplet for which 50% of the total liquid volume of sample consists of droplets of a smaller diameter (µm), also known as the mass median diameter. The present invention includes droplets having D₅₀ of less than about 80 µm. Particularly, the droplets have a D₅₀ of less than about 50 µm. More particularly, the droplets have a D₅₀ of less than about 30 µm.

The term “D₉₀,” as used herein refers the diameter of droplet for which 90% of the total liquid volume of sample consists of droplets of a smaller diameter (μm). The present invention includes droplets having D₉₀ of less than about 150 μm. Particularly, the droplets have a D₉₀ of less than about 100 μm. More particularly, the droplets have a D₉₀ of less than about 50 μm.

The term “D₁₀,” as used herein refers to the diameter of droplet for which 10% of the total liquid volume of sample consists of droplets of a smaller diameter (μm). The present invention includes droplets having D₁₀ the droplets are having a D₁₀ of less than 40 μm. Particularly, the droplets have a D₁₀ of less than 30 μm. More particularly, the droplets have a D₁₀ of less than 20 μm.

The term “span,” as used herein, refers to the measurement of the width of the distribution. The smaller the value, the narrower the distribution. Span herein is calculated as $(D_{90}-D_{10})/D_{50}$.

The D₅₀, D₉₀, D₁₀, are measured by using a Spraytec[®] instrument in which the distance between the actuator of the dispensing system and laser was kept about 4 inch.

The term “about” as used herein, refers to any value which lies within the range defined by a variation of up to ±10% of the value.

The actuation force value ranges from about 10 N to about 40 N, in particular actuation force value ranges from about 20 N to about 30 N. The term “actuation force value,” refers to any the force that presses the actuator to deliver the composition through its orifice.

The touch-free topical spray composition of halobetasol of the present invention when dispensed from a dispensing system in the form of droplets forms a spray pattern which does not substantially change. This illustrates that the composition is not showing any running of or dripping upon its delivery to the desired site and thus there is no need to rub-in the composition thereby leading to ease of application and enhanced patient compliance. The term “substantially,” as used herein means refers to any value which lies within the range defined by a variation of up to ± 25% of the value. The values of the D_{max}, D_{min}, and the ovality of the spray pattern formed from a distance of 3.5 inches up to 4 actuations given one after another on the same site with a single actuation delivering an average shot weight of ranging from about 90 mg to about 110 mg of the composition do not change by ± 25% of the initial values.

Alternatively, the values of the $D_{\max}$, $D_{\min}$, and the ovality of the spray pattern formed from a distance of 3.5 inches up to 5 actuations given one after another on the same site with a single actuation delivering an average shot weight of ranging from about 65 mg to about 95 mg of the composition do not change by $\pm 25\%$ of the initial values.

5 Spray pattern is characterized by $D_{\max}$, $D_{\min}$, and ovality. The term “ovality,” as used herein, refers to the ratio of $D_{\max}$ and $D_{\min}$. The ovality of the spray pattern indicates whether the spray is symmetrical.

10 The term “ $D_{\max}$,” as used herein, refers to the largest chord, in mm, that can be drawn within the spray pattern that crosses the COMw (*i.e.*, center of mass of the spray pattern) in base units.

 The term “ $D_{\min}$,” as used herein, refers to the smallest chord, in mm, that can be drawn within the spray pattern that crosses the COMw in base units.

 The term “COMw,” as used herein, refers to the center of mass of the detected spray pattern, where each pixel's intensity is taken into account.

15 The term “plume angle,” as used herein, refers to the angle of the emitted plume measured from the vertex of the spray cone and spray nozzle. It is measured by using SprayVIEW[®] instrument and it ranges from about 5° to about 40°. In particular, it ranges from about 10° to about 30°, more particularly, it ranges from about 15° to about 25° when measured at a distance of about 3.5 inches.

20 The term “plume width,” as used herein, refers to the width of the plume at a given distance from the spray nozzle. It is measured by using SprayVIEW[®] instrument and it ranges from about 10 mm to about 65 mm, in particular from about 15 mm to about 50 mm, more particularly from about 20 mm to about 40 mm when measured at a distance of about 3.5 inches.

25 The term “emollient,” as used herein refers to a substance that helps to retain the skin moisture and also helps to control the rate of evaporation and the tackiness of the composition. It also helps to soften the thickened epidermis of the psoriatic plaques. Additionally, emollients provide a softening or soothing effect on the skin surface. Suitable examples of emollients are selected from the group consisting of fatty acid
30 triglycerides such as mixture of caprylic and capric triglycerides (Crodamol[™] GTCC-LQ, Miglyol[™], Captex[™], Labrafac[™], Lipophile[™] WL), palmitic triglyceride, oleic triglyceride, caprylic triglyceride, capric triglyceride, and linoleic triglyceride; fatty acid

esters such as isopropyl myristate, isopropyl palmitate, dibutyl adipate, and dibutyl phthalate; polyhydric alcohols such as propylene glycol, butylene glycol, polyethylene glycol, glycerol, and sorbitol; fatty acids such as oleic acid and stearic acid; oils such as mineral oil, lanolin oil, coconut oil, cocoa butter, olive oil, jojoba oil, and castor oil; cyclomethicone; hydrogenated lanolin; waxes; lecithin; or mixtures thereof. Preferably, the emollient of the present invention is selected from the group consisting of fatty acid triglycerides, fatty acid esters, and polyhydric alcohols. More preferably, the emollient of the present invention is isopropyl palmitate. The emollient used in the present invention ranges from about 1% w/w to about 45% w/w based on the total weight of the composition. Particularly, the emollient used in the present invention ranges from about 1% w/w to about 30% w/w based on the total weight of the composition. More particularly, the emollient used in the present invention ranges from about 1% w/w to about 20% w/w based on the total weight of the composition. Even more particularly, the emollient used in the present invention ranges from about 1% w/w to about 10% w/w based on the total weight of the composition. Even more particularly, the emollient used in the present invention ranges from about 6% w/w to about 8% w/w based on the total weight of the composition.

The term “non-aqueous solvent,” as used herein refers to the solvent used to dissolve halobetasol. Suitable non-aqueous solvents are selected from the group consisting of ethyl alcohol, isopropyl alcohol, propylene glycol, butanediol, pentanediol, hexanediol, triethylene glycol, tetraethylene glycol, dipropylene glycol, dibutylene glycol, glycerin, dimethyl isosorbide, tetrahydro furfuryl alcohol polyethylene glycol ether, N-methyl-2-pyrrolidone, 1-methyl-2-pyrrolidinone, dimethylsulfoxide, dimethylacetamide, lactic acid, glycolic acid, methylene chloride, methyl-ethyl-ketone, ethyl acetate, methylene dimethyl ether, polysorbates, or mixtures thereof. In particular, ethyl alcohol is dehydrated ethyl alcohol. The non-aqueous solvent used in the present invention ranges from about 1% w/w to about 95% w/w based on the total weight of the composition. Particularly, the non-aqueous solvent is present from about 10% w/w to about 70% w/w based on the total weight of the composition. More particularly, the non-aqueous solvent is present from about 20% w/w to about 50% w/w based on the total weight of the composition. Even, more particularly, non-aqueous solvent is present from about 38% w/w to about 43% w/w based on the total weight of the composition.

