Example 2: Waterless Steroid Foamable Compositions where the Modulating Agent is a Citric Acid/Sodium Citrate buffer

[0328] The components of these waterless foamable compositions and the results of measurements of the properties of the resultant foams and of the stability of the active agent are set our below:

a) At 0.1% Sodium Citrate

Material chemical name		**% W/W**
Propylene glycol		31.00
Glycerin anhydrous		37.40
Stearyl alcohol		1.00
Hydroxypropyl cellulose		1.50
Laureth-4		2.00
Glyceryl Monostearate /PEG 100 Stearate		1.50
Citric acid		0.50
Sodium citrate		0.10
Stock solution	Betamethasone 17-Valerate	0.12
	Propylene glycol	24.88
Total		**100.00**
Results		
Quality		**good**
Color		**white**
Odor		**No odor**
Hardness [g]		**66.98**
Collapse time at 36°C [sec]		**>300**

ACCELERATED CHEMICAL STABILITY TESTS FOR **FOAM**		
Time point	**% of BMV-17 (w/w)**	**%BMV-21 of BMV 0.12% (w/w)**
ZT	0.117	0.90
2 weeks, 40°C	0.118	0.42
1month, 40°C	0.111	0.47

ACCELORATED CHEMICAL STABILITY TESTS FOR **PRE-FOAM FORMULATION**		
Time point	**% of BMV-17 (w/w)**	**%BMV-21 of BMV 0.12% (w/w)**
ZT	0.118	0.95
2 weeks, 50°C	0.115	1.34
1month, 50°C	0.109	1.40

[0329] Comment: In the presence of a modulating agent BMV-17 does not significantly break down into its unwanted isomer BMV-21 over a period of a month of accelerated stability tests indicating that the formula will be stable in the long term. The presence of a classical buffer in the waterless composition of the present invention is effective in a non classical way in providing a chemically stable environment for the active agent. It will be noted that the formulation produced good quality breakable foam with typical physical parameters of a polar waterless foam. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition.

b) At 0.4% Sodium Citrate

Material chemical name		**% W/W**
Propylene glycol		31.00
Glycerin anhydrous		37.40
Stearyl alcohol		1.00
Hydroxypropyl cellulose		1.50
Laureth-4		2.00
Glyceryl Monostearate /PEG 100 Stearate		1.50
Citric acid		0.50
Sodium citrate		0.40
Stock solution	Betamethasone 17-Valerate	0.12
	Propylene glycol	24.88
Total		**100.00**

CHEMICAL STABILITY TESTS FOR **FOAM**

Time point	% of BMV-17 (w/w)	%BMV-21 of BMV 0.12% (w/w)
ZT	0.122	0.00
2 weeks, 40°C	0.117	0.82
1month, 40°C	0.117	1.89

CHEMICAL STABILITY TESTS FOR **PRE-FOAM FORMULATION**		
Time point	**% of BMV-17 (w/w)**	**%BMV-21 of BMV 0.12% (w/w)**
ZT	0.122	0.00
2 weeks, 50°C	0.114	3.33
1month, 50°C	0.109	8.44

[0330] Comment: In the presence of a modulating agent BMV-17 does not significantly break down into its unwanted isomer BMV-21 over a period of two weeks of accelerated stability study. After a month minimal breakdown is seen indicating that the lower level of 0.1% w/w sodium citrate is preferable. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition.

Example 3: A Waterless Steroid Foamable Composition where the Modulating Agent is Stearic Acid

[0331] The components of this waterless foamable composition and the results of measurement of the stability of the active agent are set our below:

Material chemical name	% W/W
Propylene glycol	30.60
Glycerin anhydrous	37.40
Stearyl alcohol	1.00
Hydroxypropyl cellulose	1.50
Laureth-4	2.00
Glyceryl Monostearate /PEG 100 Stearate	1.50
Stearic acid	1.00

Stock solution	Betamethasone 17-Valerate	0.12
	Propylene glycol	24.88
Total		**100.00**

STABILITY TESTS FOR **FOAM**		
Time point	**% of BMV-17 (w/w)**	**%BMV-21 of BMV 0.12% (w/w)**
ZT	0.113	1.32
2 weeks, 40°C	0.112	2.20
1month, 40°C	0.096	2.41

STABILITY TESTS FOR **PRE-FOAM FORMULATION**		
Time point	**% of BMV-17 (w/w)**	**%BMV-21 of BMV 0.12% (w/w)**
ZT	0.115	0.73
2 weeks, 50°C	0.109	4.80
1month, 50°C	0.093	5.78

[0332] Comment: In the presence of a modulating agent BMV-17 does not significantly break down into its unwanted isomer BMV-21 over a period of two weeks of accelerated stability. After a month only very minimal additional breakdown is seen indicating that stability is likely to be improved with a higher level of Stearic Acid and that the formula will be stable in the long term. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition.

Example-4 A Waterless Steroid Foamable Composition With A Penetration Enhancer DMI in the absence of an added Modulating Agent.

[0333] The components of this waterless foamable composition and the results of measurements of the properties of the resultant foam and of the stability of the active agent are set our below:

a) Composition and physical results

Ingredient	**% w/w**
Stearyl alcohol	1.00
Laureth-4	2.00
Glyceryl stearate & PEG-100 stearate	1.50
Propylene glycol	45.88
Hydroxypropyl cellulose	1.50
Glycerin anhydrous	33.00
Dimethyl isosorbide	15.00
Betamethasone 17-valerate	0.12
Total:	100.00
Propellant: Mixture of propane, butane, isobutane*	8.00
Results	
Quality	good
Color	white
Odor	no odor
Density[g/mL]	0.089
Hardness [g]	94.610
Expansion time [sec]	90sec
Collapse time at 36°C [sec]	>300

b) Betamethasone Valerate Waterless Results Showing Stability at Three Months

	T-0	**T-3**	**Temp**
(w/w)%	0.117	0.113	**25C**
	0.117	0.113	**40C**
Percentage of original	100.000	96.581	**25C**
	100.000	96.581	**40C**

[0334] Comment: The above formula, in retrospect, was noted to have contained significant levels of residues of fatty acids, which were present in the raw materials. Nevertheless, the active ingredient did not significantly break down over a period of three months of accelerated stability indicating that the formula will be stable in the long term. Thus, the presence of acidic residues unexpectedly contributed to the stability of the active ingredient and it is

postulated that the stabilizing effect in the above formula is a combination of the absence of water coupled with the presence of acidic residues in the formulation and weakly acidic properties of the surfactants. In contrast the formula of Example 1 utilizing pure grade raw materials with practically no acidic residues undergoes a relatively rapid and serious breakdown.

Example 5: A Waterless Vitamin D3 Derivative Foamable Composition where the Modulating Agent is Triethoanolamine:

[0335] The components of these waterless foamable compositions and the results of measurements of the properties of the resultant foams and of the stability of the active agent are set our below:

A. Where the waterless solvent is a combination of two polyethylene glycols:

Ingredient name (INCI, CTFA)	Concentration (%w/w)
Calcipotriol	0.005
Polyethylene glycol 400	65
Polyethylene glycol 200	32.925
Hydroxypropyl cellulose	0.5
Steareth-2	1.5
Triethanolamine	0.07

Results T-0	
Quality	Good
Color	White
Odor	No odor
Density	0.096

B. Where the waterless solvent is a combination of two polyethylene glycols and propylene glycol:

Ingredient name (INCI, CTFA)	Concentration (%w/w)
Calcipotriol	0.005
Polyethylene glycol 400	65
Polyethylene glycol 200	27
Propylene glycol	4.895
Hydroxypropyl cellulose	1.5
Steareth-2	1.5
Triethanolamine	0.1

Results T-0	
Quality	Good
Color	White
Odor	No odor
Density	0.096

C. Where the waterless solvent is propylene glycol:

Ingredient name (INCI, CTFA)	Concentration (%w/w)
Calcipotriol	0.005
Propylene glycol	87.895
Stearyl alcohol	2
Hydroxypropyl cellulose	2
Laureth-4	2
Glyceryl monostearate	2
Ceteareth-20	1
PPG-15 Stearyl ether	3

Triethanolamine	0.1

Results T-0	
Quality	Good
Color	White
Odor	No odor
Density	0.064

[0336] Comment: The above three formulations demonstrate waterless breakable foams of good quality in which the active ingredient is sensitive to the presence of water and light and is stabilized by the absence of water coupled with the presence of a modulating agent triethanolamine. As will be appreciated from the results the physical characteristics are little varied following variations in the waterless solvent. Moreover, it can be seen that waterless foamable pharmaceutical and cosmetic compositions of good quality can be achieved with minimal ingredients comprising a waterless solvent, a surfactant, a polymeric agent, a propellant and an effective amount of an active ingredient. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition. In the above examples the propellant was AP70.

Example 6: A Waterless Ascorbic Acid Foamable Composition

[0337] The components of these waterless foamable compositions and the results of measurements of the properties of the resultant foam and of the stability of the active agent are set our below:

	1	2	3	4
Ingredient name (INCI, CTFA)				
Propylene glycol	88.00	78.00	46.00	78.00
Glycerin anhydrous			33.00	10.00
Stearyl Alcohol	2.00	1.00	1.00	2.00
Hydroxypropyl Cellulose	2.00	1.50	1.50	2.00
Laureth-4	2.00	2.00	2.00	2.00
Glyceyl Monostearate / PEG 100 Stearate			1.50	

	1	2	3	4
GMS NE	2.00	1.00		2.00
Macrogol Cetostearyl ether	1.00	1.50		1.00
PPG-15 stearyl ether	3.00			3.00
Dimethyl isosorbide		15.00	15.00	
total	**100.00**	**100.00**	**100.00**	**100.00**
Ingredient name (INCI, CTFA)	%w/w	%w/w	%w/w	%w/w
Stock Gel Phase preparation	95.00	95.00	95.00	95.00
Ascorbic Acid	5.00	5.00	5.00	5.00
Propellant	8.00	8.00	8.00	8.00
RESULTS				
FOAM QUALITY	GOOD	GOOD	GOOD	GOOD
COLOR	WHITE	WHITE	WHITE	WHITE
ODOR	NO ODOR	ODOR	NO ODOR	ODOR
SHAKABILITY	MODERATE	MODERATE	MODERATE	MODERATE
DENSITY	0.08	0.09	0.10	0.08
COLLAPSE TIME	>300	>300	>300	>300
HARDNESS	Not measured	Not measured	52.25	36.04

[0338] Comments; the above formulations demonstrate the preparation of good quality foam containing ascorbic acid as active ingredient is not significantly influenced by the addition of a secondary solvent or the presence of a penetration enhancer_Dimethyl isosorbide. To an extent ascorbic acid may act as its own modulating agent. Another modulating agent can be used to modify the artificial pH to be of the order of the pH at which ascorbic acid is most stable.

Example 7: Waterless Lidocaine HCl-Prilocaine base Foamable Composition

[0339] The components of this waterless foamable composition and the results of measurements of the properties of the resultant foam and of the stability of the active agent are set our below:

Material chemical name	% W/W
Propylene glycol	46.00
Hydroxypropylcellulose EF	1.50

Material chemical name	% W/W
Stearyl alcohol	1.00
Laureth-4	2.00
Glyceryl Stearate (and) PEG-100 Stearate	1.50
Lidocaine HCl	2.50
Prilocaine base	2.50
Glycerin anhydrous	28.00
Dimethyl isosorbide	15.00
Total:	**100.00**
Mixture of Propane/Butane/Isobutane	8.00

RESULTS	
FOAM QUALITY	GOOD
COLOR	WHITE
ODOR	NO ODOR
SHAKABILITY	GOOD
COLLAPSE TIME	>300
HARDNESS	85.88

[0340] Comments; the above formulations demonstrate the preparation of good quality foam containing anesthetics as active ingredient is not significantly influenced by the addition of a secondary solvent or the presence of a penetration enhancer Dimethyl isosorbide. To an extent lidocaine and prilocaine may act as its own modulating agent. Another modulating agent can be used to modify the artificial pH to be of the order of the pH at which lidocaine and prilocaine are respectively most stable.

Example 8: A Minimal Waterless Carrier

[0341] The components of this waterless foamable composition and the results of measurements of the properties of the resultant foam and of the stability of the active agent are set our below:

Material chemical name	% W/W
Propylene glycol	96.00
Hydroxypropyl cellulose	2.00
Steareth 2	2.00
Total	100.00
Results	
quality	excellent
color	white
odor	no odor

[0342] Comment: this carrier produces an excellent foam. Addition of an active agent such as active steroids in low concentrations of the order of 0.01 to 0.5% for example BMV at 0.12% w/w. together with a modulating agent should have minimal effect on the physical characteristics of the resultant foam.

Example 9: Demonstration of Excellent Minimal Foams Produced with two Different Surfactants Steareth 2 and Montanov 68 (cetearyl alcohol and cetearyl glucoside)

[0343] The components of these waterless foamable compositions and the results of measurements of the properties of the resultant foams and of the stability of the active agent are set our below:

Material chemical name	% W/W	% W/W	% W/W
Propylene glycol	96.00	95.28	97.50
Hydroxypropyl cellulose	2.00	2.00	0.50
Steareth 2	2.00	2.00	
Citric acid		0.50	
Sodium citrate		0.10	
Cetearyl Glucoside and Cetearyl Alcohol			2.00
Betamethasone 17-Valerate		0.12	
Results			
Total	**100.00**	**100.00**	**100.00**
quality	excellent	excellent	excellent
color	white	white	white
odor	no odor	no odor	no odor
shakability	shakable	shakable	shakable

[0344] Comments; the above formulations demonstrate the preparation of excellent quality foams using two different non ionic surfactants and that the addition of buffer or active agent has no significant effect on foam quality. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition.

Example 10: Examples of foams containing a steroid active agent with Carbomer (synthetic high molecular weight crosslinked polymers of acrylic acid) as the polymeric agent

[0345] The components of these waterless foamable compositions and the results of measurements of the properties of the resultant foams and of the stability of the active agent are set our below:

Material chemical name	**% W/W**	**% W/W**	**% W/W**	**% W/W**	**% W/W**	**% W/W**		
Propylene glycol	97.50	97.45	97.60	97.575	97.50	97.45	97.60	97.60
Steareth 2	2.00	2.00	2.00	2.00				
Carbomer 934	0.50	0.50	0.20	0.20	0.50	0.50	0.20	0.20
triethanolamine			0.20	0.20			0.20	0.20
Cetearyl Glucoside and Cetearyl Alcohol					2.00	2.00		
Methyl glucose sesquistearate							2.00	
Span 60								2.00
Clobetasol propionate		0.05				0.05		
Flucinolone acetonide				0.025				
Total	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**		
Results								
Quality E=excellent G=good	.E	E	E	E	E	eE	.G	.G
Color	White	white	White	white	white	white	white	white
Odor	no odor	no odor	no odor	no odor	no odor	no odor	no odor	no odo
Shakability	yes.	yes	.yes	.yes	.yes	.yes	.yes	yes

[0346] Comments; the above formulations demonstrate the preparation of excellent quality foam using Carbomer (synthetic high molecular weight crosslinked polymers of acrylic acid). Carbomer is acidic in nature and can stabilize an active agent alone or in combination with an organic base such as triethanolamine. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition.

Example 10- Chemical Stability

a) Stock Solutions 1 and 2

	Stock 1	Stock 2
chemical name		
Stearyl alcohol	1.00	
Laureth-4	2.00	
Glyceryl stearate & PEG-100 stearate	1.50	
Propylene glycol	36.00	9.88
Hydroxypropyl cellulose	1.50	
Glycerin anhydrous	33.00	
Steareth 2		
Dimethyl isosorbide	15.00	
Betamethasone 17-valerate		0.12
Total	**90.00**	**10.00**

[0347] Comments: 90mls of Stock 1 was combined with 10 mls of stock 2 to produce the basic formulations of 3, 4 and 5 below to which only a few drops of acidic Modulating Agent was added as indicated below.

b) 46% Waterless PG Formulations with BMV with different acidic Modulating Agents including one where the modulating agent is a second active agent

	003	004	005
chemical name			
Stearyl alcohol	1.00	1.00	1.00
Laureth-4	2.00	2.00	2.00
Glyceryl stearate & PEG-100 stearate	1.50	1.50	1.50
Propylene glycol (PG)	45.88	45.88	45.88
Hydroxypropyl cellulose	1.50	1.50	1.50
Glycerin anhydrous	33.00	33.00	33.00
Dimethyl isosorbide	15.00	15.00	15.00
Betamethasone 17-valerate (BMV)	0.12	0.12	0.12
Lactic acid*	To ph 4-4.5		
L-Glutamic acid*		To ph 4-4.5	
Azelaic acid*			To ph 4-4.5
Total	**100.00**	**100.00**	**100.00**

Propellant (AP-70)	8.00	8.00	8.00
foam quality	Good	Good	Good
Color	White	White	White
Odor	No	No	No
assay (T-0) FOAM	0.1183	0.1183	0.1177
assay (T-1M) 5C FOAM	0.1180	0.1182	0.1181
assay (T-1M) 25C FOAM	0.1175	0.1185	0.1180
assay (T-1M) 40C FOAM	0.1158	0.1156	0.1165
assay (T-1M) 50C PFF	0.1148	0.1165	0.1158

*Only a few drops were required to achieve the required pH, which was sufficient to provide a stabilizing effect.

[0348] Comments: All the modulated formulations provided foam of good quality, in which the active agent BMV was shown to be stable to degradation in a wide range of temperature from 5C to 50C over a period of a month. The pre foam formulation was also found to be stable for I month.

Example 11- EDTA

	006	**007**
chemical name		
Propylene glycol	97.90	98.90
Hydroxypropyl cellulose		1.00
Steareth 2	2.00	
EDTA	0.10	0.10
Total	**100.00**	**100.00**
Propellant (AP-70)	8.00	8.00

foam quality	Good	Good
Color	White	White
Odor	No	No

[0349] Comments: The formulation is modulated with EDTA and provided foam of good quality.

Example 12- Lysine

	008
chemical name	
Propylene glycol	98.00
Steareth 2	2.00
L-lysine	To ph 7
Total	**100.00**
Propellant (AP-70)	8.00
foam quality	Good
Color	White
Odor	No

[0350] Comments: The formulation modulated with a basic Modulating Agent provided foam of good quality,

Example 13- BMV

a) Minimum ingredients;

	009	010
chemical name		
Stearyl alcohol	1.00	
Laureth-4	2.00	
Glyceryl stearate & PEG-100 stearate	1.50	
Propylene glycol	45.88	97.88
Hydroxypropyl cellulose	1.50	
Glycerin anhydrous	33.00	
Steareth 2		2.00
Dimethyl isosorbide	15.00	
Betamethasone 17-valerate	0.12	0.12
Total	**100.00**	**100.00**
Propellant (AP-70)	8.00	8.00

Viscosity	4990.94	3711.21
foam quality	Good	Good
Color	White	White
Odor	No	No
Density	0.07	0.05
Collapse time	>300/G	.300/G
BUBBLE SIZE (µm)	150	139

BUBBLE SIZE (above 500 µm)	3.4	3.7
Conductivity	0.41µS	0 µS
Conductivity (+1 drop of Lactic acid)	0.55µS	0.05 µS

[0351] Comments: It is surprisingly possible to produce good quality foam without a polymeric agent. Nevertheless, the presence of polymeric agent can be not only helpful but important and sometimes critical for foam stability. Prophetically, small amounts of modulating agent may be added to the formulations without significant effect on the resultant foam. Remarkably, despite that these formulations are waterless, nevertheless a single drop of lactic acid results in a significant increase of conductivity. Also as can be seen herein the use of modulating agents is just as applicable for formulations with minimal ingredients as it is with complex formulations, perhaps the main differerence being that with complex formulations the there are more ingredients which increases the risk that one may contain a small impurity that can result in destabilization of the active ingredient. On the other hand formulations with few ingredients may have higher levels of a destabilizing impurity merely because say 90% of the formulation comprises an ingredient having the impurity albeit at low levels. Either way the importance of the presence of a small amount of modulating agent in a waterless formulation cannot be ignored or underestimated.

b) Focus group (5)

		Sum	Avg	STDV	TOTAL
MA PG0 09P	ease of application	21	4.2	0.45	**180**
	foam Texture	20	4	0.00	
	foam stability on hand	24	4.8	0.45	
	absorbance (1 min.)	17	3.4	0.55	
	spreadability	21	4.2	0.45	
	greasy feeling (after 1-2 min.)	16	3.2	1.10	
	shiny look (after 1-2 min.)	18	3.6	1.14	
	stickiness (after 1-2 min.)	17	3.4	1.14	
	odor	10	2	1.73	

	total satisfaction	16	3.2	1.10	

MA PG0 10P	ease of application	21	4.2	0.84	**201**
	foam Texture	20	4	0.71	
	foam stability on hand	22	4.4	0.55	
	absorbance (1 min.)	19	3.8	1.10	
	spreadability	21	4.2	0.84	
	greasy feeling (after 1-2 min.)	19	3.8	1.30	
	shiny look (after 1-2 min.)	18	3.6	1.14	
	stickiness (after 1-2 min.)	18	3.6	1.14	
	odor	22	4.4	0.55	
	total satisfaction	21	4.2	0.84	

[0352] Comments: The total satisfaction was surprisingly found to be significantly greater with the formulation with minimal ingredients.

Example 14- Carbopol and TEA

	011	**012**
chemical name		
Propylene glycol	99.00	97.00
Carbopol 934	1.00	1.00
Steareth 2		2.00
Triethanolamine (TEA)	neutralization (1 drop)	neutralization (1 drop)
Total	**100.00**	**100.00**
Propellant (AP-70)	8.00	8.00

Viscosity		13485.12
foam quality	P	Good
Color	White	White
Odor	No	No
Density		0.08
Collapse time		>300/G
BUBBLE SIZE (µm)		72
BUBBLE SIZE (above 500 µm)		0.0

[0353] Comments: The formulation modulated with an acidic polymer and a basic Modulating Agent TEA provided foam of good quality, Carbomer is a cross-linked polymer of acrylic acid with a high molecular weight.

Example 15- Stearic Acid

	013	014
chemical name		
Stearic acid	5.00	3.00
Isostearic acid		3.00
Propylene glycol	95.00	94.00
Total	**100.00**	**100.00**
Propellant (AP-70)	8.00	8.00

Viscosity	1887.60	
foam quality	Good	P
Color	White	White
Odor	No	No
Density	0.30	
Collapse time	>300/G	

[0354] Comments: Stearic acid a waxy solid acts as a foam adjuvant, thickener and Modulating Agent to produce good quality foam. The selection of Modulating Agent is not per se obvious with a waterless formulation. For example, the addition of isostearic acid results in poor foam presumably but without being bound by any theory suggested due to it being a liquid wax and not having the thickening effect of its closely related counterpart stearic acid plus its isostearic acids asymmetrical shape even though they both are CI8.

What is claimed is:

1. A waterless composition comprising

one or more active agents and a carrier for topical delivery of the one or more active agents suitable for stabilizing at least one of said one or more active agents, said carrier comprising a waterless solvent and an effective amount of a modulating agent;

wherein the at least one active agent is chemically unstable in the carrier in the absence of a modulating agent;

wherein the modulating agent is capable of and is selected to modulate or adjust the artificial pH of the carrier to an artificial pH or to provide an artificial pH buffering effect such that the chemical stability of the at least one active agent is increased as compared to its stability in the carrier without the modulating agent.

2. The waterless composition of claim 1 further comprising one or more agents that additionally are capable of a function selected from the group consisting of chelating an available metal ion, impeding ionization, and impeding oxidation.

3. The waterless composition of claim 1 wherein the waterless solvent comprises about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol or combinations thereof.

4. The waterless composition of claim 3 further comprising a stabilizing agent selected from the group consisting of a surface-active agent; about 0.01% to about 5% by weight of at least one polymeric agent and mixtures thereof.

5. The waterless composition of claim 1 wherein an effective amount of modulating agent is between about 5% to about 0.01% by weight of the composition and wherein if the active agent itself has a

modulating effect the amount of active agent used to obtain an effective modulating effect is less than the amount used to obtain an effective therapeutic effect.

6. The waterless composition of claim 5 wherein an effective amount of modulating agent is between about 1% to about 0.02% by weight of the composition.

7. The waterless composition of claim 1 wherein an effective amount of modulating agent is between about 0.6% to about 0.04% by weight of the composition.

8. The waterless composition of claim 1 wherein an effective amount of modulating agent is between about 1 to about 5 drops.

9. A foamable waterless composition comprising:

    a. a therapeutically effective concentration of one or more active agents;

    b. a carrier for topical delivery of the one or more active agents suitable for stabilizing at least one of said one or more active agents, comprising

        i. about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol;

        ii. 0% to about 75% of a secondary polar solvent;

        iii. an effective amount of a modulating agent

        iv. a stabilizing agent selected from the group consisting of a surface-active agent; about 0.01% to about 5% by weight of at least one polymeric agent and mixtures thereof.

v. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition

wherein the at least one active agent is chemically unstable in the carrier in the absence of a modulating agent;

wherein the modulating agent is capable of and is selected to modulate or adjust the artificial pH of the carrier to an artificial pH or to provide an artificial pH buffering effect such that the chemical stability of the at least one active agent is increased as compared to its stability in the carrier without the modulating agent.

wherein the carrier is shakable or flowable; and

wherein the composition is stored in an aerosol container and upon release expands to form a breakable foam.

10. The waterless composition of claim 9, wherein the breakable foam is of about good quality.

11. The waterless composition of claim 9, wherein the modulating agent is selected from the group consisting of sodium citrate, citric acid, lactic acid, glutamic acid, ascorbic acid, azalaeic acid, stearic acid, triethanolamine, lysine, lidocaine, prilocaine, carbomer and mixtures thereof.

12. The foamable composition of claim 9, wherein the composition is substantially non-aqueous.

13. The foamable composition of claim 9, wherein the polyol is selected from the group consisting of a diol; a triol; at least one diol and at least one triol, wherein the ratio between the diol and triol is between 9:1 and 1:1; a saccharide; and mixtures thereof.

14. The foamable composition of claim 13, wherein the diol is selected from the group consisting of propylene glycol, butanediol, butenediol, butynediol,

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pentanediol, hexanediol, octanediol, neopentyl glycol, 2-methyl-1,3-propanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, dipropylene glycol and dibutylene glycol; and or

wherein the triol is selected from the group consisting of glycerin, butane-1,2,3-triol, butane-1,2,4-triol and hexane-1,2,6-triol.

15. The foamable composition of claim 9, wherein the PEG is selected from the group consisting of PEG 200, PEG 300, PEG 400, PEG 600, PEG 1000, PEG 4000, PEG 6000 and PEG 8000.

16. The foamable composition of claim 9, wherein the foamable carrier comprises one or more PEGs in a concentration to provide viscosity of less than 12,000 CPs.

17. The foamable composition of claim 9, wherein the carrier composition comprises a mixture of at least one polyol and at least one PEG.

18. The foamable composition of claim 9, wherein the secondary polar solvent is selected from the group consisting of dimethyl isosorbide, tetrahydrofurfuryl alcohol polyethyleneglycol, ether, DMSO, a pyrrolidone, N-Methyl-2-pyrrolidone, 1-Methyl-2-pyrrolidinone, ethyl proxitol, dimethylacetamide, a PEG-type surfactant, an alpha hydroxy acid, lactic acid and glycolic acid.

19. The foamable composition of claim 9, wherein the carrier composition comprises (1) at least one polar solvent selected from a diol, a triol and PEG, and (2) at least one secondary polar solvent.

20. The foamable composition of claim 9, wherein the ratio between the polyol and/or PEG and the secondary polar solvent is between 9:1 and 1:4.

21. The foamable composition of claim 9, wherein the composition is substantially alcohol-free.

22. The foamable composition of claim 9, wherein the modulating agent is selected from the group consisting of an alpha hydroxyl acid, an aliphatic beta hydroxyacid, an aromatic acid, an aromatic hydroxyl acid, an alpha ketoacid,

an aliphatic carboxylic acid, a branched aliphatic carboxylic acid, a short chain carboxylic acid, a fatty acid, an omega-3 fatty acid, an omega-6 fatty acid, an omega-9 fatty acid, a dicarboxylic acid, a branched dicarboxylic acid, an unsaturated dicarboxylic acid, an amino acid, a dimer or oligomer of amino acids, a retinoid, a nitrogen-containing organic compound, a primary, secondary, tertiary and quaternary amine, an amide, an amine oxide and a lactam.

23. The foamable composition of claim 22,

wherein the alpha hydroxyl acid and beta hydroxyl acid are selected from the group consisting of alpha-hydroxybutyric acid, alpha-hydroxyisobutyric acid, alpha-hydroxyisocaproic acid, alpha-hydroxyisovaleric acid, atrolactic acid, beta-hydroxybutyric acid, beta-phenyl lactic acid, beta-phenylpyruvic acid, citric acid, pyruvic acid, galacturonic acid, glucoheptonic acid, glucoheptono 1,4-lactone, gluconic acid, gluconolactone, glucuronic acid, glucuronolactone, glycolic acid, lactic acid, mandelic acid, mucic acid, pyruvic acid, saccharic acid, saccharic acid 1,4-lactone, tartaric acid and tartronic acid, 3-Hydroxybutanoic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, chlorolactic acid, citramalic acid, agaricic acid, aleuritic acid, pantoic acid, lactobionic acid, piscidic acid, hexulosonic acid or the anhydride thereof;

wherein the aromatic acid is selected from the group consisting of benzoic acid, toluic acid, dimethyl benzoic acid and phthalic acid;

wherein the beta hydroxyl acid is selected from the group consisting of salicylic acids and derivatives thereof;

wherein the alpha ketoacid has the molecular structure of

(Ra)COCOO(Rb);

wherein Ra and Rb are independently selected from the group consisting of H and saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic C1-C25 alkyl, aralkyl, or aryl groups, wherein Ra may be optionally

substituted with an F, Cl, Br, I, OH, CHO, COOH, or alkoxy group having 1 to 9 carbon atoms;

wherein the aliphatic carboxylic acid is selected from the group consisting of formic acid, acetic acid and propionic acid, butyric acid, butyric acid, caproic acid, caprylic acid, nonanoic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, octacosanoic acid, oleic acid, linoleic acid, alpha-linolenic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, erucic acid, valproic acid and 12-hydroxy stearic acid;

wherein the dicarboxylic acid is selected from the group consisting of oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid, dodecanedioic acid, brassylic acid, thapsic acid, 14-methylnonacosanedioic acid, 14,15-dimethyltriacontanedioic acid (C30) undecylenic acid, maleic acid and fumaric acid;

wherein the carbon atom skeleton of the branched dicarboxylic acid is substituted with at least one group selected from the group consisting of R, F, Cl, Br, OH, OR, SH, CHO, COOH, and NRaRb, ansd wherein R, Ra and Rb are independently selected from the group consisting of H, saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic C1-C25 alkyl, aralkyl, or aryl groups;

wherein the branched dicarboxylic acid is selected from the group consisting of aspartic acid, alpha-ketoglutaric acid, adipic acid 2-amino, aconitic acid, benzene dicarboxylic acid, citramalic acid, citric acid, cystathionine, glucuronic acid, glutamic acid, itaconic acid, malic acid, mucic acid, oxalacetic acid, diamino pimelic acid, saccharic acid, dimethyl succinic acid, tartaric acid and tartronic acid;

wherein the carboxylic acid is selected from the group consisting of is selected from the group consisting of retinoic acid, isotretinoin, ascorbic

acid, isoascorbic acid, ethanesulfonic acid, glycerophosphoric acid, acetohydroxamic acid, aconitic acid, alpha-ketocaproic acid, aminomalonic acid, hippuric acid, hydrochloric acid, methanesulfonic acid, oxalic acid, phosphoric acid, sorbic acid, iminodiacetic acid and carnitine; and

wherein the amino acid is selected from the group consisting of glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, lysine, histidine, phenylalanine, tyrosine, tryptophan, praline, B-alanine (3-alanine), 4-aminobutyrate (GABA), 3-cyanoalanine (B-cyanoalanine), 2-aminobutyric acid, 2-methylene-4-aminobutyric acid, 3-methylene-4-aminobutyric acid, 2-aminoisobutyric acid, 5-aminolevulinic acid, 2-amino-4-methylhexanoic acid (homoisoleucine), 2-amino-4-methylhex-4-enoic acid, 2-amino-4-methylhex-5-ynoic acid, 2-amino-3-methylpentanoic acid, 2-aminoadipic acid, 4-ethylideneglutamic acid, 3-aminoglutaric acid, 2-aminopimelic acid, N4-ethylasparagine, N4-methylasparagine, erythro-4-methylglutamic acid, 4-methyleneglutamic acid, 4-methyleneglutamine, N5-methylglutamine, N5-ethylglutamine (theanine), N5-isopropylglutamine, 2-amino-4-(aminoxy)butyric acid (canaline), 2,4-diaminobutyrate, N4-acetyl-2,4-diaminobutyrate, N4-lactyl-2,4-diaminobutyrate, N4-oxalyl-2,4-diaminobutyrate, 2,3-diaminopropionic acid, N3-acetyl-2,3-diaminopropionic acid, N3-methyl-2,3-diaminopropionic acid, N3-oxalyl-2,3-diaminopropionic acid, N6-acetyllysine, N6-methyllysine, N6-trimethyllysine (laminine), ornithine (2,5-diaminopentanoic acid), saccharopine (N6-(2'-glutamyl)lysine, 2,6-diaminopimelic acid, N4-(2-hydroxylethyl)asparagine, erythro-3-hydroxyaspartic acid, 4-hydroxyarginine, 4-hydroxycitrulline, threo-4-hydroxyglutamic acid, 3,4-dihydroxyglutamic acid, 3-hydroxy-4-methylglutamic acid, 3-hydroxy-4-methyleneglutamic acid, 4-hydroxy-4-methylglutamic acid, 4-hydroxy-glutamine, N5-(2-hydroxyethyl)glutamine, 5-hydroxynorleucine, threo-4-hydroxyhomoarginine, homoserine, O-acetylhomoserine, O-

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oxalylhomoserine, O-phosphohomoserine, 4-hydroxyisoleucine, 5-hydroxymethylhomocysteine, threo-3-hydroxyleucine, 5-hydroxyleucine, 2-hydroxylysine, 4-hydroxylysine, 5-hydroxylysine, N6-acetyl-5-hydroxylysine, N6-trimethyl-5-hydroxylysine, 4-hydroxyornithine, mimosine, 4-hydroxynorvaline, 5-hydroxynorvaline, 2-amino-4,5-dihydroxypentanoic acid, 2-amino-4-hydroxypimelic acid, 4-hydroxyvaline, O-acetylserine, O-phosphoserine, pipecolic acid, (piperidine-2-carboxylic acid), 3-hydroxypipecolic acid, trans-4-hydroxypipecolic acid, trans-5-hydroxypipecolic acid, 5-hydroxy-6-methylpipecolic acid, 4,5-dihydroxypipecolic acid, trans-3-hydroxyproline, trans-4-hydroxyproline, trans-4-hydroxymethylproline, azetidine-2-carboxylic acid, N-(3-amino-3-carboxypropyl)azetidine-2-carboxylic acid, 4,5-dehydropipecolic acid (baikiain), 3-amino-3-carboxypyrrolidone (cucurbitine), 2-(cyclopent-2'-enyl)glycine, 5-hydroxytryptophan, albizziine (2-amino-3-ureidopropionic acid), arginosuccinic acid, canavinosuccinic acid, citrulline, homoarginine, homocitrulline, indospicine, O-ureidohomoserine, 6-hydroxykynurenine, 3-(4-aminophenyl)alanine, 3-(3-aminomethylphenyl)alanine, 3-(3-carboxyphenyl)alanine, 3-carboxytyrosine, 3-(3-hydroxymethylphenyl)alanine, 3-(3-hydroxyphenyl)alanine, 3-(3,4-dihydroxyphenyl)alanine (L-DOPA), 2-(phenyl)glycine, 2-(3-carboxyphenyl)glycine, 2-(3-carboxy-4-hydroxyphenyl)glycine, 2-(3-hydroxyphenyl)glycine, 2-(3,5-dihydroxyphenyl)glycine, 4-aminopipecolic acid, guvacine, 2-amino-4-(isoxazolin-5-one)-2-yl)butyric acid, lathyrine, tetrahydrolathyrine and ornithin and dimers or oligomers thereof.

24. The foamable composition of claim 22, wherein the modulating agent is a nitrogen-containing organic compound selected from the group consisting of primary amines, methylamine and ethylamine; an ethanolamine, monoethanolamine, monoisopropanolamines, a diamine, ethylenediamine, 1,2-diaminopropane, a dialkylamine, dimethylamine, diethylamine, diethanolamine, diisopropanolamine, N-methylethanolamine, N-

ethylethanolamine, a tertiary amine, a trialkylamine, triethylamine, triethylamine, triethanolamine, N-methyldiethanolamine and tri-isopropanolamine.

25. The foamable composition of claim 9, wherein the polymeric agent is selected from the group consisting of locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum, sodium alginate, xanthan gum, quince seed extract, tragacanth gum, guar gum, cationic guars, hydroxypropyl guar gum, starch, an amine-bearing polymer, chitosan, alginic acid, hyaluronic acid, a chemically modified starch, a carboxyvinyl polymer, polyvinylpyrrolidone, polyvinyl alcohol, a polyacrylic acid polymer, a polymethacrylic acid polymer, polyvinyl acetate, a polyvinyl chloride polymer, a polyvinylidene chloride polymer, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxy propylmethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethyl cellulose, carboxymethylcellulose carboxymethylhydroxyethylcellulose, a cationic cellulose PEG 1000, PEG 4000, PEG 6000 and PEG 8000, carbomer Carbopol® 934, Carbopol® 940, Carbopo® 941, Carbopol® 980 and Carbopol® 981.

26. The foamable composition of claim 9, wherein the polymeric agent is dispersible in the polyol or in the mixture of a polyol and an additional polar solvent.The foamable composition of claim 4, wherein the concentration of the polymeric agent is selected such that the viscosity of the composition is less than 12,000 CPs, or less than 10,000 CPs.

27. The foamable composition of claim 9, wherein the surfactant comprises at least one surfactant selected from the group consisting of a polyoxyethylene fatty ether, a polyoxyethylene fatty ester,a carbohydrate ester and a sucrose ester, glyceryl stearate, PEG-100 stearate, steareth-2, steareth-20, steareth-21, ceteareth 2, PEG-100 stearyl ether, cetearyl glucoside, methyl glucose sesquistearate, sorbitan monostearate, GMS

NE, span 20, glyceryl stearate and PEG 100 stearate, glyceryl stearate and PEG 100 stearate and laureth4; steareth 2, PEG 100 searate and laureth4, and cetearyl glucoside and cetearyl alcohol.

28. The foamable composition of claim 9, wherein the surface active agent comprises a non-ionic surface active agent.

29. The foamable composition of claim 28, wherein the surface active agent further comprises an ionic surfactant, selected from the group consisting of a cationic surfactant, a zwitterionic surfactant, an amphoteric surfactant and an ampholytic surfactant.

30. The foamable composition of claim 28, wherein the surface active agent comprises a mixture of at least one non-ionic surfactant and at least one ionic surfactant in a ratio selected from

    a. about 100:1 to about 6:1

    b. about 1:1 to about 20:1.

31. The foamable composition of claim 9, further comprising a hydrophobic solvent.

32. The foamable composition of claim 31, wherein the hydrophobic solvent is selected from the group consisting of mineral oil, isopropyl palmitate, isopropyl isostearate, diisopropyl adipate, diisopropyl dimerate, maleated soybean oil, octyl palmitate, cetyl lactate, cetyl ricinoleate, tocopheryl acetate, acetylated lanolin alcohol, cetyl acetate, phenyl trimethicone, glyceryl oleate, tocopheryl linoleate, wheat germ glycerides, arachidyl propionate, myristyl lactate, decyl oleate, ricinoleate, isopropyl lanolate, pentaerythrityl tetrastearate, neopentylglycol dicaprylate/dicaprate, isononyl isononanoate, isotridecyl isononanoate, myristyl myristate, triisocetyl citrate, octyl dodecanol, unsaturated or polyunsaturated oils, such as olive oil, corn oil, soybean oil, canola oil, cottonseed oil, coconut oil, sesame oil, sunflower oil, borage seed oil, syzigium aromaticum oil, hempseed oil, herring oil, cod-liver oil, salmon oil, flaxseed oil, wheat germ

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oil, evening primrose oils; essential oils; and silicone oils, such as dimethicone, cyclomethicone, polyalkyl siloxane, polyaryl siloxane, polyalkylaryl siloxane, a polyether siloxane copolymer and a poly(dimethylsiloxane)-(diphenyl-siloxane) copolymer.

33. The foamable composition of claim 9, further comprising a foam adjuvant selected from the group consisting of a fatty alcohol, a fatty acid and a hydroxyl fatty acid.

34. The foamable composition of claim 9, further comprising an additional component selected from the group consisting of an anti perspirant, an anti-static agent, a buffering agent, a bulking agent, a chelating agent, a colorant, a conditioner, a deodorant, a diluent, a dye, an emollient, fragrance, a humectant, an occlusive agent, a penetration enhancer, a perfuming agent, a permeation enhancer, a preservative, a skin penetration enhancer, a sunscreen, a sun blocking agent, a sunless tanning agent, and a vitamins.

35. The foamable composition of claim 9, wherein the active agent is selected from the group consisting of active herbal extracts, acaricides, age spot and keratose removing agents, allergen, analgesics, local anesthetics, antiacne agents, antiallergic agents, antiaging agents, antiinfective, antibacterials, antibiotics, antiburn agents, anticancer agents, antidandruff agents, antidepressants, antidermatitis agents, antiedemics, antifungal, antihistamines, antihelminths, antihyperkeratolyte agents, antiinflammatory agents, antiirritants, antilipemics, antimicrobials, antimycotics, antiproliferative agents, antiparasitic agents, antioxidants, anti-wrinkle agents, antipruritics, antipsoriatic agents, antirosacea agents antiseborrheic agents, antiseptic, antiswelling agents, antiviral agents, anti-yeast agents, agents that control yeast, astringents, topical cardiovascular agents, chemotherapeutic agents, corticosteroids, dicarboxylic acids, disinfectants, fungicides, hair growth regulators, hormones, hydroxy acids, immunosuppressants, immunoregulating

agents, insecticides, insect repellents, keratolytic agents, lactams, metals, metal oxides, mitocides, neuropeptides, non-steroidal anti-inflammatory agents, oxidizing agents, pediculicides, photodynamic therapy agents, retinoids, sanatives, scabicides, self tanning agents, steroids, skin whitening agents, asoconstrictors, vasodilators, vitamins, vitamin D derivatives, flavonoids,wound healing agents and wart removers.