The term "propellant," as used herein refers to the substance that helps in propelling the composition out of the container. Suitable examples of propellants are selected from the group consisting of conventional, non-ozone depleting hydrocarbon propellants. These include propane n-butane, isobutane, cyclopropane, liquefied petroleum gas, 1,1,1,2- tetrafluorethane, 1,1,1,2,3,3,3- heptafluoropropane, 1,1- difluoroethane, 1,1,1,3,3,3- hexafluoropropane, or mixtures thereof. Fluorocarbon gas may also be used as a propellant. The propellant is used in the present invention ranges from about 5% w/w to about 95% w/w based on the total weight of the composition. Particularly, the propellant is used in the present invention ranges from about 20% w/w to about 80% w/w based on the total weight of the composition. More particularly, the propellant is used in the present invention ranges from about 30% w/w to about 70% w/w based on the total weight of the composition.

The touch-free topical spray composition of the present invention further comprises solubilizers, permeation enhancers, film-formers, plasticizers, antioxidants, pH-adjusting agents, or mixtures thereof.

The solubilizer is a substance that aids in the dissolution or dispersion of halobetasol in the composition. Suitable solubilizers are selected from the group consisting of polyhydric alcohols such as propylene glycol and polyethylene glycol; fatty acids such as oleic acid and stearic acid; non-ionic and ionic surfactants such as polyoxyethyl-sorbitan-fatty acid esters such as polysorbates, ethers of sugars, ethoxylated fatty alcohols, sodium lauryl sulfate, taurocholic acid, lecithin and Labrasol™; vitamin E; vitamin E TPGS (tocopheryl polyethylene glycol 1000 succinate); caprylic triglyceride; capric triglyceride; or combinations thereof.

The permeation enhancer is a substance used to enhance the penetration rate of halobetasol through the skin. Suitable permeation enhancers are selected from the group consisting of lipophilic solvents such as dimethyl sulfoxide and dimethyl formamide; non-ionic and ionic surfactants such as polyoxyethyl-sorbitan-fatty acid esters such as polysorbates, ethers of sugars, ethoxylated fatty alcohols, sodium lauryl sulfate, taurocholic acid, lecithin and labrasol; fatty acid esters such as isopropyl myristate and isopropyl palmitate; fatty acids such as oleic acid and stearic acid; polyhydric alcohols such as propylene glycol and polyethylene glycol *e.g.*, polyethylene glycol 400; Transcutol™; essential oils *e.g.*, menthol; capric/caprylic triglycerides; or combinations thereof.

The film-former is a substance that forms a stable film on a topical surface when applied. Suitable film-formers are selected from the group consisting of acrylic polymers or copolymers such as methacrylic acid copolymers; cellulose derivatives such as cellulose acetate, hydroxypropyl methyl cellulose, hydroxy ethyl cellulose, methyl cellulose and ethyl cellulose; polyvinyl acetate; polyvinyl alcohol; povidone; povidone vinyl acetate; or combinations thereof. These film-formers can partially dissolve on exposure to moisture from the skin or air, the dissolution resulting in the formation of a porous film. This porosity can be enhanced by including additional water-soluble additives. The water-soluble additive is preferably propylene glycol, sodium lauryl sulphate, poloxamers, polyoxyl 35 castor oil, polyoxyl 40 hydrogenated castor oil, cetomacrogol, polyethylene glycol, transcitol, or combinations thereof.

The plasticizer is a substance that aids the composition in forming a flexible, adherent film on the skin. Suitable plasticizers are selected from the group consisting of citric acid esters, dimethyl isosorbide, castor oil, propylene glycol, polyethylene glycol, glycerol, oleic acid, citric acid, phosphate esters, fatty acid esters, glycol derivatives, hydrocarbons and their derivatives, adipic acid, butanediol polyesters, diethyl phthalate, dibutyl phthalate, chlorinated paraffins, or combinations thereof.

Suitable antioxidants are selected from the group consisting of butylated hydroxyl anisole, butylated hydroxy toluene, sodium metabisulfite, ascorbic acid, ascorbyl palmitate, thiourea, acetylcysteine, dithiothreitol, cysteine hydrochloride, propyl gallate, tocopherol, or combinations thereof.

Suitable pH-adjusting agents are selected from the group consisting of pharmaceutically acceptable organic or inorganic acids or bases such as sodium hydroxide, tromethamine, hydrochloric acid, citric acid, inorganic oxides, inorganic salts of weak acids, or combinations thereof.

In the present invention, the dispensing system comprises a pressurized container and a metered valve assembly as described in Figure 2. The dispensing system may further comprise a dust cap or protective cap which is fitted onto the container to shield the contents of the container from the outside environment and undesirable pressing of actuator. The metered valve assembly comprises a mounting cup, a housing, a spring, a dip tube, a metered valve having stem connected to an actuator. The mounting cup can

have an internal (Int.) gasket and an external (Ext.) gasket. Alternatively, the metered valve can have a metering chamber.

As described in Figure 2, the metered valve has a housing (6) which combines and accommodate the valve components from dip tube (7) to stem (1). Before actuation of the valve stem (1), the valve is at rest. The filling paths in the inner section of the valve stem (1) bridge the flexible section of housing, allowing free transfer through the dip tube (7) of the contents of the housing (6) and the bulk contents of the container. On actuation, the actuator depresses the valve stem (1), brings the internal cylindrical portion of the stem (1) into a sealing contact with the housing (6).

External gasket (3) in mounting cup (4) is meant for perfect sealing valve with the container. At this stage the exit hole of the stem (1) is still covered by the internal gasket (2). The metered volume to be delivered is isolated from the halobetasol composition of the container. Continued depression of the stem (1) moves the exit hole in the stem in to the isolated volume of housing (6).

The composition in the housing (6) contains a significant proportion of a volatile propellant gas in thermal equilibrium. When the exit hole enters the housing (6), the contents of the housing (6) are connected to the atmosphere, which is at a substantially lower pressure. The liquefied propellant boils vigorously to restore equilibrium and in so doing evacuates the halobetasol composition from the housing (6).

When the depressing force on the stem is removed the spring (5) returns the stem (1) back towards the rest position. The exit orifice in the stem (1) is first covered by the wall of the internal gasket (2), sealing off the flow-path to atmosphere. Further travel allows the filling paths in the inner section of the stem (1), to bridge the flexible section of the housing (6).