36. The foamable composition of claim 35, wherein the steroid is selected from the group consisting of alclometasone dipropionate, amcinafel, amcinafide, amcinonide, beclomethasone, beclomethasone dipropionate, betamethsone, betamethasone benzoate, betamethasone dexamethasone-phosphate, dipropionate, betamethasone valerate, budesonide, chloroprednisone, chlorprednisone acetate, clescinolone, clobetasol, clobetasol propionate, clobetasol valerate, clobetasone, clobetasone butyrate, clocortelone, cortisone, cortodoxone, craposone butyrate, desonide, desoxymethasone, dexamethasone, desoxycorticosterone acetate, dichlorisone, diflorasone diacetate, diflucortolone valerate, diflurosone diacetate, diflurprednate, fluadrenolone, flucetonide, flucloronide, fluclorolone acetonide, flucortine butylesters, fludroxycortide, fludrocortisone, flumethasone, flumethasone pivalate, flumethasone pivalate, flunisolide, fluocinolone, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluosinolone acetonide, fluperolone, fluprednidene acetate, fluprednisolone hydrocortamate, fluradrenolone, fluradrenolone acetonide, flurandrenolone, fluticasone, halcinonide, halobetasol, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone cyclopentylpropionate, hydrocortisone valerate, hydroxyltriamcinolone, medrysone, meprednisone, .alpha.-methyl dexamethasone, methylprednisolone, methylprednisolone acetate, mometasone furoate, paramethasone, prednisolone, prednisone, pregnenolone, progesterone,

spironolactone, triamcinolone, triamcinolone acetonide and derivatives, esters and salts thereof;

wherein the antifungal agent is selected from the group consisting of a polyene, natamycin, nystatin; an allylamine, naftifine, terbinafine; an imidazole, bifonazole, clotrimazole, econazole, fenticonazole, ketocanazole, miconazole, oxiconazole; a diazole, a triazoles, fluconazole, itraconazole, terconazole, tolnaftate, ciclopirox, undecylenic acid, sulbentine, griseofulvin, Amphotericin B, flucytosine (5FC), a morpholine compound, amorolfine, and the related morpholines and analogs, derivatives and salts thereof, and any combination thereof at a therapeutically effective concentration; and

wherein the antibacterial agent is selected from the group consisting of a beta-lactam antibiotic, an aminoglycoside, an ansa-type antibiotic, an anthraquinone, an azole, metronidazole, an antibiotic glycopeptide, a macrolide, erythromycin, clindamycin, an antibiotic nucleoside, an antibiotic peptide, polymyxin B, an antibiotic polyene, an antibiotic polyether, an antibiotic quinolone, an antibiotic steroid, fucidic acid, mupirocin, chloramphenicol, a sulfonamide, tetracycline, an antibiotic metal, silver, copper, zinc, mercury, tin, lead, bismuth, cadmium, chromium, an oxidizing agent, iodine, iodate, a periodate, a hypochlorite, a permanganate, a substance that release free radicals and/or active oxygen, a cationic antimicrobial agent, a quaternary ammonium compound, a biguanide, chlorohexidine, a triguanide, a bisbiguanide, a polymeric biguanide, a naturally occurring antibiotic compound and analogs, derivatives, salts, ions and complexes thereof.

37. The foamable composition of claim 9, wherein the active agent is unstable in the presence of water.

38. The foamable composition of claim 9, wherein the active agent is stable at an acidic pH range and the modulating agent is acidic.

39. The foamable composition of claim 9, wherein the active agent is an ester, which undergoes hydrolysis at basic pH.

40. The foamable composition of claim 9, wherein the active agent is a compound, which undergoes rearrangement at basic pH.

41. The foamable composition of claim 9, wherein the active agent is stable at a basic pH range and the modulating agent is basic.

42. The foamable composition of claim 41, wherein the active agent is selected from vitamin D, a vitamin D analog, a vitamin D derivative.

43. The foamable composition of claim 9, wherein the modulating agent is a nitrogen-containing modulating agent.

44. The foamable composition of claim 9, wherein the modulating agent is triethanolamine and the active agent is calcipotriol.

45. The foamable composition of claim 9, wherein the modulating agent is selected from the group consisting of sodium citrate, citric acid, lacic acid, glutamic acid, azaleic acid, ascorbic acid, stearic acid and mixtures thereof and the active agent is bmv.

46. The foamable composition of claim 9, wherein the modulating agent is selected from the group consisting of carbomer, and triethanolamine, and mixtures thereof and the active agent is is selected from the group consisting of clobetosol proprionate and flucinoline acetonide.

47. The foamable composition of claim 9, wherein the active agent is stable at about neutral pH range and the modulating agent is neutral.

48. The foamable composition of claim 9, wherein the modulating agent is a pharmaceutical or cosmetic active agent.

49. The foamable composition of claim 9, comprising (1) a corticosteroid; and (2) and active agent selected from the group of an antifungal agent, an antimicrobial agent, an antiviral agent, an anti-acne agent, a vitamin D3

derivative, calcipotriol, and antipsoriasis agent, a keratolytic agent and an antiacne agent.

50. The foamable composition of claim 9, comprising (1) a keratolytic agent; and (2) and active agent selected from the group of a corticosteroid, an antifungal agent, an antimicrobial agent, an antiviral agent, an anti-acne agent, a vitamin D3 derivative, calcipotriol, and antipsoriasis agent, an immunomodulator, and immunosuppressant and an antiacne agent.

51. A method of treating a disorder of mammalian subject, comprising:

administering a composition to a target site, the composition comprising:

one or more active agents and a carrier for topical delivery of the one or more active agents suitable for stabilizing at least one of said one or more active agents, said carrier comprising a waterless solvent and an effective amount of a modulating agent;

wherein the at least one active agent is chemically unstable in the carrier in the absence of a modulating agent;

wherein the modulating agent is capable of and is selected to modulate or adjust the artificial pH of the carrier to an artificial pH or to provide an artificial pH buffering effect such that the chemical stability of the at least one active agent is increased as compared to its stability in the carrier without the modulating agent.

52. A method of treating a disorder of mammalian subject, comprising:

administering a foamable composition to a target site, the composition comprising:

a foamable waterless composition comprising:

a. a therapeutically effective concentration of one or more active agents;

b. a carrier for topical delivery of the one or more active agents suitable for stabilizing at least one of said one or more active agents, comprising

i. about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol;

ii. 0% to about 75% of a secondary polar solvent;

iii. an effective amount of a modulating agent

iv. a stabilizing agent selected from the group consisting of a surface-active agent; about 0.01% to about 5% by weight of at least one polymeric agent and mixtures thereof.

v. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition

wherein the at least one active agent is chemically unstable in the carrier in the absence of a modulating agent;

wherein the modulating agent is capable of and is selected to modulate or adjust the artificial pH of the carrier to an artificial pH or to provide an artificial pH buffering effect such that the chemical stability of the at least one active agent is increased as compared to its stability in the carrier without the modulating agent.

wherein the carrier is shakable or flowable; and

wherein the composition is stored in an aerosol container and upon release expands to form a breakable foam.

53. The method of claim 52, wherein the target site is selected from the group consisting of the skin, a body cavity, a mucosal surface, the nose, the

mouth, the eye, the ear canal, the respiratory system, the vagina and the rectum.

54. The method of claim 52, wherein the disorder is selected from the group consisting of dermatological pain, dermatological inflammation, acne, acne vulgaris, inflammatory acne, non-inflammatory acne, acne fulminans, nodular papulopustular acne, acne conglobata, dermatitis, bacterial skin infections, fungal skin infections, viral skin infections, parasitic skin infections, skin neoplasia, skin neoplasms, pruritis, cellulitis, acute lymphangitis, lymphadenitis, erysipelas, cutaneous abscesses, necrotizing subcutaneous infections, scalded skin syndrome, folliculitis, furuncles, hidradenitis suppurativa, carbuncles, paronychial infections, rashes, erythrasma, impetigo, ecthyma, yeast skin infections, warts, molluscum contagiosum, trauma or injury to the skin, post-operative or post-surgical skin conditions, scabies, pediculosis, creeping eruption, eczemas, psoriasis, pityriasis rosea, lichen planus, pityriasis rubra pilaris, edematous, erythema multiforme, erythema nodosum, grannuloma annulare, epidermal necrolysis, sunburn, photosensitivity, pemphigus, bullous pemphigoid, dermatitis herpetiformis, keratosis pilaris, callouses, corns, ichthyosis, skin ulcers, ischemic necrosis, miliaria, hyperhidrosis, moles, Kaposi's sarcoma, melanoma, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, poison ivy, poison oak, contact dermatitis, atopic dermatitis, rosacea, purpura, moniliasis, candidiasis, baldness, alopecia, Behcet's syndrome, cholesteatoma, Dercum disease, ectodermal dysplasia, gustatory sweating, nail patella syndrome, lupus, hives, hair loss, Hailey-Hailey disease, chemical or thermal skin burns, scleroderma, aging skin, wrinkles, sun spots, necrotizing fasciitis, necrotizing myositis, gangrene, scarring, and vitiligo, chlamydia infection, gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranloma venereum, mucopurulent cervicitis

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(MPC), molluscum contagiosum, nongonococcal urethritis (NGU), trichomoniasis, vulvar disorders, vulvodynia, vulvar pain, yeast infection, vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), contact dermatitis, pelvic inflammation, endometritis, salpingitis, oophoritis, genital cancer, cancer of the cervix, cancer of the vulva, cancer of the vagina, vaginal dryness, dyspareunia, anal and rectal disease, anal abscess/fistula, anal cancer, anal fissure, anal warts, Crohn's disease, hemorrhoids, anal itch, pruritus ani, fecal incontinence, constipation, polyps of the colon and rectum; and wherein the active agent is suitable for treating said disorder.

55. The foamable composition of claim 9, comprising a solid, semi solid or waxy surfactant wherein the amount of surfactant or combination of surfactants is between about 0.05% to about 10%.

56. The foamable composition of claim 9, comprising a .solid, semi solid or waxy surfactant which is soluble in oil and having a HLB or weighted average HLB of less than about 12.

57. A foamable waterless composition comprising:

a. a therapeutically effective concentration of one or more active agents;

b. a carrier delivery of the one or more active agents suitable for stabilizing at least one of said one or more active agents,comprising

i. about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol;

ii. 0% to about 75% of a secondary polar solvent;

iii. an effective amount of an modulating agent

iv. a stabilizing agent selected from the group consisting of a surface-active agent; about 0.01% to about 5% by weight of at least one polymeric agent and mixtures thereof.

v. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition

wherein the at least one active agent is chemically unstable in the carrier in the absence of a modulating agent;wherein the modulating agent comprises an effective amount of one or more agents that are capable of impeding said destabilization and or are capable of stabilizing the active agent by chelating a metal ion such that the modulating agent is capable of reducing in the waterless carrier the availability of metal ions so the stability of at least one active agent is improved when compared to its stability in the carrier without the modulating agent;

wherein the carrier is shakable or flowable; and

wherein the composition is stored in an aerosol container and upon release expands to form a breakable foam.

58. The waterless composition of claim 57 further comprising one or more agents that additionally are capable of impeding said destabilization and or are capable of stabilizing the active agent primarily by modulating or adjusting the artificial pH of the carrier such that the modulating agent is capable of producing in the waterless carrier an artificial pH or an artificial pH buffering effect at about a pH or pH range in which the stability of at least one active agent is improved when compared to its stability in the carrier without the modulating agent and or by impeding ionization and or by impeding oxidation.

59. The waterless composition of claim 57, wherein the modulating agent is a chelating agent.

60. The waterless composition of claim 57, wherein the chelating agent is sufficiently soluble or functional in the waterless solvent to enable it to "mop up" or "lock" metal ions.

61. The waterless composition of claim 57, wherein the chelating agent is selected from the group consisting of ethylenediaminetetraacetic acid ("EDTA") and salts thereof, disodium EDTA, tetrasodium EDTA, calsium disodium EDTA; diethylenetriaminepentaacetic acid ("DTPA") and salts thereof; hydroxyethlethylenediaminetriacetic acid ("HEDTA") and salts thereof; and nitrilotriacetic acid ("NTA") and salts thereof; acetyl trihexyl citrate, aminotrimethylene phosphonic acid, beta-alanine diacetic acid, bismuth citrate, calcium disodium edta, citric acid, cyclohexanediamine tetraacetic acid, diammonium citrate, dibutyl oxalate, diethyl oxalate, diisobutyl oxalate, diisopropyl oxalate, dilithium oxalate, dimethyl oxalate, dipotassium edta, dipotassium oxalate, dipropyl oxalate, disodium edta, disodium edta-copper, disodium pyrophosphate, edta, etidronic acid, hedta, methyl cyclodextrin, oxalic acid, pentapotassium, triphosphate, pentasodium aminotrimethylene phosphonate, pentasodium pentetate, pentasodium triphosphate, pentetic acid, phytic acid, potassium citrate, sodium citrate, sodium dihydroxyethylglycinate, sodium gluceptate, sodium gluconate, sodium hexametaphosphate, sodium metaphosphate, sodium metasilicate, sodium oxalate, sodium trimetaphosphate, tea-edta, tetrahydroxypropyl ethylenediamine, tetrapotassium etidronate, tetrapotassium pyrophosphate, tetrasodium edta, tetrasodium etidronate, tetrasodium pyrophosphate, tripotassium edta, trisodium edta, trisodium hedta, trisodium nta, trisodium phosphate, malic acid, fumaric acid, maltol, succimer, penicillamine, dimercaprol, and desferrioxamine mesilate.

62. A foamable waterless carrier for use with a therapeutically effective concentration of one or more active agents comprising

i. about 25% to about 98% of at least polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol;0% to about 75% of a secondary polar solvent;

ii. an effective amount of a modulating agent

iii. a stabilizing agent selected from the group consisting of a surface-active agent; about 0.01% to about 5% by weight of at least one polymeric agent and mixtures thereof.

iv. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition

wherein at least one active agent if present is susceptible, to one or more of reaction, breakdown, ionization or oxidation;

wherein the modulating agent comprises an effective amount of one or more agents that are capable of impeding said destabilization and or are capable of stabilizing the active agent primarily by modulating or adjusting the artificial pH of the carrier such that the modulating agent is capable of producing in the waterless carrier an artificial pH or an artificial pH buffering effect at about a pH or pH range in which the stability of at least one active agent is improved when compared to its stability in the carrier without the modulating agent and or by chelating a metal ion such that the modulating agent is capable of reducing in the waterless carrier the availability of metal ions so the stability of at least one active agent is improved

when compared to its stability in the carrier without the modulating agent;

wherein the carrier is shakable or flowable; and

wherein the composition is stored in an aerosol container and upon release expands to form a breakable foam.

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(54) **Title:** TOPICAL PHARMACEUTICAL COMPOSITION FOR THE COMBINATION OF FUSIDIC ACID AND A CORTICOSTEROID

(57) **Abstract:** The present invention relates to topical compositions comprising combination of mometasone furoate and fusidic acid. The present invention also relates to use of topical combinations of mometasone furoate and fusidic acid for prevention and treatment of dermal infections. The present invention also relates to topical compositions comprising Halobetasol propionate and fusidic acid and their use for prevention and treatment of dermal conditions.

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TOPICAL PHARMACEUTICAL COMPOSITION FOR THE COMBINATION OF FUSIDIC ACID AND A CORTICOSTEROID

PRIORITY DETAILS

This patent application claims priority to Indian Patent Application No.1725/MUM/2007, filed on September 10, 2007, the contents of which are hereby incorporated as reference.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a combination therapy of a topical antibiotic and a topical steroid for the treatment of inflammatory dermatoses associated with secondary bacterial infections. In particular the present invention relates to topical pharmaceutical compositions comprising a combination of fusidic acid and corticosteroid such as Mometasone furoate useful in treatment of infected eczema's such as secondarily infected dermatitis, including secondarily infected contact dermatitis, psoriasis, allergic contact dermatitis and atopic dermatitis with secondary bacterial infections of skin. In particular the present invention also relates to topical pharmaceutical compositions comprising a combination of fusidic acid and corticosteroid such as Mometasone furoate useful in prevention of infection in cases of dermatitis, especially atopic dermatitis who are at risk of getting secondary bacterial infection

In particular the present invention also relates to topical pharmaceutical compositions comprising a combination of fusidic acid and corticosteroid such as Halobetasol propionate useful in treatment of infected steroid responsive dermatoses such as secondarily infected dermatoses including secondarily infected contact dermatitis, allergic contact dermatitis, atopic dermatitis, psoriasis and other corticosteroid responsive dermatoses (CRD) with secondary bacterial infections of skin. In particular the present invention also relates to topical pharmaceutical compositions comprising a combination of fusidic acid and corticosteroid such as Halobetasol propionate useful in prevention of secondary bacterial infections in patients with non-infected dermatoses

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BACKGROUND OF THE INVENTION

Bacteria such as Staphylococcus can live harmlessly on many skin surfaces, but when the skin is punctured or broken for any reason, staphylococcus bacteria can enter the wound and cause the infections. There are more than 30 species in the staphylococcus family of bacteria, and they can cause different kinds of illnesses. But most staphylococcus infections are caused by the species *Staphylococcus aureus* (S. aureus) and Streptococcus pyogenes. Skin and soft-tissue infections are among the most common infections, and may lead to serious local and systemic complications. Bacterial infections occur frequently in lesions of eczema and atopic dermatitis. One of the common causes of skin and soft-tissue infections is the occurrence of secondary bacterial infection that complicates skin lesions. Secondary bacterial skin infections are common complications of primary dermatoses, primary nonbacterial skin infections, traumatic lesions, ulcers, cutaneous infestations, and other miscellaneous skin diseases. Despite the differences in the underlying cause and clinical presentation, overt secondary bacterial infection with Staphylococcus aureus and Streptococcus pyogenes, or both is a common problem in patients with inflammatory skin diseases such as allergic contact dermatitis, atopic dermatitis, or psoriasis. Various host factors have been suggested to be the cause of secondarily infected dermatitis (SID), including the lack of expression of antimicrobial peptides on the skin, and the demonstration of increased adherence of Staphylococcus aureus to the skin of patients with atopic dermatitis, A serious consequence of atopic dermatitis, psoriasis, and allergic contact dermatitis is that the integrity of the skin barrier is compromised. Recent studies of patients with atopic dermatitis have shown that levels of both epidermal hydration and skin surface lipids are reduced, making the skin more susceptible to colonization with pathogens.

A correlation between the severity of the eczema and colonization with S. aureus has been demonstrated, and it has been determined that bacterial colonization is an important factor aggravating skin lesions. *Staphylococcus*

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aureus has also been found on the skin of more than half of the patients with chronic plaque psoriasis, and colonization with staphylococci and streptococci has been reported to exacerbate psoriasis. Staphylococcal superantigens contribute to the pathogenesis of cutaneous inflammation in atopic dermatitis through various potential mechanisms, viz. direct stimulation of antigen presenting cells and keratinocytes, stimulation of T cell proliferation (by binding to T cell receptors), expansion of skin-homing cutaneous lymphocyte antigen positive T cells. Topical corticosteroid is commonly used in the treatment of eczema and atopic dermatitis and several studies have shown the impact of such treatment on bacterial skin flora.

Antibacterials, whether topical or systemic, in combination with topical corticosteroids, may produce a more rapid decrease in S. aureus colonization than topical corticosteroids monotherapy. Corticosteroids are commonly used in treatment of eczema and Atopic dermatitis. However, when steroid application or administration is stopped, the diseases easily relapse, and when it is used for a long time it may lead to a number of adverse effects such as skin atrophy and secondary infection. Bacterial superantigens were recently shown to induce corticosteroid insensitivity. Hence the eradication of *Staphylococcus aureus* may lead to a steroid-saving effect.

Leyden et al. (Br J Dermatol 1974; 90:525–30.) first showed that the therapeutic effect of antibiotics combined with steroid was better than that of steroid monotherapy. In several open or double-blind placebo-controlled trials, topical and systemic antimicrobials were able to reduce the colonization density and led to a partial improvement of skin lesions.

Larsen FS and et al (Acta Derm Venereol. 2007;87 (1):62-8.) provides a formulation of fusidic acid and betamethasone 17-valerate as an alternative for the short-term treatment of clinically infected atopic dermatitis.

M. A. Cobb (The Veterinary Journal Volume 169, Issue 2, March 2005, Pages 276-280) and et al provides a comparative study of topical preparation containing 0.5% fusidic acid and 0.1% betamethasone-17-valerate with the systemic therapy. The study demonstrates no difference and that both treatment

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regimes represent effective treatment options for the condition such as canine acute moist dermatitis.

Strategos J. (Pharmatherapeutica. 1986; 4(9):601-6.) provides a comparison study of Fusidic acid-betamethasone combination and gentamicin-betamethasone combination.

US 6673783 assigned to Leo Pharmaceutical Products Ltd, provides compounds of Fusidic acid derivatives. The invention also provides combination of Fusidic acid derivatives with other therapeutically active components such as penicillins, cephalosporins, tetracyclines, rifamycins, erythromycins, linocomycin, clindamycin, fluoroquinolones and corticosteroids.

WO2007051468 assigned to Leo Pharma, provides the pharmaceutical composition comprising crystalline fusidic acid. The patent application also provides compositions further comprising another therapeutically active compound selected from the group consisting of antibiotics and corticosteroids.

US 6127353 assigned to Schering Corporation provides mometasone furoate monohydrate and its pharmaceutical compositions.

Combination therapy of a potent topical steroid and a topical antibiotic has been proved to be effective in a number of clinical studies. The secondary bacterial infections can occur as a side effect during long term therapy with potent steroids. These secondary bacterial infections also exacerbate the underlying inflammatory dermatoses, further increasing the amount of steroid required to control it. Advantages of the topical route for antibacterial therapy include the ability to deliver a higher concentration of antibacterial to the skin than would be possible with systemic therapy. Its use also mostly avoids severe systemic reactions

However, the above mentioned prior arts fail to disclose the composition comprising a combination of fusidic acid with corticosteroids especially Mometasone or Halobetasol. Therefore a need remains to develop the topical preparations comprising the combination of fusidic acid with corticosteroids especially Mometasone or Halobetasol. The present invention pharmaceutical compositions comprising a combination of fusidic acid and mometasone furoate

seems to be novel and a good rationale for the treatment of inflammatory dermatoses associated with secondary bacterial infections. The inventors of the present invention surprisingly found that antibiotic action of fusidic acid and the anti-inflammatory effect of corticosteroid, such as Mometasone both play important roles in reducing *S. aureus* and improving patient's symptoms and signs of skin inflammatory infections. Preferably, a combination of fusidic acid and mometasone furoate is useful for the treatment of inflammatory dermatoses associated with secondary bacterial infections, where the dermatoses is taken care of by mometasone and the bacterial infection is treated with fusidic acid.

The present invention pharmaceutical compositions comprising a combination of fusidic acid and Halobetasol propionate. Combination therapy of a potent topical steroid and a topical antibiotic has been proved to be effective in a number of clinical studies. The secondary bacterial infections can occur as a side effect during long term therapy with potent steroids. These secondary bacterial infections also exacerbate the underlying inflammatory dermatoses, further increasing the amount of steroid required to control it. *Staphylococcus aureus* and *streptococcus pyogenes* are the most common organisms infecting the inflammatory dermatoses, hence a combination of Halobetasol propionate and Fusidic acid seems to be a good rationale for the treatment of inflammatory dermatoses associated with secondary bacterial infections, where the dermatoses is taken care of by Halobetasol propionate and the bacterial infection is treated with fusidic acid. The inventors of the present invention surprisingly found that antibiotic action of fusidic acid and the anti-inflammatory effect of a corticosteroid such as Halobetasol, both play important roles in prevention of secondary bacterial infections in patients with non-infected dermatoses and in treatment of infected steroid responsive dermatoses such as secondarily infected dermatoses including secondarily infected contact dermatitis, allergic contact dermatitis, atopic dermatitis, psoriasis and other corticosteroid responsive dermatoses (CRD) with secondary bacterial infections of skin.

OBJECT OF THE INVENTION

An object of the present invention is to provide a topical pharmaceutical compositions comprising combination of a topical antibiotic and a topical steroid for the treatment of inflammatory dermatoses associated with secondary bacterial infections. In particular the present invention relates to topical pharmaceutical compositions comprising a combination of fusidic acid and corticosteroid such as Mometasone furoate useful in treatment of infected eczema's such as secondarily infected dermatitis, including secondarily infected contact dermatitis, psoriasis, allergic contact dermatitis and atopic dermatitis with secondary bacterial infections of skin. In particular the present invention also relates to topical pharmaceutical compositions comprising a combination of fusidic acid and corticosteroid such as Mometasone furoate useful in prevention of infection in cases of dermatitis, especially atopic dermatitis who are at risk of getting secondary bacterial infection

In particular the present invention also relates to topical pharmaceutical compositions comprising a combination of fusidic acid and corticosteroid such as Halobetasol propionate useful in treatment of infected steroid responsive dermatoses such as secondarily infected dermatoses including secondarily infected contact dermatitis, allergic contact dermatitis, atopic dermatitis, psoriasis and other corticosteroid responsive dermatoses (CRD) with secondary bacterial infections of skin. In particular the present invention also relates to topical pharmaceutical compositions comprising a combination of fusidic acid and corticosteroid such as Halobetasol propionate useful in prevention of secondary bacterial infections in patients with non-infected dermatoses

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SUMMARY OF THE INVENTION:

One embodiment of the present invention provides a topical pharmaceutical composition in a suitable dosage form comprising the combination of therapeutically effective amount of an antibiotic, therapeutically effective amount of corticosteroid and a pharmaceutically acceptable carrier. Suitable dosage forms include hydrous or anhydrous semisolids such as creams, gels, ointments, lotions and the like.

Another embodiment of the present invention provides the topical pharmaceutical compositions comprising the combination of a therapeutically effective amount of antibiotic agent such as fusidic acid and therapeutically effective amount of corticosteroid such as Mometasone furoate or any other pharmaceutically acceptable salts/solvates of Mometasone and a pharmaceutically acceptable carrier thereof.

Another embodiment of the present invention provides the use of topical pharmaceutical dosage forms comprising the combination of therapeutically effective amount of antibiotic agent such as fusidic acid and therapeutically effective amount of corticosteroid such as Mometasone furoate or any other pharmaceutically acceptable salts/solvates of Mometasone for the treatment of infected eczema's such as secondarily infected dermatitis, including secondarily infected contact dermatitis, allergic contact dermatitis, psoriasis and atopic dermatitis with secondary bacterial infections of skin.

Another embodiment of the present invention provides the use of topical pharmaceutical dosage forms comprising the combination of therapeutically effective amount of antibiotic agent such as fusidic acid and therapeutically effective amount of corticosteroid such as Mometasone furoate or any other pharmaceutically acceptable salts/solvates of Mometasone useful in prevention of infection in cases of dermatitis, specially atopic dermatitis who are at risk of getting secondary bacterial infection

Another embodiment of the present invention provides the topical pharmaceutical compositions comprising the combination of therapeutically

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effective amount of combination of a) 1% w/w - 5%w/w of fusidic acid; b) 0.05% w/w to 2%w/w of Mometasone furoate; and c) a pharmaceutically acceptable carrier.

Another embodiment of the present invention provides the use of topical pharmaceutical dosage forms comprising the combination of fusidic acid present in the concentration range of 1 % w/w - 5% w/w and Mometasone furoate present in the concentration range of 0.05% w/w to 2% w/w for the treatment of infected eczema's such as secondarily infected dermatitis, including secondarily infected contact dermatitis, allergic contact dermatitis and atopic dermatitis with secondary bacterial infections of skin or in prevention of infection in cases of dermatitis, specially atopic dermatitis who are at risk of getting secondary bacterial infection

Another embodiment of the present invention provides the process for preparing topical pharmaceutical dosage forms comprising a combination of a) an effective amount of fusidic acid; and b) an effective amount of mometasone furoate; and c) a pharmaceutically acceptable carrier thereof. The topical compositions of the present invention having the ratio of Mometasone furoate and fusidic acid ranging from 1:2.5 to 1:20.

Suitable dosage forms include hydrous or anhydrous semisolids such as creams, gels, ointments, creams, lotions or any other dosage form suitable for topical application and the like.

Another embodiment of the present invention provides the topical pharmaceutical compositions comprising the combination of a) a therapeutically effective amount of antibiotic agent such as fusidic acid; and b) a therapeutically effective amount of corticosteroid such as Halobetasol propionate or any other pharmaceutically acceptable salts/solvates of Halobetasol; and c) a pharmaceutically acceptable carrier thereof.

Another embodiment of the present invention provides the use of topical pharmaceutical dosage forms comprising the combination of therapeutically effective amount of antibiotic agent such as fusidic acid and therapeutically effective amount of corticosteroid such as Halobetasol propionate or any other pharmaceutically acceptable salts/solvates of Halobetasol in treatment of infected

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steroid responsive dermatoses such as secondarily infected dermatoses including secondarily infected contact dermatitis, allergic contact dermatitis, atopic dermatitis, psoriasis and other corticosteroid responsive dermatoses (CRD) with secondary bacterial infections of skin. Another embodiment of the present invention provides the use of topical pharmaceutical dosage forms comprising the combination of therapeutically effective amount of antibiotic agent such as fusidic acid and therapeutically effective amount of corticosteroid such as Halobetasol propionate or any other pharmaceutically acceptable salts/solvates of Halobetasol useful in prevention of secondary bacterial infections in patients with non-infected dermatoses.

Another embodiment of the present invention provides the topical pharmaceutical compositions comprising the combination of therapeutically effective amount of a) 1 % w/w - 5% w/w of fusidic acid; and b) 0.01% to 2% w/w of Halobetasol propionate; and c) a pharmaceutically acceptable carrier. The topical compositions of the present invention having the ratio of Halobetasol propionate and fusidic acid ranging from 1:2.5 to 1:100.

Another embodiment of the present invention provides the use of topical pharmaceutical dosage forms comprising the combination of fusidic acid present in the concentration range of 1% w/w - 5%w/w and Halobetasol propionate present in the concentration range of 0.01% to 2% for the treatment of infected steroid responsive dermatoses such as secondarily infected dermatoses including secondarily infected contact dermatitis, allergic contact dermatitis, atopic dermatitis, and other corticosteroid responsive dermatoses (CRD) with secondary bacterial infections of skin or in prevention of secondary bacterial infections in patients with non-infected dermatoses .

Another embodiment of the present invention provides the process for preparing topical pharmaceutical dosage forms comprising the combination of a) an effective amount of fusidic acid; b) an effective amount of Halobetasol propionate; and c) a pharmaceutically acceptable carrier thereof. Suitable dosage forms include hydrous or anhydrous semisolids such as creams, gels, ointments,

creams, lotions or any other dosage form suitable for topical application and the like.

DETAILED DESCRIPTION OF THE INVENTION:

Before describing the present invention in detail, it is to be understood that this invention is not limited to specific pharmacologically active carriers, formulation types, treatments, and so forth, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

DEFINITIONS:

The term "therapeutically effective amount" or "effective amount" is used herein to denote any amount of a topical formulation which will cause a substantial improvement in a disease condition when applied to the affected area. A single application can be sufficient, or the formulation can be applied repeatedly over a period of time. The amount will vary with the condition being treated, the stage of advancement of the condition, and the type and concentration of formulation applied. In the present invention, antibiotic agent such as fusidic acid is present in the concentration range of 1% w/w- 5%w/w of the total composition and corticosteroid such as Mometasone furoate is present in the concentration range of 0.05% w/w to 2% w/w of the total composition. In the present invention, antibiotic agent such as fusidic acid is present in the concentration range of 1% w/w - 5% w/w of the total composition and corticosteroid such as Halobetasol propionate is present in the concentration range of 0.01%w/w to 2%w/w of the total composition.

The terms "drug" and "pharmaceutical" are also used interchangeably to refer to a pharmacologically active substance or composition.

The term "topical composition" or "topical formulation" means a composition in which the drug may be placed for direct application to a skin surface and from which an effective amount of the drug is released. Such formulations may include creams, ointments, gels, lotions, or any other dosage

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form suitable for topical application and the like. In some aspects, such formulations may be applied to the skin in an unoccluded form with/without additional backing, structures or devices.

The term "skin" or "skin surface" is meant to include the outer skin of a subject comprising one or more of epidermal layers to which a drug composition may be administered.

The term "treating" or "treatment" of a state, disorder or condition as used herein means: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a mammal.

The term "Eczema" also known as dermatitis is a non-infectious skin disorder characterized by itching and often accompanied by small blisters. It may be caused by a variety of internal (endogenous) & external (exogenous) factors and it may be acute or chronic. There are numerous types of eczema, it can be either Atopic dermatitis or Contact dermatitis.

Atopic dermatitis is a chronic skin disease, commonest form of eczema and is closely linked with asthma and hay fever and can affect both children & adults can also be inherited and usually appears in infancy or early childhood. This disease becomes worsen after eating certain foods or after being exposed to other allergens such as pollen or dust. Most common symptoms include itchiness (or pruritus), dryness of skin, redness & inflammation. Constant scratching can also cause skin to split, leaving it prone to infection and thus bacterial infections occur frequently in lesions of atopic dermatitis.

Contact dermatitis is a localized reaction that includes redness, itching, and burning. Contact dermatitis occurs when the skin has come into contact with allergens or irritants and produces either irritant contact dermatitis or allergic contact dermatitis. Irritant contact dermatitis is a direct irritation of skin caused due to direct chemical damage that releases mediators of inflammation predominately from epidermal cells. Allergic contact dermatitis is a red, itchy, weepy reaction when the skin has come into contact with a substance that the immune system recognizes as foreign, such as poison ivy, poison oak or poison sumac or certain preservatives present in creams and lotions. This type of

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reaction reflects a specific sensitivity or allergy to a specific substance. Because of damage to the skin barrier function they have a propensity of becoming secondarily infected with bacteria; infected eczema skin may crack & weep ('wet' eczema).

The term "pharmaceutically acceptable" such as in the recitation of a "pharmaceutically acceptable carrier" or a "pharmaceutically acceptable salt/solvate or derivative" is meant a compound that is not biologically or otherwise undesirable, i.e., the compound may be incorporated into a topical formulation of the invention and administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the formulation in which it is contained.

The term "carriers" or "vehicles" as used herein refer to pharmaceutically acceptable carrier materials suitable for topical drug administration. Carriers and vehicles useful herein include any such materials known in the art that are non-toxic and do not interact with other components of the composition in a deleterious manner.

"Fusidic acid" is a steroidal antibiotic, chemically related to cephalosporin P. It interferes with amino acid transfer from amino aminoacyls RNA to protein on the ribosomes inhibiting bacterial protein synthesis. It may be bacteriostatic or bactericidal depending upon the drug concentration. Fusidic acid is active against gram-positive bacteria, particularly staphylococci, with almost no activity against gram-negative organisms. It is also active against Streptococci (including Pneumococci) and Corynebacteria. At least 99% of oxacillin-resistant staphylococcus aureus were inhibited at a concentration of 2 mg/L, 100% of oxacillin-sensitive staphylococcus aureus were inhibited at a concentration of 0.12 mg/L and 99% of staphylococcus epidermidis were inhibited at 4 mg/L. Other bacteria that demonstrated 90% of organisms inhibited at 2 mg/L or less included; Peptococcus species, Clostridium species Propionibacterium Danes, and most Bacteroides species. Fusidic acid 2% cream monotherapy or combination therapy (betamethasone, beclomethasone dipropionate, ketoconazole, and sodium

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fusidate) is effective in the treatment of secondary bacterial infections occurring in dermatitis, pyoderma, furuncle, eczema, burns, and psoriasis.

"Corticosteroids" are a class of steroid hormones that are produced in the adrenal cortex. Corticosteroids are involved in a wide range of physiologic systems such as stress response, immune response and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior.Topical corticosteroids are used to help relieve redness, swelling, itching, and discomfort of many skin problems. These medicines are like cortisone. They belong to the general family of medicines called steroids. Steroidal anti-inflammatory agents, including but not limited to, corticosteroids such as mometasone, Fluticasone, Clobetasone, hydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethasone dipropionate, alclometasone, clobetasol valerate, Desoximetasone, Diflorasone, Fluocinolone, Fluocinonide, Halobetasol, desonide, desoxycorticosterone acetate, dexamethasone, dichlorisone, deflorasonediacetate, diflucortolone valerate, fluadronolone, fluclarolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocionide, flucortine butylester, fluocortolone, flupredidene (flupredylidene) acetate, flurandronolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenalone acetonide, medrysone, amciafel, amcinafide, betamethasone and its esters, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone, triamcinolone and mixtures thereof may be used. Preferably, mometasone or halobetasol may be used.

"Mometasone" a halogenated monoester, is a synthetic corticosteroid which is highly effective but may have a lower incidence of adverse effects than

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other corticosteroids. Studies performed with Mometasone cream 0.1% indicates that it is in the medium range of potency as compared with other topical corticosteroids. Corticosteroids have multiple mechanisms of action including anti-inflammatory activity, immunosuppressive properties, and anti-proliferative actions. Anti-inflammatory effects result from decreased formation, release and activity of the mediators of inflammation (eg. kinins, histamine, liposomal enzymes, prostaglandins, leukotrienes) which reduces the initial manifestations of the inflammatory process. Corticosteroids inhibit margination and subsequent cell migration to the area of injury, and also reverse the dilation and increased vessel permeability in the area, resulting in decreased access of cells to the sites of injury. This vasoconstrictive action decreases serum extravasation, swelling and discomfort. The immunosuppressive properties decrease the response to delayed and immediate hypersensitivity reactions (eg, type III and type IV). This results from inhibition of the toxic effect from antigen and antibody complexes that precipitate in vessel walls creating cutaneous allergic vasculitis, and by inhibiting the action of lymphokines, target cells, and macrophages which together produce allergic contact dermatitis reactions. Additionally, the access of sensitized T lymphocytes and macrophages to target cells may also be prevented by corticosteroids. The anti-proliferative effects reduce hyperplastic tissue characteristic of psoriasis.

Like other topical corticosteroids, mometasone furoate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. It is postulated that lipocortins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid.

"Halobetasol", a synthetic corticosteroid, structurally related to clobetasol ,belongs to category of high potency steroids. Halobetasol propionate has been

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shown to be a super high-potency topical corticosteroid by vasoconstrictor assay in solution, cream, and ointment formulations. Like other topical corticosteroids, halobetasol propionate has anti-inflammatory, antipruritic and vasoconstrictive actions. Corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. Human and animal studies indicate that less than 6% of the applied dose of halobetasol propionate enters the circulation within 96 hours following topical administration of the cream.

Halobetasol being a steroid has multiple mechanisms of action including anti-inflammatory activity, immunosuppressive properties, and antiproliferative actions. Anti-inflammatory effects arise from decreased formation, release, and activity of the mediators of inflammation (eg, kinins, histamine, liposomal enzymes, prostaglandins, leukotrienes), which reduce the initial manifestations of the inflammatory process. Corticosteroids inhibit margination and subsequent cell migration to the area of injury, and also reverse the dilation and increased vessel permeability in the area, resulting in decreased access of cells to the sites of injury. This vasoconstrictive action decreases serum extravasation, swelling, and discomfort. The immunosuppressive properties decrease the response to delayed and immediate hypersensitivity reactions (eg, type III and type IV). This arises from inhibition of the toxic effect from antigen and antibody complexes that precipitate in vessel walls creating cutaneous allergic vasculitis, and by inhibiting the action of lymphokines, target cells, and macrophages that together produce allergic contact dermatitis reactions. Additionally, the access of sensitized T lymphocytes and macrophages to target cells may also be prevented by corticosteroids. The antiproliferative effects reduce hyperplastic tissue characteristic of psoriasis.

The topical formulations of the present invention include those suitable for topical, transdermal, rectal and buccal (e.g., sub-lingual) administration e.t.c. preferably the formulations of the present invention are administered topically and are provided in the form of semisolid dosage forms. Suitable dosage forms include hydrous or anhydrous semisolids such as creams, ointments, gels, lotions or any other dosage form suitable for topical application and the like.

The term "hydrous" as used here in means the presence of water in a concentration range of about 5% to 95% in the composition.

The term "anhydrous" as used here in means the presence of water in a concentration range of less than 5% in the composition.

The topical formulations of the present invention with Mometasone and fusidic acid are useful treatment of infected eczema's such as secondarily infected dermatitis, including secondarily infected contact dermatitis, allergic contact dermatitis and atopic dermatitis with secondary bacterial infections of skin or in prevention of infection in cases of dermatitis, psoriasis, specially atopic dermatitis who are at risk of getting secondary bacterial infection or in prevention of infection in cases of dermatitis, specially atopic dermatitis who are at risk of getting secondary bacterial infection

The topical formulations of the present invention with Halobetasol and fusidic acid are useful in the treatment of infected steroid responsive dermatoses such as secondarily infected dermatoses including secondarily infected contact dermatitis, allergic contact dermatitis, atopic dermatitis, and other corticosteroid responsive dermatoses (CRD) with secondary bacterial infections of skin or in prevention of secondary bacterial infections in patients with non-infected dermatoses .

The topical formulations for the method of treatment of the present invention may be administered from 1 to 6 times daily and more usually from 2 to 4 times daily.