The residual contents of the housing (6) are typically propellant vapour which are at low temperature and pressure. As the contents of the container are at higher pressure than the chamber, liquid is forced in to the housing (6), via the filling paths in the inner section of the stem.

The metered valve dispenses a metered quantity of composition with each actuation of the actuator. The metered quantity avoids under-dosing or overdosing that may lead to undesirable side effects.

The distance between the base of actuator to the place where it fits on to the wall of the stem is about 0.5 mm to about 10 mm, particularly 7.8 mm.

Specifically, in the present invention, the pressurized container has a capacity of 50 g and the metered valve has a capacity of 150 μ L. Further, the actuator is provided with an insert having an orifice diameter of about 0.5 mm and the actuator has a diameter of about 13.9 mm with a height of about 14.0 mm.

The dimensions of the actuator and insert determine the spray pattern characteristics such that the spray on expulsion forms a focused coverage area and also ensures that the size of droplets are sufficiently small to form a uniform spray with a characteristic of 'no-running' and yet sufficiently large to ensure that the droplets do not form a fine mist that can be inhaled.

The metered valve dispenses a metered quantity of composition with each actuation of the actuator. The metered quantity avoids under-dosing or overdosing that may lead to undesirable side effects. The dispensing system upon each actuation delivers an average shot weight in a range of from about 50 mg to about 150 mg. In particular, the average shot weight ranges from about 75 mg to about 125 mg. More particularly, the average shot weight ranges from about 90 mg to about 110 mg. The dispensing system of the present invention ensures consistent shot weight upon each actuation. The dispensing system of the present invention further ensures that with each actuation, dose uniformity is maintained. The dispensing system of the present invention also complies with other USP regulatory requirements including the leakage test.

Containers can be made from materials selected from the group consisting of stainless steel, aluminum, plastic, and glass. The plastic container can be made up of high density polyethylene (HDPE). The containers can be coated with an inert inner lining of epoxy-phenolic resins, epoxy-urea-formaldehyde resins, polytetrafluoroethylene (PTFE), perfluoroethylenepropylene (PFEP), perfluoroalkoxyalkane (PFA), ethylene tetrafluoroethylene (ETFE), polyvinylidene fluoride (PVDF), chlorinated ethylene tetrafluoroethylene, or another coating treatment that creates a barrier to chemical interaction between the composition and the container. The dust cap can be made of any suitable material such as plastic or metal.

The following examples represent various embodiments according to the present invention. The examples are given solely for the purpose of illustration and are not to be

construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

EXAMPLES

Example 1

Ingredients	Quantity (% w/w)
Halobetasol propionate	0.05
Ethyl alcohol	42.65
Isopropyl palmitate	7.30
Liquefied petroleum gas	50.00

5 Procedure:

1. Halobetasol propionate was dissolved into a portion of ethyl alcohol with stirring.
2. Isopropyl palmitate was added while stirring into the solution of step 1.
3. The remaining quantity of ethyl alcohol was added into the solution of step 2 and mixed.
- 10 4. The solution of step 3 was filled into an aluminum container with an inert liner.
5. The container of step 4 was then crimped with a metered valve as described in Figure 2.
6. Liquefied petroleum gas was then charged into the container of step 5.
7. The container of step 6 was then fitted with an actuator which is then fitted with a dust
15 cap to form halobetasol spray.

Example 2

Ingredients	Quantity (% w/w)
Halobetasol propionate	0.05
Ethyl alcohol	42.65
Isopropyl palmitate	7.30
Isobutane	50.00

Procedure:

1. Halobetasol propionate is dissolved into a portion of ethyl alcohol with stirring.
2. Isopropyl palmitate is added while stirring into the solution of step 1.
- 20 3. The remaining quantity of ethyl alcohol is added into the solution of step 2 and mixed.
4. The solution of step 3 is filled into an aluminum container with an inert liner.

5. The container of step 4 is then crimped with a metered valve as described in Figure 2.
6. Isobutane is charged into the filled container of step 5.
7. The container of step 6 is then fitted with an actuator which is then fitted with a dust cap to form halobetasol spray.

5 **Example 3**

Ingredients	Quantity (% w/w)
Halobetasol propionate	0.05
Ethyl alcohol	20.00
Caprylic and capric triglycerides (Crodamol™ GTCC-LQ)	29.95
Isobutane	50.00

Procedure:

1. Halobetasol propionate is dissolved into a portion of ethyl alcohol with stirring.
2. Crodamol™ GTCC-LQ is added while stirring into the solution of step 1.
3. The remaining quantity of ethyl alcohol is added into the solution of step 2 and mixed.
- 10 4. The solution of step 3 is filled into an aluminum container with an inert liner.
5. The container of step 4 is then crimped with a metered valve as described in Figure 2.
6. Isobutane is then charged into the container of step 5.
7. The container of step 6 is then fitted with an actuator which was then fitted with a dust cap to form halobetasol spray.

15 **Example 4**

Ingredients	Quantity (% w/w)
Halobetasol propionate	0.05
Ethyl alcohol	20.00
Caprylic and capric triglycerides (Crodamol™ GTCC-LQ)	29.95
Liquefied petroleum gas	50.00

Procedure:

1. Halobetasol propionate is dissolved into a portion of ethyl alcohol with stirring.
2. Crodamol™ GTCC-LQ is added while stirring into the solution of step 1.
3. The remaining quantity of ethyl alcohol is added into the solution of step 2 and mixed.
- 20 4. The solution of step 3 is filled into an aluminum container with an inert liner.

5. The container of step 4 is then crimped with a metered valve as described in Figure 2.
6. Liquefied petroleum gas is then charged into the container of step 5.
7. The container of step 6 is then fitted with an actuator which is then fitted with a dust cap to form halobetasol spray.

5 **Example 5**

Ingredients	Quantity (% w/w)
Halobetasol propionate	0.05
Ethyl alcohol	52.65
Isopropyl palmitate	7.30
Liquefied petroleum gas	40.00

Procedure:

1. Halobetasol propionate is dissolved into a portion of ethyl alcohol with stirring.
2. Isopropyl palmitate is added while stirring into the solution of step 1.
3. The remaining quantity of ethyl alcohol is added into the solution of step 2 and mixed.
- 10 4. The solution of step 3 is filled into an aluminum container with an inert liner.
5. The container of step 4 is then crimped with a metered valve as described in Figure 2.
6. Liquefied petroleum gas is then charged into the container of step 5.
7. The container of step 6 is then fitted with an actuator which is then fitted with a dust cap to form halobetasol spray.

15 **Example 6**

Ingredients	Quantity (% w/w)
Halobetasol propionate	0.05
Ethyl alcohol	32.65
Isopropyl palmitate	7.30
Isobutane	60.00

Procedure:

1. Halobetasol propionate is dissolved into a portion of ethyl alcohol with stirring.
2. Isopropyl palmitate is added while stirring into the solution of step 1.
3. The remaining quantity of ethyl alcohol is added into the solution of step 2 and mixed.
- 20 4. The solution of step 3 is filled into an aluminum container with an inert liner.
5. The container of step 4 is then crimped with a metered valve as described in Figure 2.

6. Isobutane is then charged into the container of step 5.
7. The container of step 6 is then fitted with an actuator which is then fitted with a dust cap to form halobetasol spray.

Example 7

Ingredients	Quantity (% w/w)
Halobetasol propionate	0.05
Ethyl alcohol	32.65
Isopropyl myristate	7.30
n-Butane	60.00

- 5 Procedure:
 1. Halobetasol propionate is dissolved into a portion of ethyl alcohol with stirring.
 2. Isopropyl palmitate is added while stirring into the solution of step 1.
 3. The remaining quantity of ethyl alcohol is added into the solution of step 2 and mixed.
 4. The solution of step 3 is filled into an aluminum container with an inert liner.
 - 10 5. The container of step 4 is then crimped with a metered valve as described in Figure 2.
 6. n-Butane is then charged into the container of step 5.
 7. The container of step 6 is then fitted with an actuator which is then fitted with a dust cap to form halobetasol spray.

Example 8

Ingredients	Quantity (% w/w)
Halobetasol propionate	0.05
Ethyl alcohol	52.65
Isopropyl myristate	7.30
Liquefied petroleum gas	40.00

- 15 Procedure:
 1. Halobetasol propionate is dissolved into a portion of ethyl alcohol with stirring.
 2. Isopropyl myristate is added while stirring into the solution of step 1.
 3. The remaining quantity of ethyl alcohol is added into the solution of step 2 and mixed.
 4. The solution of step 3 is filled into an aluminum container with an inert liner as
 - 20 described in Figure 2.
 5. The container of step 4 is then crimped with a metered valve.

6. Liquefied petroleum gas is then charged into the container of step 5.
7. The container of step 6 is then fitted with an actuator which is then fitted with a dust cap to form halobetasol spray.

Example 9

Ingredients	Quantity (% w/w)
Halobetasol propionate	0.05
Ethyl alcohol	32.65
Isopropyl palmitate	7.30
Isobutane	60.00

5 Procedure:

1. Halobetasol propionate is dissolved into a portion of ethyl alcohol with stirring.
2. Isopropyl myristate is added while stirring into the solution of step 1.
3. The remaining quantity of ethyl alcohol is added into the solution of step 2 and mixed.
4. The solution of step 3 is filled into an aluminum container with an inert liner as
10 described in Figure 2.
5. The container of step 4 is then crimped with a metered valve.
6. Isobutane is then charged into the container of step 5.
7. The container of step 6 is then fitted with an actuator which is then fitted with a dust cap to form halobetasol spray.

15 **Example 10**

Ingredients	Quantity (% w/w)
Halobetasol propionate	0.05
Ethyl alcohol	19.95
Propylene glycol	30.00
Isobutane	50.00

Procedure:

1. Halobetasol propionate is dissolved into a portion of ethyl alcohol with stirring.
2. Propylene glycol is added while stirring into the solution of step 1.
3. The remaining quantity of ethyl alcohol is added into the solution of step 2 and mixed.
- 20 4. The solution of step 3 is filled into an aluminum container with an inert liner.
5. The container of step 4 is then crimped with a metered valve as described in Figure 2.

6. Isobutane is then charged into the container of step 5.
7. The container of step 6 is then fitted with an actuator which is then fitted with a dust cap to form halobetasol spray.

Example 11

Ingredients	Quantity (% w/w)
Halobetasol propionate	0.05
Ethyl alcohol	19.95
Propylene glycol	30.00
Liquefied petroleum gas	50.00

- 5 Procedure:
1. Halobetasol propionate is dissolved into a portion of ethyl alcohol with stirring.
 2. Propylene glycol is added while stirring into the solution of step 1.
 3. The remaining quantity of ethyl alcohol is added into the solution of step 2 and mixed.
 4. The solution of step 3 is filled into an aluminum container with an inert liner.
 - 10 5. The container of step 4 is then crimped with a metered valve as described in Figure 2.
 6. Liquefied petroleum gas is then charged into the container of step 5.
 7. The container of step 6 is then fitted with an actuator which is then fitted with a dust cap to form halobetasol spray.

Shot weight per actuation (Valve delivery)

- 15 The shot weight of the halobetasol spray as per Example 1 was determined for five dispensing systems with three sprays made for each dispensing system. The average of these 15 sprays was taken and found to be 103 mg per actuation. Further, when a target of 103 mg per actuation was set, the maximum % difference of individual dispensing system was determined to be 3.7 and the mean % difference of dispensing system was determined
- 20 to be 2. The data ensures consistent shot weight upon each actuation with minimum variation.

Delivered Dose Uniformity (DDU)

- The Delivered Dose Uniformity (DDU) of the halobetasol spray prepared as per Example 1 was determined. Twenty sprays were made (10 from beginning and 10 from
- 25 end of the doses) from each dispensing system and the amount of halobetasol propionate

was determined in each spray. The same procedure was performed on 10 dispensing systems. The halobetasol content in the mean of beginning 10 sprays and end 10 sprays were determined to be 99.2% and 101.6% respectively. The mean halobetasol content from these 20 determinations was found to be 100.4%. The results ensure uniform delivery of the halobetasol upon each actuation with minimum variation.

Leakage Test

12 aerosol containers were selected and the weight of each container to the nearest mg (W1) was noted. The date and time to the nearest half hour were recorded and the containers were charged into a humidity chamber maintained at $25\pm 2^{\circ}\text{C}/60^{\circ}\pm 5$ R.H. by keeping each container in upright position for not less than 3 days (not less than 72 hours). The containers were removed from the humidity chamber and date and time to the nearest half hour at the time of removal from the humidity chamber were recorded. The weight of each container (W2) was noted to the nearest mg. The time T, in hours, was determined during which the containers were under test.

The leakage rate was calculated, in mg per year, of each container taken by the formula:

$$\text{Leakage rate (mg/year)} = 365 \times 24 \times (W1 - W2) / T$$

Where,

W1 = weight of the container (in mg)

W2 = weight of the container after leakage test (in mg)

T = Time point (in hours) for which the leakage test has been carried out.