The topical pharmaceutical composition of the present invention may include suitable pharmaceutically acceptable carriers. A wide range of ingredients including, emollients; emulsifying agents; emulsion stabilizers and viscosity builders; humectants; odorants; preservatives, antioxidants, and chemical stabilizers; solvents; and thickening, stiffening, suspending agents; buffers, neutralizing agents and agents to adjust pH; coloring agents, opacifiers and decoloring agents, pigments; and antifoaming agents, skin feel modifiers and the like. Exemplary emollients include octyldodecanol, caprylic/capric triglycerides, castor oil, ceteareth-20, ceteareth-30, cetostearyl alcohol, ceteth 20, cetostearyl

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alcohol, cetyl alcohol, cetyl stearyl alcohol, cocoa butter, diisopropyl adipate, glycerin, gyceryl monooleate, glyceryl monostearate, glyceryl stearate, isopropyl myristate, isopropyl palmitate, lanolin, lanolin alcohol, hydrogenated lanolin, liquid paraffins, linoleic acid, mineral oil, oleic acid, white petrolatum, polyethylene glycol, polyoxyethylene glycol fatty alcohol ethers, polyoxypropylene 15-stearyl ether, propylene glycol stearate, propylene glycol mono stearate squalane, steareth-2 or -100, stearic acid, stearyl alcohol, urea and the like. Exemplary emulsifying agents include Propylene glycol stearate, aluminum starch octenylsuccinate, ammonium hydroxide, amphoteric-9, beeswax, white beeswax, synthetic beeswax, carbomer 934, carbomer 934P, carbomer 940, ceteareth-20, ceteareth-30, cetearyl alcohol, ceteth 20, cetyl alcohol, cholesterol, cyclomethicone, diglycerides, dimethicone (e.g., dimethicone 350), disodium monooleamido sulfosuccinate, NF emulsifying wax, fatty acid pentaerythritol ester, glycerides, glyceryl monooleate, glyceryl monostearate, glyceryl stearate, lanolin, lanolin alcohol, hydrogenated lanolin, magnesium stearate, mineral oil, monoglycerides, polyethylene glycol, PEG stearate, polyethylene glycol 6000 distearate, polyethylene glycol 1000 monocetyl ether, polyethylene glycol monostearate, polyethylene glycol 400 monostearate, polyoxyethylene glycol fatty alcohol ethers, polyoxyl 20 cetostearyl ether, polyoxyl 40 stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polysorbates, PPG-26 oleate, propylene glycol stearate, quaternium-15, simethicone, sodium laureth sulfate, sodium lauryl sulfate, sorbitan esters, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan palmitate, sorbitan sesquioleate, steareth-2, steareth-100, stearic acid, stearyl alcohol, triethanolamine, trolamine and the like. Exemplary emulsion stabilizers and viscosity builders include carbomer 934, carbomer 934P, carbomer 940, cetearyl alcohol, cetostearyl alcohol, cetyl alcohol, cetyl stearyl alcohol, dextrin, diglycerides, disodium edetate, edetate disodium, glycerides, glyceryl monostearate, glyceryl stearate, hydroxypropyl cellulose, monoglycerides, plasticized hydrocarbon gel, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 1450, polyethylene glycol 8000, polyethylene glycols,

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propylene glycol stearate, stearyl alcohol and the like. Exemplary humectants include glycerin, propylene glycol, sorbitol, urea and the like. Exemplary odorants include hypoallergenic perfume, menthol and the like. Exemplary preservatives, antioxidants, and chemical stabilizers include alcohol, benzyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, butylparaben, calcium acetate, caster oil, chlorocresol, Potassium sorbate, 4chloro-m-cresol, citric acid, disodium edetate, Dowicil 200 (Dow), edetate disodium, ethoxylated alcohol, ethyl alcohol, glycerin, Glydant Plus (Lonza), 1,2,6-hexanetriol, Kathon CG (Rohm & Haas), Liquid Germall Plus (ISP Sutton Labs), Liquipar (ISP Sutton Labs), methylparaben, parabens, potassium sorbate, propyl gallate, propylene glycol, propylparaben, sodium bisulfite, sodium citrate, sodium metabisulfite, sorbic acid, tannic acid, triglycerides of saturated fatty acids, Ucarcide (Union Carbide), Vitamin E, zinc stearate and the like. Exemplary solvents include alcohol, castor oil, diisopropyl adipate, ethoxylated alcohol, ethyl alcohol, fatty alcohol citrate, glycerin, 1,2,6-hexanetriol, hexylene glycol, isopropyl alcohol, isopropyl myristate, isopropyl palmitate, mineral oil, phosphoric acid, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 1450, polyethylene glycol 8000, polyethylene glycol 1000 monocetyl ether, polyethylene glycol monostearate, polyethylene glycol 400 monostearate, polyethylene glycols, polyoxyl 20 cetostearyl ether, polyoxypropylene 15-stearyl ether, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polysorbates, octyldodecanol, propylene carbonate, propylene glycol, purified water, and SD alcohol 40, triglycerides of saturated fatty acids and the like. Exemplary thickening, stiffening and suspending agents include aluminum stearate, beeswax, white beeswax, synthetic beeswax, carbomer 934, carbomer 934P, carbomer 940, cetostearyl alcohol, cetyl alcohol, cetyl esters wax, dextrin, glyceryl monostearate, hydroxypropyl cellulose, kaolin, paraffin, white soft paraffin, petrolatum, white petrolatum polyethylene, propylene glycol stearate, starch, stearyl alcohol, wax, white wax, xanthan gum, bentonite and the like. Exemplary buffers, neutralizing agents and agents to adjust pH include phosphoric acid, ammonium hydroxide, citric acid, diisopropanolamine, hydrochloric acid, lactic acid, monobasic sodium phosphate, sodium citrate,

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sodium hydroxide, sodium phosphate, triethanolamine, trolamine and the like. Exemplary opacifiers/colorants include suitable for use may be organic and/or inorganic and the like. Suitable examples include titanium dioxide, and pre-dispersed titanium dioxide. Exemplary antifoaming agents include cyclomethicone, dimethicone (e.g., dimethicone 350), simethicone and the like. Exemplary skin feel modifiers Aluminum starch octenylsuccinate (gamma irradiated) and the like.

The invention is further exemplified with following examples and is not necessarily limited to the present formulations. It is obvious to those skilled in the art to find out the composition for other dosage forms and substitute the equivalent excipients as described in this specification or with the one known to the art.

Example 1 : Mometasone furoate and Fusidic acid Topical formulation.

Steps	Ingredients	% w/w
I	White Soft Paraffin	63.869
	White Bees Wax	5.000
	Promulgen G™	7.000
	Propylene Glycol Monostearate	8.000
	Aluminium Starch Octenylsuccinate (Dry Flow Pure™)	5.000
II	Purified water	3.000
	Hexylene Glycol	6.000
	Phosphoric Acid (10%w/v)	*
	Mometasone Furoate, Micronised	0.100
	Fusidic Acid(Micronised)	2.000

* Quantity required to adjust pH of Hexylene Glycol & water solution up to pH 4.0

Brief Manufacturing Process

1. Preparation of Oil Phase : White Soft Paraffin, White Bees Wax, Promulgen G™, Propylene Glycol Monostearate, Aluminium Starch Octenylsuccinate (Dry Flow Pure™) were heated to the temperature range 70-72°C.

2. Preparation of Drug Phase : pH of Hexylene Glycol & water solution was adjusted up to pH 4.0 using Phosphoric acid. This was heated up to 70°C to

72°C. Mometasone Furoate and Fusidic Acid was added to this solution and dissolved with stirring.

3. Emulsification: Added drug phase to oily phase under stirring maintaining the temperature at 70°C to 72°C.And then homogenized for 10 minutes. After homogenization, the mixed phase was slowly cooled to get a white to off white topical cream.

Example 2 : Mometasone furoate and Fusidic acid Topical formulation.

Step	Ingredients	% w/w
I	White Soft Paraffin	6.000
	Liquid Paraffin	6.000
	White Bees Wax	1.500
	Promulgen G	4.000
	Propylene Glycol Monostearate	2.000
	Polysorbate 60	1.500
	Cetostearyl Alcohol	6.000
	Butylated Hydroxytoluene (BHT)	0.050
	Butylated Hydroxyanisole (BHA)	0.050
II	Purified water	46.569
III	Purified water	1.000
	Potassium Sorbate	0.200
IV	Phenoxyethanol	0.500
V	Purified water	5.000
	Polysorbate 60	0. 500
	Glycerin	8.000
	Fusidic Acid	2.000
VI	Purified Water	3.000
	Hexylene Glycol	6.000
	Phosphoric Acid solution (10%)	*
	Mometasone Furoate	0.100

* Quantity required for adjusting pH of Hexylene Glycol & water solution up to pH 4.0 and then adjusting the final pH.

Brief Manufacturing Process

1. Preparation of Oil Phase : White Soft Paraffin, Liquid Paraffin, White Bees Wax, Promulgen G™, Propylene Glycol Monostearate, Polysorbate 60, Cetostearyl Alcohol to the temperature range 70-72°C. Butylated Hydroxytoluene and Butylated Hydroxyanisole were added.

2. Preparation of Aqueous Phase :Purified water was heated to the temperature range 70-72°C

3. Emulsification Phase : Added oil phase to aqueous phase at 70°C to 72°C and homogenized for 15 minutes.

4. Mometasone Furoate Phase : Adjusted the pH of Hexylene Glycol & water solution up to pH 4.0 with phosphoric acid, followed by heating up to 70°C to 72°C. Dissolved Mometasone Furoate under stirring . Add drug solution of Mometasone furoate to emulsification phase at 70°C.

5.Fusidic Acid Phase :_Purified water & Glycerin were taken and Polysorbate 60 was added to it. Dispersed under stirring Fusidic Acid. Added Fusidic acid solution to emulsification phase at 70°C.

6. Added previously dissolved potassium sorbate solution in water to bulk at 40° C under stirring.

7. Added Phenoxyethanol to the bulk at 40° C under stirring. The bulk was then cooled under stirring slowly to get a cream.

Physical Parameters tested :

Description : white coloured cream
pH : 5.0 to 5.5

Example 3 : Mometasone furoate and Fusidic acid Topical formulation.

Step	Ingredients	% w/w
I	White Soft Paraffin	6.000
	Light Liquid Paraffin	6.000
	Sorbitan Monosterate (SMS)	2.000
	Polyoxyl 20 Cetyl Ether **(Brij 58)**	2.000
	Cetostearyl alcohol	8.000
	White Bees Wax	3.000
	Butylated Hydroxyanisole **(BHA)**	0.050
	Butylated Hydroxytoluene **(BHT)**	0.050
II	Purified water	52.069
	Glycerin	8.000
III	Purified water	1.000
	Potassium Sorbate	0.200
IV	Phenoxyethanol	0.500
V	Purified water	3.000
	Hexylene Glycol	6.000
	Phosphoric Acid (10%w/v)	*
	Mometasone Furoate	0.100
	Fusidic Acid	2.000

* Quantity required for adjusting pH of Hexylene Glycol & water solution up to pH 4.0 and then adjusting the final pH.

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Brief Manufacturing Process

1. Preparation of Oil Phase ; White Soft Paraffin, Light Liquid Paraffin, Sorbitan Monostearate , Polyoxyl 20 Cetyl Ether, Cetostearyl Alcohol, White Bees Wax to the temperature range 70-72°C. Butylated Hydroxytoluene and Butylated Hydroxyanisole were added.

2. Preparation of Aqueous Phase : Purified water and glycerine mixture was heated to a temperature range 70°C to 72°C

3. Emulsification Phase : Added oil phase to aqueous phase at 70°C to 72°C and homogenized for 15 minutes.

4. Preparation of Drug Phase: Adjusted the pH of Hexylene Glycol & water solution up to pH 4.0 with phosphoric acid. Followed by heating upto 70°C to 72°C. Mometasone Furoate and Fusidic Acid were dissolved under stirring. Then added to emulsification phase at 70°C.

5.Added previously dissolved potassium sorbate solution in water to bulk at 40° C under stirring.

6. Added Phenoxyethanol to the bulk at 40° C under stirring. The bulk was then cooled under stirring slowly to get a cream.

Physical Parameters:

Description	: white coloured cream
pH	: 5.0 to 5.5

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Example 4 : Halobetasol Propionate and Fusidic acid Topical formulation

Steps	Ingredients	% w/w
I	White Soft Paraffin	4.000
	Polyoxyl 20 Cetyl Ether **(Brij 58)**	1.800
	Cetyl Alcohol	2.000
	Cetostearyl alcohol	8.000
	Dimethicone 350	0.500
	Isopropyl Palmitate	5.500
	Butylated Hydroxytoluene (BHT)	0.100
	Phenoxyethanol	0.700
II	Purified water	58.626
	Potassium Sorbate	0.200
III	Glycerin	2.000
	Polyoxyl 20 Cetyl Ether (Brij 58)	0.050
	Water	0.750
	Halobetasol Propionate	0.050
IV	Glycerin	6.000
	Polyoxyl 20 Cetyl Ether *(Brij 58)*	0.200
	Purified Water	7.000
	Fusidic Acid	2.000
V	Phosphoric Acid solution 10%	0.524

Brief Manufacturing Process

1. Preparation of Oil Phase ; White Soft Paraffin, part of Polyoxyl 20 Cetyl Ether , Cetyl alcohol, Cetostearyl Alcohol, Dimethicone 350, Isopropyl Palmitate, Butylated Hydroxytoluene and Phenoxyethanol to the temperature range 70-72°C.
2. Preparation of Aqueous phase :Dissolved potassium sorbate in water and heated to a temperature range 70-72°C.
3. Emulsification : Added oil phase to aqueous phase at 70°C to 72°C and homogenized for 15 minutes, followed by cooling.
4. Heated glycerin up to 60°C then added Polyoxyl 20 Cetyl Ether (Brij 58) to melt completely and added water to maintain temperature up to 40° to 42°C. At 42°C added under stirring Halobetasol Propionate to disperse completely.
5. Heated glycerin up to 60°C then added Polyoxyl 20 Cetyl Ether (Brij 58) to melt completely and added water to maintain temperature up to 40° to 42°C. At 42°C added under stirring Fusidic Acid to disperse completely.
6. Added Halobetasol solution to the bulk at 50° C under stirring.

7. Added Fusidic Acid solution to the bulk at 40° C under stirring.

8. Added Phosphoric Acid solution 10% to the bulk at 40° C under stirring. The bulk was then cooled under stirring slowly to get a cream.

Physical Parameters:

Description : white coloured cream

pH at 25°C : 4.5 - 6.00

Example 5 : Halobetasol Propionate and Fusidic acid Topical formulation

STEP	INGREDIENTS	% w/w
I	White Soft Paraffin	4.000
	Polyoxyl 20 Cetyl Ether (Brij 58)	1.800
	Cetyl Alcohol	2.000
	Cetostearyl alcohol	8.000
	Dimethicone 350	0.500
	Isopropyl Palmitate	5.500
	Butylated Hydroxytoluene (BHT)	0.100
	Benzyl Alcohol	1.000
II	Purified water	63.320
	Potassium Sorbate	0.200
III	Glycerin	2.000
	Polyoxyl 20 Cetyl Ether (Brij 58)	0.050
	Water	0.750
	Halobetasol Propionate (Micronized)	0.050
IV	Glycerin	6.000
	Polyoxyl 20 Cetyl Ether ***(Brij 58)***	0.200
	Purified Water	2.000
	Fusidic Acid(Micronized)	2.000
V	Phosphoric Acid solution (10%)	0.530

Brief Manufacturing Process

1. Preparation of Oil Phase ; White Soft Paraffin, part of Polyoxyl 20 Cetyl Ether , Cetyl alcohol, Cetostearyl Alcohol, Dimethicone 350, Isopropyl Palmitate, Benzyl alcohol to the temperature range 70-72°C.

2. Preparation of Aqueous phase :Dissolved potassium sorbate in water and heated to a temperature range 70-72°C.

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3. Emulsification:Added oil phase to aqueous phase at 70°C to 72°C and homogenized for 15 minutes, followed by cooling.

4. Heated glycerin up to 60°C then added Polyoxyl 20 Cetyl Ether (Brij 58) to melt completely and added water to maintain temperature up to 40° to 42°C. At 42°C added under stirring Halobetasol Propionate to disperse completely.

5. Heated glycerin up to 60°C then added Polyoxyl 20 Cetyl Ether (Brij 58) to melt completely and added water to maintain temperature up to 40° to 42°C. At 42°C added under stirring Fusidic Acid to disperse completely.

6. Added Halobetasol solution to the bulk at 50° C under stirring.

7. Added Fusidic Acid solution to the bulk at 40° C under stirring.

8. Added Phosphoric Acid solution 10% to the bulk at 40° C under stirring. The bulk was then cooled under stirring slowly to get a cream.

Example 6 : Halobetasol Propionate and Fusidic acid Topical formulation

STEP	INGREDIENTS	% w/w
I	White Soft Paraffin	4.000
	Polyoxyl 20 Cetyl Ether (Brij 58)	2.000
	Cetyl Alcohol	2.000
	Cetostearyl alcohol	8.000
	Dimethicone 350	0.500
	Isopropyl Palmitate	6.000
	Butylated Hydroxytoluene (BHT)	0.100
	Benzyl Alcohol	1.000
II	Purified water	63.350
III	Diethylene Glycol Monoethyl Ether (Transcutol P)	1.000
	Halobetasol Propionate	0.050
IV	Hexylene Glycol	5.000
	Glycerin	4.000
	Polysorbate 60 (Tween 60)	1.000
	Fusidic Acid	2.000

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Brief Manufacturing Process

1. Preparation of Oil Phase ; White Soft Paraffin, Polyoxyl 20 Cetyl Ether , Cetyl alcohol, Cetostearyl Alcohol, Dimethicone 350, Isopropyl Palmitate, BHT, Benzyl alcohol to the temperature range 70-72°C.
2. Preparation of Aqueous phase : Heated water to a temperature range 70-72°C.
3. Emulsification : Added oil phase to aqueous phase at 70°C to 72°C and homogenized for 15 minutes, followed by cooling.
4. In Separate container Diethylene Glycol Monoethyl Ether (Transcutol P) was taken, to this added under stirring Halobetasol Propionate. Continued stirring for 5 minutes to dissolve completely and added to the bulk at 50° C under stirring.
5. Heated Hexylene Glycol up to 50°C then added glycerin and Polysorbate 60 (Tween 60) and maintained temperature up to 50° - 52°C. At 52°C added under stirring Fusidic Acid to dissolve completely. Added the Fusidic Acid solution to the main bulk at 40° C under stirring. The bulk was then cooled under stirring slowly to get a cream.

Example 7 : Halobetasol Propionate and Fusidic acid Topical formulation

STEP	INGREDIENTS	% w/w
I	White Soft Paraffin	9.000
	Cetostearyl Alcohol	10.000
	liquid Paraffin	7.000
	Polysorbate 60 (Tween 60)	2.000
	Vitamin E (As dl-alpha Tocopherol Acetate)	0.050
	Butylated Hydroxytoluene	0.050
II	Purified Water	57.580
	Potassium sorbate	0.270
III	Diethylene Glycol Monoethyl Ether (Transcutol P)	1.000
	Halobetasol Propionate	0.050
IV	Glycerin	10.000
	Polysorbate 60 (Tween 60)	1.000
	Fusidic Acid	2.000

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Brief Manufacturing Process

1. Preparation of Oil Phase ; White Soft Paraffin, Cetostearyl Alcohol, Liquid paraffin, Polysorbate 60, Vitamin E, Butylated Hydroxytoluene to the temperature range 70-72ºC.
2. Preparation of Aqueous phase : Potassium sorbate dissolved in water and heated to a temperature range 70-72ºC.
3. Emulsification :Added oil phase to aqueous phase at 70°C to 72°C and homogenized for 15 minutes, followed by cooling.
4. In Separate container Diethylene Glycol Monoethyl Ether (Transcutol P) was taken, to this added under stirring Halobetasol Propionate. Continued stirring for 5 minutes to dissolve completely and added to the bulk at 50° C under stirring.
5. Heated glycerin and Polysorbate 60 (Tween 60) up to 50°C then added Fusidic Acid to disperse completely. Added the Fusidic Acid dispersion to the main bulk at 40° C under stirring. The bulk was then cooled under stirring slowly to get a cream.

Example 8 : Halobetasol Propionate and Fusidic acid Topical formulation

STEP	INGREDIENTS	% w/w
I	Cetyl Alcohol	12.000
	Isopropyl Isostearate (Prisorin 2021)	3.000
	Isopropyl Palmitate	2.000
	Polyoxyl 20 Cetyl Ether (Brij 58)	2.000
	Polyoxyethylene (21) Stearyl Ether (Brij 721)	3.000
II	Purified Water	56.663
III	Purified Water	5.000
	Imiduria	0.200
IV	Purified Water	3.000
	Methylisothiazolinone & Methylchloroisothiazolinone (Kathon CG)	0.050
V	Glycerin	8.000
	Polyoxyl 20 Cetyl Ether (Brij 58)	1.000
	Fusidic Acid (Micronized)	2.037
VI	Glycerin	2.000
	Halobetasol Propionate (Micronized)	0.050
	Total	100.000

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Brief Manufacturing Process

1. Preparation of Oil Phase : Heated Cetostearyl Alcohol, Isopropyl Isostearate, Polyoxyl 20 Cetyl Ether *(Brij 58),* Polyoxyethylene (21) Stearyl Ether *(Brij 721)* to the temperature range 70-72°C.

2. Preparation of Aqueous phase :Heated part of water to a temperature range 70-72°C.

3. Emulsification :Added oil phase to aqueous phase at 70°C to 72°C and homogenized for 15 minutes, followed by cooling.

4. Added Imiduria solution in water to the bulk at 40°-42° C under stirring.

5. Added Kathon CG dispersion to the bulk at 40°-42° C under stirring.

6. Heated glycerin and Polyoxyl 20 Cetyl Ether (Brij 58) up to 50°C then added Fusidic Acid to disperse completely. Added Fusidic Acid dispersion to the main bulk at 40° C under stirring.

7. In Separate container , Glycerin was taken, to this added under stirring Halobetasol Propionate. Continued stirring for 5 minutes to disperse completely and added to the bulk at 40° C under stirring. The bulk was then cooled under stirring slowly to get a cream.

The compositions of the present invention, example 1 and 4 were tested for clinical efficacy on human volunteers for indications described herein.

The formulation of the present invention were assessed for efficacy, safety and tolerability of combination of Mometasone 0.1%w/w plus Fusidic acid 2%w/w cream, Example 1 vs Mometasone 0.1%w/w cream for prevention of secondary bacterial infections in patients with corticosteroid-responsive dermatoses. The combination preparation of Momometasone and Fusidic acid of the present invention was compared with marketed preparation Momate® containing 0.1%w/w Momatasone furoate, available in India, Malaysia and Philippines, marketed by Glenmark Pharmaceutical Ltd..

Prospective, randomized, multicentre, open label study .was conducted with 50 Male & female (post-menopausal, surgically sterilized or practicing a reliable method of birth control) patients with age ranging from 12 to 65 years..

The duration of the study was 3 weeks, including a 2-week active treatment period, preceded by a 1-week washout phase. The patients selected were clinically diagnosed for corticosteroid-responsive dermatoses without secondary bacterial infections. The exclusion criteria for the patients were pregnant and lactating women, Serious skin disorders, dyspigmentation and extensive scarring in the affected areas., Hypersensitivity to Mometasone or Fusidic acid or cream base., Immuno-compromised states and patients with systemic infections., Patients who have participated in a new drug study in the past 6 months., Patients with severe cardiac, hepatic, renal, or cerebrovascular disease, malignancy, chronic uncontrolled systemic diseases e.g., diabetes, hypertension, asthma, collagen disorders, etc. or any other serious medical illness.

Study Plan

Activity/Observation	Screening Visit (Day -7)	Visit I (Baseline /Day 0)	Visit II (Day 6-7)	Visit III (Day 13-14)
Demographic Variables	X			
History and Physical Examination	X			
Inclusion/Exclusion Criteria	X			
Informed Consent	X			
Clinical Evaluation	X	X	X	X
Laboratory and other investigations	X			
Study drug treatment		X	X	X
Adverse Events		X	X	X
Patient Compliance			X	X
Overall Assessment of Efficacy			X	X
Bacteriological evaluation	X			X

Screening visit:

Demographic data and history of the patients were recorded and a brief physical examination was performed. Patients were recruited based on the inclusion and exclusion criteria. Written, informed consent was obtained from these patients. Clinical assessment of the condition under study, laboratory investigations, chest

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x-ray & ECG were carried out at this visit. Patients were given a 1-week washout period following which study treatment was initiated.

Clinical Efficacy Parameters assessed:

The study was designed to monitor clinical signs and symptoms such as Scaling, Erythema, Itching, Induration/Edema, Pain, Exudation/Crusting and Total sign/ symptom. In addition Severity of lesion, Discharge for lesion, Bacteriological findings and Bacteriological findings including *Staphylococcus aureus*, *Staphylococcus epidermidis*, Streptococcus spp, Enterobacteriaceae were also monitored.

Study Treatment

Patients received Mometasone 0.1% plus Fusidic acid 2% cream to be applied over the affected area/s twice daily as a thin film and rubbed in gently and completely, with each application separated by about 12 hours.

Overall Global Assessment of Efficacy

At the end of study, an overall assessment of the efficacy of the medication was performed by both the investigator and the patient.

Physician's Global Evaluation included the following parameters:

Grade	Evaluation
1	Complete resolution (100 % remission of signs and symptoms)
2	Excellent (90-99 % improvement)
3	Marked (75-89 % improvement)
4	Moderate (50-74 % improvement)
5	Slight (30-49 % improvement)
6	No appreciable improvement (0-29 %)
7	Worse (< 0 %)

Patient's Global Evaluation

Grade	Evaluation
1	Greatly improved
2	Somewhat improved
3	Same
4	Somewhat worse
5	Much worse

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Patient Compliance was assessed on visits II, III and IV by direct questioning to the patients.

Results of the study :

The study data for assessment for efficacy of combination of Mometasone 0.1%w/w and Fusidic acid 2%w/w cream(Example 1 of the present invention) vs Mometasone 0.1%w/w cream, Momate® for prevention of secondary bacterial infections in patients with corticosteroid-responsive dermatoses were pooled and results were analyzed using a non-parametric test. All tests were two tailed & $p<0.05$ were considered to be significant.

Table 1 : Results of Clinical symptoms assessment with combination of Mometasone 0.1% w/w and Fusidic acid 2% w/w cream(Example 1 of the present invention) vs Mometasone 0.1% w/w cream, Momate® for prevention of secondary bacterial infections in patients with corticosteroid-responsive dermatoses.

Table 1	Mean Total Score ($\overline{X} \pm$ SD)					
Indication	**Effect on Scaling**		**Effect on Erythema**		**Effect on Itching**	
Duration in days	Example 1	Momate®	Example 1	Momate®	Example 1	Momate ®
Baseline	2.52 ± 0.95	2.60 ± 0.91	2.46 ± 0.88	2.35 ± 0.73	2.39 ± 0.80	2.44 ± 0.93
6 - 7	*1.72 ± 0.69	*1.95 ± 0.77	*1.23 ± 0.72	@ *1.64 ± 0.90	*1.28 ± 0.67	@*1.78± 0.59
13 – 14	*0.54 ± 0.55	@ *1.01 ± 0.63	*0.40 ± 0.49	@ *0.98 ± 0.73	*0.59 ± 0.63	@*1.04± 0.65
Indication	**Effect on Induration/Edema**		**Effect on Pain**		**Effect on Exudation**	
Duration i days	Example 1	Momate®	Example 1	Momate ®	Example 1	Momate ®
Baseline	2.01 ± 0.76	1.98 ± 0.85	2.27 ± 0.90	2.19 ± 0.78	1.72 ± 0.78	1.65 ± 0.59
6 - 7	*0.98 ± 0.52	@ *1.30 ± 0.57	*1.09 ± 0.71	@*1.59± 0.66	*0.80 ± 0.68	@ *1.08 ± 0.79
13 – 14	*0.39 ± 0.45	@ *0.94 ± 0.77	*0.40 ± 0.59	@*0.85± 0.71	*0.41 ± 0.49	@ *0.72 ± 0.66

By Wilcoxon Sign Rank Test *P < 0.05 Vs Basal, Significant

By Mann Whitney U Test @Between Groups P < 0.05 Significant

Table 1 shows that mean score of scaling were 2.52 and 2.60 respectively in patients treated with composition as described in Example 1 of the present invention and patients treated with Momate® at baseline which was same and difference was not statistically significant. After the end of treatment, mean score had a fall of 78.6% among Example 1 group, which was significantly more as compared to 61.2% in Momate® group. After the end of treatment, mean score for Erythema had a fall of 83.7% among patients treated with Example 1 of the present invention which was significantly more as compared to 58.3% in Momate® group. After the end of treatment, mean score for itching had a fall of 75.3% among Example 1 group which was significantly more as compared to 57.4% in Momate® group. After the end of treatment for Induration/edema, mean

score had a fall of 80.6% among Example 1 group which was significantly more as compared to 52.5% in Momate® group. After the end of treatment, mean score for pain had a fall of 82.4% among Example 1 group which was significantly more as compared to 61.2% in Momate® group. After the end of treatment, mean score for exudation had a fall of 76.2% among Example 1 group which was significantly more as compared to 56.4% in Momate® group. After the end of treatment, mean score for total signs/symptoms had a fall of 79.6% among Example 1 group which was significantly more as compared to 58.1% in Momate® group.

Table 2 : Results of changes in severity of lesions with combination of Mometasone 0.1%w/w and Fusidic acid 2%w/w cream(Example 1 of the present invention) vs Mometasone 0.1%w/w cream, Momate® for prevention of secondary bacterial infections in patients with corticosteroid-responsive dermatoses

Table 2	Changes In Severity Of Lesions Between Two Groups					
	Example 1			Momate®		
Severity	Baseline (N = 25) No. %	Day 6 - 7 (N = 25) No. %	Day 13 - 14 (N = 25) No. %	Baseline (N = 26) No. %	Day 6 - 7 (N = 26) No. %	Day 13 - 14 (N = 26) No. %
Mild	05 (20.0)	08 (32.0)	*22(88.0)	06 (23.1)	07 (26.9)	12 (46.2)
Moderate	10 (40.0)	12 (48.0)	02 (08.0)	09 (34.6)	11 (42.3)	09 (34.6)
Severe	10 (40.0)	05 (20.0)	01 (04.0)	11 (42.3)	08 (30.8)	05 (19.2)

By Chi - Square test *P < 0.05 Significant

72.1 - 80.0% of the total study cases had a mild to moderate severity of lesions in both the groups at baseline. At the end of treatment 88.0% of total cases had mild severity of lesion in Example 1 group which was significantly low as compared to 46.2% among Momate® group.

Table 3 : Results of changes in discharge of lesions with combination of Mometasone 0.1%w/w and Fusidic acid 2%w/w cream(Example 1 of the present

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invention) vs Mometasone 0.1%w/w cream, Momate® for prevention of secondary bacterial infections in patients with corticosteroid-responsive dermatoses

Table 3	Changes In Discharge For Lesions Between Two Groups					
	Example 1			Momate®		
Type of Discharge	Baseline (N = 25) No. %	Day 6 - 7 (N = 25) No. %	Day 13 - 14 (N = 25) No. %	Baseline (N = 26) No. %	Day 6 - 7 (N = 26) No. %	Day 13 - 14 (N = 26) No. %
Absent	- (-)	*07 (28.0)	16 (64.0)	- (-)	03 (11.5)	06 (23.1)
Serous	04 (16.0)	*10 (40.0)	06 (24.0)	05 (19.2)	06 (23.1)	09 (34.6)
Purulent	14 (56.0)	05 (20.0)	*02 (08.0)	15 (57.7)	12 (46.2)	07 (26.9)
Mucopurulent	07 (28.0)	03 (12.0)	*01 (04.0)	06 (23.1)	05 (19.2)	04 (15.4)

By Chi - Square test *P < 0.05 Significant

In this study group 80.8 – 84.0% of the total study cases had a purulent to mucopurulent type of discharge for lesion in both the groups at baseline. After treatment at the end of 6 – 7 days, 68.0% of the total cases had a serous to no discharges in Example 1 group which was significantly more as compared to 34.6% among Momate® group . At the end of treatment 12.0% of total cases had purulent to mucopurulent type of discharge in Example 1 group which was significantly low as compared to 42.3% among Momate® group.

The bacteriological findings in the study indicated that 80.8 - 88.0% of the total cases had a significant bacteriological growth in both the groups at baseline. The common bacteriological isolates were staphylococcus aureus, streptococcus spp followed by epidermidis and proteus spp in both the groups. After the treatment only 16.0% of the cases had a significant growth among the patients treated with Example 1 of the present invention which was significantly very low as compared

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to 57.5% in patients treated with Momate® cream. As per Global assessment of efficacy of treatment by Physicians, 76.0% of total cases showed complete resolution to 90 – 99% resolution among total sign & symptoms in Example 1group which was significantly more as compared to 23.1% among Momate® group. As per Global assessment of efficacy of treatment by patients, 80.0% of total cases had greatly improvement in Example 1 group which was significantly more as compared to 23.1% among Momate® group.

The formulation of the present invention were also assessed for efficacy, safety and tolerability of combination of mometasone 0.1%w/w and fusidic acid 2%w/w cream, Example 1 in treatment of patients of corticosteroid-responsive dermatoses with secondary bacterial infections. Prospective, randomized, monocentre, open label study was conducted in one centre with 25 Male & female (post-menopausal, surgically sterilized or practicing a reliable method of birth control) patients with age ranging from 12 to 65 years.. The duration of the study was 3 weeks, including a 2-week active treatment period, preceded by a 1-week washout phase. The efficacy variables included changes in mean scores of scaling, erythema, pruritus/itching, induration/edema, pain, exudation/crusting, total sign/ symptom score, severity of lesion, discharge from lesions and overall global assessment of efficacy by physician/patients and monitoring of treatment–emergent adverse events. The study data was pooled and results were analyzed using a non-parametric test. All tests were two tailed & $p<0.05$ were considered to be significant.

Table 4 : Results of clinical symptoms with combination of Mometasone 0.1% w/w and Fusidic acid 2%w/w cream(Example 1 of the present invention) in treatment of patients of corticosteroid-responsive dermatoses with secondary bacterial infections

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Table 4	Mean Total Score ($\bar{X} \pm$ SD)					
Indication	Effect on Scaling		Effect on Erythema		Effect on Itching	
Duration in days	Example 1	%change	Example 1	%change	Example 1	%change
Baseline	2.48 ± 0.89	-	2.36 ± 0.75	-	2.40 ± 0.61	-
6 - 7	*1.86 ± 0.55	25.0	*1.27 ± 0.89	46.2	*1.32 ± 0.81	45.0
13 – 14	*0.52 ± 0.61	79.0	*0.36 ± 0.48	84.7	*0.67 ± 0.52	72.1
Indication	Effect on Induration/Edema		Effect on Pain		Effect on Exudation	
Duration in days	Example 1	%change	Example 1	%change	Example 1	%change
Baseline	1.95 ± 0.62	-	2.11 ± 0.63	-	1.67 ± 0.72	-
6 - 7	*1.00 ± 0.49	48.7	*1.17 ± 0.55	44.5	*0.84 ± 0.65	49.7
13 – 14	*0.42 ± 0.67	78.5	*0.32 ± 0.49	84.8	*0.32 ± 0.51	80.8

By Wilcoxon Sign Rank Test *P < 0.05 Vs Basal, Significant

In this study group mean total score of symptoms were 12.97 at baseline. After the treatment at the end of 6 – 7 days mean score had a significant reduction i.e. 42.5%. At the end of 13 - 14 days mean score had a fall of 82.7% from baseline.

Results showed that there was a significant decrease ($p<0.05$) in the mean symptom/sign scores as well as the total scores 1st week onwards and was significant sustained till two weeks ($p<0.05$)

Table 5 : Results of changes in severity of lesions with combination of Mometasone 0.1% w/w and Fusidic acid 2%w/w cream(Example 1 of the present invention) in treatment of patients of corticosteroid-responsive dermatoses with secondary bacterial infections

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Table 5 : Results of changes in severity of lesions

Severity	Baseline (N = 25) No.	%	Day 6 – 7 (N = 25) No.	%	Day 13 – 14 (N = 25) No.	%
Mild	04	16.0	*07	28.0	*20	80.0
Moderate	09	36.0	*14	56.0	03	12.0
Severe	12	48.0	04	16.0	02	08.0

By Chi – Square Test * P < 0.05 Vs Baseline, Significant

Table 5 shows that 52.0% of the total study cases had a mild to moderate severity of lesions at baseline. After treatment at the end of 6 – 7 days, 84.0% of the total cases showed mild to moderate severity of lesions which was considerable change and difference was significant. At the end of treatment 80.0% of the cases had a mild severity of lesions which was significant change from baseline.

Table 6 : Results of changes in discharge of lesions with combination of Mometasone 0.1% w/w and Fusidic acid 2%w/w cream(Example 1 of the present invention) in treatment of patients of corticosteroid-responsive dermatoses with secondary bacterial infections

Table 6 : Results of changes in discharge of lesions

Type of Discharge	Day 3 (N = 25) No.	%	Day 6 – 7 (N = 25) No.	%	Day 13 – 14 (N = 25) No.	%
Absent	-	-	06	24.0	*17	68.0
Serous	05	20.0	11	44.0	04	16.0
Purulent	14	56.0	*06	24.0	03	12.0
Mucopurulent	06	24.0	*02	08.0	01	04.0

By Chi – Square Test * P < 0.05 Vs Baseline, Significant

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Table 6 indicates 80.0% of the total study cases had a purulent to mucopurulent type of discharge for lesions at baseline. After treatment at the end of 6 – 7 days, only 32.00% of the total cases showed same type of discharge for lesions which was statistically significant from baseline. At the end of treatment 68.0% of the cases did not had a discharge and 16.0% serous discharge.

88.0% of the total cases had a bacteriological growth at baseline. Out of which 56.0% had a Staphylococcus aureus, 20.0% Streptococcus Spp and 8.0% Staphylococcus. epidermidis. At the end of treatment only 8.0% of the cases had a growth. There was a significant decrease (92%) in bacteriological growth compared to baseline ($P < 0.05$). According to the physician's assessment, 32.0% of the total study cases had a 100% remission of sign and symptoms, 44.0% showed a 90 – 99% improvement followed by 20.0% cases showed a moderate improvement. According to patients assessment, 84.0% of the total study cases showed a greatly improvement and 16.0% had a somewhat improvement after the treatment.

Treatment with combination of Mometasone furoate 0.1%w/w and Fusidic acid 2%w/w cream, Example 1 of the present invention, proved to be effective in 100 % cases with 96% cases showing marked improvement to complete resolution of symptoms, the remaining 4% cases also showed moderate improvement. These results are interpreted to be superior to the results obtained by Javier PR et al 1986 (Ref : Javier PR, Ortiz M, Torralba L, Montinola FL, Ke ML, Canete R. Fusidic acid/betamethasone in infected dermatoses--a double-blind comparison with neomycin/betamethasone. Br J Clin Pract. 1986;40:235-8), with the combination of betamethasone 0.1% plus fusidic acid 2% cream, where efficacy was seen in 85 % cases. The combination of Mometasone furoate 0.1% w/w and Fusidic acid 2%w/w cream, Example 1 of the present invention, also proved to be effective in eradication of the bacterial organisms in 92% of cases. This was found to be superior to the results obtained by Hjorth N, et al 1985 (Ref : Hjorth N, Schmidt H, Thomsen K.. Fusidic acid plus betamethasone in infected or potentially infected eczema. Pharmatherapeutica. 1985;4:126-31.), where bacteriological cures were 67% and by Javier PR et al 1986, where bacteriological

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cures were 78%.Therapy with the combination of Mometasone furoate 0.1%w/w and Fusidic acid 2%w/w cream of the present invention provided a fast, better efficacy and safe tolerability.

The formulation of the invention were assessed for efficacy, safety and tolerability of combination of Halobetasol propionate 0.05%w/w and Fusidic acid 2%w/w cream, Example 4 vs Halobetasol propionate 0.05%w/w cream, Halbate®, marketed by Glenmark Pharmaceutical Ltd. in India, for prevention of secondary bacterial infections in patients with non-infected dermatoses.

Prospective, randomized, multicentre, open label study was conducted with 25 Male & female (post-menopausal, surgically sterilized or practicing a reliable method of birth control) patients with age ranging from 12 to 65 years.. The duration of the study was 3 weeks, including a 2-week active treatment period, preceded by a 1-week washout phase. The patients selected were clinically diagnosed for non-infected dermatoses. The exclusion criteria for the patients were pregnant and lactating women, Serious skin disorders, dyspigmentation and extensive scarring in the affected areas., Hypersensitivity to halobetasol or Clobetasol or salicylic acid or ointment base., Immuno-compromised states and patients with systemic infections., Patients who have participated in a new drug study in the past 6 months., Patients with severe cardiac, hepatic, renal, or cerebrovascular disease, malignancy, chronic uncontrolled systemic diseases e.g., diabetes, hypertension, asthma, collagen disorders, etc. or any other serious medical illness.

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Study Plan

Activity/Observation	Screening Visit (Day -7)	Visit I (Baseline /Day 0)	Visit II (Day 4-6)	Visit III (Day 8-10)
Demographic Variables	X			
History and Physical Examination	X			
Inclusion/Exclusion Criteria	X			
Informed Consent	X			
Clinical Evaluation	X	X	X	X
Laboratory and other investigations	X			
Study drug treatment		X	X	X
Adverse Events		X	X	X
Patient Compliance			X	X
Overall Assessment of Efficacy			X	X
Bacteriological evaluation	X			X

Screening visit:

Demographic data and history of the patients were recorded and a brief physical examination was performed. Patients were recruited based on the inclusion and exclusion criteria. Written, informed consent was obtained from these patients. Clinical assessment of the condition under study, laboratory investigations, chest x-ray & ECG were carried out at this visit. Patients were given a 1-week washout period following which study treatment was initiated.

Clinical Efficacy Parameters assessed:

The study was designed to monitor Clinical signs and symptoms such as Scaling, Erythema, Itching, Induration/Edema, Pain, Exudation/Crusting and Total sign/ symptom. In addition Severity of lesion, Discharge for lesion , Bacteriological findings and Bacteriological findings including *Staphylococcus aureus*, *Staphylococcus epidrmidis*, Streptococcus spp, Enterobacteriaceae were also monitored.

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Study Treatment

Patients received combination of Halobetasol propionate 0.05%w/w and Fusidic acid 2%w/w cream or Halobetasol propionate 0.05%w/w cream according to randomization to be applied over the affected area/s twice daily as a thin film and rubbed in gently and completely, with each application separated by about 12 hours.

Overall Global Assessment of Efficacy

At the end of study, an overall assessment of the efficacy of the medication was performed by both the investigator and the patient.

Physician's Global Evaluation included the following parameters:

Grade	Evaluation
1	Complete resolution (100 % remission of signs and symptoms)
2	Excellent (90-99 % improvement)
3	Marked (75-89 % improvement)
4	Moderate (50-74 % improvement)
5	Slight (30-49 % improvement)
6	No appreciable improvement (0-29 %)
7	Worse (< 0 %)

Patient's Global Evaluation

Grade	Evaluation
1	Greatly improved
2	Somewhat improved
3	Same
4	Somewhat worse
5	Much worse

Patient Compliance was assessed on visits II, III and IV by direct questioning to the patients.

Results of the study :

The study data for assessment for efficacy of combination of Halobetasol propionate 0.05% w/w and Fusidic acid 2%w/w cream, Example 4 of the present invention vs Halobetasol propionate 0.05%w/w cream, Halbate® in prevention of secondary bacterial infections in patients with non-infected dermatoses were pooled and results were analyzed using a non-parametric test. All tests were two tailed & $p<0.05$ were considered to be significant.