All the containers were kept in a freezer for chilling to reduce the internal pressure for about 15 minutes. Each container was cut and all the contents of the container were removed. The container was thoroughly washed with methanol. All associated parts of container were retained as a unit and dry them in an air oven at 100°C for about 5 minutes to ensure complete evaporation of methanol. The containers were cooled to room temperature and the weight of each empty container (as a unit) (W3) was recorded to the nearest mg. The net fill weight was determined as $W1 - W3$ for each container.

The leakage rate (% year) was calculated using the following formula:

Leakage rate (% of net fill weight/year) = Leakage rate (mg/year) x 100/W1-W3

Average leakage rate (% of net fill weight/year) = Sum of leak rate of each
containers/Number of containers

where,

5 W1-W3= net fill weight (in mg)

W1= weight of the container (in mg)

W2 = weight of the container after leakage test (in mg)

T= Time point (in hours) for which the leakage test has been carried out.

The Average % leakage rate was determined to be 0.9 and Maximum % Leakage /
10 year of individual container was determined to be 1.1. The results complied with the USP
limits.

Stability Data

The halobetasol spray of Example 1 was stored at a temperature of 40°C and a
relative humidity (R.H.) of 75% for a period of three months and six months in both
15 upright and inverted positions of the dispensing systems, and analyzed for halobetasol
propionate content by an HPLC method. The results of the analysis are represented in
Table 1.

Table 1: Stability Data for the Halobetasol Spray as per Example 1

Time	Assay (%)		Related substances (% w/w)	
	Upright	Inverted	Upright	Inverted
Initial	99.7		Not detected	
3 months (40°C/75% R.H.)	97.8	97.9	0.19	0.21
6 months (40°C/75% R.H.)	99.0	97.8	0.35	0.34

From the above data, it is clear that the halobetasol composition remains stable for
20 six months when stored at accelerated conditions of 40°C/75% R.H.

Microbial Test

The halobetasol spray as per Example 1 was stored at a temperature of 40°C and a relative humidity (R.H.) of 75% for a period of six months, and analyzed for microbial count (Table 2).

5 **Table 2: Microbial Test**

	Total aerobic microbial count (cfu/g)	Total combined yeast/moulds count (cfu/g)	Staphylococcus aureus (per g)	Pseudomonos aeruginosa (per g)
Initial	Less than 10	Less than 10	Absent	Absent
6 months (40°C/75% R.H.)	Less than 10	Less than 10	Absent	Absent

From the above data, it is clear that the halobetasol composition remains microbiologically stable for six months when stored at accelerated conditions of 40°C/75% R.H.

Internal pressure

10 The internal pressure of halobetasol composition of Example 1 was found to be 80 psig.

Ease of Application

The touch-free topical spray composition of halobetasol of the present invention when dispensed from a dispensing system in the form of droplets form a spray pattern
 15 which did not substantially change upon its delivery to the desired site. This illustrates that the composition is not showing any running of or dripping and there is no need to rub-in, thereby leading to ease of application. It was further observed that the specific characteristics of the halobetasol spray of the present invention such as droplet size and specific gravity are responsible for this surprising result.

20 The halobetasol spray as per Example 1 was sprayed at a distance of 3.5 inches onto a surface such as Whatman filter paper fixed on a wall. The angle between the paper and spray container was kept 90°C. Four actuations one after another on the same surface were made by keeping a gap 1-2 seconds and a picture of the formed spray pattern was taken initially after four actuations, and after five minutes. The average shot weight for
 25 five actuations was found to be 102 mg. Similar experiment was done with Clobex® spray wherein the average shot weight for five actuations was 104 mg.

From these pictures, the values for $D_{\max}$ and $D_{\min}$ were recorded initially and after five minutes. The value for ovality was also calculated initially and after five minutes. These pictures are herein presented in Figure 3 and the data is shown in Table 3.

Table 3: $D_{\max}$, $D_{\min}$, and ovality of the spray pattern of halobetasol spray as per

5 **Example 1**

Parameter	Initial	After 5 minutes
$D_{\max}$ (mm)	44.0	50.0
$D_{\min}$ (mm)	41.0	45.0
Ovality	1.07	1.11

From this data, it is clear that the values of $D_{\max}$, $D_{\min}$, and ovality remain substantially same after 5 minutes for halobetasol spray as per Example 1 of the present invention. The same has been illustrated in Figure 3. An unusual, non-oval, wide spray pattern was noted with Clobex[®] spray which illustrated the running of initially as well as after five minutes. It was noted that Clobex[®] spray starts to drip off even with a single application.

Droplet size

The droplet size of Halobetasol spray of Example 1 was determined for three sprays with an average shot weight of 101.6 mg in which initial 6 sprays were used for priming. Similarly, the droplet size of Clobex[®] spray was determined for four sprays with an average shot weight of 104 mg in which initial 4 sprays were used for priming. The droplet size was determined by using a Spraytec[®] instrument in which the distance between the actuator and laser was kept at 4 inch. Data were collected for D_{10} , D_{50} , D_{90} , and % <10 μm and is shown in Table 4.

20 **Table 4: Droplet size of Halobetasol spray of Example 1 and Clobex[®] spray**

Droplet Size	Example 1 (Mean of 3 sprays)	Clobex [®] Spray (Mean of 4 sprays)
$D(10)$ (μm)	9.664	48.13
$D(50)$ (μm)	18.60	96.17
$D(90)$ (μm)	33.99	188.95
Span	1.308	1.47
% <10 μm	11.17	0.02

Specific gravity

Specific gravity was measured by using a relative density apparatus. The specific gravity of the bulk solution of Example 1 was found to be 0.794 g/mL at 25°C. The

specific gravity of the final composition was found to be 0.634g/mL considering the specific gravity of liquefied petroleum gas as 0.5277 g/mL at 25°C. The specific gravity of Clobex[®] spray composition was found to be 0.8425 g/mL at 25°C.

Plume geometry

5 The plume geometry of Halobetasol spray of Example 1 was determined for three sprays with an average shot weight of 103.4 mg in which initial 6 sprays were used for priming. Similarly, the plume geometry of Clobex[®] spray was determined for three sprays with an average shot weight of 104 mg in which initial five sprays were used for priming. The plume geometry of Halobetasol spray of Example 1 and Clobex[®] Spray was
10 determined by SprayVIEW[®] with instrument parameters of velocity =70mm/sec, acceleration=3000mm/sec², frame=250, frame rate=500 frames/sec, stroke length=3.6mm, and hold time=360ms. Distance between the actuator orifice and laser was kept 3.5 inch. Plume geometry is characterised by the plume angle and plume width and is provided in Table 5.

15 **Table 5: Plume geometry of Halobetasol spray of Example 1 and Clobex[®] spray**

Parameter	Halobetasol spray (Mean of 3 sprays)	Clobex [®] Spray (Mean of 3 sprays)
Plume angle	17.9°	44.8°
Width (mm)	27.97	73.47

The plume angle as well as plume width herein depicts the coverage area. A smaller plume angle and plume width observed with the halobetasol spray of the present invention illustrates the focused coverage area whereas a broader plume angle and plume width observed with the Clobex[®] spray illustrates the wider coverage area.

20 **In-vitro Permeation Studies**

The *in-vitro* skin permeation studies were performed on halobetasol spray of Example 1 (halobetasol propionate 0.05% w/w) and halobetasol cream formulation manufactured by Perrigo[®] (halobetasol propionate 0.05% w/w) using a Franz diffusion cell (FDC). For this, human cadaver skin from two different donors and 3 FDCs for each formulation were
25 used. The following parameters were evaluated, amount of: analyte un-absorbed on skin through surface wash, analyte in stratum corneum through tape stripping, analyte absorbed in epidermis, analyte absorbed in dermis. Analysis was carried out with an HPLC method.

Before in vitro skin permeation test skin integrity was checked by electrical resistance method using precision component analyzer (LCR meter). Following parameters were set on Precision Component Analyzer, 1) Frequency: 1000 Hz (1 KHz), 2) AC databridge: 300 mV in parallel circuit mode.

- 5 Normal saline solution was filled in donor chamber. One electrode was inserted through sampling arm into centre of receptor chamber and another electrode was placed in saline solution over skin in donor chamber. The resistance values observed in $K\Omega$ or Ω were noted.

- 10 After skin integrity test, receptor solution was filled into receptor chamber. The assembly was kept on magnetic stirrer and heating circulator bath were switched ON. The skin was equilibrated until temperature on skin surface reaches at $32 \pm 1^\circ\text{C}$. Prior to dose application on skin surface, pre-dose sample (0.300 mL) was collected from each FDC and the receptor solution was replaced with stock receptor solution. For application of spray formulation, dispensing tube with actuator was placed on spray nozzle of can. Donor
15 chamber of FDCs were occluded with parafilm before application of spray formulation. The dispensing tube was inserted into donor chamber through parafilm and single spray stroke were dispensed gently. The actual amount of halobetasol propionate in topical spray formulation was 50000ng (in single spray). The parafilm were removed from the donor chamber after 10 minute of spray formulation application and were dipped into 5 mL of
20 methanol. Similarly 100 μL of cream formulation was applied using positive displacement pipettes (here donor chamber were left unoccluded). The actual amount of halobetasol propionate in cream formulation was 47362 ng (in 100 μL of cream).

- 25 At each sampling time point, 0.300 mL of receptor solution were removed from centre of receptor chamber using a dosing syringe and was replaced with fresh stock of receptor solution up to the mark on the sampling arm. At the end of the 24 hour duration, the surface of the skin was washed with 1 mL, five times (5 mL) in succession, with methanol to collect un-absorbed formulation from the skin surface and was pooled. These surfaces washed samples were further diluted two times with receptor solution before analysis.

30 **In vitro permeation test method:**

Apparatus: Franz diffusion cells – 20 mL; Sampling time points: Predose, 1 h, 22 h and 24 h ; Sample aliquot: 0.300 mL at each sampling time point; Heating circulator

- bath temperature: $40^{\circ}\text{C} \pm 1.0^{\circ}\text{C}$; Temperature on membrane surface: $32^{\circ}\text{C} \pm 1.0^{\circ}\text{C}$;
 Skin: Human cadaver skin (Dermatomed); Receptor solution: $0.025\% \pm 0.001\%$ brij-
 98 in 10 mM Phosphate buffered saline (w/v); Extraction solution: Methanol (for
 surface washing and extraction of analyte from dermis and epidermis); receptor
 5 solution (for extraction of analyte from stratum corneum).

HPLC Method:

- Column: Synergy 4 μ Max-RP 80A (150 $\times$ 4.6mm, 4 μ); Mobile Phase: Buffer-1 (10 mM
 ammonium bicarbonate):Acetonitrile: Methanol; 35:35:30, v/v; Flow Rate: 1.000 mL/min;
 Column Oven Temperature: $40^{\circ}\text{C} \pm 1.0^{\circ}\text{C}$; Sample Cooler Temperature: $10^{\circ}\text{C} \pm 1.0^{\circ}\text{C}$;
 10 Injection Volume: 50 μL ; UV Detection: 240 nm; RT: Halobetasol Propionate: 8.0 to 10.0
 min; Rinsing solution: Water: Methanol: Acetonitrile, 60:20:20 v/v; Total Run Time: 16.0
 min.

The results for in-vitro permeation studies are summarized in Table 6A and 6B

Table 6A

Skin donor	Formulation	* Analyte unabsorbed on skin through surface wash (%)	* Analyte unabsorbed on skin through surface wash (ng)	Analyte in stratum corneum (%)	Analyte in stratum corneum (ng)
1	Spray	*18.99	9496.67	0.20	98.70
	Cream	99.42	47088.27	0.00	0.00
2	Spray	*38.10	19051.13	0.61	305.93
	Cream	106.51	50444.00	0.00	0.00

- 15 *For spray formulation unabsorbed amount of analyte on skin is the sum of recoveries obtained from surface wash and parafilm samples

Mean recovery (n=3)

Table 6B

Skin donor	Formulation	Analyte absorbed in epidermis (%)	Analyte absorbed in epidermis (ng)	Analyte absorbed in dermis (%)	Analyte absorbed in dermis (ng)
1	Spray	3.86	1932.40	36.02	18011.23
	Cream	0.23	107.53	0.70	332.10
2	Spray	6.99	3495.33	29.23	14616.00
	Cream	1.15	545.77	1.42	671.33

We Claim:

- 1 1. A touch-free topical spray for the treatment of skin disorders, wherein the spray is
2 formed from a composition delivered through a dispensing system, wherein the
3 composition comprises from about 0.01% w/w to about 0.5% w/w of halobetasol based on
4 the total weight of the composition, wherein the dispensing system comprises a metered
5 valve assembly comprising a metered valve having a stem connected to an actuator,
6 wherein the actuator is provided with an insert having an orifice diameter in a range of
7 about 0.2 mm to about 1.5 mm, wherein the topical spray is in the form of droplets, and
8 wherein no rubbing-in is required when said composition is applied to affected skin.
- 1 2. The touch-free topical spray of claim 1 wherein the composition comprises about
2 0.05% w/w of halobetasol based on the total weight of the composition.
- 1 3. The touch-free topical spray of claim 1, wherein the halobetasol is halobetasol
2 propionate.
- 1 4. The touch-free topical spray of claim 1, wherein when the composition is delivered
2 through the dispensing system, one actuation of the dispensing system delivers an average
3 shot weight of about 50 mg to about 150 mg of the composition.
- 1 5. The touch-free topical spray of claim 1, wherein the composition is stable.
- 1 6. The touch-free topical spray of claim 1, wherein the composition is a solution.
- 1 7. The touch-free topical spray of claim 1, wherein the metered valve assembly
2 further comprises a mounting cup attached to the pressurized container by crimping, a
3 housing, a spring, a dip tube, and a gasket.
- 1 8. The touch-free topical spray of claim 1, wherein the actuator diameter is about 5.0
2 mm to about 20.0 mm.
- 1 9. The touch-free topical spray of claim 1, wherein the actuator has a height of about
2 5.0 mm to about 20.0 mm.
- 1 10. The touch-free topical spray of claim 1, wherein the composition has a specific
2 gravity of 0.5 g/mL to about 0.8 g/mL.
- 1 11. The touch-free topical spray of claim 1, wherein the droplets have a D_{90} of less
2 than 150 μm .