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Table 1A : Results of Clinical symptoms assessment with combination of Halobetasol propionate 0.05% plus Fusidic acid 2% cream, Example 4 of the present invention vs Halobetasol propionate 0.05% cream, Halbate® in prevention of secondary bacterial infections in patients with non-infected dermatoses

Table 1A	**Mean Total Score ($\overline{X} \pm$ SD)**					
Indication	**Effect on Scaling**		**Effect on Erythema**		**Effect on Itching**	
Duration in days	Example 4	Halbate®	Example 4	Halbate®	Example 4	Halbate®
Baseline	2.51 ± 0.89	2.47 ± 0.83	2.49 ± 0.98	2.32 ± 0.86	2.29 ± 0.70	2.21 ± 0.81
6 - 7	*1.66 ± 0.72	*1.86 ± 0.78	*1.38 ± 0.77	@ *1.82 ± 0.68	*1.07 ± 0.65	@ *1.67 ± 0.72
13 – 14	*0.49 ± 0.57	@ *0.98 ± 0.85	*0.41 ± 0.54	@ *0.91 ± 0.70	*0.50 ± 0.67	@ *1.03 ± 0.66
Indication	**Effect on Induration/Edema**		**Effect on Pain**		**Effect on Exudation**	
Duration i days	Example 4	Halbate®	Example 4	Halbate®	Example 4	Halbate®
Baseline	2.11 ± 0.54	1.97 ± 0.77	2.31 ± 0.88	2.22 ± 0.73	1.83 ± 0.71	1.78 ± 0.78
6 - 7	*1.01 ± 0.66	@ *1.34 ± 0.52	*1.13 ± 0.75	@ *1.70 ± 0.65	*0.92 ± 0.56	@ *1.40 ± 0.55
13 – 14	*0.36 ± 0.49	@ *1.06 ± 0.49	*0.46 ± 0.52	@ *0.95 ± 0.59	*0.49 ± 0.53	@ *0.79 ± 0.48

By Wilcoxon Sign Rank Test *P < 0.05 Vs Basal, Significant

By Mann Whitney U Test @Between Groups P < 0.05 Significant

Table 1A indicates that after the end of treatment, mean score for scaling of 80.5% among patients treated with combination of Halobetasol and Fusidic Acid Cream, Example 4, which was significantly more as compared to those treated with 60.3% in Halobetasol Cream, Halbate® . After the end of treatment, mean score of erythema, had a fall of 83.5% among patients treated with combination of Halobetasol and Fusidic Acid Cream, Example 4, which was significantly more as compared to 60.8% in patients treated with Halobetasol Cream, Halbate®. After

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the end of treatment, mean score of itching, had a fall of 78.2% among patients treated with combination of Halobetasol and Fusidic Acid Cream, Example 4, which was significantly more as compared to 53.4% in patients treated with Halobetasol Cream, Halbate®. After the end of treatment, mean score of induration/edema had a fall of 82.9% among patients treated with combination of Halobetasol and Fusidic Acid Cream, Example 4 which was significantly more as compared to 46.2% in patients treated with Halobetasol Cream, Halbate®. After the end of treatment, mean score for pain had a fall of 80.1% among patients treated with combination of Halobetasol and Fusidic Acid Cream, Example 4, which was significantly more as compared to 57.2% in patients treated with Halobetasol Cream. After the end of treatment, mean score for exudation had a fall of 73.2% among patients treated with combination of Halobetasol and Fusidic Acid Cream, Example 4, which was significantly more as compared to 55.6% in patients treated with Halobetasol Cream, Halbate®. After the end of treatment, mean score for total signs and symptoms had a fall of 80.9% among patients treated with combination of Halobetasol and Fusidic Acid Cream, Example 4, which was significantly more as compared to 55.9% in those treated with Halobetasol Cream, Halbate®

Table 2A : Results of changes in severity of lesions with combination of Halobetasol and Fusidic Acid Cream (Example 4 of the present invention) vs Halobetasol propionate 0.05% cream, Halbate® in prevention of secondary bacterial infections in patients with non-infected dermatoses.

Table 2A	Changes in Severity Of Lesions Between Two Groups					
	Example 4			Halbate®		
Severity	Baseline (N = 28) No. %	Day 6 - 7 (N = 28) No. %	Day 13 - 14 (N = 28) No. %	Baseline (N = 27) No. %	Day 6 - 7 (N = 27) No. %	Day 13 - 14 (N = 27) No. %
Mild	04 (14.2)	08 (28.6)	*22(78.7)	05 (18.6)	06 (22.2)	10 (37.0)
Moderate	12 (42.9)	13 (46.4)	04 (14.2)	11 (40.7)	12 (44.5)	11 (40.8)
Severe	12 (42.9)	07 (25.0)	02 (07.1)	11 (40.7)	09 (33.3)	06 (22.2)

At the end of treatment 78.7% of total cases had mild severity of lesion in patients treated with combination of Halobetasol and Fusidic Acid Cream, Example 4, which was significantly more as compared to 37.0% among those treated with Halobetasol Cream , Halbate®

Table 3A : Results of changes in discharge of lesions with combination of Halobetasol and Fusidic Acid Cream (Example 4 of the present invention) vs Halobetasol propionate 0.05% cream, Halbate® in prevention of secondary bacterial infections in patients with non-infected dermatoses.

Table 3A	**Changes in Discharge For Lesions Between Two Groups**					
	Example 4			**Halbate®**		
Type of Discharge	**Baseline (N = 28) No. %**	**Day 6 - 7 (N = 28) No. %**	**Day 13 - 14 (N = 28) No. %**	**Baseline (N = 27) No. %**	**Day 6 - 7 (N = 27) No. %**	**Day 13 - 14 (N = 27) No. %**
Absent	23(82.2)	24 (85.7)	*22 (78.5)	23 (85.2)	13 (48.2)	*06 (22.2)
Serous	05 (17.8)	04 (14.3)	04 (14.3)	04 (14.8)	06 (22.2)	10 (37.0)
Purulent	00 (00)	00 (00)	*01 (03.6)	00 (00)	6 (22.2)	*08 (29.7)
Mucopurulent	00 (00)	00 (00)	01 (03.6)	00 (00)	02 (7.4)	03 (11.1)

By Chi - Square test *P < 0.05 Significant

Results showed that there was a significant decrease ($p<0.05$) in the mean symptom/sign scores as well as the total scores 1st week onwards and was significant sustained till two weeks ($p<0.05$) in patients treated with combination of Halobetasol propionate 0.05%w/w and Fusidic acid 2%w/w cream, Example 4 compared to patients treated with Halobetasol propionate 0.05% cream, Halbate®. In both the groups at baseline did not show purulent to mucopurulent type of discharge. At the end of treatment 7.2% of total cases had purulent to mucopurulent type of discharge in Patients treated with combination of Halobetasol propionate 0.05%w/w and Fusidic acid 2%w/w cream which was significantly low

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as compared to 40.8% among patients treated with Halobetasol propionate 0.05%w/w cream, Halbate® ($p<0.05$).89.2 – 92.5% of the total cases had no significant bacteriological growth in both the groups at baseline and difference was not significant between the groups. The common bacteriological isolates were *Staphylococcus aureus* in both the groups. After the treatment only 7.2% of the cases had a significant growth among patients treated with combination of Halobetasol propionate 0.05%w/w and Fusidic acid 2%w/w cream, Example 4 which was significantly very low as compared to 55.6% in patients treated with Halbate® ($p<0.05$). According to Physician's global assessment, 78.6% of total cases showed complete resolution among total signs & symptoms in patients treated with combination of Halobetasol propionate 0.05%w/w and Fusidic acid 2% w/w cream, Example 4 group which was significantly more as compared to 26.0% among those treated with Halbate® ($p<0.05$). According to patients global evaluation, 78.6% of total cases had greatly improvement in combination of Halobetasol propionate 0.05%w/w and Fusidic acid 2%w/w cream, Example 4 group which was significantly more as compared to 25.9% among Halbate® group ($p<0.05$).

The formulations of the present invention were also assessed for efficacy, safety and tolerability of combination of Halobetasol 0.05%w/w and Fusidic acid 2%w/w cream, Example 4 in treatment of patients with infected dermatoses. Prospective, randomized, monocentre, open label study was conducted with 25 Male & female (post-menopausal, surgically sterilized or practicing a reliable method of birth control) patients with age ranging from 12 to 65 years with a clinical diagnosis of infected dermatoses with secondary bacterial infections confirmed by laboratory evaluation (gram stain & culture). Patients fulfilling the selection criteria were assigned to treatment with combination of Halobetasol propionate 0.05%w/w and Fusidic acid 2%w/w cream, Example 4, topically daily every 12 hours for 2 weeks after obtaining their informed consent. The duration of the study was 3 weeks including a 2-week week active treatment period preceded by a 1-week washout period. The efficacy variables included changes in mean

scores of scaling, erythema, pruritus/itching, induration/edema, pain, exudation/crusting, total sign/ symptom score, severity of lesion, discharge from lesions and overall global assessment of efficacy by physician/patients and monitoring of treatment–emergent adverse events. The study data was pooled and results were analyzed using a non-parametric test. All tests were two tailed & $p<0.05$ were considered to be significant.

Table 4A : Results of clinical symptoms with combination of Halobetasol propionate 0.05% w/w and Fusidic acid 2%w/w cream, Example 4 in treatment of patients with infected dermatoses

Table 4A	**Mean Total Score ($\bar{X} \pm$ SD)**					
Indication	**Effect on Scaling**		**Effect on Erythema**		**Effect on Itching**	
Duration in days	Example 4	%change	Example 4	%change	Example 4	%change
Baseline	2.39 ± 0.69	-	2.44 ± 0.79	-	2.30 ± 0.90	-
6 - 7	*1.69 ± 0.53	29.3	*1.19 ± 0.70	51.2	*1.22 ± 0.64	46.9
13 – 14	*0.33 ± 0.48	86.2	*0.28 ± 0.50	88.5	*0.49 ± 0.53	78.7
Indication	**Effect on Induration/Edema**		**Effect on Pain**		**Effect on Exudation**	
Duration in days	Example 4	%change	Example 4	%change	Example 4	%change
Baseline	2.13 ± 0.75	-	2.33 ± 0.83	-	1.61 ± 0.74	-
6 - 7	*1.12 ± 0.66	47.4	*1.21 ± 0.67	48.1	*0.85 ± 0.49	47.2
13 – 14	*0.51 ± 0.59	76.1	*0.42 ± 0.60	81.9	*0.36 ± 0.48	77.6

By Wilcoxon Sign Rank Test *P < 0.05 Vs Basal, Significant

In this study, the mean total score of symptoms were 13.20 at baseline. After the treatment at the end of 6 – 7 days mean score had a significant reduction i.e. 44.8%. At the end of 13 - 14 days mean score had a fall of 81.9% from baseline.

Table 5A : Results of changes in severity of lesions for combination of Halobetasol propionate 0.05% w/w and Fusidic acid 2%w/w cream, Example 4 in treatment of patients with infected dermatoses

Table 5A : Results of changes in severity of lesions

Severity	Baseline (N = 28) No.	%	Day 6 – 7 (N = 28) No.	%	Day 13 – 14 (N = 28) No.	%
Mild	05	17.9	*09	32.1	*23	82.1
Moderate	10	35.7	*13	46.5	03	10.8
Severe	13	46.4	06	21.4	02	07.1

By Chi – Square Test * P < 0.05 Vs Baseline, Significant

Table 5A shows that 53.6% of the total study cases had a mild to moderate severity of lesions at baseline. After treatment at the end of 6 – 7 days, 78.6% of the total cases showed mild to moderate severity of lesions which was considerable change and difference was significant. At the end of treatment 82.1% of the cases had a mild severity of lesions which was significant change from baseline.

Table 6A : Results of changes in discharge of lesions for combination of Halobetasol propionate 0.05% w/w and Fusidic acid 2%w/w cream, Example 4 in treatment of patients with infected dermatoses

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Table 6A : Results of changes in discharge of lesions

Type of Discharge	Day 3 (N = 28) No.	%	Day 6 – 7 (N = 28) No.	%	Day 13 – 14 (N = 28) No.	%
Absent	-	-	07	25.0	*19	67.9
Serous	06	21.4	11	39.3	05	17.9
Purulent	15	53.6	*07	25.0	02	07.1
Mucopurulent	07	25.0	*03	10.7	02	07.1

By Chi – Square Test * P < 0.05 Vs Baseline, Significant

Table 6A indicates, 78.6% of the total study cases had a purulent to mucopurulent type of discharge for lesions at baseline. After treatment at the end of 6 – 7 days, only 35.7% of the total cases showed same type of discharge for lesions which was statistically significant from baseline. At the end of treatment 67.9% of the cases did not had a discharge and 17.9% serous discharge after treatment with Example 4..

Results showed that there was a significant decrease ($p<0.05$) in the mean symptom/sign scores as well as the total scores 1st week onwards and was significant sustained till two weeks ($p<0.05$) in case of treatment with combination of Halobetasol 0.05%w/w and Fusidic acid 2%w/w cream, Example 4 in treatment of patients with infected dermatoses. 82.1% of the total cases had significant bacteriological growth at baseline. Out of which 46.4% had a *Staphylococcus aureus,* 1.4% Streptococcus Spp and 7.1% Proteus Spp. After the treatment only 10.7% of the cases had a growth which was significantly low from baseline. There was a significant decrease (89.3%) in bacteriological growth compared to baseline ($P < 0.05$). Combination of Halobetasol propionate 0.05%w/w and Fusidic acid 2%w/w cream of the present invention proved to be effective in 100% cases with 92.9% cases showing marked improvement to complete resolution of symptoms, the remaining 7.1 % cases also showed moderate improvement. A total of 6.7% of total cases had an adverse event. Out of this each one of them had a burning,

irritation and dry skin. The severity of events was mild to moderate in both the cases which were disappeared during the treatment. Combination of Halobetasol propionate 0.05%w/w and Fusidic acid 2%w/w cream of the present invention proved to be effective in 100% cases with 92.9% cases showing marked improvement to complete resolution of symptoms, the remaining 7.1 % cases also showed moderate improvement.

This is superior to the results obtained by Javier PR et al 1986 (Ref: Javier PR, Ortiz M, Torralba L, Montinola FL, Ke ML, Canete R. Fusidic acid/betamethasone in infected dermatoses - a double-blind comparison with neomycin/betamethasone. Br J Clin Pract. 1986;40:235-8), with the fixed dose combination of betamethasone 0.1%w/w and fusidic acid 2%w/w cream, where efficacy was seen in 85 % cases. In a study of Halobetasol propionate 0.05%w/w by Kantor et al 1991 (Ref: Kantor I, Cook PR, Cullen SI, et al. Double-blind bilateral paired comparison of 0.05% halobetasol propionate cream and its vehicle in patients with chronic atopic dermatitis and other eczematous dermatoses. J Am Acad Dermatol 1991 Dec; 25(6 Pt 2):1184-6), in patients of atopic dermatitis and other eczematous dermatoses, showed excellent to good clinical improvement in 87% cases. Combination of Halobetasol propionate 0.05%w/w and Fusidic acid 2%w/w cream of the present invention also proved to be effective in eradication of the bacterial organisms in 89.3% of cases. This was found to be superior to the results obtained by Hjorth N, et al 1985 (Ref: Hjorth N, Schmidt H, Thomsen K.. Fusidic acid plus betamethasone in infected or potentially infected eczema. Pharmatherapeutica. 1985;4:126-31), where bacteriological cures were 67% and by Javier PR et al 1986, where bacteriological cures were 78%.

Therapy with the combination of Halobetasol propionate 0.05%w/w and Fusidic acid 2%w/w cream of the present invention provided a fast, better efficacy and safe tolerability.

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode

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for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention.

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We claim :

1. A topical composition comprising a combination of
a) a therapeutically effective amount of Mometasone furoate or its salts;
b) a therapeutically effective amount of Fusidic acid or its salts; and
c) a pharmaceutically acceptable carrier.

2. The topical composition according to claim 1, wherein, mometasone furoate, constitutes from about 0.05%w/w to about 2%w/w, and fusidic acid, constitutes from about 1% to about 5%w/w of the total composition.

3. The topical composition according to claim 1, wherein, mometasone furoate, constitutes 0.1% w/w, and fusidic acid, constitutes 2% w/w of the total composition.

4. The topical composition according to claim 1, wherein the ratio of Mometasone furoate and fusidic acid ranges from 1:2.5 to 1:20.

5. Use of mometasone furoate and fusidic acid for the preparation of topical composition, according to claims 1-4, for the treatment of infected eczema's such as secondarily infected dermatitis, including secondarily infected contact dermatitis, psoriasis, allergic contact dermatitis and atopic dermatitis with secondary bacterial infections of skin.

6. Use of mometasone furoate and fusidic acid for the preparation of topical composition, according to claims 1-4, for the prevention of infection in cases of dermatitis.

7. Use of mometasone furoate and fusidic acid for the preparation of topical composition, according to claim 6, for the prevention of cases of atopic dermatitis with the risk of getting secondary bacterial infection.

8. A topical composition comprising a combination of
d) a therapeutically effective amount of Halobetasol propionate or its salts;
e) a therapeutically effective amount of Fusidic acid or its salts; and
f) a pharmaceutically acceptable carrier.

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9. The topical composition according to claim 8, wherein, Halobetasol propionate, constitutes from about 0.01%w/w to about 2%w/w and fusidic acid, constitutes from about 1%w/w to about 5%w/w of the total composition.

10. The topical composition according to claim 9, wherein, Halobetasol propionate, constitutes 0.05% w/w and fusidic acid, constitutes 2% w/w of the total composition.

11. The topical composition according to claim 8, wherein the ratio of Halobetasol propionate and fusidic acid ranges from 1:2.5 to 1:100.

12. Use of halobetasol propionate and fusidic acid for the preparation of topical composition, according to claims 8-11, for the treatment of infected steroid responsive dermatoses such as secondarily infected dermatoses including secondarily infected contact dermatitis, allergic contact dermatitis, atopic dermatitis, psoriasis and other corticosteroid responsive dermatoses (CRD) with secondary bacterial infections of skin.

13. Use of halobetasol propionate and fusidic acid for the preparation of topical composition, according to claims 8-11, for the prevention of secondary bacterial infections in patients with non-infected dermatoses.

14. A method of treating infected eczema's such as secondarily infected dermatitis, including secondarily infected contact dermatitis, psoriasis, allergic contact dermatitis and atopic dermatitis with secondary bacterial infections of skin, wherein the said method comprises topical application to the afflicted area, the composition comprising a combination of

a) a therapeutically effective amount of Mometasone furoate or its salts; and

b) a therapeutically effective amount of Fusidic acid or its salts, to a subject in need thereof.

15. A method of prevention of infection in cases of dermatitis, wherein the said method comprises topical application to the afflicted area, the composition comprising a combination of

a)a therapeutically effective amount of Mometasone furoate or its salts; and

b) a therapeutically effective amount of Fusidic acid or its salts, to a subject in need thereof.

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16. A method of prevention according to claim 15, wherein the composition is used for prevention of cases of atopic dermatitis with the risk of getting secondary bacterial infection.

17. A method according to claims 14-16, wherein, mometasone furoate, constitutes from about 0.05%w/w to about 2%w/w, and fusidic acid, constitutes from about 1%w/w to about 5%w/w of the total composition

18. A method according to claim 17, wherein, mometasone furoate, constitutes about 0.1%w/w and fusidic acid, constitutes about 2% w/w of the total composition

19. A method of treating infected steroid responsive dermatoses such as secondarily infected dermatoses including secondarily infected contact dermatitis, allergic contact dermatitis, atopic dermatitis, psoriasis and other corticosteroid responsive dermatoses (CRD) with secondary bacterial infections of skin, wherein the said method comprises topical application to the afflicted area, the composition comprising a combination of

a) a therapeutically effective amount of Halobetasol propionate or its salts; and

b) a therapeutically effective amount of Fusidic acid or its salts, to a subject in need thereof.

20. A method of prevention of secondary bacterial infections in patients with non-infected dermatoses, wherein the said method comprises topical application to the afflicted area, the composition comprising a combination of

a) a therapeutically effective amount of Halobetasol propionate or its salts; and

b) a therapeutically effective amount of Fusidic acid or its salts, to a subject in need thereof.

21. A method according to claim 19-20, wherein, halobetasol propionate, constitutes from about 0.01%w/w to about 2%w/w, and fusidic acid, constitutes from about 1%w/w to about 5%w/w of the total composition

22. A method according to claim 21, wherein, halobetasol propionate, constitutes about 0.05%w/w and fusidic acid, constitutes about 2% w/w of the total composition.

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(54) **Title:** TOPICAL COMPOSITION COMPRISING HALOBETASOL AND SALICYLIC ACID

(57) **Abstract:** The present invention relates to topical pharmaceutical compositions, their uses an methods of manufacturing. Specifically, the present invention relates to topical composition comprising combination of halobetasol and salicylic acid.

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"TOPICAL COMPOSITION COMPRISING HALOBETASOL AND SALICYLIC ACID"

PRIORITY DETAILS

This patent application claims priority to Indian Patent Application No. 2074/MUM/2007, filed on October 18, 2007, the contents of which are hereby incorporated as reference.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to topical pharmaceutical compositions, their uses and methods of manufacturing. Specifically, the present invention relates to topical formulations comprising combination of halobetasol propionate and salicylic acid.

BACKGROUND OF THE INVENTION

The corticosteroids constitute a class of primarily synthetic steroids used topically as an anti-inflammatory and anti-pruritic agents. Halobetasol is used to treat swelling, inflammation, and, itching associated with skin conditions such as eczema, dermatitis, rashes, insect bites, and allergies.

Corticosteroids are medicines used for reducing inflammation. Inflammation of the skin happens due to the irritation of the skin, and is caused by the release of various substances that are important in the immune system. These substances cause blood vessels to widen, resulting in the irritated area becoming red, swollen, itchy and painful. When corticosteroid is applied to the skin it works by acting inside the skin cells to decrease the release of these inflammatory substances. This reduces swelling, redness and itch.

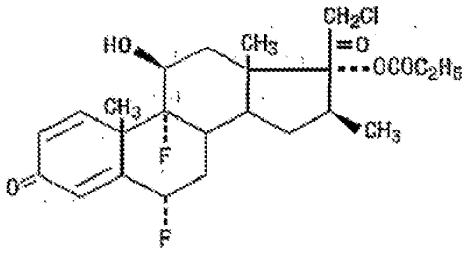
The different forms of superficial inflammatory diseases of the skin represent the most common reaction pattern seen by the dermatologist. The treatment of such diseases needs to be individualized. It is important to note that in conditions such as psoriasis and chronic eczema, the excessive amounts of keratin in the skin cells causes these cells to harden, and makes the skin

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become thickened and scaly. This not only makes the skin itchy and inflamed, but also reduces the degree to which anti-inflammatory medicines can penetrate through the skin to treat the inflammation, as a result decreasing the efficacy of the drug and consequently lead to inadequate treatment. Hence there is a need for such an effective formulation which can be effectively help penetrate the required drug in adequate amounts to enhance the efficacy of the formulation.

Halobetasol propionate

Chemically halobetasol propionate is 21-chloro-6 α, 9-difluoro-1 1 β - methylpregna-1 , 4-diene-3-20-dione, 17-propionate, $C_{25}H_{31}ClF2O5$. It has the following structural formula:



Like other topical corticosteroids, halobetasol propionate has anti-inflammatory, antipruritic and vasoconstrictive actions. The mechanism of the anti-inflammatory activity of the topical corticosteroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic , acid, is released from membrane phospholipids by phospholipase A_2

Halobetasol is a synthetic super-potent corticosteroid structurally related to clobetasol, meant for topical dermatological use.

Being a steroid Halobetasol has multiple mechanisms of action including anti-inflammatory activity, immunosuppressive properties, and antiproliferative

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actions. Anti-inflammatory effects arise from decreased formation, release, and activity of the mediators of inflammation (eg, kinins, histamine, liposomal enzymes, prostaglandins, leukotrienes), which reduce the initial manifestations of the inflammatory process. Corticosteroids inhibit margination and subsequent cell migration to the area of injury, and also reverse the dilation and increased vessel permeability in the area, resulting in decreased access of cells to the sites of injury. This vasoconstrictive action decreases serum extravasation, swelling, and discomfort. The immunosuppressive properties decrease the response to delayed and immβdiate hypersensitivity reactions (eg, type UI and type IV). This arises from inhibition of the toxic effect from antigen and antibody complexes that precipitate in vessel walls creating cutaneous allergic vasculitis, and by inhibiting the action of lymphokines, target cells, and macrophages that together produce allergic contact dermatitis reactions. Additionally, the access of sensitized T lymphocytes and macrophages to target cells may also be prevented by corticosteroids. The < antiproliferative effects reduce hyperplastic tissue characteristic of psoriasis.

Halobetasol propionate' is effective for the short-term (2 weeks or less) topical treatment of moderate-to-severe inflammatory and pruritic dermatoses such as atopic dermatitis, contact dermatitis, eczema, chronic eczematous dermatoses seborrheic dermatitis, and psoriasis.

Salicylic Acid:

Salicylic acid is a member of the class Non-steroidal anti-inflammatory drugs useful in the treatment of various dermatological disorders. In lower concentrations, it is an effective keratolytie used in the treatment of conditions such as dermatoses, psoriasis, and dandruff;' Salicylic acid is thus a valuable adjunct to dermatological therapy. Salicylic acid- in concentrations of 3% to 6% is useful in the treatment of various dermatological disorders.

Salicylic acid is a type of medicine called a keratolytie. It works by breaking down keratin, which is a protein that forms part of the skin structure. In conditions such as psoriasis and chronic eczema, excessive amounts of keratin in the skin

cells causes these cells to harden, and makes the skin become thickened and scaly. This not only makes the skin itchy and inflamed, but also reduces the degree to which anti-inflammatory medicines can penetrate through the skin to treat the inflammation. Salicylic acid breaks down the keratin in the hardened and thickened skin, helping to shed skin cells from the area to which it is applied, and soften and improve the appearance of scaly skin. It also helps improve the penetration of the corticosteroid into the skin, making it more effective than if the corticosteroid was applied on its own. The combination of corticosteroid and salicylic acid in this medicine is therefore used to treat dry, scaly, inflammatory skin disorders such as eczema, dermatoses and psoriasis, where the thickened skin could otherwise prevent absorption of the corticosteroid.

US patent no. 4,619,921 assigned to Ciba-Geigy is directed to halobetasol propionate.

US patent publication no. 2006/0286177 assigned to CombinatoRx, Inc describes composition comprising bufexamac and a corticosteroid selected from clobetasol, triamcinolone, betamethasone, hydrocortisone, halobetasol, diflorasone, mometasone, halcinonide, fluticasone, prednisone, and dexamethasone.

DE2744826A assigned to EXPL. MARQUES describes topical compositions for the treatment of dermatoses containing corticosteroids and salicylic acid.

EP735885B assigned to Schering describes combination of mometasone furoate and salicylic acid.

There remains the need to develop new pharmaceutical compositions that can be effectively used for treating skin diseases with lower side effects for the treatment of Lichenified skin lesions.

Without being bound by any theory, the inventors of the present invention believe that the topical composition^ comprising halobetasol propionate together with salicylic acid, of the present invention can be very effective for the topical treatment of Lichenified skin lesions.

SUMMARY OF THE INVENTION

One embodiment of the present invention provides a topical pharmaceutical composition comprising the combination of therapeutically effective amount of halobetasol propionate or its pharmaceutically acceptable salts/solvates there of, salicylic acid or its pharmaceutically acceptable salts/solvates of salicylic acid and a pharmaceutically acceptable carrier.

According to another embodiment of the present invention, suitable dosage forms for the combination of halobetasol propionate and salicylic acid include hydrous or anhydrous semisolids such as creams, gels, ointments, lotions and the like.

Another embodiment of the present invention provides the use of topical pharmaceutical composition comprising the combination of therapeutically effective amount of keratolytic agent such as salicylic acid and therapeutically effective amount of corticosteroid such as Halobetasol propionate or any other pharmaceutically acceptable salts/solvates there of for the topical treatment of Lichenified skin lesions.

Another embodiment of the present invention provides topical pharmaceutical composition comprising about 0.025 %w/w to 0.075 % w/w of halobetasol propionate and 3 %w/w to 6 % w/w of salicylic acid.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the terms "treating" or "treatment" of a state, disorder or condition mean: (1) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof, or (2) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms. The benefit to a patient to be treated is either statistically significant or at least perceptible to the patient or to the physician.

The term "pharmaceutically acceptable" as used in connection with components includes those components approved by a governmental regulatory

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agency or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in mammals, such as humans.

As used herein, the terms "effective amount" or a "therapeutically effective amount" of a drug refers to a non-toxip but sufficient amount of the drug to provide the desired effect. The "effective amount" will vary depending on the disease and its severity and the age, weight, physical condition and responsiveness of the mammal to be treated. An appropriate "effective amount" in any individual case may be determined by methods known in the art.

Active ingredient in the context of, present invention includes halobetasol propionate and salicylic acid.

The topical pharmaceutical compositions of the present invention are useful in delivering a combination of halobetasol propionate and micronised salicylic acid for the treatment of lichenified skin lesions.

Lichenified skin lesions:

The term lichenification refers to a thickening of the skin cells of the epidermis, which is the outermost layer of the skin, into a leather-like or bark-like formation, there is also hyperpigmentation of the thickened skin surface and an accentuation of the normal, crisscross diamond shaped skin markings, it is the important feature of chronic phase of eczema. It is usually seen with chronic coalescence of popular lesions and also occurs as a response to persistent rubbing or scratching.

Lichenified lesions are very difficult to treat; once established, they may persist for months even with adequate therapy and avoidance of rubbing or scratching. Histologically the lesions may show hyperkeratosis and parakeratosis and a thickened layer of epidermis.

The disorders that have lichenified skin lesions are skin disorders like Psoriasis, atopic dermatitis, neurodermatitis (Lichen simplex chronicus), all the types of eczemas which hyperkeratotic in the chronic phase including chronic

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allergic and irritant contact dermatitis, asteatotic dermatitis, nummular eczema, stasis dermatitis, and hand eczema.

Topical pharmaceutical composition in accordance with the present invention comprises about 0.025 % w/w to 0.075 % w/w of halobetasol propionate and about 3% w/w to 6 % w/w of salicylic acid.

Salicylic acid according to the present invention is preferably micronised salicylic acid. The term micronised salicylic acid as described in the present invention refers to salicylic acid having particle size with D_{90} less than about 50 microns, preferably less than about 35 microns and more preferably less than about 25 microns. The particle size of salicylic acid is measured by dry method using Malvern Particle size analyzer (Malvern Mastersizer "S").

The topical pharmaceutical compositions according to the present invention refers to use of composition externally over the skin in the form of ointment, cream, lotion, emulsion, paste, gel or the like and may contain appropriate conventional and pharmaceutically acceptable excipients/ additives selected from, but are not limited to preservatives, solvents, chelating agents, gelling agents, surfactants, buffering agents, viscosity builders, stiffening agents, emulsifiers, emollients, pH modifiers, Vehicles and the like and mixtures thereof that are typically used in the art for locally applied semisolid dosage forms.

Ointments are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. The specific ointment base to be used, as will be appreciated by those skilled in the art, is one that will provide for optimum drug delivery, and, preferably, will provide for other desired characteristics as well, e.g., emollie ηcy or the like. Ointment bases may be grouped in four classes: oleaginous bases; emulsifiable -bases; emulsion bases; and water-soluble bases.

Process for preparing topical ointment composition involves the following steps: (a) oil phase excipients were melted at about 65°C to 85^{0}Q, (b) drug is dissolved in propylene glycol at about 65°C to 85°C, (c) the contents of step (b)

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and step (a) were added at about 65°C to 85^{0}C to form a base, (d) the mixture of step (c) is homogenized for about 15 minutes for uniform mixing; and (e) homogenized mixture is cooled under stirring to about 30^{0}C.

Creams are semisolid dosage forms containing one or more drug substances dissolved or dispersed in a suitable base, possessing relatively fluid consistency formulated as either water-in-oil or oil-in-water emulsions.

The cream base may be prepared by conventional techniques well known to those skilled in the art. Generally, a suitable process comprises admixing the various ingredients of the cream in appropriate relative amounts in any order that is convenient and thereafter, if necessary adjusting the pH to the final desired value. For example, the components, of the base may be mixed together at an elevated temperature of 65-75 ^{0}C until an emulsion has formed, and therapeutic agent may be added after cooling the emulsified cream base, or during mixing, if it is stable to the temperatures employed. .

Stiffening agents used according to the present invention are selected from, but are not limited to fatty alcohols or esters such as white soft paraffin, white bees wax, stearyl alcohol, cetyl alcohol, myristyl alcohol, cetomacrogol emulsifying wax, cetyl stearyl alcohol, glycerin monostearate and mixtures there of.

Emulsifiers according to the present invention are selected from, but are not limited to polyoxyethylene glycol monocetyl ethers, white beeswax, DEHYMULS® E, (dicotyl pentaerythrityl distearyl citrate, sorbitan sesquioleate, aluminium stearates), cetomacrogol, pojyoxyethylene 21 stearyl ether, polyoxyethylene 20 cetyl ether, polydxyethlene sorbitan monostearates, Polysorbate 60, polyoxyethylene sorbitan monoleates, tween 80, sorbitol monostearate (Span 60), glyceryl monostearate and mixtures there of.

Humectants according to the present invention include, but are not limited to, propylene glycol, glycerin, butylend glycol, sorbitol, triacetin and mixtures there of.

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As used herein, the term "viscosity builders" is intended to mean an agent which helps for increasing the viscosity of the final formulation and helps in building the consistency to the final formulation. The viscosity built up is dependent upon the degree of polymerization and the ability of the polymer to swell. Such compounds include, by way of example and without limitation, carbomer, xanthan gum and the like.

Buffering agents are used to maintain a suitable pH and are selected from sodium dihydrogen phosphate dihydrate, dibasic sodium phosphate anhydrous (anhydrous sodium phosphate), alkali metal hydroxides such as spdium hydroxide, potassium hydroxide, ammonium hydroxide and the like and mixtures there of.

As used herein, the term "chelating agent" is intended to mean a compound which forms complex with metal ions and thus prevents the unwanted chemical reactions catalyzed by these ions. Such compounds include, by way of example and without limitation, disodium edetate and the like.

Preservatives according to the present invention are selected from, but are not limited to phenoxyethanol, benzyl alcohol, methylparaben, propylparaben, methylchloroisothiazolinone, methylisothiazolinone, Dimethicone 350, and poloxamer and mixtures thereof.

Solvents/vehicles used according to the present invention are selected from, but are not limited to propylene glycol, water, liquid paraffin, diethylene glycol monoethyl ether and mixtures thereof.

The composition of the present invention may also include minor amounts of conventional additives such as antioxidants like butylated hydroxytoluene, penetration enhancers, co-solvents, humectants, pH modifiers like triethanolamine, sodium hydroxide, emollients such as isopropyl palmitate, 2-Octyldodecanol, light liquid paraffin or mixtures there of.

The invention is further exemplified with following examples and is not intended to limit the scope of the invention. It is obvious to those skilled in the art

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to find out the composition for other dosage forms and substitute the equivalent excipients as described in this specification or With the one known to the industry.

EXAMPLES

Example - 1: Ointment composition comprising Halobetasol propionate and salicylic acid.

Steps	Ingredients	Concentration (% w/w)
I	White soft paraffin	87.95
	White beeswax	4.000
	DEHYMULS® E (Dicocoyl pentaerythrityl distearyl citrate, sorbitan sesquioleate, beeswax and aluminum stearates)	2.000
II	Propylene glycol	3.000
	Halobetasol propionate (micronised)	0.050
III	Salicylic acid (micronised)	3.000
	Total	**100**

Brief manufacturing process:

(a) The excipients of step (I) (white soft paraffin; white bees wax, DEHYMULS(R) E (dicQcoyl pentaerythrityl distearyl citrate, sorbitan sesquioleate, beeswax, and aluminum stearates)) were heated at about 65°C to 85°C.

(b) Halobetasol propionate was dissolved in propylene glycol at about 65^{0}C to 85°C.

(c) The contents of step (b) were added to the contents of step (a) under stirring at about 65°C to 85°C to form a base.

(d) Salicylic acid was added to the base obtained from step (c) at about 6O^{0}C to 68°C.

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(e) The mixture of step (d) is homogenized for about 15 minutes for uniform mixing and cooled under stirring to about 30°C.

Example 2: Cream composition comprising Halobetasol propionate and salicylic acid.

Steps	Ingredients	Concentration (% w/w)
I	White soft paraffin	6.000
	Cetomacrogol emulsifying wax	11.500
	Cetyl alcohol	2.500
	Glyceryl monostearate (SE)	1.500
	Polyoxyl 20 cetyl ether	0.500
	Liquid paraffin	6.000
	Methylparaben	0.200
	Propylparaben	0.020
	Dimethicone 350	0.100
II	Purified water	57.630
	Disodium edetate	0.050
III	Purified water	3.000
	Dibasic sodium phosphate anhydrous	0.100
IV	Diethylene glycol monoethyl ether	1.500
	Halobetasol propionate (Micronized)	0.050
V	Propylene glycol	4.000
	Salicylic acid, micronised	3.000
VI	Triethanolamine	2.000
VII	Sodium hydroxide	0.250
	Total	**100**

Brief manufacturing process:

(a) Oil phase: The excipients of step (i) were heated at about 65°C to 85°C.

(b) Aqueous phase: Disodium edetate was dissolved in water at about 65°C to 85°C.

(c) Emulsification and homogenization: The contents of step (b) were added to the contents of step (a) under stirring at about 65^{0}C to 85^{0}C, and homogenized for 10 minutes, and cooled to form cream base.

(d) Buffer phase: Dibasic sodium phosphate anhydrous was dissolved in water and added to the base of step (c) at about 40^{0}C.

(e) Qrug phase: Halobetasol propionate (dissolved in diethylene glycol monoethyl ether) and salicylic acid (dissolved in propylene glycol) were added to cream base of step (d) at about 40°C.

(f) Triethanolamine and sodium hydroxide phase: Triethanolamine was added to cream base at 40^{0}C and pH was adjusted to 5.0 with sodium hydroxide solution.

(g) Mixing: Stirring was continued and cooled to room temperature to form cream.

Example 3: Cream composition comprising Halobetasol propionate and salicylic acid.

Steps	Ingredients	Concentration (% w/w)
I	Cetyl alcohol	7.000
	Isopropyl isostearate	8.000
	Isopropyl palmitate	8.000
	Steareth-21	3.200
II	Diazolidinyl urea	0.200
	Purified water	65.500
III	Methylchloroisothiazolinone & Methylisothiazolinone (Kathon CG)	0.050
IV	Halobetasol propionate	0.050
	Salicylic acid	3.000
	Glycerin	5.000
	Total	**100**

Brief manufacturing process:

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(a) Oil Phase: Cetyl Alcohol, isopropyl isostearate, isopropyl palmitate and steareth-21 were heated up to 70^{0}C to 72^{0}C in stainless steel container.

(b) Aqueous Phase: Diazolidinyl urea was dissolved in purified water and heated up to 70^{0}C to 72°C in stainless steel container.

(c) Emulsification: The contents of step (b) were added to the contents of step (a) under stirring at about 65^{0}C to 85^{0}C, and homogenized for 15 minutes and cooled.

(d) Drug phase: Halobetasol propionate and salicylic acid were dispersed in glycerin and added to cream base at about 40^{0}C.

(e) Methylchloroisothiazolinone and methylisothiazolinone were added to cream base at about 40°C.

(f) Mixing: Stirring was continued for about 25 minutes and cooled to room temperature.

Example 4:

The topical ointment composition of the present invention, Example 1, comprising combination of Halobetasol propionate 0.05% w/w and salicylic acid (micronized) 3%w/w was evaluated for efficacy, safety and tolerability as compared to topical ointment composition containing combination of mometasone furoate 0.1%w/w and salicylic acid 3% w/w; halobetasol propionate Q-05%w/w ointment, mometasone furoate 0.05% ointment and placebo in the treatment of lichenified skin lesions, plaque psoriasis and chronic dermatoses.

Methods:

A prospective, randomized, double blind, multicentre, phase III study was undertaken in approximately 110 patients with a clinical diagnosis of plaque psoriasis and chronic dermatoses, Patients fulfilling the selection criteria were assigned to treatment with the composition as coded below for Groups A-E, topically daily every 12 hours for 2 weeks after obtaining their informed consent. The duration of the study was 3 weeks including a 2-week active treatment period preceded by a 1-week washout period.

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Coding:

GROUP A = Halobetasol U.ut>%w/w + Salicylic MCIU ^VII<JI UMI<-.CU; ɔ /OW/W ointment (Example 1 of the present invention).

GROUP B = Mometasone Furoate 0.1% + salicylic acid 3% ointment (Sensicort S® from Zuventus Pharmaceuticals Ltd).

GROUP C = Halobetasol 0.05% ointment (Halovate ® from Glenmark Pharmaceuticals Ltd).

GROUP D = Mometasone 0.05% ointment (Elocon ® from Fulford).

GROUP E = Placebo.

The efficacy variables included changes in mean scores of pruritus/itching, scaling, erythema, oozing/crusting, lichenification and overall global assessment of efficacy by physician/patients and monitoring of treatment-emergent adverse events.

Overall Global Assessment of Efficacy:

At the end of study, an overall assessment of the efficacy of the medication was performed by both the physician and the patient by using 7 point scale. Physician's and Patients Gjobal evaluation is graded as:.

Grade	Evaluation
1	Complete resolution (100 % remission of signs and symptoms)
2	Excellent (90-99 % improvement)
3	Marked (75-89 % improvement)
4	Moderate (50-74 % improvement)
5	Slight (30-49 % improvement)
6	No appreciable improvement (0-29 %)
7	Worse (< 0 %)

Results of the study:

The study data for assessment for efficacy of combination of Halobetasol 0.05%w/w and Salicylic acid 3%w/w ointment (Example 1 of the present invention) vs combination of mometasone furoate 0.1%w/w and salicylic acid 3% w/w ointment, halobetasol propionate 0.05%w/w ointment, mometasone furoate 0.05% ointment and placebo in the treatment of lichenified skin lesions, plaque psoriasis and chronic dermatoses were pooled and results were analyzed using a

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non-parametric test. All tests were two tailed & $p<0.05$ were considered to be significant.

Table 1: Results of itching with combination of Halobetasol propionate 0.05% w/w and salicylic acid 3% w/w ointment (Example 1 of the present invention) vs combination of mometasone furoate 0.1%w/w and salicylic acid 3% w/w, halobetasol propionate 0.05%w/w ointment, mometasone furoate 0.05% ointment and placebo in the treatment of lichenified skin lesions, plaque psoriasis and chronic dermatoses

Table 1

Duration in Days	Mean Score of Itching ($\bar{X} \pm SD$)				
	Group A	Group B	Group C	Group D	Group E
Baseline	2.35 ± 0.95	2.30 ± 0.77	2.33 ± 0.98	2.29 ± 0.97	2.24 ± 0.99
3	*1.18 ± 0.50	*1.54 ± 0.60	*1.58 ± 0.74	*1.87 ± 0.81	@ 2.19 ± 0.78
7	*0.81 ± 0.78	*1.14 ± 0.70	*1.23 ± 0.70	*1.72 ± 0.70	@ 2.02 ± 0.95
14	*0.44 ± 0.19	*0.77 ± 0.18	*0.69 ± 0.26	*0.92 ± 0.54	@ 1.90 ± 0.85

By ANOVA *P < 0.05 Significant @ Between Group P < 0.05 Significant

Table 1 shows that mean score of itching were 2.35 among Group A, 2.30 in Group B, 2.33 in Group C, 2.29 in Group D and 2.24 among Group E at baseline which was same and difference was not significant. After treatment at the end of 3rd day mean score of itching had a significant fall in all the groups except in Group E, i.e. 49.8 % among Group A, 33.0 % in Group B, 32.2% in Group C, 18.3% in Group D and only 02.2% among Group E. Group A had more fall as compared to Group B, C and D and the difference was statistically significant. After the treatment at the end of 14th day mean score of itching had a significant fall i.e. 81.3 % in Group A, 66.2 % in Group B, 77.40 % in Group C, 59.8% in Group D and 15.2% among Group E.