- 1 12. The touch-free topical spray of claim 1, wherein the droplets have a D_{50} of less
2 than 80 μm .
- 1 13. The touch-free topical spray of claim 1, wherein the droplets have a D_{10} of less than
2 40 μm .
- 1 14. The touch-free topical spray of claim 1, wherein the droplets have a droplet size
2 distribution of D_{90} of less than 150 μm , a D_{50} of less than 80 μm , a D_{10} of less than 40 μm .
- 1 15. The touch-free topical spray of claim 1, wherein the droplets have a droplet span in
2 a range of about 1.1 to about 1.40.
- 1 16. The touch-free topical spray of claim 1, wherein when the composition is
2 delivered through a dispensing system the droplets form a plume with a plume angle
3 ranging from about 5° to about 40° .
- 1 17. The touch-free topical spray of claim 1, wherein when the composition is delivered
2 through a dispensing system the droplets form a plume with a plume width ranging from
3 about 10 mm to about 65 mm.
- 1 18. A method for treating skin disorders comprising: topically spraying a touch-free
2 topical spray composition comprising halobetasol to a surface, wherein the composition is
3 delivered in the form of droplets from a dispensing system in up to 4 actuations one after
4 another on to the same surface, wherein the droplets form a spray pattern when dispensed
5 from a distance of 3.5 inches onto the surface, wherein the spray pattern does not
6 substantially change, and a single actuation of the dispensing system delivers an average
7 shot weight of about 90 mg to about 110 mg of the composition.
- 1 19. A method for treating skin disorders comprising: topically spraying a touch-free
2 topical spray composition comprising halobetasol to a surface, wherein the composition is
3 delivered in the form of droplets from a dispensing system in up to 4 actuations one after
4 another on to the same surface, wherein the droplets form a spray pattern when dispensed
5 from a distance of 3.5 inches onto the surface, wherein the droplets are characterized by
6 having an droplet size such that the spray pattern does not substantially change and a
7 single actuation of the dispensing system delivers an average shot weight of about 90 mg
8 to about 110 mg of the composition.
- 1 20. The method of claim 19, wherein the droplets have a D_{90} of less than 150 μm .
- 1 21. The method of claim 19, wherein the droplets have a D_{50} of less than 80 μm .

- 1 22. The method of claim 19, wherein the droplets have a D_{10} of less than 40 μm .
- 1 23. The method of claim 19, wherein the droplets are having a droplet size distribution
2 of D_{90} of less than 150 μm , a D_{50} of less than 80 μm , a D_{10} of less than 40 μm .
- 1 24. The method of claim 19, wherein the droplets have a droplet span in a range of
2 about 1.1 to about 1.40.
- 1 25. The method of claim 19, wherein the droplets form a plume with a plume angle
2 ranging from about 5° to about 40° .
- 1 26. The method of claim 19, wherein the droplets form a plume with a plume width
2 ranging from about 10 mm to about 65 mm.
- 1 27. A method of treating skin disorders, comprising: topically spraying a touch-free
2 topical spray composition comprising halobetasol to a surface, wherein the composition is
3 delivered in the form of droplets from a dispensing system, in up to 4 actuations one after
4 another on to the same surface, wherein the droplets form a spray pattern when dispensed
5 from a distance of 3.5 inches from the surface, wherein the composition has a specific
6 gravity such that the spray pattern does not substantially change, and wherein a single
7 actuation of the dispensing system delivers an average shot weight ranges from about 90
8 mg to about 110 mg of the composition..
- 1 28. The method of claim 27, wherein the composition has a specific gravity of 0.5
2 g/mL to about 0.8 g/mL.

Figure 1

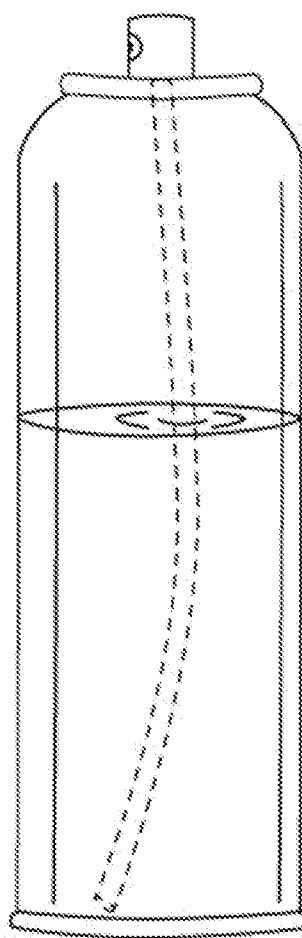
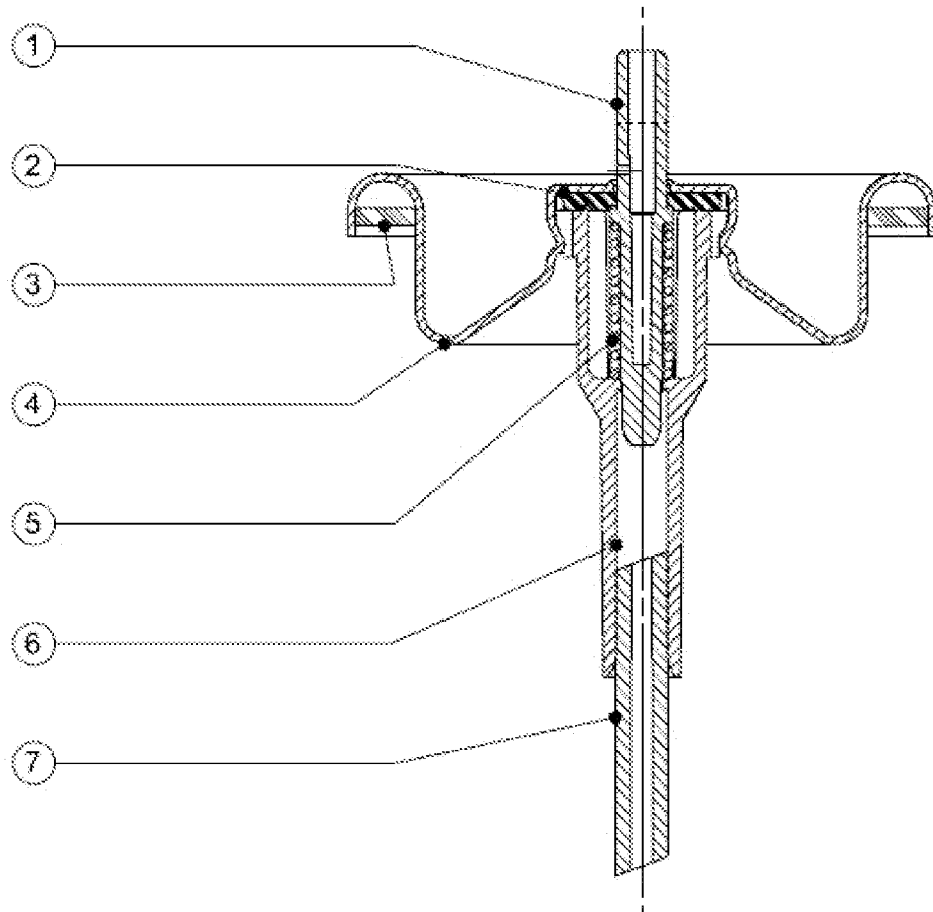
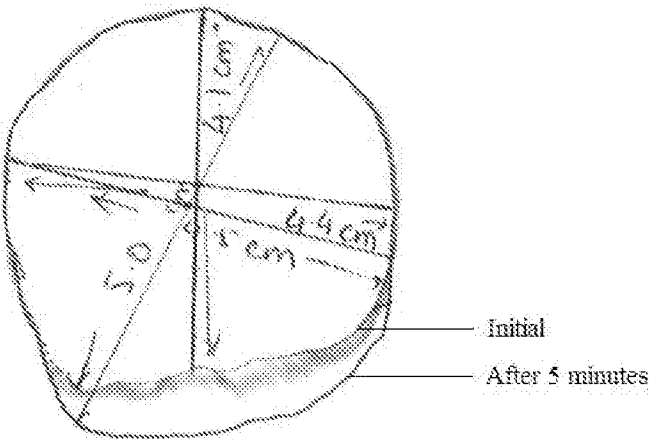