Table 2: Results of changes in mean score of thickness with combination of Halobetasol propionate 0.05% w/w and salicylic acid 3%w/w ointment (Example 1 of the present invention) vs combination of mometasone furoate 0.1%w/w and salicylic acid 3%w/w, halobetasol propionate 0.05%w/w ointment, mometasone

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furoate 0.05% ointment and placebo in the treatment of lichenified skin lesions, plaque psoriasis and chronic dermatoses.

Table 2

Duration in Days	Mean Score of Thickness ($\bar{X} \pm SD$)				
	Group A	Group B	Group C	Group D	Group E
Baseline	2.32 ± 0.85	2.29 ± 0.75	2.30 ± 0.82	2.36 ± 0.88	2.40 ± 0.91
3	*1.22 ± 0.61	*1.54 ± 0.80	*1.61 ± 0.80	*1.88 ± 0.75	@2.28 ± 0.90
7	*0.61 ± 0.66	*0.83 ± 0.58	*0.91 ± 0.71	*1.18 ± 0.80	@2.10 ± 0.87
14	*0.18 ± 0.39	*0.49 ± 0.41	*0.54 ± 0.48	*0.68 ± 0.55	@2.01 ± 0.89

By ANOVA P < 0.05 Significant @ Between Group P < 0.05 Significant

Table 2 shows that mean score of thickness were 2.32 among Group A, 2.29 in Group B, 2.30 in Group C, 2.36 in Group D and 2.40 among Group E at baseline which was same and difference was not significant. After treatment at the end of 3rd day mean score of thickness had a significant fall in all the groups except in Group E i.e. 47.4% among Group A, 32.8% in Group B, 30.0% in Group C, 20.3% in Group D and only 5.0 among Group E. Group A had more fall as compared to Group B, C and D. After the treatment at the end of 14th day mean score of thickness had a significant fall i.e. 92.2% in Group A, 78.6% in Group B, 76.5% in Group C, 71.2% in Group D and 16.3% among Group E. If you compare fall was more among Group A as compared to Group B, C and D.

Table 3: Results of changes in mean score of pain with combination of Halobetasol propionate 0.05% w/w and salicylic acid 3% w/w ointment (Example 1 of the present invention) vs combination of mometasone furoate 0.1%w/w and salicylic acid 3% w/w, halobetasol propionate 0-05%w/w ointment, mometasone furoate 0.05% ointment and placebo in the treatment of lichenified skin lesions, plaque psoriasis and chronic dermatoses.

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Table 3					
Duration in Days	Mean Score of Pain SD)				
	Group A	Group B	Group C	Group D	Group E
Baseline	1.72 ± 0.94	1.69 ± 0.70	1.62 ± 0.77	1.59 ± 0.78	1.66 ± 0.80
3	*1.09 ± 0.67	*1.43 ± 0.58	*1.40 ± 0.66	*1.50 ± 0.69	1.60 ± 0.90
7	*0.44 ± 0.70	*0.65 ± 0.60	*0.55 ± 0.71	*0.80 ± 0.58	@1.50 ± 0.57
14	*0.12 ± 0.42	*0.28 ± 039	*0.26 ± 0.48	*0.43 ± 0.70	@1.48 ± 0.66

By ANOVA *P < 0.05 Significant @ Between Group P < 0.05 Significant

Table 3 shows that Mean score of pain were 1.72 among Group A, 1.69 in Group B, 1.62 in Group C, 1.59 in Group D and 1.66 among Group E at baseline which was same and difference was not significant. After treatment at the end of 3rd day mean score of pain had a fall in all the groups except in Group E i.e. 36.6% among Group A, 15.4% in Group B, 13.6% in Group C, 5.7% in Group D and 3.7% among Group E. After the treatment at the end of 14th day mean score of pain had a significant fall i.e. 93.0% in Group A, 83.4% in Group B, 84.0% in Group C, 73.0% in Group D and 7.5% among Group E. The fall was more among Group A as compared tp Group B, C and Q.

Table 4: Results of changes in mean score of crusting with combination of Halobetasol propionate 0.05% w/w and salicylic acid 3% w/w ointment (Example 1 of the present invention) vs combination of mometasone furoate 0.1%w/w and salicylic acid 3% w/w, halobetasol propionate 0.05%w/w ointment, mometasone furoate 0.05% ointment and placebo in the treatment of lichenified skin lesions, plaque psoriasis and chronic dermatoses.

Table 4					
Duration in Days	Mean Score of Crusting (X± SD)				
	Group A	Group B	Group C	Group D	Group E
Baseline	1.44 ± 0.72	1.39 ± 0-70	1.36 ± 0.δδ	1.38 ± 0.78	1.40 ± 0.79
3	*0.74 ± 0.71	*1.15± 0.72	*1.11 ± 0.69	*1.20 ± 0.55	@1.35 ± 0.66
7	*Q.39 ± 0.58	*0.52 ± 0.66	*0.57 ± 0.66	*0.84 ± 0.67	@1.30 ± 0.70
14	*0.09 ± 0.32	*0.21 ± Q.40	*0.24 ± 0.37	*0.40 ± 0.52	@1.28 ± 0.59

By ANOVA *P < 0.05 Significant: @ Between Group P < 0.05 Significant

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Table 4 reveals that mean score of crusting were 1.44 among Group A, 1.39 in Group B, 1.36 in Group C, 1.38 in Group D and 1.40 among Group E at baseline which was same and difference was not significant. After treatment at the end of 3rd day mean score of crusting had a significant fall in all the groups except in Group E i.e. 48.6% among Group A, 17.3% in Group B, 18.4% in Group C, 13.0% in Group D and only 3.6 among Group E. After the treatment at the end of 14th day mean score of crusting had a significant fall, i.e. 93.8% in Group A, 84.9% in Group B, 82.44% in Group C, 71.0% in Group D and 8.6% among Group E. The fall was more among Group A as compared to Group B, C and D.

Table 5: Results of changes in mean score of scaling with combination of Halobetasol propionate 0.05% w/w and salicylic acid 3% w/w ointment (Example 1 of the present invention) vs combination of mometasone furoate 0.1%w/w and salicylic acid 3% w/w, halobetasol propionate 0.05%w/w ointment, mometaspne furoate 0.05% ointment and placebo in the treatment of lichenified skin lesions, plaque psoriasis and chronic dermatoses.

Table 5

Duration in Days	Mean Score of Scaling ($\bar{X} \pm SD$)				
	Group A	Group B	Group C	Group D	Group E
Baseline	2.39 ± 0.88	2.42 ± 0.90	2.51 ± 1.01	2.49 ± 0.95	2.44 ± 0.98
3	*1.05 ± 0.66	*1.40 ± 0.88	*1.44 ± 0.90	*1.88 ± 0.88	@2.31 ± 0.79
7	*0.71 ± 0.65	*0.94 ± 0.78	*1.03 ± 0.75	*1.39 ± 0.90	@2.24 ± 1.01
14	*0.24 ± 0.60	*0.41 ± 0.53	*0.51 ± 0.54	*0.74 ± 0.71	@2.19 ± 0.94

By ANOVA *P < 0-05 Significant @ Between Group P < 0-05 Significant

Table 5 indicates that mean score of scaling were 2.42 among Group A, 2.39 in Group B, 2.51 in Group C_1 2.49 in Group D and 2.44 among Group E at baseline which was same and difference was not significant. After treatment at the end of 3rd day, mean score pf scaling had a significant fall in all the groups except in Group E i.e. 56.1 % among Group A; 42.1% in Group B, 42.6% in Group C, 24.5% in Group D and 05.3 among Group E. After the treatment at the end of 14th day, mean score of spaling had a significant fall i.e. 90.0% in Group A, 83.1 % in Group B, 79.7% in Group C, 70.3% in Group D and 10.2% among

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Group E. The fall was more among Group A as compared to Group B, C and D but difference was not significant.

Table 6: Results of changes in mean score of redness with combination of Halobetasol propionate 0.05% w/w and salicylic acid 3% w/w ointment (Example 1 of the present invention) vs combination of mometasone furoate 0.1 %w/w and salicylic acid 3% w/w, halobetasol propionate 0.05%w/w, ointment, mometasone furoate 0.05% ointment and placebo in the treatment of lichenified skin lesions, plaque psoriasis and chronic dermatoses.

Table 6

Duration in Days	Mean Score of Redness ($\bar{X} \pm SD$)				
	Group A	Group B	Group C	Group D	Group E
Baseline	2.01 ± 0.81	1.95 ± 0.78	1.89 ± 0.67	1.90 ± 0.71	1.93 ± 0.79
3	*1.28 ± 0.67	*1.62 ± 0.66	*1.69 ± 0.70	*1.79 ± 0.80	1.84 ± 0.80
7	*0.93 ± 0.60	*1.23 ± 0.65	*1.18 ± 0.58	*1.44 ± 0.58	@1.78 ± 0.67
14	*0.40 ± 0.59	*0.58 ± 0.53	*0.61 ± 0.60	*0.99 ± 0.77	@1.70 ± 0.74

By ANOVA *P < 0.05 Significant @Between Group P < 0.05 Significant

Table 6 shows that mean score of redness were 1.95 among Group A, 2.01 in Group B, 1.89 in Group C, 1.90 in Group D and 1.93 among Group E at baseline which was same and difference was hot significant. After treatment at the end of 3rd day, mean score of redness had a significant fall in group A but in other groups reduction were not significant i.e. 36.3% among Group A, 16.9% in Group B, 10.6% in Group C, 5.8% in Group D and only 4.7 among Group E. The fall was low in Group D & E as compared to other groups and Group A had more fall as compared to Group C and P. After the treatment at the end of 14th day, mean score of redness had a significant fall i.e. 80.1 % in Group A, 70.3% in Group B, 67.7% in Group C, 47.9% in Group D and 11.9% among Group E.

Table 7: Results of changes in mean score of oozing with combination of Halobetasol propionate 0.05% w/w and salicylic acid 3% w/w ointment (Example 1 of the present invention) vs combination of mometasone furoate 0.1%w/w and salicylic acid 3% w/w, halobetasol propionate 0.05%w/w ointment, mometasone furoate 0.05% ointment and placebo in the treatment of lichenified skin lesions, plaque psoriasis and chronic dermatoses.

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Table 7

Duration in Days	Mean Score of Oozing ($\bar{X} \pm SD$)				
	Group A	Group B	Group C	Group D	Group E
Baseline	1.78 ± 0.92	1.75 ± 0.88	1.70 ± 0.77	1.81 ± 0.79	1.82 ± 0.95
3	*1.01 ± 0.57	*1.34 ± 0.58	*1.33 ± 0.70	*1.64 ± 0.66	@1.75 ± 0.82
7	*0.85 ± 0.52	*0.98 ± 0.66	*0.95 ± 0.68	*1.44 ± 0.52	@1.70 ± 0.78
14	*0.29 ± 0.37	*0.41 ± 0.49	*0.47 ± 0.71	*0.79 ± 0.58	@1.68 ± 0.55

By ANOVA *P < 0.05 Significant @ Between Group P < 0.05 Significant

Table 7 indicates mean score of oozing were 1.78 among Group A, 1.75 in Group B, 1.70 in Group C, 1.81 in Group D and 1.82 among Group E at baseline which was same and difference was not significant. After treatment at the end of 3rd day, mean score of oozing had a significant fall in all the groups except in Group D & E i.e. 43.3% among Group A, 23.4% in Group B, 21.9% in Group C, 9.4% in Qroup D and only 3.8 among Group E. The fall was significantly low in Group P & E as compared to Group A and had more fall as compared to Group B, C and D. After the treatment at the eiid of 14th day, mean score of oozing had a significant fall i.e. 83.7% in Group A, 76.6% in Group B, 72.4% in Group C, 56.4% in Group D and 07.7% among Group E.

Table 8: Results of overall global assessment of efficacy of treatment by physician with combination of Halobetasol propionate 0.05% w/w and salicylic acid 3% w/w ointment (Example 1 of the present invention) vs combination of mometasone furoate 0.1%w/w and salicylic acid 3% w/w, halobetasol propionate 0.05%w/w ointment, mometasone furoate 0.05% ointment and placebo in the treatment of lichenified skin lesions, plaque psoriasis and chronic dermatoses.

Table 8

Assessment	Group A (N=21)		Group B (N=20)		Group C (N=21)		Group D (N=20)		Group E (N=20)	
	No	%	No	%	No	%	No	%	No	%
Complete Resolution	*08	38.1	05	25.0	04	19.0	02	10.0	-	-
Excellent	*10	47.6	04	20.0	06	28.6	02	10.0	-	-
Marked	02	09.6	03	15.0	06	28.6	06	30.0	-	-
Moderate	01	04.7	08	40.0	05	23..8	010	50.0	-	-
Slight	-	-	-	-	-	-	-	-	01	05.0

No Appreciable Improvement	-	-	-	-	-	-	-	-	13	65.0
Worse	-	-	-	-	-	-	-	-	06	30.0

By Chi - Square Test *P < 0.05 Significant compared to placebo

As per overall global assessment of efficacy of treatment by physicians, at the end of 14th day, 95.3% of the cases treated with topical ointment composition of the present invention comprising combination of Halobetasol propionate 0.05% w/w and salicylic acid (micronized) 3%w/w,Group A, had a marked to complete resolution after the treatment which was more as compared to all other groups i.e. 60.0% in Group B, 76.2 % in Group C, 50.0% in Group D and not a single patient in Group E.

In cases treated with topical ointment composition of the present invention comprising combination of Halobetasol propionate 0.05% w/w and salicylic acid (micronized) 3% w/w (Group A) the results of marked to complete resolution were statistically significant as compared to Group B, C and D in global assessment for efficacy by physicians.

Table 9: Results of overall global assessment of efficacy of treatment by patients with combination of Halobetasol propionate 0.05% w/w and salicylic acid 3% w/w ointment (Example 1 of the present invention) vs combination of mometasone furoate 0.1%w/w and salicylic acid 3% w/w, halobetasol propionate 0.05%w/w ointment, mometasone furoate 0.05% ointment and placebo in the treatment of lichenified skin lesions, plaque psoriasis and chronic dermatoses.

Table 9

Assessment	Group A (N=21)		Group B (N=20)		Group C (N=21)		Group D (N=20)		Group E (N=20)	
	No	%	No	%	No	%	No	%	No	%
Complete Resolution	*09	42.9	05	25.0	04	19.0	03	15.0	-	-
Excellent	*09	42.9	03	15.0	08	38.1	06	30.0	-	-
Marked	02	09.5	05	25.0	05	23.9	02	10.0	-	-

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Moderate	01	4.7	07	35.0	04	19.0	09	45.0	-	-
Slight	-	-	-	-	-	-	-	-	02	10.0
No Appreciable Improvement	-	-	-	-	-	-	-	-	12	60.0
Worse	-	-	-	-	-	-	-	-	06	30.0

By Chi - Square Test *P < 0.05 Significant

As per overall global assessment of efficacy of treatment by patients, at the end of 14th day, 95.3 % of the cases treated with topical ointment composition of the present invention comprising combination of Halobetasol propionate 0.05% w/w and salicylic acid (micronized) 3%w/w; Group A had a marked to complete resolution after the treatment which was more as compared to all other groups i.e. 65.0% in Group B, 81.0% in Group. C, 55.0% in Group D and not a single patient in Group E. Group A results of marked to complete resolution were statistically significant as compared to Group B, C and D.

For cases treated with topical ointment composition of the present invention comprising combination of Halobetasol propionate 0.05% w/w and salicylic acid (micronized) 3% w/w (Group A), results of marked to complete resolution were statistically significant as compared to Mometasone 0.1%w/w + Salicylic Acid 3% w/w ointment group, Halobetasol propionate 0.Q5 %w/w ointment group, and Mometasone 0.05% w/w ointmeht ($P < 0.05$).

Treatment with the combination of Halobetasol propionate 0.05%w/w + Salicylic Acid (micronized) 3%w/w ointment proved to be effective in 95.3. % of the cases showing marked improvement to complete resolution of symptoms, the remaining 4.7 % cases also showed moderate improvement. This is superior to the results obtained by Bemhard J et al 1991 with Halobetasol, where efficacy was seen in 72.2 % cases and results obtained by Koo J et al 1998, with the combination of Mometasone 0.-1% w/w + Salicylic Acid 3%w/w ointment group, where efficacy was seen in 52.6 % cases.

Results showed that there was a faster and significant decrease ($p<0.05$) in the mean symptom/sign scores as well as the total scores 3rd day onwards in the Halobetasol 0.05% w/w + Salicylic Acid (Micronized) 3% w/w ointment group

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as compared to other groups and this was significantly sustained till end of treatment ($p<0.05$). On further observation, it was noticed that thicker lesion (palmoplantar psoriasis and hyperkeratotic lesions) response was considerably superior in Halobetasol 0.05%w/w.+ Salicylic Acid (micronized) 3%w/w ointment group as compared with Mometasone 0.1 %w/w + Salicylic Acid 3%w/w ointment group which suggests that the difference is more marked due to presence of halobetasol in the combination as against Mometasone in combination with Salicylic acid.

Therapy with the combination of Halobetasol 0.05% w/w + Salicylic Acid (micronized) 3% w/w ointment of the present invention provided a better efficacy, quick relief from signs and symptoms, and had good tolerability.

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We claim:

1. A topical composition comprising a combination of
a) a therapeutically effective amount of halobetasol propionate or its salts;
b) a therapeutically effective amount of salicylic acid or its salts; and
c) a pharmaceutically acceptable carrier.

2. The topical pharmaceutical composition according to claim 1, wherein said composition is an ointment, cream, lotion, solution or gel.

3. The topical composition according to claim 1, wherein, halobetasol propionate constitutes from about 0.025w/w % to 0.075% w/w, and salicylic acid constitutes from about 3% to about 6%w/w of the total composition.

4. The topical composition according to claim 1, wherein, halobetasol propionate constitutes 0.05 %w/w, and salicylic acid constitutes 3% w/w of the total composition.

5. The topical composition according to claim 1, wherein the weight ratio of halobetasol propionate and salicylic acid ranges from 1:40 to 1:240.

6. The topical composition according to claims 1-5, further comprising solvents, vehicles, ointment/cream bases, emulsifiers, preservatives, buffers, emollients, humectants, surfactants, and transport enhancers or mixtures there of.

7. Use of halobetasol propionate and salicylic acid for the preparation of topical composition, according to claims 1-6, for the treatment of lichenified skin lesions, plaque psoriasis and chronic dermatoses.

8. A method of treatment according to claim 7, wherein the composition is used for treatment of lichenified skin lesions caused by skin disorders including psoriasis, atopic dermatitis, neurodermatitis (Lichen simplex chronicus), eczemas which are hyperkeratotic in the chronic phase including chronic allergic and irritant contact dermatitis, asteatotic dermatitis, nummular eczema, stasis dermatitis, and hand eczema.

9. A method of treating lichenified skin lesions, plaque psoriasis and chronic dermatoses, wherein the said method comprises topical application to the afflicted area, the composition comprising a combination of:
a) a therapeutically effective amount of halobetasol propionate or its salts; and

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b) a therapeutically effective amount of salicylic acid or its salts, to a subject in need thereof.

10. A method of treatment according to claim 9, wherein the composition is used for treatment of lichenified skin lesions caused by skin disorders like psoriasis, atopic dermatitis, neurodermatitis (Lichen simplex chronicus), eczemas which are hyperkeratotic in the chronic phase including chronic allergic and irritant contact dermatitis, asteatotic dermatitis, nummular eczema, stasis dermatitis, and hand eczema.

11. A method according to claims 9-10, wherein, halobetasol propionate constitutes from about 0.025 %w/w to 0.075 %w/w, and salicylic acid constitutes from about 3%w/w to about 6%w/w of the total composition.

12. A method according to claim 11, wherein, halobetasol propionate constitutes about 0.05%w/w, and salicylic acid constitutes about 3%w/w of the total composition.

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(54) Title: DERMAL DELIVERY

(57) Abstract: The present invention describes systems and methods for treating disorders and/or conditions associated with the dermal level of the skin. Such disorders include acne, hyperhidrosis, bromhidrosis, chromhidrosis, rosacea, hair loss, dermal infection, and/or actinic keratosis. Methods generally involve administering nanoemulsions (*e.g.*, nanoparticle compositions) comprising at least one therapeutic agent, such as botulinum toxin. In some embodiments, nanoemulsions are prepared, *e.g.*, by high pressure microfluidization, and comprise a particle size distribution exclusively between 10 nm and 300 nm.

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DERMAL DELIVERY

Related Applications

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application, U.S.S.N. 60/076,065, filed June 26, 2008 ("the '065 application"). The entire contents of the '065 application are incorporated herein by reference.

Background

[0002] Conditions or disorders associated with sweat glands or sebaceous glands can cause a great deal of unhappiness and psychological debilitation for those who suffer from them, and current treatments are not very successful and often have undesirable side effects. For example, according to studies, acne often leads to reduced self esteem, and sometimes even to depression or suicide (see, *e.g.*, Goodman, 2006, *Aust. Fam. Physician* 35:503, 2006; Purvis *et al.*, 2006, *J. Paediatr. Child. Health* 42:793; both of which are incorporated herein by reference). Similar challenges are observed with hyperhidrosis (excessive sweating), bromhidrosis (body odor), chromhidrosis (colored sweat), psoriasis, dermal infection (*e.g.*, herpes simplex virus infection, human papillomavirus infection, fungal infection, *etc.*), hair loss, actinic keratosis, rosacea, and other afflictions of the skin.

Summary of the Invention

[0003] The present invention provides methods of treating conditions or disorders associated with dermal structures (*e.g.*, sweat glands, sebaceous glands, hair follicles, *etc.*). Specifically, the present invention demonstrates that nanoparticle compositions (*e.g.*, nanoemulsions) can deliver active agents efficiently and specifically to the dermis. For example, the present invention demonstrates dermal delivery without significant side effects associated with delivery to other areas (*e.g.*, to subdermal or extradermal structures and/or to tissues other than dermis).

[0004] The present invention therefore provides methods of treating conditions or disorders associated with dermal structures by applying to a skin surface a composition containing a nanoparticle composition (*e.g.*, a nanoemulsion) that includes a therapeutic agent useful in the treatment of the condition or disorder. In general, a nanoparticle composition is arranged and constructed such that an amount of therapeutic agent is delivered to dermal structures that is sufficient to treat the condition or disorder. In general, a nanoparticle

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composition is arranged and constructed such that it does not induce unwanted clinical effects inside and/or outside of the dermis.

[0005] For example, in some embodiments, the present invention provides methods comprising dermal administration of a nanoparticle composition containing a therapeutic agent without clinically significant side effects such as systemic side effects, damage to nervous tissue underlying the dermis (*e.g.*, neuronal paralysis), unwanted effects on muscles (*e.g.*, muscle paralysis), undesirable blood levels of therapeutic agent, *etc.*

[0006] To give but one example, the present invention provides methods for treating conditions associated with skin glands utilizing nanoparticle compositions (*e.g.*, nanoemulsions) containing botulinum toxin. Furthermore, the data presented herein demonstrate effective and efficient delivery of botulinum toxin to the dermis (which houses the sweat and sebaceous glands) using such nanoparticle compositions. Additionally, the data presented herein demonstrate that delivery of botulinum toxin to the dermis can be achieved without unwanted clinical effects associated with such delivery (*e.g.*, one or more of systemic side effects, damage to underlying nervous tissue [*e.g.*, neuronal paralysis], unwanted effects on muscles [*e.g.*, muscle paralysis], undesirable blood levels, *etc.*).

[0007] The present invention therefore also demonstrates the usefulness of such botulinum nanoparticle compositions in the treatment of other disorders and conditions associated with the dermis, or defects therein. For example, as addressed below in Example 5, the present invention provides methods of using botulinum nanoparticle compositions in the treatment of acne. For example, as addressed below in Example 6, the present invention provides methods of using botulinum nanoparticle compositions in the treatment of rosacea.

[0008] According to the present invention, nanoparticle compositions containing one or more therapeutic agents are useful in various cosmetic and medical applications. In some embodiments, such nanoparticle compositions are utilized to treat acne. In some embodiments, such nanoparticle compositions are utilized to treat hyperhidrosis. In some embodiments, such nanoparticle compositions are utilized to treat bromhidrosis. In some embodiments, such nanoparticle compositions are utilized to treat chromhidrosis. In some embodiments, such nanoparticle compositions are used to treat disorders or conditions associated with sweat glands. In some embodiments, such nanoparticle compositions are used to treat disorders or conditions associated with sebaceous glands, such as excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*). In some embodiments, such nanoparticle compositions are used to treat disorders or conditions associated with any component of the dermis that is present at around the same level of depth as sweat and

sebaceous glands. In some embodiments, such nanoparticle compositions are used to treat rosacea. In some embodiments, such nanoparticle compositions are used to treat hair loss. In some embodiments, such nanoparticle compositions are used to treat psoriasis. In some embodiments, such nanoparticle compositions are used to treat dermal infections (*e.g.*, herpes simplex infections, human papillomavirus infection, fungal infection, *etc.*). In some embodiments, such nanoparticle compositions are used to treat actinic keratosis. In some embodiments, such nanoparticle compositions are used to treat eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*). In some embodiments, such nanoparticle compositions are used to treat excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*). In some embodiments, such nanoparticle compositions are used to treat Raynaud's phenomenon. In some embodiments, such nanoparticle compositions are used to treat lupus erythematosus. In some embodiments, such nanoparticle compositions are used to treat hyperpigmentation disorders (*e.g.*, melasma, *etc.*). In some embodiments, such nanoparticle compositions are used to treat hypopigmentation disorders (*e.g.*, vitiligo, *etc.*). In some embodiments, such nanoparticle compositions are used to treat skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*).

[0009] Nanoparticle compositions formulated and used according to the present invention achieve transdermal delivery of therapeutic agents. Such compositions therefore avoid problems often associated with other delivery systems, including injection and oral delivery systems. Botulinum toxin, for example, is most commonly delivered by injection. Indeed, injection is currently the only delivery method that is approved by the United States Food and Drug Administration (USFDA). Improper injection techniques can damage tissue and /or can deliver therapeutic agents (*e.g.*, botulinum toxin) to unintended and/or undesirable locations. Pain, hematoma, ecchymosis, and bruising can also occur. Efforts have been made to develop transdermal delivery systems, including for botulinum toxin; however, these systems typically employ one or more agents that disrupt the skin, either chemically or mechanically. The present invention, by contrast, provides the surprising finding that certain nanoparticle compositions can efficiently and appropriately deliver therapeutic agents, including botulinum toxin, to the dermal layer (*e.g.*, to sebaceous gland regions and sweat gland regions) of the skin. The present invention therefore surprisingly demonstrates that inventive nanoparticle compositions are useful in the treatment of a variety of disorders or conditions associated with the sweat or sebaceous glands, and not just with certain of such disorders or conditions (*e.g.*, ones that might be tolerant of less precise or less efficient delivery). The present invention also demonstrates the effective and efficient delivery of therapeutically

active agents to the dermis and therefore illustrates the usefulness of nanoparticle compositions in the treatment of disorders or conditions of the dermis (*e.g.*, rosacea).

[00010] The inventors have discovered that certain nanoparticle compositions can achieve transdermal delivery of therapeutic agents without changing or altering the structure of the skin (see, *e.g.*, co-pending U.S. Patent Application U.S.S.N. 11/607,436, entitled "BOTULINUM NANOEMULSIONS," filed December 1, 2006; incorporated herein by reference). For example, abrasive agents or agents that erode or deteriorate the superficial layer of the skin are not required to achieve transdermal delivery of botulinum toxin according to the present invention. Thus, in many embodiments, transdermal delivery of therapeutic agents (*e.g.*, botulinum toxin) is accomplished without significant irritation of the skin.

[00011] In some embodiments, nanoparticle compositions for use in accordance with the present invention are prepared by exposure to high shear forces; in some embodiments, nanoparticle compositions are prepared by microfluidization; in some embodiments, nanoparticle compositions are prepared by high pressure homogenization.

[00012] According to the present invention, transdermal delivery of therapeutic agents (*e.g.*, botulinum toxin) may be accomplished in any of a variety of formats. In some embodiments, a nanoparticle composition comprising one or more therapeutic agents (*e.g.*, botulinum toxin) is incorporated within a cream, gel, powder, or lotion such that the therapeutic agent(s) are administered to a subject by application to the skin. In some embodiments, a nanoparticle composition comprising one or more therapeutic agents (*e.g.*, botulinum toxin) is incorporated within an ointment and/or liniment such that the therapeutic agent(s) are administered to a subject by application to the skin. In some embodiments, a nanoparticle composition comprising one or more therapeutic agents (*e.g.*, botulinum toxin) is incorporated within a suspension, microemulsion, nanoemulsion, and/or liposome such that the therapeutic agent(s) are administered to a subject by application to the skin. In some embodiments, a nanoparticle composition is incorporated within a transdermal patch such that a therapeutic agent (*e.g.*, botulinum toxin) is administered to a subject from the patch.

[00013] In some embodiments, nanoparticle compositions are emulsions containing a population of particles having maximum and minimum diameters, wherein the difference between the maximum and minimum diameters does not exceed about 600 nanometers (nm), about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 100 nm, about 90 nm, about 80 nm, about 70 nm, about 60 nm, about 50 nm, or fewer than about 50 nm.

[00014] In some embodiments, particles (*e.g.*, particles containing one or more therapeutic agents) within nanoparticle compositions have diameters that are smaller than about 600 nm, about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 130 nm, about 120 nm, about 115 nm, about 110 nm, about 100 nm, about 90 nm, about 80 nm, about 70 nm, about 60 nm, about 50 nm, about 40 nm, about 30 nm, about 20 nm, or less than about 20 nm.

[00015] In some embodiments, particles (*e.g.*, particles containing one or more therapeutic agents) within nanoparticle compositions have diameters within the range of about 10 and about 600 nm. In some embodiments, particles within nanoparticle compositions have diameters within the range of about 10 nm and about 300 nm, about 10 nm and about 200 nm, about 10 nm and about 150 nm, about 10 nm and about 130 nm, about 10 nm and about 120 nm, about 10 nm and about 115 nm, about 10 nm and about 110 nm, about 10 nm and about 100 nm, or about 10 nm and about 90 nm.

[00016] In some embodiments, particles (*e.g.*, particles containing one or more therapeutic agents) within nanoparticle compositions have an average particle size that is under about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 130 nm, about 120 nm, about 115 nm, about 110 nm, about 100 nm, or about 90 nm. In some embodiments, the average particle size is within the range of about 10 nm and about 300 nm, about 50 nm and about 250 nm, about 60 nm and about 200 nm, about 65 nm and about 150 nm, about 70 nm and about 130 nm. In some embodiments, the average particle size is about 80 nm and about 110 nm, about 70 nm and about 90 nm, about 60 nm and about 80 nm, about 50 nm and about 70 nm, about 10 nm and about 50 nm. In some embodiments, the average particle size is about 90 nm and about 100 and nm.

[00017] In some embodiments, a majority of the particles (*e.g.*, particles containing one or more therapeutic agents) within compositions in accordance with the invention have diameters below a specified size or within a specified range. In some embodiments, the majority is more than 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9% or more of the particles in the composition.

[00018] In some embodiments, nanoparticle compositions are substantially free of particles (*e.g.*, particles containing one or more therapeutic agents) having diameters greater than about 120 nm. In some embodiments, particles (*e.g.*, particles containing one or more therapeutic agents) within nanoparticle compositions have diameters within the range of about 30 nm and about 115 nm. In some embodiments, most of the particles within the composition have diameters within this range; in some embodiments, such compositions are

substantially free of particles having diameters larger than about 115 nm. In some embodiments, particles within nanoparticle compositions have diameters within the range of about 30 nm to about 70 nm or 40 nm to 90 nm. In some embodiments, most of the particles within such compositions have diameters within this range; in some embodiments the compositions are substantially free of particles with diameters larger than about 70 nm.

[00019] In some embodiments, nanoparticle compositions have at least two distinct populations of particles. For example, in some such embodiments, a majority of the particles in nanoparticle compositions have diameters within the range of about 30 nm and about 70 nm, while a second population of particles has diameters within the range of about 70 nm and about 120 nm. In some such embodiments, the composition is not contaminated with particles greater than 120 nm in diameter.

[00020] In some embodiments, at least one therapeutic agent (*e.g.*, botulinum toxin) is present partially or entirely within nanoparticles in nanoparticle compositions; in some embodiments, at least one therapeutic agent is adsorbed on the surface of nanoparticles in nanoparticle compositions; in some embodiments, at least one therapeutic agent is associated with the interface between the nanoparticles and the dispersion medium. In some embodiments, at least one therapeutic agent is found in two or more of these locations within the nanoparticle composition.

[00021] In some embodiments, a therapeutic agent to be incorporated within and/or associated with nanoparticles is any agent that is useful for treating skin disorders at the dermal level (*e.g.*, any agent useful for treating acne, hyperhidrosis, bromhidrosis, chromhidrosis, rosacea, hair loss, psoriasis, actinic keratosis, eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*), excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*), Raynaud's phenomenon, lupus erthythematosus, hyperpigmentation disorders (*e.g.*, melasma, *etc.*), hypopigmentation disorders (*e.g.*, vitiligo, *etc.*), skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*) and/or dermal infection (*e.g.*, fungal infection, herpes simplex virus infection, human papillomavirus infection, *etc.*).

[00022] In some embodiments, a therapeutic agent is botulinum toxin. In some embodiments, a therapeutic agent is an antibiotic. In some embodiments, a therapeutic agent is an antibody. In some embodiments, a therapeutic agent is benzoyl peroxide. In some embodiments, a therapeutic agent is isotretinoin. In some embodiments, a therapeutic agent is azelaic acid.

[00023] In some embodiments, botulinum toxin is selected from the group consisting of type A, type B, type C1, type C2, type D, type E, type F, and type G. In some embodiments,

botulinum toxin is present as an isolated protein; in some embodiments, botulinum toxin is present as part of a protein complex.

[00024] This application refers to various patent publications, all of which are incorporated herein by reference.

Definitions

[00025] *Abrasion:* The term "abrasion," as used herein, refers to any means of altering, disrupting, removing, or destroying the top layer of the skin. In some embodiments, abrasion refers to a mechanical means of altering, disrupting, removing, or destroying the top layer of the skin. In some embodiments, abrasion refers to a chemical means of altering, disrupting, removing, or destroying the top layer of skin. To give but a few examples, agents such as exfoliants, fine particles (*e.g.*, magnesium or aluminum particles), acids (*e.g.*, alpha-hydroxy acids or beta-hydroxy acids), and/or alcohols may cause abrasion. In general, permeation enhancers such as those described, for example, by Donovan (see, *e.g.*, U.S. Patent Publications 2004/009180 and 2005/175636; and PCT Publication WO 04/06954; all of which are incorporated herein by reference), and Graham (see, *e.g.*, U.S. Patent 6,939,852 and U.S. Patent Publication 2006/093624; both of which are incorporated herein by reference), *etc.*, are expected to cause abrasion. Of course, those of ordinary skill in the art will appreciate that a particular agent may cause abrasion when present at one concentration, or in association with one or more other agents, but may not cause abrasion under different circumstances. Thus, whether or not a particular material is an "abrasive agent" depends on context. Abrasion can readily be assessed by those of ordinary skill in the art, for example by observation of redness or irritation of the skin and/or histologic examination of skin showing alteration, disruption, removal, or erosion of the stratum corneum.

[00026] *Administration:* The term "administration," as used herein to refers to the delivery of a nanoparticle composition to a subject, is not limited to any particular route but rather refers to any route accepted as appropriate by the medical community. For example, the present invention contemplates routes of delivering or administering that include, but are not limited to, transdermal.

[00027] *Amino acid*: As used herein, term "amino acid," in its broadest sense, refers to any compound and/or substance that can be incorporated into a polypeptide chain. In some embodiments, an amino acid has the general structure H_2N–C(H)(R)–COOH. In some embodiments, an amino acid is a naturally-occurring amino acid. In some embodiments, an amino acid is a synthetic amino acid; in some embodiments, an amino acid is a D-amino acid;

in some embodiments, an amino acid is an L-amino acid. "Standard amino acid" refers to any of the twenty standard L-amino acids commonly found in naturally occurring peptides. "Nonstandard amino acid" refers to any amino acid, other than the standard amino acids, regardless of whether it is prepared synthetically or obtained from a natural source. Amino acids, including carboxy- and/or amino-terminal amino acids in peptides, can be modified by methylation, amidation, acetylation, and/or substitution with other chemical groups that can change the peptide's circulating half-life without adversely affecting their activity. Amino acids may participate in a disulfide bond. The term "amino acid" is used interchangeably with "amino acid residue," and may refer to a free amino acid and/or to an amino acid residue of a peptide. It will be apparent from the context in which the term is used whether it refers to a free amino acid or a residue of a peptide.

[00028] *Animal:* As used herein, the term "animal" refers to any member of the animal kingdom. In some embodiments, "animal" refers to humans, at any stage of development. In some embodiments, "animal" refers to non-human animals, at any stage of development. In certain embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, and/or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, and/or worms. In some embodiments, an animal may be a transgenic animal, genetically-engineered animal, and/or a clone.

[00029] *Approximately:* As used herein, the terms "approximately" or "about" in reference to a number are generally taken to include numbers that fall within a range of 5%, 10%, 15%, or 20% in either direction (greater than or less than) of the number unless otherwise stated or otherwise evident from the context (except where such number would be less than 0% or exceed 100% of a possible value).

[00030] *Biologically active agent*: As used herein, the phrase "biologically active agent" refers to any substance that has activity in a biological system and/or organism. For instance, a substance that, when administered to an organism, has a biological effect on that organism is considered to be biologically active. In particular embodiments, where a polypeptide (*e.g.*, botulinum toxin) is biologically active, a portion of that polypeptide that shares at least one biological activity of the whole polypeptide is typically referred to as a "biologically active" portion.

[00031] *Botulinum nanoparticle composition*: The term "botulinum nanoparticle composition," as used herein, refers to any nanoparticle composition in which at least one nanoparticle includes botulinum toxin. The botulinum toxin may be present within the

nanoparticle, on the nanoparticle surface and/or within a micellar membrane defining the nanoparticle.

[00032] *Botulinum toxin:* The term "botulinum toxin," as used herein, refers to any neurotoxin produced by *Clostridium botulinum*. Except as otherwise indicated, the term encompasses fragments or portions (*e.g.*, the light chain and/or the heavy chain) of such neurotoxin that retain appropriate activity (*e.g.*, muscle relaxant activity). The phrase "botulinum toxin," as used herein, encompasses the botulinum toxin serotypes A, B, C, D, E, F, and G; mutants thereof; variants thereof; fragments thereof; characteristic portions thereof; and/or fusions thereof. Botulinum toxin, as used herein, also encompasses both a botulinum toxin complex (*i.e.*, for example, the 300, 600, and 900 kD complexes) as well as the purified (*i.e.*, for example, isolated) botulinum toxin (*i.e.*, for example, about 150 kD). "Purified botulinum toxin" is defined as a botulinum toxin that is isolated, or substantially isolated, from other proteins, including proteins that form a botulinum toxin complex. A purified toxin may be greater than 80% pure, greater than 85% pure, greater than 90 % pure, greater than 95% pure, greater than 98% pure, and/or greater than 99% pure. Those of ordinary skill in the art will appreciate that the present invention is not limited to any particular source of botulinum toxin. For example, botulinum toxin for use in accordance with the present invention may be isolated from *Clostridium botulinum*, may be chemically synthesized, may be produced recombinantly (*i.e.*, in a host cell or organism other than *Clostridium botulinum*), *etc.*

[00033] *Cosmetic formulation:* The term "cosmetic formulation" is used herein to refer to a topically applied composition that contains one or more agents having cosmetic properties. To give but a few examples, a cosmetic formulation may be a skin softener, nutrition lotion type emulsion, cleansing lotion, cleansing cream, skin milk, emollient lotion, massage cream, emollient cream, make-up base, lipstick, facial pack or facial gel, cleaner formulation such as shampoos, rinses, body cleanser, hair-tonics, or soaps, and/or a dermatological composition such as a lotion, ointment, gel, cream, patch, deodorant, and/or spray.

[00034] *Cream:* The term "cream" refers to a spreadable composition, typically formulated for application to the skin. Creams typically contain an oil and/or fatty acid based-matrix. Creams formulated according to the present invention may contain nanoparticles and may be capable of substantially complete penetration (*e.g.*, of such nanoparticles) through the skin upon topical administration. Such a cream could also act as a carrier for incorporated materials (*e.g.*, for example, for one or more therapeutic agents).

[00035] *Dispersion medium*: The term "dispersion medium" as used herein, refers to a liquid medium in which particles (*e.g.*, nanoparticles) are dispersed. In general, a dispersion is formed when at least two immiscible materials are combined. An "oil-in-water" dispersion is one in which oily particles are dispersed within an aqueous dispersion medium. A "water-in-oil" dispersion is one in which aqueous particles are dispersed within an oily dispersion medium. Those of ordinary skill in the art will appreciate that a dispersion can be formed from any two immiscible media and is not limited strictly to combinations of aqueous and oily media. The term "dispersion medium" therefore applies broadly to *any* dispersion medium notwithstanding that it is common to refer to "aqueous" and "oily" categories.

[00036] *Encapsulated:* The term "encapsulated" (also "encapsulate" or "encapsulating") is used herein to mean that the encapsulated entity is completely surrounded by another material. To give but one example, a biologically active agent (*e.g.*, botulinum toxin) may be encapsulated within a nanoparticle in an emulsion in accordance with the invention. Such encapsulation may be achieved, for example, during formation of a nanoparticle composition (*e.g.*, a nanoemulsion), for example during microfluidization.