Figure 2

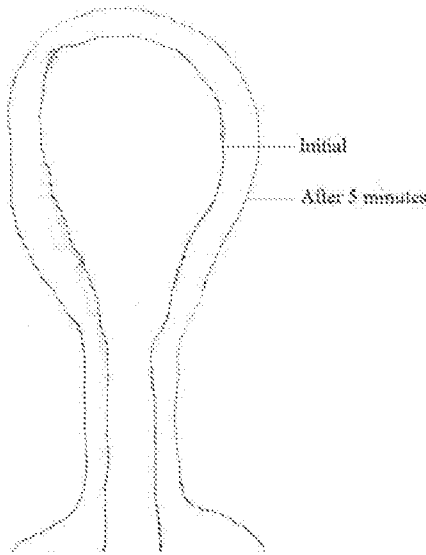


Stem - 1, Int. Gasket - 2, Ext. Gasket - 3, Mounting Cup - 4,
Soft Spring - 5, Housing - 6, Dip Tube - 7

Figure 3

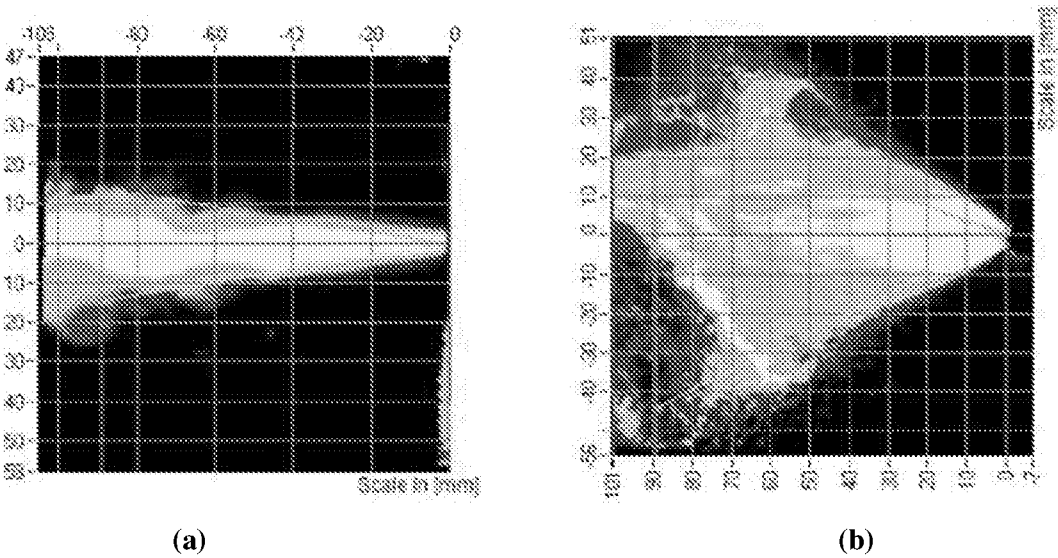


(a)



(b)

Figure 4



INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 17/54447

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/56; A61K 31/573; A61Q 19/00; B65D 83/16; B65D 83/54 (2017.01)

CPC - A61K 9/0014; A61K 9/7015; A61K 31/56; A61K 31/573; A61Q 19/00; B65D 83/16; B65D 83/54; Y10S 514/887

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2012/0214776 A1 (Ubaidulla et al.) 23 August 2012 (23.08.2012); entire document, but especially: para [0001], para [0051], para [0052], para [0068], para [0094], para [0096], para [0098], para [0101], para [0103], para [0105], para [0123], para [0174], example 6	1-6, 8-28 ----- 7
Y --- A	US 2015/0157729 A1 (LEO Pharma A/S) 11 June 2015 (11.06.2015); entire document, but especially: para [0001], para [0017], para [0018], para [0022], para [0067], para [0069], para [0092]	7 ----- 1-6, 8-28
X, P	US 2017/0165275 A1 (Therapeutics Inc.) 15 June 2017 (15.06.2017); entire document	1-28
X, P	US 2016/0235766 A1 (Sun Pharmaceutical Industries Limited) 18 August 2016 (18.08.2016); entire document	1-28
A	WO 2015/044879 A1 (Ranbaxy Laboratories Limited) 02 April 2015 (02.04.2015); entire document	1-28
A	US 2015/0258119 A1 (Promius Pharma, LLC) 17 September 2015 (17.09.2015); entire document	1-28

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

31 October 2017

Date of mailing of the international search report

01 DEC 2017

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