[00037] *In conjunction with*: As used herein, the phrase "delivered in conjunction with" refers to the co-delivery of two or more substances or agents. In particular, according to the present invention, the phrase is used herein in reference to delivery of a biologically active agent with nanoparticles and/or nanoparticle compositions in accordance with the invention. A substance or agent is delivered in conjunction with nanoparticles when the substance or agent is combined with nanoparticles and/or nanoparticle compositions; is encapsulated or completely surrounded by nanoparticles; is embedded within a nanoparticle micellar membrane; and/or is associated with the outer surface of a nanoparticle micellar membrane. A substance or agent to be delivered in conjunction with nanoparticles and/or nanoparticle compositions may or may not be covalently linked to the nanoparticles and/or nanoparticle compositions. A substance or agent to be delivered in conjunction with nanoparticles and/or nanoparticle compositions may or may not be attached to the nanoparticles and/or nanoparticle compositions by adsorption forces.

[00038] *Isolated*: As used herein, the term "isolated" refers to a substance and/or entity that has been (1) separated from at least some of the components with which it was associated when initially produced (whether in nature and/or in an experimental setting), and/or (2) produced, prepared, and/or manufactured by the hand of man. Isolated substances and/or entities may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with

which they were initially associated. In some embodiments, isolated substances and/or entities are more than 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% pure.

[00039] *Microfluidized*: As used herein, the term "microfluidized" means exposed to high shear forces. In some embodiments, such exposure to high shear forces is accomplished by exposure to high pressure; in some embodiments such high pressure is within the range of about 15,000 psi to about 26,000 psi. In some embodiments, such exposure to high shear forces is accomplished by cavitation. In some embodiments, such exposure to high shear forces is accomplished by passing a sample through an instrument such as, for example, a Microfluidizer® (Microfluidics Corporation/MFIC Corporation) or other like device that may be useful in creating a uniform nanoparticle composition. In some embodiments, a sample is microfluidized through exposure to high shear forces for a period of time less than about 10 minutes. In some embodiments, the period of time is less than about 9, about 8, about 7, about 6, about 5, about 4, about 3, about 2, or about 1 minute(s). In some embodiments, the period of time is within the range of about 1 – about 2 minutes. In some embodiments, the period of time is about 30 seconds. In some embodiments, a sample is "microfluidized" through a single exposure to high shear forces; such embodiments are referred to as "single pass" microfluidization.

[00040] *Nanoemulsion*: An emulsion is traditionally defined in the art "as a system … consisting of a liquid dispersed with or without an emulsifier in an immiscible liquid usually in droplets of larger than colloidal size" *Medline Plus Online Medical Dictionary, Merriam Webster* (2005). The term "nanoemulsion," as used herein, refers to an emulsion in which at least some of the droplets (or particles) have diameters in the nanometer size range. As will be understood by those of ordinary skill in the art, a nanoemulsion is characterized by droplets or particles one thousand fold smaller than microemulsion droplets or particles.

[00041] *Nanoparticle*: As used herein, the term "nanoparticle" refers to any particle having a diameter of less than 1000 nanometers (nm). In some embodiments, a nanoparticle has a diameter of less than 300 nm, as defined by the National Science Foundation. In some embodiments, a nanoparticle has a diameter of less than 100 nm as defined by the National Institutes of Health. In some embodiments, nanoparticles are micelles in that they comprise an enclosed compartment, separated from the bulk solution by a micellar membrane. A "micellar membrane" comprises amphiphilic entities which have aggregated to surround and enclose a space or compartment (*e.g.*, to define a lumen).

[00042] *Nanoparticle composition*: As used herein, the term "nanoparticle composition" refers to any substance that contains at least one nanoparticle. In some embodiments, a

nanoparticle composition is a uniform collection of nanoparticles. In some embodiments, nanoparticle compositions are dispersions or emulsions. In general, a dispersion or emulsion is formed when at least two immiscible materials are combined. An "oil-in-water" dispersion is one in which oily particles (or hydrophobic or non-polar) are dispersed within an aqueous dispersion medium. A "water-in-oil" dispersion is one in which aqueous (or hydrophilic or polar) particles are dispersed within an oily dispersion medium. Those of ordinary skill in the art will appreciate that a dispersion can be formed from any two immiscible media and is not limited strictly to combinations of aqueous and oily media. The term "dispersion medium" therefore applies broadly to *any* dispersion medium notwithstanding that it is common to refer to "aqueous" and "oily" categories. In some embodiments, nanoparticle compositions are nanoemulsions. In some embodiments, nanoparticle compositions comprise micelles. In some particular embodiments, a nanoparticle composition comprises amphiphilic entity nanoparticles as described in co-pending PCT application serial number PCT/US07/86018, entitled "Amphiphilic Entity Nanoparticles" and filed on November 30, 2007 (incorporated herein by reference). In some particular embodiments, a nanoparticle composition comprises a nanoemulsion as described in co-pending U.S. Patent Application U.S.S.N. 11/607,436, entitled "BOTULINUM NANOEMULSIONS," filed December 1, 2006 (incorporated herein by reference). In some embodiments, a nanoparticle composition is stable. In some embodiments, a nanoparticle composition includes one or more biologically active agents to be delivered in conjunction with the nanoparticles.

[00043] *Not contaminated with*: The phrase "not contaminated with," when used herein to refer to a nanoparticle composition, is synonymous with "substantially free of" and describes a nanoparticle composition containing no more than about 50% of the recited material. For example, if a nanoparticle composition is said to be "substantially free of" particles whose diameter is outside of a stated range, then no more than about 50% of the particles in that composition have diameters outside of the range. In some embodiments, no more than 25% of the particles are outside of the range. In some embodiments, no more than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have diameters outside of the stated range.

[00044] *Nucleic acid*: As used herein, the term "nucleic acid," in its broadest sense, refers to any compound and/or substance that is or can be incorporated into an oligonucleotide chain. In some embodiments, a nucleic acid is a compound and/or substance that is or can be incorporated into an oligonucleotide chain via a phosphodiester linkage. In some embodiments, "nucleic acid" refers to individual nucleic acid residues (*e.g.*, nucleotides

and/or nucleosides). In some embodiments, "nucleic acid" refers to an oligonucleotide chain comprising individual nucleic acid residues. As used herein, the terms "oligonucleotide" and "polynucleotide" can be used interchangeably. In some embodiments, "nucleic acid" encompasses RNA as well as single and/or double-stranded DNA and/or cDNA. Furthermore, the terms "nucleic acid," "DNA," "RNA," and/or similar terms include nucleic acid analogs, *e.g.*, analogs having other than a phosphodiester backbone. For example, the so-called "peptide nucleic acids," which are known in the art and have peptide bonds instead of phosphodiester bonds in the backbone, are considered within the scope of the present invention. The term "nucleotide sequence encoding an amino acid sequence" includes all nucleotide sequences that are degenerate versions of each other and/or encode the same amino acid sequence. Nucleotide sequences that encode proteins and/or RNA may include introns. Nucleic acids can be purified from natural sources, produced using recombinant expression systems and optionally purified, chemically synthesized, *etc.* Where appropriate, *e.g.*, in the case of chemically synthesized molecules, nucleic acids can comprise nucleoside analogs such as analogs having chemically modified bases or sugars, backbone modifications, *etc.* A nucleic acid sequence is presented in the 5' to 3' direction unless otherwise indicated. The term "nucleic acid segment" is used herein to refer to a nucleic acid sequence that is a portion of a longer nucleic acid sequence. In many embodiments, a nucleic acid segment comprises at least 3, 4, 5, 6, 7, 8, 9, 10, or more residues. In some embodiments, a nucleic acid is or comprises natural nucleosides (*e.g.*, adenosine, thymidine, guanosine, cytidine, uridine, deoxyadenosine, deoxythymidine, deoxyguanosine, and deoxycytidine); nucleoside analogs (*e.g.*, 2-aminoadenosine, 2-thiothymidine, inosine, pyrrolo-pyrimidine, 3-methyl adenosine, 5-methylcytidine, C-5 propynyl-cytidine, C-5 propynyl-uridine, 2-aminoadenosine, C5-bromouridine, C5-fluorouridine, C5-iodouridine, C5-propynyl-uridine, C5-propynyl-cytidine, C5-methylcytidine, 2-aminoadenosine, 7-deazaadenosine, 7-deazaguanosine, 8-oxoadenosine, 8-oxoguanosine, O(6)-methylguanine, and 2-thiocytidine); chemically modified bases; biologically modified bases (*e.g.*, methylated bases); intercalated bases; modified sugars (*e.g.*, 2'-fluororibose, ribose, 2'-deoxyribose, arabinose, and hexose); and/or modified phosphate groups (*e.g.*, phosphorothioates and 5'-*N*-phosphoramidite linkages). In some embodiments, the present invention is specifically directed to "unmodified nucleic acids," meaning nucleic acids (*e.g.*, polynucleotides and residues, including nucleotides and/or nucleosides) that have not been chemically modified in order to facilitate or achieve delivery (*e.g.*, transdermal delivery).

[00045] *Patient:* As used herein, the term "patient" or "subject" refers to any organism to which a composition in accordance with the invention may be administered, *e.g.*, for experimental, diagnostic, prophylactic, cosmetic, and/or therapeutic purposes. Typical patients include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and humans). In some embodiments, a patient is a human.

[00046] *Pharmaceutically acceptable*: The term "pharmaceutically acceptable" as used herein, refers to agents that, within the scope of sound medical judgment, are suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00047] *Premix*: As used herein, the term "premix" refers to any combination of components that is subsequently used to generate a nanoparticle composition according to the present invention. For example, a premix is any collection of ingredients that, when subjected to high shear forces, generates nanoparticles according to the present invention. In some embodiments, a premix contains two or more immiscible solvents. In some embodiments, a premix contains components that self-assemble into nanoparticles. In some embodiments, a premix contains components that self-assemble into micelles. In some embodiments, a premix contains one or more amphiphilic entities as described in co-pending PCT application serial number PCT/US07/86018, entitled "Amphiphilic Entity Nanoparticles" and filed on November 30, 2007. In some embodiments, a premix contains one or more therapeutic agents; in some embodiments, a premix contains at least one other biologically active agent. In some embodiments, a premix is agitated, mixed, and/or stirred; in some embodiments, a premix is agitated, mixed, and/or stirred prior to being subjected to high shear force. In some embodiments, a premix comprises at least one solubilized component (*i.e.*, at least one component that is in solution); in some such embodiments, the premix is subjected to high shear force after such solubilization is achieved.

[00048] *Pure*: As used herein, a substance and/or entity is "pure" if it is substantially free of other components. For example, a preparation that contains more than about 90% of a particular substance and/or entity is typically considered to be a pure preparation. In some embodiments, a substance and/or entity is at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% pure.

[00049] *Refractory:* The term "refractory" as used herein, refers to any subject that does not respond with an expected clinical efficacy following the delivery of a biologically active agent or pharmaceutical composition as normally observed by practicing medical personnel.

[00050] *Self-administration:* The term "self-administration," as used herein, refers to the situation where a subject has the ability to administer a composition to him or herself without requiring medical supervision. In some embodiments, self-administration may be performed outside of a clinical setting. To give but one example, in some embodiments, a facial cosmetic cream may be administered by a subject in one's own home.

[00051] *Shear force*: As used herein, the term "shear force" refers to a force that is parallel or tangential to the face of a material, as opposed to a force that is perpendicular to the face of a material. In some embodiments, a composition is exposed to high shear forces in order to produce a uniform nanoparticle composition. Any method known in the art can be used to generate high shear forces. In some embodiments, cavitation is used to generate high shear forces. In some embodiments, high pressure homogenization is used to generate high shear forces. Alternatively or additionally, high shear force may be administered by exposure to high pressure, for example about 15,000 psi. In some embodiments, such high pressure is within the range of about 18,000 psi to about 26,000 psi; in some embodiments, it is within the range of about 20,000 psi to about 25,000 psi. In some embodiments, and to give but one example, a Microfluidizer® Processor (Microfluidics Corporation/MFIC Corporation) or other like device is used to generate high shear force. Microfluidizer® Processors provide high pressure and a resultant high shear rate by accelerating a composition through microchannels (typically having dimensions on the order of 75 microns) at a high velocity (typically in the range of 50 m/s – 300 m/s) for size reduction to the nanoscale range. As the fluid exits the microchannels it forms jets which collide with jets from opposing microchannels. In the channels the fluid experiences high shear (up to 10^7 1/s) which is orders of magnitude higher than that of conventional technologies. Jet collisions result in mixing at submicron levels. Therefore, in such devices, high shear and/or impact can achieve particle size reduction and mixing of multiphase. In some embodiments, a sample is exposed to high shear forces for a period of time less than about 10 minutes. In some embodiments, the period of time is less than about 9 minutes, about 8 minutes, about 7 minutes, about 6 minutes, about 5 minutes, about 4 minutes, about 3 minutes, about 2 minutes, or about 1 minute. In some embodiments, the period of time is within the range of about 1 minute to about 2 minutes; in some embodiments, the period of time is less than about 1 minute; in some embodiments, the period of time is about 30 seconds. In some embodiments, a sample is "microfluidized" through a single exposure to high shear forces; such embodiments are referred to herein as "single pass" microfluidization.

[00052] *Small Molecule:* In general, a "small molecule" is a molecule that is less than about 5 kilodaltons (kD) in size. In some embodiments, the small molecule is less than about 4 kD, 3 kD, about 2 kD, or about 1 kD. In some embodiments, the small molecule is less than about 800 daltons (D), about 600 D, about 500 D, about 400 D, about 300 D, about 200 D, or about 100 D. In some embodiments, a small molecule is less than about 2000 g/mol, less than about 1500 g/mol, less than about 1000 g/mol, less than about 800 g/mol, or less than about 500 g/mol. In some embodiments, small molecules are non-polymeric. In some embodiments, in accordance with the present invention, small molecules are not proteins, polypeptides, oligopeptides, peptides, polynucleotides, oligonucleotides, polysaccharides, glycoproteins, proteoglycans, *etc.*

[00053] *Stable*: The term "stable," when applied to nanoparticle compositions herein, means that the compositions maintain one or more aspects of their physical structure (*e.g.*, size range and/or distribution of particles) over a period of time. In some embodiments, a stable nanoparticle composition is one for which the average particle size, the maximum particle size, the range of particle sizes, and/or the distribution of particle sizes (*i.e.*, the percentage of particles above a designated size and/or outside a designated range of sizes) is maintained for a period of time. In some embodiments, the period of time is at least about one hour; in some embodiments the period of time is about 5 hours, about 10 hours, about one (1) day, about one (1) week, about two (2) weeks, about one (1) month, about two (2) months, about three (3) months, about four (4) months, about five (5) months, about six (6) months, about eight (8) months, about ten (10) months, about twelve (12) months, about twenty-four (24) months, about thirty-six (36) months, or longer. In some embodiments, the period of time is within the range of about one (1) day to about twenty-four (24) months, about two (2) weeks to about twelve (12) months, about two (2) months to about five (5) months, *etc.* For example, if a nanoparticle composition is subjected to prolonged storage, temperature changes, and/or pH changes and a majority of the nanoparticles in the composition maintains a diameter within a stated range (for example, between approximately 10 nm and approximately 120 nm), the nanoparticle composition is stable. For some such populations, a majority is more than about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 99.5%, about 99.6%, about 99.7%, about 99.8%, about 99.9% or more. In some embodiments, where a nanoparticle composition comprises at least one biologically active agent, the nanoparticle composition is considered stable if the concentration of biologically active agent (*e.g.*,

botulinum toxin) is maintained in the composition over the designated period of time under a designated set of conditions.

[00054] *Substantially*: As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[00055] *Substantially free of*: A nanoparticle composition is said to be "substantially free of" particles whose diameter is outside of a stated range when no more than about 50% of the particles in that composition have diameters outside of the range. In some embodiments, no more than 25% of the particles are outside of the range. In some embodiments, no more than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have diameters outside of the stated range.

[00056] *Suffering from*: An individual who is "suffering from" a disease, disorder, or condition (*e.g.*, a condition associated with sweat glands or sebaceous glands, such as acne; hyperhidrosis; bromhidrosis; chromhidrosis; hair loss; psoriasis; actinic keratosis; dermal infection; eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*); excess sebum-producing disorder; Raynaud's phenomenon; lupus erthythematosus; hyperpigmentation disorder; hypopigmentation disorder; skin cancer; *etc.*) has been diagnosed with or exhibits symptoms of the disease, disorder, or condition.

[00057] *Symptoms are reduced:* According to the present invention, "symptoms are reduced" when one or more symptoms of a particular disease, disorder or condition is reduced in magnitude (*e.g.*, intensity) or frequency. For purposes of clarity, a delay in the onset of a particular symptom is considered one form of reducing the frequency of that symptom. To give but a few examples, where the condition in question is acne, symptoms of that condition are reduced when the size and/or severity of one or more blemishes in the selected area is reduced, and/or when the number of total blemishes is reduced (*e.g.*, on a subject's face, back, *etc.*). Where the condition in question is hyperhidrosis, symptoms are reduced when the subject produces less sweat. It is not intended that the present invention be limited only to cases where the symptoms are eliminated. The present invention specifically contemplates treatment such that one or more symptoms is/are reduced (and the condition of the subject is thereby "improved"), albeit not completely eliminated.

[00058] *Therapeutically effective amount:* As used herein, the term "therapeutically effective amount" means an amount that is sufficient, when administered to an individual suffering from or susceptible to a disease, disorder, and/or condition, to treat the disease, disorder, and/or condition. Those of ordinary skill in the art will appreciate that the term "therapeutically effective amount" does not in fact require successful treatment be achieved in a particular individual. Rather, a therapeutically effective amount may be that amount that provides a particular desired pharmacological response in a significant number of subjects when administered or delivered to patients in need of such treatment. It is specifically understood that particular subjects may, in fact, be "refractory" to a "therapeutically effective amount." To give but one example, a refractory subject may have a low bioavailability such that clinical efficacy is not obtainable. In some embodiments, reference to a therapeutically effective amount may be a reference to an amount as measured in one or more specific tissues.

[00059] *Therapeutic agent*: As used herein, the phrase "therapeutic agent" refers to any agent that has a therapeutic effect and/or elicits a desired biological and/or pharmacological effect, when administered to a subject.

[00060] *Toxic solvent:* As used herein, the term "toxic solvent" refers to any substance that may alter, disrupt, remove, or destroy an animal's tissue. As would be understood by one of ordinary skill in the art, an animal's tissue can include living cells, dead cells, extracellular matrix, cellular junctions, biological molecules, *etc.* To give but a few examples, toxic solvents include dimethyl sulfoxide, dimethyl acetimide, dimethyl formamide, chloroform, tetramethyl formamide, acetone, acetates, and alkanes.

[00061] *Treatment*: As used herein, the term "treatment" (also "treat" or "treating") refers to any administration of a biologically active agent that partially or completely alleviates, ameliorates, relives, inhibits, delays onset of, reduces severity of and/or reduces incidence of one or more symptoms or features of a particular disease, disorder, and/or condition. Such treatment may be of a subject who does not exhibit signs of the relevant disease, disorder and/or condition and/or of a subject who exhibits only early signs of the disease, disorder, and/or condition. Alternatively or additionally, such treatment may be of a subject who exhibits one or more established signs of the relevant disease, disorder and/or condition.

[00062] *Uniform*: The term "uniform," when used herein in reference to a nanoparticle composition, refers to a nanoparticle composition in which the individual nanoparticles have a specified range of particle diameter sizes. For example, in some embodiments, a uniform nanoparticle composition is one in which the difference between the minimum diameter and

maximum diameter does not exceed about 600 nm, about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 100 nm, about 90 nm, about 80 nm, about 70 nm, about 60 nm, about 50 nm, or fewer nm. In some embodiments, particles (*e.g.*, botulinum toxin-containing particles) within uniform nanoparticle compositions in accordance with the invention have diameters that are smaller than about 600 nm, about 550 nm, about 500 nm, about 450 nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 130 nm, about 120 nm, about 115 nm, about 110 nm, about 100 nm, about 90 nm, about 80 nm, or less. In some embodiments, particles (e.g., particles containing one or more therapeutic agents) within uniform nanoparticle compositions in accordance with the invention have diameters within the range of about 10 nm and about 600 nm. In some embodiments, particles within uniform nanoparticle compositions in accordance with the invention have diameters within the range of about 10 nm and about 300 nm, about 10 nm and about 200 nm, about 10 nm and about 150 nm, about 10 nm and about 130 nm, about 10 nm and about 120 nm, about 10 nm and about 115 nm, about 10 nm and about 110 nm, about 10 nm and about 100 nm, or about 10 nm and about 90 nm. In some embodiments, particles within nanoparticle compositions in accordance with the invention have an average particle size that is under about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 130 nm, about 120 nm, about 115 nm, about 110 nm, about 100 nm, or about 90 nm. In some embodiments, the average particle size is within the range of about 10 nm and about 300 nm, about 50 nm and about 250 nm, about 60 nm and about 200 nm, about 65 nm and about 150 nm, about 70 nm and about 130 nm. In some embodiments, the average particle size is between about 80 nm and about 110 nm. In some embodiments, the average particle size is about 90 nm to about 100 nm. In some embodiments, a majority of the particles within uniform nanoparticle compositions in accordance with the invention have diameters below a specified size or within a specified range. In some embodiments, the majority is more than 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9% or more of the particles in the composition. In some embodiments, a uniform nanoparticle composition is achieved by microfluidization of a sample. In some embodiments, a uniform nanoparticle composition is prepared by exposure to high shear force, *e.g.*, by microfluidization.

[00063] *Unwanted side effects*: As used herein, the term "unwanted side effects" refers to effects and/or symptoms associated with administration of a therapeutic agent to a patient that are not the desired and/or intended effect. Exemplary unwanted side effects include pain; bruising; ecchymosis; hematoma; botulism poisoning; unwanted systemic effects; undesirable

blood levels of a substance (*e.g.*, the therapeutic agent, a metabolite of the therapeutic agent, *etc.*); damage to underlying nervous tissue (*e.g.*, neuronal paralysis); unwanted effects on muscles (*e.g.*, muscle paralysis); flu-like symptoms; morbidity; mortality; alteration in body weight; alteration in enzyme levels; pathological changes detected at the microscopic, macroscopic, and/or physiological levels; infection; hemorrhage; inflammation; scarring; loss of function; changes in local blood flow; fever; malaise; teratogenesis; pulmonary hypertension; stroke; heart disease; heart attack; neuropathy; nausea; vomiting; dizziness; diarrhea; headache; dermatitis; dry mouth; addiction; miscarriage; abortion; uterine hemorrhage; birth defects; bleeding; cardiovascular disease; deafness; kidney damage and/or failure; liver damage and/or failure; dementia; depression; diabetes; erectile dysfunction; glaucoma; hair loss; anaemia; insomnia; lactic acidosis; melasma; thrombosis; priapism; rhabdomyolysis; seizures; drowsiness; increase in appetite; decrease in appetite; increase in libido; decrease in libido; tardive dyskinesia; non-axillary sweating; injection site pain and hemorrhage; pharyngitis; neck pain; back pain; pruritus; anxiety; follicular obstruction; and/or combinations thereof. In some embodiments, topical administration of a therapeutic agent reduces unwanted side effects by about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99%, or about 100% relative to non-topical administration (*e.g.*, injection, oral administration, *etc.*) of the same therapeutic agent.

Brief Description of the Drawing

[00064] *Figure 1* shows one embodiment of a particle diameter distribution of a microfluidized botulinum toxin nanoemulsion.

[00065] *Figure 2* shows one embodiment of a particle diameter distribution of homogenized botulinum toxin microemulsion.

[00066] *Figure 3* shows a patient attempting maximal brow elevation prior to (Panel A) and two weeks after (Panel B) topical administration of a composition comprising a botulinum nanoparticle composition.

[00067] *Figure 4a* illustrates a subject prior to treatment with a botulinum nanoemulsion. Darkened skin areas and sweat demonstrate profuse sweating at rest.

[00068] *Figure 4b* illustrates a subject two weeks following treatment with a botulinum nanoemulsion, demonstrating a profound diminishment of sweating at rest as demonstrated by the minor areas of skin darkening.

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Description of Certain Preferred Embodiments

[00069] The present invention relates to the treatment of certain disorders or conditions associated with the dermal layer of the skin (*e.g.*, conditions associated with sweat or sebaceous glands or hair follicles) through the transdermal application of nanoemulsion compositions comprising at least one therapeutic agent. In some embodiments, the present invention provides treatments for acne. In some embodiments, the present invention provides treatments for hyperhidrosis, bromhidrosis, and/or chromhidrosis. In some embodiments, the present invention provides treatments for rosacea. In some embodiments, the present invention provides treatments for hair loss. In some embodiments, the present invention provides treatments for psoriasis. In some embodiments, the present invention provides treatments for dermal infection (*e.g.*, herpes simplex virus infection, human papillomavirus infection, fungal infection, *etc.*). In some embodiments, the present invention provides treatments for actinic keratosis. In some embodiments, the present invention provides treatments for eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*). In some embodiments, the present invention provides treatments for excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*). In some embodiments, the present invention provides treatments for Raynaud's phenomenon. In some embodiments, the present invention provides treatments for lupus erythematosus. In some embodiments, the present invention provides treatments for hyperpigmentation disorders (*e.g.*, melasma, *etc.*). In some embodiments, the present invention provides treatments for hypopigmentation disorders (*e.g.*, vitiligo, *etc.*). In some embodiments, the present invention provides treatments for skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*).

Nanoparticle Compositions

[00070] As described herein, the present invention provides, among other things, novel nanoparticle compositions that contain at least one therapeutic agent (*e.g.*, botulinum toxin). The present invention provides novel uses for such nanoparticle compositions. In some embodiments, the invention provides use of nanoparticle compositions for treatment of disorders or conditions associated with the dermal layer of the skin, such as dermal gland disorders (*e.g.*, acne, hyperhidrosis, bromhidrosis, and/or chromhidrosis). In some embodiments, the invention provides use of nanoparticle compositions for treatment of rosacea. In some embodiments, the invention provides use of nanoparticle compositions for treatment of hair loss. In some embodiments, the invention provides use of nanoparticle compositions for treatment of psoriasis. In some embodiments, the invention provides use of

nanoparticle compositions for treatment of dermal infection (*e.g.*, herpes simplex virus infection, human papillomavirus infection; fungal infection, *etc.*). In some embodiments, the present invention provides use of nanoparticle compositions for treatment of actinic keratosis. In some embodiments, the present invention provides use of nanoparticle compositions for treatment of eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*). In some embodiments, the present invention provides use of nanoparticle compositions for treatment of excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*). In some embodiments, the present invention provides use of nanoparticle compositions for treatment of Raynaud's phenomenon. In some embodiments, the present invention provides use of nanoparticle compositions for treatment of lupus erythematosus. In some embodiments, the present invention provides use of nanoparticle compositions for treatment of hyperpigmentation disorders (*e.g.*, melasma, *etc.*). In some embodiments, the present invention provides use of nanoparticle compositions for treatment of hypopigmentation disorders (*e.g.*, vitiligo, *etc.*). In some embodiments, the present invention provides use of nanoparticle compositions for treatment of skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*).

[00071] In general, a nanoparticle composition is any composition that includes at least one nanoparticle. In some embodiments, nanoparticle compositions comprise at least one therapeutic agent (*e.g.*, botulinum toxin). A therapeutic agent may be encapsulated or completely surrounded by one or more nanoparticles; associated with the nanoparticle interface; and/or adsorbed to the outer surface of one or more nanoparticles. A therapeutic agent may or may not be covalently linked to the nanoparticles and/or nanoparticle compositions; a therapeutic agent may or may not be attached to nanoparticles and/or nanoparticle compositions by adsorption forces.

[00072] In some embodiments, nanoparticle compositions in accordance with the invention are stable. In some embodiments, nanoparticle compositions in accordance with the invention are uniform. For example, in some embodiments, the difference between the minimum diameter and maximum diameter of the nanoparticles in a nanoparticle composition does not exceed approximately 600 nm, approximately 550 nm, approximately 500 nm, approximately 450 nm, approximately 400 nm, approximately 350 nm, approximately 300 nm, approximately 250 nm, approximately 200 nm, approximately 150 nm, or approximately 100 nm, approximately 90 nm, approximately 80 nm, approximately 70 nm, approximately 60 nm, approximately 50 nm, or fewer nm.

[00073] In some embodiments, particles within nanoparticle compositions have diameters that are smaller than about 1000 nm, about 600 nm, about 550 nm, about 500 nm, about 450

nm, about 400 nm, about 350 nm, about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 130 nm, about 120 nm, about 115 nm, about 110 nm, about 100 nm, about 90 nm, about 80 nm, about 50 nm, or less.

[00074] In some embodiments, particles within nanoparticle compositions have diameters within the range of about 10 nm and about 600 nm. In some embodiments, particles within nanoparticle compositions have diameters within the range of about 10 nm to about 300 nm, about 10 nm to about 200 nm, about 10 nm to about 150 nm, about 10 nm to about 130 nm, about 10 nm to about 120 nm, about 10 nm to about 115 nm, about 10 nm to about 110 nm, about 10 nm to about 100 nm, or about 10 nm to about 90 nm. In some embodiments, particles within nanoparticle compositions have diameters within the range of 1 nm to 1000 nm, 1 nm to 600 nm, 1 nm to 500 nm, 1 nm to 400 nm, 1 nm to 300 nm, 1 nm to 200 nm, 1 nm to 150 nm, 1 nm to 120 nm, 1 nm to 100 nm, 1 nm to 75 nm, 1 nm to 50 nm, or 1 nm to 25 nm. In some embodiments, particles within nanoparticle compositions have diameters of 1 nm to 15 nm, 15 nm to 200 nm, 25 nm to 200 nm, 50 nm to 200 nm, or 75 nm to 200 nm.

[00075] In some embodiments, the total particle distribution is encompassed within the specified range of particle diameter size. In some embodiments, less than 50%, 25%, 10%, 5%, or 1% of the total particle distribution is outside of the specified range of particle diameter sizes. In some embodiments, less than 1% of the total particle distribution is outside of the specified range of particle diameter sizes. In certain embodiments, the nanoparticle composition is substantially free of particles having a diameter larger than 300 nm, 250 nm, 200 nm, 150 nm, 120 nm, 100 nm, 75 nm, 50 nm, or 25 nm.

[00076] In some embodiments, particles within nanoparticle compositions have an average particle size that is under about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 130 nm, about 120 nm, about 115 nm, about 110 nm, about 100 nm, about 90 nm, or about 50 nm. In some embodiments, the average particle size is within the range of about 10 nm and about 300 nm, about 50 nm and about 250, about 60 nm and about 200 nm, about 65 nm and about 150 nm, or about 70 nm and about 130 nm. In some embodiments, the average particle size is about 80 nm and about 110 nm. In some embodiments, the average particle size is about 90 nm and about 100 nm.

[00077] In some embodiments, a majority of the particles within nanoparticle compositions have diameters below a specified size or within a specified range. In some embodiments, the majority is more than 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9% or more of the particles in the composition.

[00078] In some embodiments, nanoparticle compositions are substantially free of particles having a diameter in excess of 300 nm. Specifically, in some embodiments, fewer than 50%, of the nanoparticles in nanoparticle compositions have a diameter in excess of 120 nm. In some embodiments, fewer than 25% of the particles have a diameter in excess of 120 nm. In some embodiments, fewer than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have a diameter in excess of 120 nm. Furthermore, in some embodiments, the nanoparticles in nanoparticle compositions have diameters within the range of 10 nm and 300 nm.

[00079] In some embodiments, nanoparticle compositions are substantially free of particles having a diameter in excess of 200 nm. Specifically, in some embodiments, fewer than 50%, of the nanoparticles in nanoparticle compositions have a diameter in excess of 120 nm. In some embodiments, fewer than 25% of the particles have a diameter in excess of 120 nm. In some embodiments, fewer than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have a diameter in excess of 120 nm. Furthermore, in some embodiments, the nanoparticles in nanoparticle compositions have diameters within the range of 10 nm and 200 nm.

[00080] In some embodiments, nanoparticle compositions are substantially free of particles having a diameter in excess of 120 nm. Specifically, in some embodiments, fewer than 50%, of the nanoparticles in nanoparticle compositions have a diameter in excess of 120 nm. In some embodiments, fewer than 25% of the particles have a diameter in excess of 120 nm. In some embodiments, fewer than 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5% or less of the particles have a diameter in excess of 120 nm. Furthermore, in some embodiments, the nanoparticles in nanoparticle compositions have diameters within the range of 10 nm and 120 nm.

[00081] In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters between 10 nm and 120 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters between 20 nm and 120 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters between 20 nm and 110 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters between 20 nm and 100 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters between 20 nm and 90 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters between 20 nm and 80 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters between 20 nm and 70 nm. In some embodiments,

a majority of nanoparticles in a nanoparticle composition have diameters between 20 nm and 60 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters between 20 nm and 50 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters between 20 nm and 40 nm. In some embodiments, a majority of nanoparticles in a nanoparticle composition have diameters between 20 nm and 30 nm.

[00082] In certain embodiments, about 50% of nanoparticles in a nanoparticle composition have diameters between 10 nm and 40 nm. In certain embodiments, about 90% of nanoparticles in a nanoparticle composition have diameters between 10 nm and 80 nm. In certain embodiments, about 90% of nanoparticles in a nanoparticle composition have diameters between 10 nm and 90 nm. In certain embodiments, about 95% of nanoparticles in a nanoparticle composition have diameters between 10 nm and 110 nm. In certain embodiments, about 95% of nanoparticles in a nanoparticle composition have diameters between 10 nm and 120 nm.

[00083] In certain embodiments, about 50% of the aggregate volume of all nanoparticles in a nanoparticle composition comprises or consists of nanoparticles having diameters between 10 nm and 40 nm. In certain embodiments, about 90% of the aggregate volume of all nanoparticles in a nanoparticle composition comprises or consists of nanoparticles having diameters between 10 nm and 80 nm. In certain embodiments, about 95% of the aggregate volume of all nanoparticles in a nanoparticle composition comprises or consists of nanoparticles having diameters between 10 nm and 110 nm. In certain embodiments, about 95% of the aggregate volume of all nanoparticles in a nanoparticle composition comprises or consists of nanoparticles having diameters between 10 nm and 120 nm.

[00084] Zeta potential is a measurement of the electric potential at a shear plane. A shear plane is an imaginary surface separating a thin layer of liquid bound to a solid surface (*e.g.*, nanoparticle surface) and showing elastic behavior from the rest of liquid (*e.g.*, liquid dispersion medium) showing normal viscous behavior. In some embodiments, nanoparticles have a zeta potential ranging between -80 mV and +80 mV. In some embodiments, nanoparticles have a zeta potential ranging between -50 mV and +50 mV. In some embodiments, nanoparticles have a zeta potential ranging between -25 mV and +25 mV. In some embodiments, nanoparticles have a zeta potential ranging between n -10 mV and +10 mV. In some embodiments, nanoparticles have a zeta potential of about -80 mV, about -70 mV, about -60 mV, about 50 mV, about -40 mV, about -30 mV, about -25 mV, about -20 mV, about -15 mV, about -10 mV, or about -5 mV. In some embodiments, nanoparticles

have a zeta potential of about +50 mV, about +40 mV, about +30 mV, about +25 mV, about +20 mV, about +15 mV, about +10 mV, or about +5 mV. In some embodiments, nanoparticles have a zeta potential that is about 0 mV.

[00085] In some embodiments, nanoparticles have a zeta potential that is about -5 mV to about -80 mV. In some embodiments, nanoparticles have a zeta potential that is about -5 mV to about -70 mV. In some embodiments, nanoparticles have a zeta potential that is about -5 mV to about -60 mV. In some embodiments, nanoparticles have a zeta potential that is about -5 mV to about -50 mV. In some embodiments, nanoparticles have a zeta potential that is about -5 mV to about -40 mV. In some embodiments, nanoparticles have a zeta potential that is about -5 mV to about -30 mV. In some embodiments, nanoparticles have a zeta potential that is about -5 mV to about -20 mV.

[00086] In some embodiments, nanoparticles have a zeta potential that is about -10 mV to about -15 mV. In some embodiments, nanoparticles have a zeta potential that is about -10 mV to about -80 mV. In some embodiments, nanoparticles have a zeta potential that is about -10 mV to about -70 mV. In some embodiments, nanoparticles have a zeta potential that is about -10 mV to about -60 mV. In some embodiments, nanoparticles have a zeta potential that is about -10 mV to about -50 mV. In some embodiments, nanoparticles have a zeta potential that is about -10 mV to about -40 mV. In some embodiments, nanoparticles have a zeta potential that is about -10 mV to about -30 mV. In some embodiments, nanoparticles have a zeta potential that is about -10 mV to about -20 mV.

[00087] In some embodiments, nanoparticles have a zeta potential that is about -80 mV to about -70 mV. In some embodiments, nanoparticles have a zeta potential that is about -70 mV to about -60 mV. In some embodiments, nanoparticles have a zeta potential that is about -60 mV to about -50 mV. In some embodiments, nanoparticles have a zeta potential that is about -50 mV to about -40 mV. In some embodiments, nanoparticles have a zeta potential that is about -40 mV to about -30 mV. In some embodiments, nanoparticles have a zeta potential that is about -30 mV to about -20 mV. In some embodiments, nanoparticles have a zeta potential that is about -20 mV to about -10 mV. In some embodiments, nanoparticles have a zeta potential that is about -10 mV to about 0 mV.

[00088] In some embodiments, nanoparticles have a zeta potential that is about -15 mV to about -20 mV. In some embodiments, nanoparticles have a zeta potential that is about -5 mV, about -6 mV, about -7 mV, about -8 mV, about -9 mV, -10 mV, about -11 mV, about -12 mV, about -13 mV, about -14 mV, about -15 mV, about 16 mV, about -17 mV, about -18

mV, about
-19 mV, or about -20 mV.

[00089] Nanoparticle compositions are typically emulsions or dispersions. In some embodiments, the compositions are "oil-in-water" dispersions (*i.e.*, dispersions in which oily particles are dispersed within an aqueous dispersion medium); in some embodiments, the compositions are "water-in-oil" dispersions (*i.e.*, dispersions in which aqueous particles are dispersed within an oily dispersion medium).

[00090] In some embodiments, nanoparticle compositions do not require toxic solvents. By contrast, many conventional strategies for inducing formation of nanoparticles in a composition utilize toxic (typically organic) solvents. In some embodiments, nanoparticle compositions do not require polymers. By contrast, many conventional strategies for preparing compositions that contain nanoparticle structures require polymers.

[00091] In some embodiments, nanoparticle compositions have better tissue absorption and/or better biocompatibility than other nanoparticle compositions. For example, in some embodiments, nanoparticle compositions have better tissue absorption and/or better biocompatibility than nanoparticle compositions that are not uniform, that utilize one or more toxic (*e.g.*, organic) solvents, and/or that utilize one or more polymers.

[00092] In some embodiments, nanoparticle compositions are stable. In some embodiments, a stable nanoparticle composition is one for which the average particle size, the maximum particle size, the range of particle sizes, and/or the distribution of particle sizes (*i.e.*, the percentage of particles above a designated size and/or outside a designated range of sizes) is maintained for a period of time. In some embodiments, the period of time is at least about one hour; in some embodiments the period of time is about 5 hours, about 10 hours, about one (1) day, about one (1) week, about two (2) weeks, about one (1) month, about two (2) months, about three (3) months, about four (4) months, about five (5) months, about six (6) months, about eight (8) months, about ten (10) months, about twelve (12) months, about twenty-four (24) months, or longer. In some embodiments, the period of time is within the range of about one (1) day to about twenty-four (24) months, about two (2) weeks to about twelve (12) months, about two (2) months to about five (5) months, *etc.* For example, if a population of nanoemulsion particles is subjected to prolonged storage, temperature changes, and/or pH changes and a majority of the nanoparticles in the population maintain a diameter within a stated range (*i.e.*, for example, between approximately 10 nm and about 120 nm), the nanoparticle composition is stable. For some such populations, a majority is more than about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%, about 97%,

about 98%, about 99%, about 99.5%, about 99.6%, about 99.7%, about 99.8%, about 99.9%, or more than about 99.9% pure. In some embodiments, where a nanoparticle composition comprises at least one biologically active agent, the nanoparticle composition is considered stable if the concentration of biologically active agent (*e.g.*, botulinum toxin) is maintained in the composition over the designated period of time under a designated set of conditions.

[00093] As described herein, nanoparticle compositions are useful in various cosmetic and/or medical applications. Such compositions may be delivered to a subject by transdermal delivery. In some embodiments, such compositions comprise botulinum toxin. It should be noted that botulinum nanoparticle compositions are readily distinguishable from other botulinum-toxin-containing compositions that have been described. For example, Donovan has described a preparation in which botulinum toxin has been incorporated into a lipid vesicle for transdermal delivery (U.S. Patent Publication 2004/0009180; incorporated herein by reference). Such vesicles also require the incorporation of an enhancing agent, such as an alcohol, to facilitate the absorption of botulinum toxin through the skin. Donovan also describes a neurotoxin that is incorporated into a transfersome, which are deformable carriers containing lipids and membrane softeners (Hofer *et al.*, 2000, *World J. Surg.*, 24:1187; and U.S. Patent 6,165,500; both of which are incorporated herein by reference). Donovan specifically describes the preparation of phosphatidyl choline + sodium cholate liposomes incorporating botulinum toxin.

[00094] Suvanprakorn *et al.* have also described suspensions of liposome-encapsulated materials in discrete macro-beads; one of the literally hundreds of compounds that is said to be amendable to encapsulation is "BOTOX®" (U.S. Patent Publication 2004/0224012; incorporated herein by reference). Included in contemplated methods of making these multi-lamellar vesicular liposomes are lyophilization/rehydration and organic solution dehydration/aqueous rehydration. These conventional methods of producing liposomes would be expected to produce microparticle-sized vesicles.

Methods of Making Nanoparticle Compositions

[00095] In general, nanoparticle compositions may be prepared by any available method. In some embodiments, nanoparticle compositions are prepared by chemical means. However, chemical means often require toxic (typically organic) solvents; in some embodiments, nanoparticle compositions are prepared in accordance with the present invention without utilizing such solvents.

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High Shear Force

[00096] In some embodiments, nanoparticle compositions in accordance with the invention self-assemble from a collection of combined components. In some embodiments, nanoparticle compositions are prepared by subjecting a combination of components (*i.e.*, a "premix") to high shear force. As used herein, the term "shear force" refers to a force that is parallel or tangential to the face of a material, as opposed to a force that is perpendicular to the face of a material. In some embodiments, high shear force is applied by high pressure, by cavitation, by homogenization, and/or by microfluidization. In some embodiments, combined nanoparticle-forming components are agitated, stirred, or otherwise mixed. In some such embodiments, the components are subjected to high shear force after having been mixed. In some specific embodiments, mixing may be performed for a period of time such as, for example, about 1 minute, about 3 minutes, about 5 minutes, about 10 minutes, about 15 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, or about 15 hours. In some specific embodiments, mixing may be performed for a period of time such as, for example, more than 15 minutes, more than 30 minutes, more than 45 minutes, more than 1 hour, more than 2 hours, more than 3 hours, more than 4 hours, more than 5 hours, more than 6 hours, more than 7 hours, more than 8 hours, more than 9 hours, more than 10 hours, more than 11 hours, more than 12 hours, more than 13 hours, more than 14 hours, or more than 15 hours. In some specific embodiments, mixing may be performed for a period of time such as, for example, less than 15 minutes, less than 30 minutes, less than 45 minutes, less than 1 hour, less than 2 hours, less than 3 hours, less than 4 hours, less than 5 hours, less than 6 hours, less than 7 hours, less than 8 hours, less than 9 hours, less than 10 hours, less than 11 hours, less than 12 hours, less than 13 hours, less than 14 hours, or less than 15 hours. In some embodiments, solubilization is achieved.

[00097] Any method known in the art can be used to generate high shear forces. In some embodiments, cavitation is used to generate high shear forces. According to the present invention, the use of mechanical energy (*i.e.*, high shear forces) can replace or minimize any requirement to use costly and/or toxic chemical solvents; can increase the speed at which nanoparticles assemble, can increase the yield of nanoparticles generated in a particular mix of components, and/or can greatly reduce the overall cost of preparing nanoemulsion compositions. Furthermore, in those embodiments in which an agent such as a biologically active agent (*e.g.*, botulinum toxin) is incorporated into nanoparticle compositions, the use of

high shear force can increase the loading capacity of the nanoparticle as compared to traditional methods of forming nanoparticles. In traditional methods, loading of agents within or on the surface of nanoparticles typically relies on diffusion of the agent to the interior and/or to the surface of the nanoparticle. According to the present invention, the use of high shear force can allow for the manufacture of smaller particles (*e.g.*, on average) and/or a more narrow distribution of particle sizes in a nanoparticle composition.

[00098] In some embodiments, high shear forces are achieved by exposure to high pressure, for example by continuous turbulent flow at high pressure, for example about 15,000 psi. In some embodiments, such high pressure is within the range of about 18,000 psi to about 26,000 psi; in some embodiments, it is within the range of about 20,000 psi to about 25,000 psi; in some embodiments, it is within the range of about 25,000 psi to about 30,000 psi; in some embodiments, it is within the range of about 30,000 psi to about 35,000 psi; in some embodiments, it is within the range of about 30,000 psi to about 40,000 psi; in some embodiments, it is within the range of about 40,000 psi to about 50,000 psi.

[00099] In some embodiments, high shear force or high pressure may be administered by cavitation or high pressure homogenization.

[000100] In some embodiments, high shear force may be administered by passage through an instrument such as, for example, a Microfluidizer® Processor (Microfluidics Corporation/MFIC Corporation) or other like device. Microfluidizer® Processors provide high pressure and a resultant high shear rate by accelerating the product through microchannels to a high velocity for size reduction to the nanoscale range. The fluid is split in two and is pushed through microchannels with typical dimensions in the order of 75 microns at high velocities (in the range of 50 m/s to 300 m/s). As the fluid exits the microchannels it forms jets which collide with jets from opposing microchannels. In the channels the fluid experiences high shear (up to 10^7 1/s) which is orders of magnitude higher than that of conventional technologies. Jet collisions result in mixing in submicron level. Therefore, high shear and impact are responsible for particle size reduction and mixing of multiphase fluids in the Microfluidizer® technology.

[000101] More generally, a microfluidizer may be any device that powers a single acting intensifier pump. The intensifier pump amplifies the hydraulic pressure to a selected level which, in turn, imparts that pressure to the product stream. As the pump travels through its pressure stroke, it drives the product at constant pressure through the interaction chamber. Within the interaction chamber are specially designed fixed-geometry microchannels through which the product stream will accelerate to high velocities, creating high shear and impact

forces that can generate a uniform nanoparticle composition (*e.g.*, nanoemulsion) as the high velocity product stream impinges on itself and on wear-resistant surfaces.

[000102] As the intensifier pump completes its pressure stroke, it reverses direction and draws in a new volume of product. At the end of the intake stroke, it again reverses direction and drives the product at constant pressures, thereby repeating the process.

[000103] Upon exiting the interaction chamber, the product flows through an onboard heat exchanger which regulates the product to a desired temperature. At this point, the product may be recirculated through the system for further processing or directed externally to the next step in the process (U.S. Patents 4,533,254; and 4,908,154; both of which are incorporated herein by reference).

[000104] In some embodiments, a sample is "microfluidized" through exposure to high shear forces for a period of time less than about 10 minutes. In some embodiments, the period of time is less than about 9, about 8, about 7, about 6, about 5, about 4, about 3, about 2, or about 1 minute(s). In some embodiments, the period of time is within the range of about 1 to about 2 minutes or less; in some embodiments, the period of time is about 30 seconds.

[000105] In some embodiments, a sample is "microfluidized" through a single exposure to high shear forces; such embodiments are referred to herein as "single pass" microfluidization.

Premix Composition

[000106] The present invention encompasses the recognition that subjecting a premix to high shear forces can generate a nanoparticle composition, and in particular can generate a uniform nanoparticle composition.

[000107] In general, the premix from which nanoparticle compositions are prepared through the application of high shear force is expected to contain at least two immiscible materials, one of which will constitute the dispersion medium (*i.e.*, the liquid medium in which particles (*e.g.*, nanoparticles) are dispersed in the ultimate nanoparticle composition). An "oil-in-water" dispersion is one in which oily particles are dispersed within an aqueous dispersion medium. A "water-in-oil" dispersion is one in which aqueous particles are dispersed within an oily dispersion medium. Those of ordinary skill in the art will appreciate that a dispersion can be formed from any two immiscible media and is not limited strictly to combinations of aqueous and oily media. The term "dispersion medium" therefore applies broadly to *any* dispersion medium notwithstanding that it is common to refer to "aqueous" and "oily" categories.

[000108] Thus, in some embodiments, a premix will contain an aqueous dispersion medium and an oily medium that becomes dispersed in nanoparticle form in the dispersion medium; in

some embodiments, a premix contains an oily dispersion medium and an aqueous medium that becomes dispersed in nanoparticle form in the oily dispersion medium.

[000109] Those of ordinary skill in the art will be well aware of suitable aqueous media that can be used as dispersion media or as media to be dispersed in accordance with the present invention. Representative such aqueous media include, for example, water, saline solutions (including phosphate buffered saline), water for injection, short chain alcohols, 5% dextrose, Ringer's solutions (lactated Ringer's injection, lactated Ringer's plus 5% dextrose injection, acylated Ringer's injection), Normosol-M, Isolyte E, and the like, and combinations thereof.

[000110] Those of ordinary skill in the art will also be well aware of suitable oily media that can be used as dispersion media or as media to be dispersed in accordance with the present invention. In some embodiments, the oil may comprise one or more fatty acid groups or salts thereof. In some embodiments, the fatty acid group may comprise digestible, long chain (*e.g.*, C_8-C_{50}), substituted or unsubstituted hydrocarbons. In some embodiments, the fatty acid group may be a C_{10}-C_{20} fatty acid or salt thereof. In some embodiments, the fatty acid group may be a C_{15}-C_{20} fatty acid or salt thereof. In some embodiments, the fatty acid group may be a C_{15}-C_{25} fatty acid or salt thereof. In some embodiments, the fatty acid group may be a medium chain triglyceride. In some embodiments, the fatty acid group may be unsaturated. In some embodiments, the fatty acid group may be monounsaturated. In some embodiments, the fatty acid group may be polyunsaturated. In some embodiments, a double bond of an unsaturated fatty acid group may be in the *cis* conformation. In some embodiments, a double bond of an unsaturated fatty acid may be in the *trans* conformation.

[000111] In some embodiments, the fatty acid group may be one or more of butyric, caproic, caprylic, capric, lauric, myristic, palmitic, stearic, arachidic, behenic, or lignoceric acid. In some embodiments, the fatty acid group may be one or more of palmitoleic, oleic, vaccenic, linoleic, alpha-linolenic, gamma-linoleic, arachidonic, gadoleic, arachidonic, eicosapentaenoic, docosahexaenoic, or erucic acid.

[000112] In some embodiments, the oil is a liquid triglyceride. In some embodiments, the oil is a medium chain triglyceride. In general, medium chain triglycerides are fatty acids containing 6–12 carbons atoms (*e.g.*, caprylic acid, octanoic acid, capric acid, decanoic acid, lauric acid, *etc.*) and may be obtained from coconut oil or palm kernel oil. In some embodiments 1349 oil is a medium-chain triglyceride that can be utilized in accordance with the invention.

[000113] Representative such oily media include, for example, saturated and unsaturated almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade,

camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macadamia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils; butyl stearate; caprylic triglyceride; capric triglyceride; cyclomethicone; diethyl sebacate; dimethicone 360; isopropyl myristate; mineral oil; octyldodecanol; oleyl alcohol; silicone oil; medium-chain triglyceride oils; 1349 oil; and combinations thereof.

[000114] In addition to the two immiscible media, a premix according to the present invention may include, for example, one or more surfactants or emulsifying agents. Suitable such surfactants or emulsifying agents include, but are not limited to, phosphoglycerides; phosphatidylcholines; dipalmitoyl phosphatidylcholine (DPPC); dioleylphosphatidyl ethanolamine (DOPE); dioleyloxypropyltriethylammonium (DOTMA); dioleoylphosphatidylcholine; cholesterol; cholesterol ester; diacylglycerol; diacylglycerolsuccinate; diphosphatidyl glycerol (DPPG); hexanedecanol; fatty alcohols such as polyethylene glycol (PEG); polyoxyethylene-9-lauryl ether; a surface active fatty acid, such as palmitic acid or oleic acid; fatty acids; fatty acid monoglycerides; fatty acid diglycerides; fatty acid amides; sorbitan trioleate (SPAN®85) glycocholate; sorbitan monolaurate (SPAN®20); polysorbate 20 (TWEEN®20); polysorbate 60 (TWEEN®60); polysorbate 65 (TWEEN®65); polysorbate 80 (TWEEN®80); polysorbate 85 (TWEEN®85); super-refined polysorbate 20 (SR TWEEN®20); super-refined polysorbate 60 (SR TWEEN®60); super-refined polysorbate 65 (SR TWEEN®65); super-refined polysorbate 80 (SR TWEEN®80); super-refined polysorbate 85 (SR TWEEN®85); polyoxyethylene monostearate; surfactin; a poloxomer; a sorbitan fatty acid ester such as sorbitan trioleate; lecithin; lysolecithin; phosphatidylserine; phosphatidylinositol; sphingomyelin; phosphatidylethanolamine (cephalin); cardiolipin; phosphatidic acid; cerebrosides; dicetylphosphate; dipalmitoylphosphatidylglycerol; stearylamine; dodecylamine; hexadecyl-amine; acetyl palmitate; glycerol ricinoleate; hexadecyl stearate; isopropyl myristate; tyloxapol; poly(ethylene glycol)5000-phosphatidylethanolamine; poly(ethylene glycol)400-monostearate; phospholipids; synthetic and/or natural detergents having high surfactant properties; deoxycholates; cyclodextrins; chaotropic salts; ion pairing agents; and combinations thereof. The surfactant component may be a mixture of different surfactants.

These surfactants may be extracted and purified from a natural source or may be prepared synthetically in a laboratory. In some embodiments, the surfactants are commercially available.

[000115] In some embodiments, all of the components present in the final nanoparticle composition are present in the premix and are subjected to high shear force to produce the nanoparticle composition. In some embodiments, one or more of the components that are present in the final nanoparticle composition is/are missing from the premix or is/are present in the premix in a smaller amount than in the final nanoparticle composition. That is, in some embodiments, one or more materials are added to the nanoparticle composition after the premix is subjected to high shear force.

[000116] In certain embodiments, the premix is prepared as a solution prior to application of high shear force. In particular, for nanoparticle compositions that include at least one therapeutic agent (*e.g.*, botulinum toxin), it is often desirable for the therapeutic agent to be dissolved in the premix before the high shear force is applied. Thus, in many embodiments, the therapeutic agent is soluble in at least one of the media (or in a combination of media utilized in the premix). In some embodiments, such dissolution requires heating; in other embodiments it does not.

[000117] In some embodiments, the premix components may assemble into particles before the application of high shear force. At least some of such particles may be microparticles or even nanoparticles. In some embodiments, a nanoparticle composition is prepared from a premix, wherein the premix is selected from the group comprising a suspension or a microemulsion. In some embodiments, however, particle structures do not form in the premix before application of high shear force.

[000118] In certain embodiments, relative amount of premix components are selected or adjusted to generate nanoparticles having desired characteristics. In some embodiments, the premix comprises oil and surfactant at a ratio ranging between 0.5 – 10. In some embodiments, the ratio of oil to surfactant is approximately 0.5:1, approximately 1:1, approximately 2:1, approximately 3:1, approximately 4:1, approximately 5:1, approximately 6:1, approximately 7:1, approximately 8:1, approximately 9:1 or approximately 10:1. In some embodiments, the ratio of surfactant to oil is approximately 0.5:1, approximately 1:1, approximately 2:1, approximately 3:1, approximately 4:1, approximately 5:1, approximately 6:1, approximately 7:1, approximately 8:1, approximately 9:1 or approximately 10:1.

[000119] In some embodiments, oil and surfactant are utilized at a ratio ranging between 0.5 and 2. In certain embodiments, the ratio of oil to surfactant is approximately 0.5:1,

approximately 1:1, or approximately 2:1. In certain embodiments, the ratio of surfactant to oil is approximately 0.5:1, approximately 1:1, or approximately 2:1. In certain specific embodiments, the ratio of oil to surfactant is approximately 1:1.

[000120] In some embodiments, the water and surfactant are utilized at a ratio ranging between 0.5 and 10. In some embodiments, the ratio of water to surfactant is approximately 0.5:1, approximately 1:1, approximately 2:1, approximately 3:1, approximately 4:1, approximately 5:1, approximately 6:1, approximately 7:1, approximately 8:1, approximately 9:1 or approximately 10:1. In some embodiments, the ratio of surfactant to water is approximately 0.5:1, approximately 1:1, approximately 2:1, approximately 3:1, approximately 4:1, approximately 5:1, approximately 6:1, approximately 7:1, approximately 8:1, approximately 9:1 or approximately 10:1. In some embodiments, water and surfactant are utilized at a ratio ranging between 0.5 and 2. In certain embodiments, the ratio of water to surfactant is approximately 0.5:1, approximately 1:1, or approximately 2:1. In certain embodiments, the ratio of surfactant to water is approximately 0.5:1, approximately 1:1, or approximately 2:1. In certain specific embodiments, the ratio of water to surfactant is approximately 1:1. In some embodiments, compositions utilizing such ratios of water to surfactant comprise water-in-oil emulsions.

[000121] In some embodiments, the percent of oil in the premix ranges between 0% and 30%. In some embodiments, the percent of oil in the premix ranges between 0% and 5%, between 5% and 10%, between 10% and 15%, between 15% and 20%, between 20% and 25%, or between 25% and 30%. In some embodiments, the percent of oil in the premix ranges between 0% and 10%, between 0% and 20%, or between 0% and 30%. In some embodiments, the percent of oil in the premix ranges between 10% and 20% or between 10% and 30%. In some embodiments, the percent of oil in the premix ranges between 20% and 30%.

[000122] In some embodiments the percent of oil in the premix is approximately 1%, approximately 2%, approximately 3%, approximately 4%, approximately 5%, approximately 6%, approximately 7%, approximately 9%, approximately 10%, approximately 11%, approximately 12%, approximately 13%, approximately 14%, approximately 15%, approximately 16%, approximately 17%, approximately 18%, approximately 19%, approximately 20%, approximately 21%, approximately 22%, approximately 23%, approximately 24%, approximately 25%, approximately 26%, approximately 27%, approximately 28%, approximately 29% or approximately 30%. In some embodiments the percent of oil is approximately 10%. In some embodiments the percent of oil is

approximately 9%. In some embodiments the percent of oil is approximately 8%. In some embodiments the percent of oil is approximately 7%. In some embodiments the percent of oil is approximately 6%. In some embodiments the percent of oil is approximately 5%. In some embodiments the percent of oil is approximately 4%. In some embodiments the percent of oil is approximately 3%. In some embodiments the percent of oil is approximately 2%. In some embodiments the percent of oil is approximately 1%.

[000123] The percent of water in the premix can range from 0% to 99%, from 10% to 99%, from 25% to 99%, from 50% to 99%, or from 75% to 99%. In some embodiments, the percent of water in the premix can range from 0% to 75%, from 0% to 50%, from 0% to 25%, or from 0% to 10%. In some embodiments, the percent of water in the premix ranges between 0% and 30%. In some embodiments the percent of water is approximately 1%, approximately 2%, approximately 3%, approximately 4%, approximately 5%, approximately 6%, approximately 7%, approximately 9%, approximately 10%, approximately 11%, approximately 12%, approximately 13%, approximately 14%, approximately 15%, approximately 16%, approximately 17%, approximately 18%, approximately 19%, approximately 20%, approximately 21%, approximately 22%, approximately 23%, approximately 24%, approximately 25%, approximately 26%, approximately 27%, approximately 28%, approximately 29%, approximately 30%, approximately 35%, approximately 40%, approximately 45%, approximately 50%, approximately 55%, approximately 60%, approximately 65%, approximately 70%, approximately 71%, approximately 72%, approximately 73%, approximately 74%, approximately 75%, approximately 76%, approximately 77%, approximately 78%, approximately 79%, approximately 80%, approximately 81%, approximately 82%, approximately 83%, approximately 84%, approximately 85%, approximately 86%, approximately 87%, approximately 88%, approximately 89%, approximately 90%, approximately 91%, approximately 92%, approximately 93%, approximately 94%, approximately 95%, approximately 96%, approximately 97%, approximately 98%, or approximately 99%,. In some embodiments the percent of water is approximately 83%. In some embodiments the percent of water is approximately 9%. In some embodiments the percent of water is approximately 5%.

[000124] In some embodiments, the percent of surfactant in the premix ranges between 0% –30%. In some embodiments the percent of surfactant in the premix is about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about

19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, or about 30%. In some embodiments the percent of surfactant is approximately 10%. In some embodiments the percent of surfactant is approximately 9%. In some embodiments the percent of surfactant is approximately 8%. In some embodiments the percent of surfactant is approximately 7%. In some embodiments the percent of surfactant is approximately 6%. In some embodiments the percent of surfactant is approximately 5%.

[000125] In some embodiments, a nanoparticle composition does not contain more than one oil. In some embodiments, a nanoparticle composition may comprise two or more oils. In some embodiments, a nanoparticle composition does not contain more than one surfactant. In some embodiments, a nanoparticle composition may comprise two or more surfactants.

[000126] In some embodiments, a nanoparticle composition consists essentially of water, an oil, a surfactant, and a therapeutic agent (*e.g.* botulinum toxin). In some embodiments, a nanoparticle composition consists essentially of water, an oil, a surfactant, at least one therapeutic agent (*e.g.*, botulinum toxin), and at least one substance used to produce and/or preserve the nanoparticle composition (*e.g.*, proteins, salts, *etc.*).

[000127] In some embodiments, a nanoparticle composition consists of water, an oil, a surfactant, and a therapeutic agent (*e.g.*, botulinum toxin). In some embodiments, a nanoparticle composition consists of water, an oil, a surfactant, at least one therapeutic agent (*e.g.*, botulinum toxin), and at least one substance used to produce and/or preserve the nanoparticle composition (*e.g.*, proteins, salts, *etc.*).

Therapeutic Agents

[000128] In some embodiments, a nanoparticle composition may comprise one or more therapeutic agents. In some embodiments, one or more therapeutic agents may be incorporated into a premix which is subjected to high shear force to generate nanoparticle compositions. In some embodiments, one or more therapeutic agents may be mixed with nanoparticle compositions when preparing a pharmaceutical composition.

Botulinum Toxin

[000129] Botulinum toxin (BTX) BTX is produced in nature by the anaerobic, gram positive bacillus *Clostridium botulinum* and is a potent polypeptide neurotoxin. Most notably, BTX causes a neuroparalytic illness in humans and animals referred to as botulism. BTX can apparently pass through the lining of the gut and attack peripheral motor neurons. Symptoms of botulinum toxin intoxication can progress from difficulty walking, swallowing, and speaking to paralysis of the respiratory muscles, and death.

[000130] BTX-A is the most lethal natural biological agent known to man. The LD_{50} in female Swiss Webster mice (18 g – 20 g) for commercially available BTX-A is about 50 picograms; this amount is defined as 1 Unit of BTX-A. On a molar basis, BTX-A is about 1.8 billion times more lethal than diphtheria, about 600 million times more lethal than sodium cyanide, about 30 million times more lethal than cobra toxin and about 12 million times more lethal than cholera (Singh, *et al.*, ed., "Critical Aspects of Bacterial Protein Toxins" *Natural Toxins II*, pp. 63-84, Plenum Press, New York, 1996).

[000131] The different serotypes of botulinum toxin vary in the animal species that they affect and in the severity and duration of the paralysis they evoke. For example, it has been determined that BTX-A is 500 times more potent than is BTX-B, as measured by the rate of paralysis produced in the rat. Additionally, BTX-B has been determined to be non-toxic in primates at a dose of 480 U/kg, which is about 12 times the primate LD_{50} for BTX-A. Furthermore, it is known that botulinum toxin type B has, upon intramuscular injection, a shorter duration of activity and is also less potent than BTX-A at the same dose level.

[000132] Botulinum toxin apparently binds with high affinity to cholinergic motor neurons, is translocated into the neuron and blocks the release of acetylcholine and other pre-formed mediators and transmitters. For example, *in vitro* studies performed on neurons other than motor neurons revealed that botulinum toxin not only blocks acetylcholine release, but can also prevent liberation of other neurotransmitters (*e.g.*, neurotransmitters stored in vesicles), including small organic molecules and neuropeptides (*e.g.*, adrenaline; noradrenaline; dopamine; glutamate; aspartate; glycine; GABA; ATP that is co-stored with neurotransmitters such as acetylcholine and/or glutamate; substance P; and/or CGRP) (Poulain, 2008, *Botulinum J.*, 1:14; incorporated herein by reference).

[000133] Botulinum toxins have been used in clinical settings for the treatment of certain neuromuscular disorders. In particular, BTX-A has been approved by the U.S. Food and Drug Administration for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia; the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents; the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above; and for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients $\leq$ 65 years of age.

[000134] Clinical effects of peripheral intramuscular BTX-A are usually seen within one week of injection. The typical duration of symptomatic relief from a single intramuscular injection of BTX-A averages about three months.

[000135] Although all the botulinum toxins serotypes apparently inhibit release of the neurotransmitter acetylcholine at the neuromuscular junction, they do so by affecting different neurosecretory proteins and/or cleaving these proteins at different sites. For example, botulinum types A and E both cleave the 25 kilodalton (kD) synaptosomal associated protein (SNAP-25), but they target different amino acid sequences within this protein. Botulinum toxin types B, D, F and G act on vesicle-associated membrane protein (VAMP, also called synaptobrevin), with each serotype cleaving the protein at a different site. Finally, botulinum toxin type C_1 has been shown to cleave both syntaxin and SNAP-25. These differences in mechanism of action may affect the relative potency and/or duration of action of the various botulinum toxin serotypes. The cytosol of pancreatic islet B cells contains at least SNAP-25 (Gonelle-Gispert *et al.*, 1999, *Biochem. J.*, 339 (pt 1): 159-65; incorporated herein by reference), and synaptobrevin (1995, *Mov. Disord.*, 10: 376; incorporated herein by reference).

[000136] The molecular weight of a botulinum toxin protein molecule, for all seven of the known botulinum toxin serotypes, is about 150 kD. Botulinum toxins are released by the *Clostridium* bacterium as complexes comprising the 150 kD botulinum toxin protein molecule along with associated non-toxin proteins. Thus, the BTX-A complex can be produced by the *Clostridium* bacterium as 900 kD, 500 kD and 360 kD forms. Botulinum toxin types B and C_1 are apparently produced as only a 500 kD complex. Botulinum toxin type D is produced as both 300 kD and 500 kD complexes. Finally, botulinum toxin types E and F are produced as only approximately 300 kD complexes.

[000137] BTX complexes (*i.e.*, those compositions having molecular weights greater than about 150 kD) are believed to contain a non-toxin hemagglutinin protein and a non-toxin and non-toxic non-hemagglutinin protein. These two non-toxin proteins (which along with the botulinum toxin molecule comprise the relevant neurotoxin complex) may act to provide stability against denaturation to the botulinum toxin molecule and protection against digestive acids when toxin is ingested.

[000138] Either BTX proteins or BTX complexes may be utilized in accordance with the present invention. Indeed, it will be appreciated by those of ordinary skill in the art that any portion or fragment of a BTX protein or complex that retains the appropriate activity may be utilized as described herein.

[000139] *In vitro* studies have indicated that botulinum toxin inhibits potassium cation induced release of both acetylcholine and norepinephrine from primary cell cultures of brainstem tissue. Additionally, it has been reported that botulinum toxin inhibits the evoked release of both glycine and glutamate in primary cultures of spinal cord neurons and that in brain synaptosome preparations botulinum toxin inhibits the release of each of the neurotransmitters acetylcholine, dopamine, norepinephrine, CGRP and glutamate.

[000140] As noted above, the source of botulinum toxin is not critical to the present invention. For purposes of completeness, however, we note that a variety of sources, including commercial sources, for certain botulinum toxin preparations are readily available.

[000141] For example, BTX or BTX complex can be obtained by establishing and growing cultures of *Clostridium botulinum* in a fermenter and then harvesting and purifying the fermented mixture in accordance with known procedures. All the botulinum toxin serotypes are initially synthesized as inactive single chain proteins which must be cleaved or nicked by proteases to become neuroactive. The bacterial strains that make botulinum toxin serotypes A and G possess endogenous proteases. Therefore, serotypes A and G can be recovered from bacterial cultures in predominantly their active form. In contrast, botulinum toxin serotypes C_1, D and E are synthesized by nonproteolytic strains and are therefore typically unactivated when recovered from culture. Serotypes B and F are produced by both proteolytic and nonproteolytic strains and therefore can be recovered in either the active or inactive form. However, even the proteolytic strains that produce, for example, the BTX-A serotype typically only cleave a portion of the toxin produced. The exact proportion of nicked to unnicked molecules can depend on the length of incubation and the temperature of the culture. Therefore, a certain percentage of any preparation of, for example BTX-A, is likely to be inactive. The presence of inactive botulinum toxin molecules in a clinical preparation will contribute to the overall protein load of the preparation, which has been linked in some commercially available botulinum toxin preparations to increased antigenicity, without contributing to its clinical efficacy.

[000142] High quality crystalline botulinum toxin type A can be produced from the Hall A strain of *Clostridium botulinum* with characteristics of $\geq 3 \times 10^7$ U/mg, an A_{260}/A_{278} of less than 0.60 and a distinct pattern of banding on gel electrophoresis. The known Schantz process can be used to obtain crystalline botulinum toxin including type A (Shantz *et al.*, 1992, *Microbiol. Rev.*, 56:80; incorporated herein by reference).

[000143] Generally, the botulinum toxin complex can be isolated and purified from an anaerobic fermentation by cultivating *Clostridium botulinum* (*e.g.*, type A) in a suitable

medium. The known process can be used, upon separation out of the non-toxin proteins, to obtain pure botulinum toxins, such as for example: purified botulinum toxin type A with an approximately 150 kD molecular weight with a specific potency of 1-2 × 10^8 LD_{50} U/mg or greater; purified botulinum toxin type B with an approximately 156 kD molecular weight with a specific potency of 1-2 × 10^8 LD_{50} U/mg or greater, and; purified botulinum toxin type F with an approximately 155 kD molecular weight with a specific potency of 1-2 × 10^7 LD_{50} U/mg or greater.

[000144] Alternatively or additionally, already prepared and purified botulinum toxins and toxin complexes can be obtained from, for example, List Biological Laboratories, Inc., Campbell, CA; the Centre for Applied Microbiology and Research, Porton Down, U.K.; Wako (Osaka, Japan) as well as from Sigma Chemicals of St. Louis, MO.

[000145] Pure botulinum toxin, when administered as a free solution, is so labile that it is generally not used to prepare a pharmaceutical composition. Furthermore, the botulinum toxin complexes, such the toxin type A complex can also be susceptible to denaturation due to surface denaturation, heat, and alkaline conditions. In some cases, inactivated toxin forms toxoid proteins which may be immunogenic. Resulting antibodies can render a patient refractory to toxin injection.

[000146] In some embodiments, the present invention provides botulinum toxin nanoparticle compositions (*e.g.*, nanoemulsions) in which the botulinum toxin has improved stability when compared to currently administered free solutions. That is, in some embodiments, botulinum toxin present in a nanoparticle composition is protected, at least in part, from at least one adverse condition such as heat, alkaline conditions, acidic conditions, degradative enzymes, host organism antibodies, *etc.* Alternatively or additionally, botulinum toxin present in nanoparticle compositions may show less surface denaturation than an otherwise comparable preparation of botulinum toxin in free solution. Surface denaturation refers to protein degradation that results from interactions of proteins with surfaces (*e.g.*, walls of a container in which proteins are stored) or with air (*e.g.*, at the interface between a nanoparticle composition and air).

[000147] Indeed, one surprising aspect of the present invention encompasses the recognition that botulinum toxin may be stabilized by incorporation into a nanoparticle composition. Those of ordinary skill in the art will readily appreciate that a nanoparticle composition according to this aspect of the present invention may be prepared by any available means. In some embodiments, the present invention allows use of isolated

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botulinum toxin rather than botulinum toxin complex, at least in part due to the additional stability imparted by incorporation into a nanoparticle composition.

[000148] The present invention further provides botulinum toxin nanoparticle compositions (*e.g.*, nanoemulsions) in which the botulinum toxin has improved ability to permeate skin when compared to currently administered free solutions. In some embodiments, the minimal time between administration and intracellular accumulation results in a method of administration having improved efficacy and decreased side effects.

[000149] Moreover, as demonstrated herein, the present invention provides botulinum toxin nanoparticle compositions from which botulinum toxin can cross the skin without requiring alteration or disruption of skin structures. For example, commercially available technologies for transdermal administration of biologically active agents traditionally require chemical, physical, electrical or other disruption of at least the outer layer of skin. Such disruption can cause irritation, undesirable medical side-effects, and/or unwanted aesthetic outcomes. The present invention provides botulinum toxin nanoparticle compositions that, when administered to skin, do not significantly or noticeably irritate the skin and/or erode the stratum corneum, and yet allow botulinum toxin to permeate the skin to have its biological effects.

[000150] As with proteins generally, the biological activities of the botulinum toxins (which are intracellular peptidases) can be affected by changes in three dimensional conformation. Thus, botulinum toxin type A can be detoxified by heat, various chemicals, surface stretching and surface drying. Additionally, it is known that dilution of the toxin complex obtained by the known culturing, fermentation and purification to the much, much lower toxin concentrations used for pharmaceutical composition formulation results in rapid detoxification of the toxin unless a suitable stabilizing agent is present. Dilution of the toxin from milligram quantities to a solution containing nanograms per milliliter presents significant difficulties because of the rapid loss of specific toxicity upon such great dilution. Since the toxin may be used months or years after the toxin containing pharmaceutical composition is formulated, solution preparations of the toxin may be formulated with a stabilizing agent, such as albumin.

[000151] As noted above, the present invention may provide stabilized preparations of botulinum toxin. Notwithstanding the additional stability that may be imparted by the formulation itself, in some embodiments, use of additional stabilizers is contemplated. For example, in some embodiments, at least one additional protein is used together with the botulinum toxin. In some embodiments, this additional protein comprises albumin. In some

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embodiments, this additional protein comprises one or more of the proteins naturally found in a botulinum toxin complex. Indeed, in some embodiments, a complete botulinum toxin complex is employed. In some such embodiments, albumin is also utilized. Thus, in some embodiments, the present invention provides a botulinum nanoemulsion (*e.g.*, microfluidized nanoemulsion) comprising albumin.

[000152] In some embodiments, the botulinum toxin utilized is BOTOX® (Allergan, Inc.). BOTOX® consists of a purified botulinum toxin type A complex, albumin and sodium chloride packaged in sterile, vacuum-dried form.

[000153] The botulinum toxin type A present in BOTOX® is made from a culture of the Hall strain of *Clostridium botulinum* grown in a medium containing N-Z amine and yeast extract. The botulinum toxin type A complex is purified from the culture solution by a series of acid precipitations to a crystalline complex (see, *e.g.*, Shantz *et al.*, 1992, *Microbiol. Rev.*, 56:80; incorporated herein by reference) consisting of the active high molecular weight toxin protein and at least one associated hemagglutinin protein. The crystalline complex is re-dissolved in a solution containing saline and albumin and sterile filtered (0.2 microns) prior to vacuum-drying. BOTOX® can be reconstituted with sterile, non-preserved saline prior to intramuscular injection. Each vial of BOTOX® contains about 100 units (U) of *Clostridium botulinum* toxin type A purified neurotoxin complex, 0.5 milligrams of human serum albumin, and 0.9 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative.

[000154] Currently, BOTOX® is typically reconstituted with 0.9% sodium chloride for administration by injection. Since there is a concern that BOTOX® can be denatured by bubbling or similar violent agitation, it is recommended that the diluent be gently injected into the vial. BOTOX®, as a free solution, is recommended to be administered within four hours after reconstitution. Further, between reconstitution and injection, it is further recommended that reconstituted BOTOX® be stored in a refrigerator (*i.e.*, for example, between 2° to 8° C). Reconstituted BOTOX® is clear, colorless and free of particulate matter.

[000155] It has been reported that BOTOX® has been used in clinical settings as follows (for a review, see, *e.g.*, Poulain, 2008, *Botulinum J.*, 1:14; incorporated herein by reference):

(1) about 75 U – 125 U of BOTOX® per intramuscular injection (multiple muscles) to treat cervical dystonia;

(2) 5 U – 10 U of BOTOX® per intramuscular injection to treat glabellar lines (brow furrows) (5 units injected intramuscularly into the procerus muscle and 10 units injected intramuscularly into each corrugator supercilli muscle);

(3) about 30 U – 80 U of BOTOX® to treat constipation by intrasphincter injection of the puborectalis muscle;

(4) about 1 U – 5 U per muscle of intramuscularly injected BOTOX® to treat blepharospasm by injecting the lateral pre-tarsal orbicularis oculi muscle of the upper lid and the lateral pre-tarsal orbicularis oculi of the lower lid.

(5) to treat strabismus, extraocular muscles have be in injected intramuscularly with between about 1 U –5 U of BOTOX®, the amount injected varying based upon both the size of the muscle to be injected and the extent of muscle paralysis desired (*i.e.*, amount of diopter correction desired).

(6) to treat upper limb spasticity following stroke by intramuscular injections of BOTOX® into five different upper limb flexor muscles, as follows:

(a) flexor digitorum profundus: 7.5 U to 30 U

(b) flexor digitorum sublimus: 7.5 U to 30 U

(c) flexor carpi ulnaris: 10 U to 40 U

(d) flexor carpi radialis: 15 U to 60 U

(e) biceps brachii: 50 U to 200 U

Each of the five indicated muscles has been injected at the same treatment session, so that the patient receives from 90 U to 360 U of upper limb flexor muscle BOTOX® by intramuscular injection at each treatment session.

(7) to treat migraine, pericranial injected (injected symmetrically into glabellar, frontalis and temporalis muscles) injection of 25 U of BOTOX® has showed significant benefit as a prophylactic treatment of migraine compared to vehicle as measured by decreased measures of migraine frequency, maximal severity, associated vomiting and acute medication use over the three month period following the 25 U injection.

[000156] The present invention demonstrates (see, for example, Examples 4 and 5) that a botulinum nanoparticle composition, when incorporated into a cream that is applied to the skin for transdermal delivery of the toxin, achieves biological results (*i.e.*, reduction of wrinkles) comparable to those historically observed with injection of a botulinum toxin solution containing approximately the same amount of BOTOX®.

[000157] The positive clinical responses of botulinum toxin type A has led to interest in other botulinum toxin serotypes. A study of two commercially available botulinum type A

preparations (BOTOX® and DYSPORT®) and preparations of botulinum toxins type B and F (both obtained from Wako Chemicals, Japan) has been carried out to determine local muscle weakening efficacy, safety and antigenic potential in mice. Botulinum toxin preparations were injected into the head of the right gastrocnemius muscle (0.5 to 200.0 U/kg) and muscle weakness was assessed using the mouse digit abduction scoring assay (DAS). ED_{50} values were calculated from dose response curves.

[000158] Additional mice were given intramuscular or peritoneal injections to determine LD_{50} doses. The therapeutic index was calculated as LD_{50} /ED_{50}. Separate groups of mice received hind limb injections of BOTOX® (5.0 to 10.0 U/kg) or botulinum toxin type B (50.0 to 400.0 U/kg), and were tested for muscle weakness and increased water consumption, the later being a putative model for dry mouth. Peak muscle weakness and duration were dose related for all serotypes.

[000159] DAS ED_{50} values (U/kg) were as follows: BOTOX®: 6.7, DYSPORT®: 24.7, botulinum toxin type B: 27.0 to 244.0, botulinum toxin type F: 4.3. BOTOX® had a longer duration of action than botulinum toxin type B or botulinum toxin type F. Therapeutic index values were as follows: BOTOX®: 10.5, DYSPORT®: 6.3, botulinum toxin type B: 3.2. Water consumption was greater in mice injected with botulinum toxin type B than with BOTOX®, although botulinum toxin type B was less effective at weakening muscles. DAS results indicate relative peak potencies of botulinum toxin type A being equal to botulinum toxin type F, and botulinum toxin type F being greater than botulinum toxin type B. With regard to duration of effect, botulinum toxin type A was greater than botulinum toxin type B, and botulinum toxin type B duration of effect was greater than botulinum toxin type F. As shown by the therapeutic index values, the two commercial preparations of botulinum toxin type A (BOTOX® and DYSPORT ®) are different. The increased water consumption behavior observed following hind limb injection of botulinum toxin type B indicates that clinically significant amounts of this serotype entered the murine systemic circulation. The results also indicate that in order to achieve efficacy comparable to botulinum toxin type A, it may be necessary to increase doses of the other serotypes examined. Increased dosage, however, can compromise safety.

[000160] Antigenic potential was assessed by monthly intramuscular injections in rabbits (1.5 or 6.5 ng/kg for botulinum toxin type B or 0.15 ng/kg for BOTOX®). After four months of injections, 2 of 4 rabbits treated with 1.5 ng/kg and 4 of 4 animals treated with 6.5 ng/kg developed antibodies against botulinum toxin type B. In a separate study, 0 of 9 BOTOX® treated rabbits demonstrated antibodies against botulinum toxin type A. Therefore, in rabbits,

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botulinum toxin type B was more antigenic than was BOTOX®, possibly because of the higher protein load injected to achieve an effective dose of botulinum toxin type B (Aoki, 1999, *Eur. J. Neurol.*, 6:S3-S10).

[000161] As indicated herein, the present invention contemplates use of botulinum toxin of any serotype. Those of ordinary skill in the art will readily be able to assess the appropriateness of a particular serotype for a particular use and, according to the teachings herein, will be able to prepare nanoparticle compositions containing such botulinum toxin. Thus, the present invention provides nanoparticle compositions containing botulinum toxin of any serotype, including compositions containing only botulinum toxin proteins and compositions containing one or more other proteins. In some embodiments, such other proteins comprise or consist of albumin; in some embodiments, botulinum toxin complexes are employed.

[000162] Commercially available sources of botulinum toxin that may be utilized in accordance with the present invention include, but are not limited to, BOTOX®, DYSPORT® (*Clostridium botulinum* type A toxin hemagglutinin complex with human serum albumin and lactose; Ispen Limited, Berkshire U.K.), Xeomin®, PurTox®, Medy-Tox, NT-201 (Merz Pharmaceuticals), and/or MYOBLOC® (an injectable solution consisting of botulinum toxin type B, human serum albumin, sodium succinate, and sodium chloride, pH 5.6, Elan Pharmaceuticals, Dublin, Ireland), *etc.*

Therapeutic Agents Useful for Acne Treatment

[000163] In some embodiments, a therapeutic agent is useful for treating acne. In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating acne is botulinum toxin. In some embodiments, a therapeutic agent useful for treatment of acne is a topical bactericidal, for example, benzoyl peroxide, triclosan, and/or chlorhexidine gluconate. In addition to its therapeutic effect as a keratolytic (*i.e.*, a substance that dissolves keratin plugging pores), benzoyl peroxide can prevent new lesions by killing *P. acnes*. Benzoyl peroxide is also thought to decrease the presence of free fatty acids, resulting in a decrease in inflammation and follicular obstruction. In one study, roughly 70% of participants using a 10% benzoyl peroxide solution experienced a reduction in acne lesions after 6 weeks (Dogra *et al.*, 1993, *Indian J. Dermatol. Venereol. Leprol.*, 59:243-6; incorporated herein by reference). Benzoyl peroxide routinely causes dryness, local irritation, and redness. Nanoemulsions in accordance with the present invention may be prepared with ingredients (*e.g.*, oil, surfactant, aqueous medium, excipients, *etc.*) that can help reduce or ameliorate one or more of these side effects. In some embodiments, a topical

bactericidal is present in a premix at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, a topical bactericidal is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%. In some embodiments, a topical bactericidal is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 0.1% to about 25%, about 0.1% to about 10%, or about 0.1% to about 5%. In some embodiments, a topical bactericidal is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 5% to about 50%, about 10% to about 50%, or about 25% to about 50%.

[000164] In some embodiments, a therapeutic agent useful for treatment of acne is a topical antibiotic, for example, erythromycin, clindamycin, Stiemycin, doxycycline, and/or tetracycline. Topical antibiotics typically aim to kill the bacteria (*e.g.*, *P. acnes*) that are harbored in follicles. While topical use of antibiotics can be equally as effective as oral use, topical administration may avoid side effects including upset stomach and drug interactions (*e.g.*, it will not affect use of the oral contraceptive pill). In some embodiments, a topical antibiotic is present in a premix at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, a topical antibiotic is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%. In some embodiments, a topical antibiotic is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 0.1% to about 25%, about 0.1% to about 10%, or about 0.1% to about 5%. In some embodiments, a topical antibiotic is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 5% to about 50%, about 10% to about 50%, or about 25% to about 50%.

[000165] In some embodiments, a therapeutic agent useful for treatment of acne is a hormone, for example, cortisone. Injected cortisone has the effect of flattening a pimple, thereby making it less conspicuous, and can also aid in the healing process. Side effects of injection may include a temporary whitening of the skin around the injection point, formation of a small depression, and/or scarring. In some embodiments, a hormone such as cortisone is present in a premix at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about

2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, a hormone such as cortisone is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%. In some embodiments, a hormone such as cortisone is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 0.1% to about 25%, about 0.1% to about 10%, or about 0.1% to about 5%. In some embodiments, a hormone such as cortisone is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 5% to about 50%, about 10% to about 50%, or about 25% to about 50%.

[000166] In some embodiments, a therapeutic agent useful for treatment of acne is a topical retinoid, for example, tretinoin (RETIN-A®), adapalene (DIFFERIN®), and tazarotene (TAZORAC®), retinol, *etc.* Topical retinoids may function by influencing cell creation and cell death in the follicle lining, thereby preventing hyperkeratinization of these cells. Topical retinoids can cause significant irritation of the skin, and they often cause an initial flare up of acne and facial flushing. In some embodiments, a topical retinoid is present in a premix at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, a topical retinoid is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%. In some embodiments, a topical retinoid is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 0.1% to about 25%, about 0.1% to about 10%, or about 0.1% to about 5%. In some embodiments, a topical retinoid is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 5% to about 50%, about 10% to about 50%, or about 25% to about 50%.

[000167] In some embodiments, a therapeutic agent useful for treatment of acne is a natural product with anti-acne activity, for example, aloe vera, aruna, haldi (*i.e.*, turmeric), papaya, *etc.* (Mantle *et al.*, 2001, *Adverse Drug Reactions and Toxicological Reviews*, 20:89-103; incorporated herein by reference). In some embodiments, a natural product with anti-acne activity is present in a premix at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, a natural

product with anti-acne activity is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000168] In some embodiments, a therapeutic agent useful for treatment of acne is azelaic acid (brand names AZELEX™, FINACEA®, FINEVIN®, SKINOREN, *etc.*). In some embodiments, azelaic acid is present in a premix at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, azelaic acid is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%. In some embodiments, azelaic acid is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 0.1% to about 25%, about 0.1% to about 10%, or about 0.1% to about 5%. In some embodiments, azelaic acid is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 5% to about 50%, about 10% to about 50%, or about 25% to about 50%.

[000169] In some embodiments, a therapeutic agent useful for treatment of acne is nicotinamide (*i.e.*, vitamin B3) (Shalita *et al.*, 1995, *Int. J. Dermatol.*, 34:434-7; incorporated herein by reference). Topical nicotinamide is thought to have anti-inflammatory activity and/or to result in increased synthesis of collagen, keratin, involucrin and/or flaggrin. In some embodiments, nicotinamide is present in a premix at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, nicotinamide is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%. In some embodiments, nicotinamide is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 0.1% to about 25%, about 0.1% to about 10%, or about 0.1% to about 5%. In some embodiments, nicotinamide is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 5% to about 50%, about 10% to about 50%, or about 25% to about 50%.

[000170] In some embodiments, a therapeutic agent useful for treatment of acne is tea tree oil (melaleuca oil). Tea tree oil has been shown to be an effective anti-inflammatory in skin infections (Mantle *et al.*, 2001, *Adverse Drug Reactions and Toxicological Reviews*, 20:89-

103; Koh *et al.*, 2002, *Br. J. Dermatol.*, 147:1212-7; and Khalil *et al.*, 2004, *J. Invest. Dermatol.*, 123:683-90; all of which are incorporated herein by reference). In some embodiments, tea tree oil is present in a premix at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, tea tree oil is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%. In some embodiments, tea tree oil is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 0.1% to about 25%, about 0.1% to about 10%, or about 0.1% to about 5%. In some embodiments, tea tree oil is present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 5% to about 50%, about 10% to about 50%, or about 25% to about 50%.

[000171] In some embodiments, a therapeutic agent useful for treatment of acne is aminolevulinic acid, azithromycin, methylaminolevuninate, nadifloxacine, PRK124, talarozole, zileuton, and/or combinations thereof. In some embodiments, such agents are present in a premix at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, such agents are present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%. In some embodiments, such agents are present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 0.1% to about 25%, about 0.1% to about 10%, or about 0.1% to about 5%. In some embodiments, such agents are present in a premix and/or in a nanoparticle composition at a concentration ranging between about 0.1% to about 50%, about 5% to about 50%, about 10% to about 50%, or about 25% to about 50%.

[000172] Various acne treatments are described, for example, in Krowchuk (2000, *Pediatric Dermatology*, 47:841-857; incorporated herein by reference); and Johnson *et al.* (2000, *American Family Physician*, 62:1823-1830 and 1835-1836; incorporated herein by reference).

[000173] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of acne (*e.g.*, may be present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of

the therapeutic agents useful for treatment of acne can be utilized in any combination with one another. Such agents, when used in combination, may be present in the same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination with one or more of the acne therapeutics described herein. In some embodiments, botulinum toxin is not utilized in combination with any of the acne therapeutics described herein. Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

Therapeutic Agents Useful for Treatment of Sweat Gland Disorders

[000174] In some embodiments, a therapeutic agent is useful for treating sweat gland disorders, such as hyperhidrosis (excessive sweating), bromhidrosis (body odor), and/or chromhidrosis (colored sweat). In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating sweat gland disorders is botulinum toxin. In some embodiments, such a therapeutic agent is an antiperspirant, for example, aluminum chloride, aluminum chlorohydrate, aluminum-zirconium compounds, aluminum zirconium tetrachlorohydrex gly, aluminum zirconium trichlorohydrex gly, ammonium alum, *etc.* Aluminum-based complexes react with electrolytes in sweat to form a gel plug in the duct of the sweat gland. Plugs prevent glands from excreting liquid and are removed over time by the natural sloughing of the skin. Blockage of a large number of sweat glands reduces the amount of sweat produced in the underarms, though this may vary from person to person. In some embodiments, an antiperspirant is present in a premix at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, an antiperspirant is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000175] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of sweat gland disorders (*e.g.*, may be present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of the therapeutic agents useful for treatment of sweat gland disorders can be utilized in any combination with one another. Such agents, when used in combination, may be present in the same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination

with one or more of the sweat gland disorder therapeutics described herein. In some embodiments, botulinum toxin is not utilized in combination with any of the sweat gland disorder therapeutics described herein. Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

Therapeutic Agents Useful for Treatment of Rosacea

[000176] In some embodiments, a therapeutic agent is useful for treating rosacea. In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating rosacea is botulinum toxin. In some embodiments, such a therapeutic agent is an oral antibiotic, for example, tetracycline, doxycycline, minocycline, metronidazole, macrolide antibiotic, and/or combinations thereof. In some embodiments, an additional therapeutic agent is oral isotretinoin. In some embodiments, such a therapeutic agent is a topical antibiotic (*e.g.*, metronidazole, clindamycin, erythromycin, *etc.*). In some embodiments, such a therapeutic agent is a topical azelaic acid (*e.g.*, FINACEA, AZELEX™, FINEVIN®, SKINOREN, *etc.*); topical sulfacetamide; topical sulfur; topical calcineurin inhibitor (*e.g.*, tacrolimus, pimecrolimus, *etc.*); topical benzoyl peroxide; topical permethrin; a combination of plant-sourced Methylsulfonylmethane (MSM) and Silymarin; and/or combinations thereof. In some embodiments, such a therapeutic agent is brimonidine, dapsone, IDP-115, PRK124, SR-01, tretinoin, zinc sulfate, and/or combinations thereof.

[000177] In some embodiments, one or more of the therapeutic agents described above is present in a premix at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, one or more of the therapeutic agents described above is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000178] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of rosacea (*e.g.*, may be present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of the therapeutic agents useful for treatment of rosacea can be utilized in any combination with one another. Such agents, when used in combination, may be present in the same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination with one or more of the rosacea therapeutics described herein. In some embodiments, botulinum toxin is

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not utilized in combination with any of the rosacea therapeutics described herein. Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

Therapeutic Agents Useful for Treatment of Hair Loss

[000179] In some embodiments, a therapeutic agent is useful for treating hair loss. In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating hair loss is botulinum toxin. In some embodiments, such a therapeutic agent is an aza-steroid, such as finasteride (PROPECIA®; PROSCAR®; *etc.*) or dutasteride (AVODART®). In some embodiments, such a therapeutic agent is topically applied minoxidil (ROGAINE®; a vasodilator). In some embodiments, such a therapeutic is an antiandrogen (*e.g.*, ketoconazole, fluconazole, spironolactone, *etc.*); saw palmetto; caffeine; copper peptides; nitroxide spin labels TEMPO and TEMPOL; unsaturated fatty acids (*e.g.*, gamma linolenic acid); hedgehog agonists; azelaic acid and zinc in combination; Chinese knotweed; pumpkin seed; tretinoin; zinc; stinging nettle; Tempol alcohol-based gel (*e.g.*, MTS-01, *etc.*); Aldara; alefacept; AS101; bimatoprost; capsaicin; efalizumab; FK506; GP11046; GP11511; hydroxychloroquine; latanoprost; MK0906; roxithromycin; Targretin Gel 1%; tetrapeptide aldehyde proteasome inhibitor (*e.g.*, NEOSH101, *etc.*); and/or combinations thereof.

[000180] In some embodiments, one or more of the therapeutic agents described above is present in a premix at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, one or more of the therapeutic agents described above is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000181] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of hair loss (*e.g.*, may be present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of the therapeutic agents useful for treatment of hair loss can be utilized in any combination with one another. Such agents, when used in combination, may be present in the same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination with one or more of the hair loss therapeutics described herein. In some embodiments, botulinum toxin is not utilized in combination with any of the hair loss therapeutics described herein.

Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

Therapeutic Agents Useful for Treatment of Psoriasis

[000182] In some embodiments, a therapeutic agent is useful for treating psoriasis. In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating psoriasis is botulinum toxin. In some embodiments, such a therapeutic agent is coal tar; dithranol (anthralin); a corticosteroid such as desoximetasone (TOPICORT); a vitamin D3 analog (*e.g.*, calcipotriol); a retinoid; argan oil; topical administration of psoralen with exposure to ultraviolet A (UVA) light; milk thistle; methotrexate; cyclosporine A; the antimetabolite tioguanine; hydroxyurea; sulfasalazine; mycophenolate mofetil; azathioprine; tacrolimus, pimecrolimus, and similar drugs; and/or antibody-based therapeutics (*e.g.*, alefacept [AMEVIEVE®], etanercept [EMBREL®], infliximab [REMICADE®], rituximab, efalizumab, adalimumab, ustekinumab, *etc.*); 4,4-dimethyl-benziso-2H-selenazine; abatacept; ABT-874; acitretin; ACT-128800; AEB071; AIN457; AMG 714; Aminopeptidase N; AN2728; apremilast; BCT194; Bicillin L-A; bimosiamose; BTT1023; Calcipotriene; CC10004; CD 2027; certolizumab pegol; CF101; clobetasol propionate; CNTO 1275; CP-690,550; CRx-197; CTA018; CTLA4Ig; daclizumab; dipeptidyl peptidase; doxercalciferol; E6201; fludarabine; fluphenazine decanoate; halobetasol; ILV-094; INCB018424; LEO 29102; MM-093; mometasone furoate; nortriptyline HCl; NYC 0462; paclitaxel; parathyroid hormone; pazopanib; pioglitazone; QRX-101; roflumilast; RWJ-445380; SCH 527123; taclonex; talarozole; tetrathiomolybdate; U0267; vitamin B12; voclosporin; zidovudine; and/or combinations thereof.

[000183] In some embodiments, one or more of the therapeutic agents described above is present in a premix at a concentration of about 0.01%, about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, one or more of the therapeutic agents described above is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000184] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of psoriasis (*e.g.*, may be present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of the therapeutic agents useful for treatment of psoriasis can be utilized in any combination with one another. Such agents, when used in combination, may be present in the

same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination with one or more of the psoriasis therapeutics described herein. In some embodiments, botulinum toxin is not utilized in combination with any of the psoriasis therapeutics described herein. Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

Therapeutic Agents Useful for Treatment of Dermal Infections

[000185] In some embodiments, a therapeutic agent is useful for treating dermal infections (*e.g.*, bacterial, viral, and/or fungal infections). In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating dermal infections is botulinum toxin. In some embodiments, therapeutic agents useful for treatment of conditions or disorders associated with bacterial infection of the dermis include, but are not limited to, antibiotics (*e.g.*, penicillin, dicloxacillin, cephalexin, erythromycin, clindamycin, gentamicin, *etc.*), topical antibiotics (*e.g.* clindamycin, erythromycin, mupirocin *etc.*), topical mixture of bacitracin and polymyxin (*e.g.*, NEOSPORIN®, POLYSPORIN®), topical fusidic acid cream, and combinations thereof.

[000186] In some embodiments, therapeutic agents useful for treatment of conditions or disorders associated with viral infection of the dermis include, but are not limited to, antiviral therapeutics (*e.g.*, acyclovir, famciclovir, valacyclovir, *etc.*), topical treatments (*e.g.*, trichloroacetic acid, salicylic acid, podophyllin, canthacur, imiquimod cream, *etc.*), cidofovir; foscarnet sodium; trifluridine; ionic zinc; ME-609; glutamine; ganciclovir; fialuridine; ASP2151; hydroxypropyl-beta-caclodextrin; penciclovir; and/or combinations thereof.

[000187] In some embodiments, therapeutic agents useful for treatment of conditions or disorders associated with fungal infection of the dermis include, but are not limited to, topical therapeutics (*e.g.*, terbinafine [LAMISIL], clotrimazole [LOTRIMIN®, MYCELEX®], or econazole [SPECTAZOLE®], selenium sulfide shampoo, ketoconazole shampoo, *etc.*), oral therapeutics (*e.g.*, itraconazole [SPORANOX®], terbinafine, *etc.*), amphotericin B, anidulafungin; caspofungin; fluconazole; isavuconazole; micafungin; posaconazole; voriconazole; pramiconazol; AN2690; and/or combinations thereof.

[000188] In some embodiments, one or more of the therapeutic agents described above is present in a premix at a concentration of about 0.01%, about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, one or more of the therapeutic agents described above is present in a nanoparticle composition at a

concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000189] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of dermal infection (*e.g.*, may be present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of the therapeutic agents useful for treatment of dermal infection can be utilized in any combination with one another. Such agents, when used in combination, may be present in the same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination with one or more of the dermal infection therapeutics described herein. In some embodiments, botulinum toxin is not utilized in combination with any of the dermal infection therapeutics described herein. Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

Therapeutic Agents Useful for Treatment of Actinic Keratosis

[000190] In some embodiments, a therapeutic agent is useful for treating actinic keratosis. In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating actinic keratosis is botulinum toxin. In some embodiments, therapeutic agents useful for treatment of actinic keratosis include, but are not limited to, 5-fluorouricil, imiquimod, diclofenac, crocodile oil, ingenol mebutate, oleogel-S-10, aminolevulinic acid, methyl aminolevulinate, T4N5, eflornithine, kunecatechins, and/or combinations thereof.

[000191] In some embodiments, one or more of the therapeutic agents described above is present in a premix at a concentration of about 0.01%, about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, one or more of the therapeutic agents described above is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000192] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of actinic keratosis (*e.g.*, may be present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of the therapeutic agents useful for treatment of actinic keratosis can be utilized in any combination with one another. Such agents, when used in combination, may be present in the same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination with one or

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more of the actinic keratosis therapeutics described herein. In some embodiments, botulinum toxin is not utilized in combination with any of the actinic keratosis therapeutics described herein. Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

Therapeutic Agents Useful for Treatment of Eczematous Dermatitis

[000193] In some embodiments, a therapeutic agent is useful for treating eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*). Eczematous dermatitis and atopic dermatitis are also known in the art as "eczema." In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating eczematous dermatitis is botulinum toxin. In some embodiments, therapeutic agents useful for treatment of eczematous dermatitis include, but are not limited to, glucocorticosteroids, coal tar, calcineurin inhibitors (*e.g.*, tacrolimus, pimecrolimus, *etc.*), antihistamines (*e.g.*, diphenhydramine, *etc.*), cyclosporine, interferon, omalizumab, rituximab, mycophenolate mofetil, AMG 157, JNJ-26113100, CD 2027, SUN13834, S-777469, GW842470X, TS022, roflumilast, calcipotriol, pitrakinra, and/or combinations thereof.

[000194] In some embodiments, one or more of the therapeutic agents described above is present in a premix at a concentration of about 0.01%, about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, one or more of the therapeutic agents described above is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000195] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*) (*e.g.*, may be present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of the therapeutic agents useful for treatment of eczematous dermatitis can be utilized in any combination with one another. Such agents, when used in combination, may be present in the same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination with one or more of the eczematous dermatitis therapeutics described herein. In some embodiments, botulinum toxin is not utilized in combination with any of the eczematous dermatitis therapeutics described herein. Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

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Therapeutic Agents Useful for Treatment of Excess Sebum-Producing Disorders

[000196] In some embodiments, a therapeutic agent is useful for treating excess sebum-producing disorders *(e.g.*, seborrhea, seborrheic dermatitis, *etc.*). In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating excess sebum-producing disorders is botulinum toxin. In some embodiments, therapeutic agents useful for treatment of excess sebum-producing disorders *(e.g.*, seborrhea, seborrheic dermatitis, *etc.*) include, but are not limited to, salicylic acid, azelaic acid, selnium sulfide, imidazoles (*e.g.*, ketoconazole, miconazole, fluconazole, econazole, bifonazole, climazole, ciclopirox, ciclopiroxolamine, *etc.*), itraconazole, terbinafine, zinc pyrithione, benzoyl peroxide, coal tar, juniper tar, glucocorticosteroids (*e.g.*, hydrocortisone, *etc.*), metronidazole, lithium, calcineurin inhibitors (*e.g.*, tacrolimus, pimecrolimus, *etc.*), Vitamin D3, isotretinoin, and/or combinations thereof.

[000197] In some embodiments, one or more of the therapeutic agents described above is present in a premix at a concentration of about 0.01%, about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, one or more of the therapeutic agents described above is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000198] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of excess sebum-producing disorders *(e.g.*, seborrhea, seborrheic dermatitis, *etc.*) (*e.g.*, may be present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of the therapeutic agents useful for treatment of excess sebum-producing disorders can be utilized in any combination with one another. Such agents, when used in combination, may be present in the same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination with one or more of the excess sebum-producing disorder therapeutics described herein. In some embodiments, botulinum toxin is not utilized in combination with any of the excess sebum-producing disorder therapeutics described herein. Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

Therapeutic Agents Useful for Treatment of Hyperpigmentation Diseases

[000199] In some embodiments, a therapeutic agent is useful for treating hyperpigmentation diseases (*e.g.*, melasma, *etc.*). In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating hyperpigmentation diseases is botulinum toxin. In some embodiments, therapeutic agents useful for treatment of hyperpigmentation diseases include, but are not limited to, phenols (*e.g.*, hydroxyquinone, mequinol, *etc.*), retinoids (*e.g.*, tretinoin, isotretinoin, *etc.*), alpha-hydroxy acids (*e.g.*, glycolic acid, salicyclic acid, azelaic acid), and/or combinations thereof.

[000200] In some embodiments, one or more of the therapeutic agents described above is present in a premix at a concentration of about 0.01%, about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, one or more of the therapeutic agents described above is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000201] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of hyperpigmentation diseases (*e.g.*, melasma) (*e.g.*, may be present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of the therapeutic agents useful for treatment of hyperpigmentation diseases can be utilized in any combination with one another. Such agents, when used in combination, may be present in the same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination with one or more of the hyperpigmentation disease therapeutics described herein. In some embodiments, botulinum toxin is not utilized in combination with any of the hyperpigmentation disease therapeutics described herein. Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

Therapeutic Agents Useful for Treatment of Hypopigmentation Diseases

[000202] In some embodiments, a therapeutic agent is useful for treating hypopigmentation diseases (*e.g.*, vitiligo, *etc.*). In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating hypopigmentation diseases is botulinum toxin. In some embodiments, therapeutic agents useful for treatment of hypopigmentation diseases include, but are not limited to, corticosteriods, calcineurin inhibitors (*e.g.*, tacrolimus, pimecrolimus, *etc.*), calcipotriol, psoralen, and/or combinations thereof.

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[000203] In some embodiments, one or more of the therapeutic agents described above is present in a premix at a concentration of about 0.01%, about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, one or more of the therapeutic agents described above is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000204] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of hypopigmentation diseases (*e.g.*, vitiligo, *etc.*) (*e.g.*, may be present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of the therapeutic agents useful for treatment of hypopigmentation diseases can be utilized in any combination with one another. Such agents, when used in combination, may be present in the same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination with one or more of the hypopigmentation disease therapeutics described herein. In some embodiments, botulinum toxin is not utilized in combination with any of the hypopigmentation disease therapeutics described herein. Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

Therapeutic Agents Useful for Treatment of Skin Cancer

[000205] In some embodiments, a therapeutic agent is useful for treating skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*). In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating skin cancer is botulinum toxin. In some embodiments, therapeutic agents useful for treatment of squamous cell skin carcinoma include, but are not limited to, 5-aminolevulinic acid, 5-fluorouracil, acitretin, afamelanotide, API 31510, API 31510, cetuximab, dasatinib, eflornithine, erlotinib, GDC-0449, efitinib, HPPH, imiquinod, methyl aminolevulinate, PEG-interferon alfa-2a, PEP005, silicon phthalocyanine 4, tazarotene, tretinoin, verteporfin, and/or combinations thereof.

[000206] In some embodiments, therapeutic agents useful for treatment of basal cell skin carcinoma include, but are not limited to, 5-aminolevulinic acid, 5-fluorouracil, acitretin, afamelanotide, API 31510, API 31510, cetuximab, dasatinib, eflornithine, erlotinib, GDC-0449, gefitinib, HPPH, imiquinod, methyl aminolevulinate, PEG-interferon alfa-2a, PEP005, silicon phthalocyanine 4, tazarotene, Tretinoin, verteporfin, and/or combinations thereof.

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[000207] In some embodiments, one or more of the therapeutic agents described above is present in a premix at a concentration of about 0.01%, about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, one or more of the therapeutic agents described above is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000208] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*) (*e.g.*, may be present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of the therapeutic agents useful for treatment of skin cancer can be utilized in any combination with one another. Such agents, when used in combination, may be present in the same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination with one or more of the skin cancer therapeutics described herein. In some embodiments, botulinum toxin is not utilized in combination with any of the skin cancer therapeutics described herein. Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

Therapeutic Agents Useful for Treatment of Lupus Erthythematosus

[000209] In some embodiments, a therapeutic agent is useful for treating lupus erthythematosus. In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating lupus erthythematosus is botulinum toxin. In some embodiments, therapeutic agents useful for treatment of lupus erthythematosus include, but are not limited to, nonsteriodal anti-inflammatory medications (*e.g.*, ibuprofen, *etc.*), aspirin, antimalarial drugs (*e.g.*, chloroquine, hydroxychloroquine, *etc.*), corticosteroids (*e.g.*, hydroxycortisone, *etc.*), immunosuprresive medications (*e.g.*, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, methotrexate, therapeutic antibodies, *etc.*), and/or combinations thereof.

[000210] In some embodiments, one or more of the therapeutic agents described above is present in a premix at a concentration of about 0.01%, about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, one or more of the therapeutic agents described above is present in a nanoparticle composition at a

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concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000211] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of lupus erythythematosus (*e.g.*, may be present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of the therapeutic agents useful for treatment of lupus erythythematosus can be utilized in any combination with one another. Such agents, when used in combination, may be present in the same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination with one or more of the lupus erythythematosus therapeutics described herein. In some embodiments, botulinum toxin is not utilized in combination with any of the lupus erythythematosus therapeutics described herein. Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

Therapeutic Agents Useful for Treatment of Raynaud's Phenomenon

[000212] In some embodiments, a therapeutic agent is useful for treating Raynaud's phenomenon. In accordance with the present invention, in some embodiments, a therapeutic agent that is useful for treating Raynaud's phenomenon is botulinum toxin. In some embodiments, therapeutic agents useful for treatment of Raynaud's phenomenon include, but are not limited to, calcium channel blockers (*e.g.*, nifedipine, *etc.*), alpha blockers (*e.g.*, hydralazine, *etc.*), nitroglycerin, angiotensin II receptor antagonists (*e.g.*, losartan, *etc.*), selective serotonin reuptake inhibitors (*e.g.*, fluoxetine, *etc.*), glyceryl trinitrate, tadalafil, *Ginkgo biloba* extract, SLx-2101, St. John's Wort, fasudil, cilostazol, iloprost, relaxin, treprostinil diethanolamine, sildenafil, atorvastatin, imatinib mesylate, treprostinil diethanolamine, and/or combinations thereof.

[000213] In some embodiments, one or more of the therapeutic agents described above is present in a premix at a concentration of about 0.01%, about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, or about 50%. In some embodiments, one or more of the therapeutic agents described above is present in a nanoparticle composition at a concentration of about 0.1%, about 0.5%, about 0.75%, 1%, about 2%, about 2.5%, about 5%, about 7.5%, about 10%, about 15%, about 20%, or about 25%.

[000214] Any of the therapeutic agents described herein may be incorporated in nanoparticle compositions to be used for treatment of Raynaud's phenomenon (*e.g.*, may be

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present in a premix and/or in a nanoparticle composition at any of the concentrations specified above). Any of the therapeutic agents useful for treatment of Raynaud's phenomenon can be utilized in any combination with one another. Such agents, when used in combination, may be present in the same nanoparticle composition, or they may be present in different nanoparticle compositions. In some embodiments, botulinum toxin is utilized in combination with one or more of the Raynaud's phenomenon therapeutics described herein. In some embodiments, botulinum toxin is not utilized in combination with any of the Raynaud's phenomenon therapeutics described herein. Additional considerations for combination therapies are described in further detail below, in the section entitled "Treatment Applications of Nanoparticle Compositions."

Administration

[000215] The present invention provides methods of delivering nanoparticle compositions for various applications including, for example, cosmetic and/or medical applications. Such nanoparticle compositions may include one or more biologically active agents. In certain embodiments, nanoparticle compositions include botulinum toxin.

[000216] In some embodiments, the present invention contemplates methods of delivering nanoparticle compositions including, but not limited to transdermal, topical, or intradermal, routes of administration. These routes of administration are particularly favored for formulations (*e.g.*, certain nanoparticle compositions comprising particular therapeutic agents) that are intended to have a localized effect. Subsequent tissue absorption of the formulation's ingredients, however, is not always predictable.

[000217] In some embodiments, nanoparticle compositions in accordance with the invention may be encapsulated for example using lipid-based carriers, *e.g.*, to facilitate entry into cells. Lipid-based carrier efficacies, however, may be dependent upon; i) lipid composition (*i.e.*, for example, molecular size and charge); ii) the structure (*e.g.*, molecular size and pH ionization) of any biologically active agent or other entity included in the composition; and iii) the overall health of the subject. The present invention contemplates compositions and methods related to uniform nanoemulsions (*e.g.*, microfluidized nanoemulsions) comprising lipid-based carriers thereby improving the bioavailability of cosmeceuticals.

[000218] The present invention specifically provides methods of administering therapeutic agents, and particularly of administering nanoparticle compositions comprising therapeutic agents, for the treatment of disorders or conditions associated with the dermal level of the

skin, such as acne, hyperhidrosis, bromhidrosis, chromhidrosis, rosacea, hair loss, psoriasis, actinic keratosis, eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*), excess sebum-producing disorders *(e.g.*, seborrhea, seborrheic dermatitis, *etc.*), Raynaud's phenomenon, lupus erthythematosus, hyperpigmentation disorders *(e.g.*, melasma, *etc.*), hypopigmentation disorders *(e.g.*, vitiligo, *etc.*), skin cancer *(e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*) and/or dermal infection *(e.g.*, fungal infection, herpes simplex virus infection, human papillomavirus infection, *etc.*)

[000219] In some embodiments, such a therapeutic agent is botulinum toxin. Clinical effects of topically applied transdermal administration of botulinum toxins may be seen within one week, similar to botulinum toxins administered by injection. The typical duration of symptomatic relief (*i.e.*, for example, flaccid muscle paralysis) from a single intramuscular injection of botulinum toxin type A can be present for up to four months or longer; durations of clinical effect following transdermal administration of botulinum toxins according to the present invention can be present for up to four months or longer, depending on the characteristics of the individual subject and/or one the specific formulation of botulinum nanoparticle preparation.

[000220] It will be appreciated by those of ordinary skill in the art that botulinum toxin is currently administered almost exclusively by injection, and in particular by injection of a liquid saline solution, usually reconstituted from a lyophilized preparation.

[000221] As has already been discussed, BOTOX® (a purified *Clostridium botulinum* toxin type A complex, human serum albumin, and sodium chloride packaged in a sterile vacuum-dried form) is currently reconstituted for injection using sterile normal saline without a preservative (0.9% sodium chloride, injection grade). Specifically, standard injection protocols involve drawing up the proper amount of diluent in the appropriate size syringe. Since BOTOX® is denatured by bubbling or similar violent agitation, the diluent is gently injected into a vial containing a designated amount of lyophilized BOTOX®. Standard injection protocols involve administering aqueous BOTOX® solutions within four hours after reconstitution.

[000222] Although problems with the available botulinum toxin preparations (including stability issues, sterility issues, *etc.*) have been well known, few improved formulations have been developed. Furthermore, injection remains the standard approach for delivering botulinum toxin, notwithstanding the undesirability of invasive techniques in general, patient discomfort, *etc.*

[000223] The present invention provides methods for treating acne, hyperhidrosis, bromhidrosis, chromhidrosis, and/or rosacea utilizing topical administration of nanoparticle compositions comprising one or more therapeutic agents (including, but not limited to, botulinum toxin).

[000224] In certain embodiments, the present invention provides methods of administering a therapeutic agent (*e.g.*, botulinum toxin) transdermally. Human skin comprises the dermis and the epidermis. The epidermis has several layers of tissue, namely, stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale (identified in order from the outer surface of the skin inward).

[000225] The stratum corneum presents the most significant hurdle in transdermal delivery of medications. The stratum corneum is typically about 10 μm – 15 μm thick, and it comprises flattened, keratised cells (corneocytes) arranged in several layers. The intercellular space between the corneocytes is filled with lipidic structures, and may play a role in the permeation of substances through skin (Bauerova *et al.*, 2001, *Eur. J. Drug Metabolism Pharmacokinetics*, 26:85; incorporated herein by reference).

[000226] The rest of the epidermis below the stratum corneum is approximately 150 μm thick. The dermis is about 1 mm – 2 mm thick and is located below the epidermis. The dermis is supported by various capillaries as well as neuronal processes.

[000227] Transdermal administration of pharmaceuticals generally has been the subject of research in an attempt to provide an alternative route of administration of medications without undesirable consequences associated with injections and oral delivery. For example, needles often cause localized pain, bleeding and bruising, and potentially expose patients to transmissible diseases. Oral administration often suffers from poor bioavailability of medications due to the extremely acidic environment of the patient's stomach.

[000228] Efforts have been made to develop transdermal administration techniques for certain pharmaceuticals in an attempt to overcome these shortcomings by providing noninvasive administration. It is generally desirable with transdermal administration to reduce damage to a patient's skin. Thus, transdermal administration of medication may reduce or eliminate pain associated with injections and/or reduce the likelihood of infection.

[000229] Traditionally, attempts at transdermal administration of medication have been focused on increasing the permeability of the stratum corneum. Some attempts have included using chemical penetration enhancing agents that increase the permeability of molecules through the skin. Some attempts have included using mechanical apparatus to bypass or ablate portions of the stratum corneum. In addition, attempts have included use of ultrasound

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or iontophoresis to facilitate the permeation of pharmaceuticals through the skin. In most cases, the goal has been to deliver a pharmaceutical agent, typically a small molecule, through the skin so that an agent may pass to the capillary bed in the dermis where the agent may be systemically incorporated into the subject to achieve a therapeutic effect.

[000230] Although small molecules have been a major focus of transdermal administration techniques, it is important to note that it appears that large molecules, such as polypeptides, and protein complexes, are also amenable to transdermal administration. Erythropoietin, which is about 48 kD, has also been successfully transdermally administered with the assistance of ultrasound (Mitragotri *et al.*, 1995, *Science*, 269:850; and U.S. Patents 5,814,599 and 6,002,961; all of which are incorporated herein by reference).

[000231] The present invention provides, among other things, methods of treating acne, hyperhidrosis, bromhidrosis, chromhidrosis, and/or rosacea utilizing topical application of therapeutic agents (*e.g.*, botulinum toxin) that does not require use of abrasive or other disrupting agents (whether chemical, mechanical, electrical, magnetic, *etc.*). The inventors have surprisingly found that therapeutic agents (*e.g.*, botulinum toxin) incorporated into nanoparticle compositions are effectively delivered transdermally without further steps to permeabilize or disrupt the stratum corneum. Use of such agents or steps with nanoparticle compositions is not necessarily precluded in all embodiments, but is also not required.

[000232] In some embodiments, a nanoparticle composition is applied directly to the skin and for absorption through the epidermal layers. In some embodiments, the nanoparticle composition can penetrate the top layer of the skin, including the stratum corneum, dermal pores, and/or dermal glands, without the use of chemical or mechanical skin permeation enhancers or other agents that cause abrasion.

[000233] It will be appreciated by those of ordinary skill in the art that compositions for topical administration may have a cosmetic formulation such as skin softener, nutritional lotion type emulsion, cleansing lotion, cleansing cream, skin milk, emollient lotion, massage cream, emollient cream, make-up base, lipstick, facial pack or facial gel, cleaner formulation such as shampoos, rinses, body cleanser, hair-tonics, or soaps, or dermatological composition such as lotions, ointments, gels, creams, patches, deodorants, or sprays.

[000234] A composition for topical administration in accordance with the invention may be formulated and/or administered such that an amount of therapeutic agent between about 10^{-3} U/kg and 10 U/kg passes through a patient's skin (*i.e.*, reaches the dermal layer). In some embodiments, a composition is formulated and/or administered so that between about 10^{-2} U/kg and about 1 U/kg pass through a patient's skin. In some embodiments, a composition is

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formulated and/or administered so that between about 10^{-1} U/kg and about 1 U/kg pass through a patient's skin. In some embodiments, a composition is formulated and/or administered so that between about 1 U/kg and about 3 U/kg pass through a patient's skin. In some embodiments, a composition is formulated and/or administered so that between about 3 U/kg and about 5 U/kg pass through a patient's skin. In some embodiments, a composition is formulated and/or administered so that between about 5 U/kg and about 10 U/kg pass through a patient's skin. In some embodiments, a composition is formulated and/or administered so that between about 10 U/kg and about 50 U/kg pass through a patient's skin. In some embodiments, a composition is formulated and/or administered so that between about 0.1 Units and about 5 Units pass through a patient's skin. In some embodiments, a composition is formulated and/or administered at about 1U /ng, 10 U/ng, 100 U/ng, about 250 U/ng, about 500 U/ng, about 750 U/ng, about 0.1 U/pg, about 0.25 U/pg, about 0.5 U/pg, about 1.0 U/pg, about 10 U/pg, or about 100 U/pg. In some embodiments, between about 1 U and about 500 U, about 5 U and about 400 U, about 10 U and about 300 U, about 50 U and about 200 U, or about 100 U and about 150 U botulinum toxin will be administered to a patient treatment area. In some embodiments, about 1 U, about 2 U, about 3 U, about 4 U, about 5 U, about 6 U, about 7 U, about 8 U, about 9 U, about 10 U, about 11 U, about 12 U, about 13 U, about 14 U, about 15 U, about 16 U, about 17 U, about 18 U, about 19 U, about 20 U, about 30 U, about 40 U, about 50 U, about 75 U, about 100 U, about 200 U, about 300 U, about 400 U, or about 500 U botulinum toxin will be administered to a patient treatment area.

[000235] Those of ordinary skill in the art will appreciate that units herein relate to Units that are biologically equivalent or bioactively equivalent to Units defined by commercial manufacturers of any given therapeutic agent.

[000236] Therapeutic effects of a therapeutic agent administered according to the present invention may persist as long as do the effects of an injected solution. To give but one example, the effects of such injected botulinum toxin solution can persist for up to about 4 months, about 6 months, about 9 months, about 12 months, or longer. Furthermore, use of a synthetic polymer carrier that can retain the therapeutic agent so that it is released slowly may prolong the effects for up to about five years (U.S. Patent 6,312,708; incorporated herein by reference).

[000237] In certain embodiments, the present invention provides novel uses for topical formulations of a therapeutic agent (*e.g.*, botulinum toxin) that avoid potential complications. To give but a few examples, such complications might include systemic toxicity or botulism poisoning. In some embodiments, dosages of a therapeutic agent (*e.g.*, botulinum toxin,

including types A, B, C, D, E, F, or G) can range from as low as about 1 unit to as high as about 20,000 units, with minimal risk of adverse side effects. The particular dosages may vary depending on the condition being treated and therapeutic regime being utilized. For example, if a therapeutic agent is botulinum toxin, treatment of subdermal, hyperactive muscles may require high transdermal dosages (*e.g.*, 10 units to 20,000 units) of botulinum toxin. In comparison, treatment of neurogenic inflammation or hyperactive sweat glands may require relatively small transdermal dosages (*e.g.*, about 1 unit to about 1,000 units) of botulinum toxin.

[000238] The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the condition, the particular composition, its mode of administration, its mode of activity, and the like. Compositions in accordance with the invention are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions in accordance with the invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of clearance of the specific composition; the duration of the treatment; therapeutic agents and/or procedures used in combination or coincidental with the specific compositions employed; and like factors well known in the medical arts.

[000239] In certain embodiments, compositions in accordance with the invention may be administered at dosage levels sufficient to deliver from about 0.001 ng/kg to about 100 ng/kg, from about 0.01 ng/kg to about 50 ng/kg, from about 0.1 ng/kg to about 40 ng/kg, from about 0.5 ng/kg to about 30 ng/kg, from about 0.01 ng/kg to about 10 ng/kg, from about 0.1 ng/kg to about 10 ng/kg, or from about 1 ng/kg to about 25 ng/kg, or from about 25 ng/kg to about 50 ng/kg of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect. In certain embodiments, compositions in accordance with the invention may be administered at dosage levels sufficient to deliver from about 0.01 U/kg to about 100 U/kg, from about 0.1 U/kg to about 50 U/kg, from about 0.2 U/kg to about 20 U/kg, from about 0.5 U/kg to about 15 U/kg, from about 0.1 U/kg to about 10 U/kg, or from about 0.5 U/kg to about 5 U/kg of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

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[000240] The desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, every four weeks, every six weeks, every 2 months, every 3 months, every 4 months, every 6 months, every 9 months, once a year, or longer. In certain embodiments, the desired dosage may be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

Pharmaceutical Compositions

[000241] In some embodiments, the present invention provides pharmaceutical compositions comprising at least one therapeutic agent (*e.g.*, botulinum toxin) for transdermal delivery into a human patient. A composition can comprise between about 1 unit to about 20,000 units of therapeutic agent, and a composition can comprise an amount of therapeutic agent sufficient to achieve a therapeutic effect lasting between 1 month and 5 years.

[000242] The present invention further provides pharmaceutical compositions comprising one or more nanoparticle compositions, together with one or more pharmaceutically acceptable excipients. In accordance with some embodiments, a method of administering pharmaceutical compositions comprising nanoparticle compositions to a subject in need thereof is provided. In some embodiments, compositions are administered to humans. For the purposes of the present disclosure, the phrase "active ingredient" generally refers to nanoparticle compositions as described herein.

[000243] In some embodiments, the present invention provides topical formulations of therapeutic agents (*e.g.*, botulinum toxin) that allow the therapeutic agent to permeate through a subject's skin without permeating in significant amount through a blood vessel. For example, in some embodiments, less than about 25%, less than 20%, less than 15%, less than 10%, less than 10%, or even less than about 5%, of the therapeutic agent present in a pharmaceutical composition permeates into a blood vessel upon application of a topical and/or transdermal preparation.

[000244] In some embodiments, the present invention provides topical formulations of therapeutic agents (*e.g.*, botulinum toxin) that allow the therapeutic agent to permeate to the dermal level of the skin without permeating in significant amount to the subdermal level. For example, in some embodiments, less than about 35%, about 25%, less than 20%, less than 15%, less than 10%, less than 10%, less 5%, or even less than about 1%, of the therapeutic agent present in a pharmaceutical composition permeates into the subdermal level of the skin upon application of a topical and/or transdermal preparation.

[000245] Formulations of pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with an excipient and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

[000246] A pharmaceutical composition in accordance with the invention may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[000247] Relative amounts of active ingredient, pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, a composition may comprise between 0.1% and 100% (w/w) active ingredient.

[000248] Pharmaceutical formulations may additionally comprise at least one pharmaceutically acceptable excipient, which, as used herein, includes any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's *The Science and Practice of Pharmacy*, 21st Edition, A. R. Gennaro (Lippincott, Williams & Wilkins, Baltimore, MD, 2005; incorporated herein by reference) discloses various excipients used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional excipient medium is incompatible with a substance or its derivatives, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this invention.

[000249] In some embodiments, a pharmaceutically acceptable excipient is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved by United States Food and Drug Administration. In some embodiments, an excipient is pharmaceutical grade. In some embodiments, an excipient

meets the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or other International Pharmacopoeia.

[000250] Pharmaceutically acceptable excipients used in the manufacture of pharmaceutical compositions include, but are not limited to, inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Such excipients may optionally be included in pharmaceutical formulations. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and/or perfuming agents can be present in the composition, according to the judgment of the formulator.

[000251] Exemplary diluents include, but are not limited to, calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, *etc.*, and/or combinations thereof.

[000252] Exemplary granulating and/or dispersing agents include, but are not limited to, potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (VEEGUM®), *etc.*, and/or combinations thereof.

[000253] Exemplary surface active agents and/or emulsifiers include, but are not limited to, natural emulsifiers (*e.g.*, acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.*, bentonite [aluminum silicate] and VEEGUM® [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (*e.g.*, stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.*, carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.*, carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.*, polyoxyethylene sorbitan

monolaurate [TWEEN®20], polyoxyethylene sorbitan [TWEEN ®60], polyoxyethylene sorbitan monooleate [TWEEN ®80], sorbitan monopalmitate [SPAN®40], sorbitan monostearate [SPAN®60], sorbitan tristearate [SPAN®65], glyceryl monooleate, sorbitan monooleate [SPAN®80]), polyoxyethylene esters (*e.g.*, polyoxyethylene monostearate [MYRJ®45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and SOLUTOL®), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.*, CREMOPHOR®), polyoxyethylene ethers, (*e.g.*, polyoxyethylene lauryl ether [BRIJ®30]), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, PLURONIC®F 68, POLOXAMER®188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, *etc.* and/or combinations thereof.

[000254] Exemplary binding agents include, but are not limited to, starch (*e.g.*, cornstarch and starch paste); gelatin; sugars (*e.g.*, sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol,); natural and synthetic gums (*e.g.*, acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (VEEGUM®), and larch arabogalactan); alginates; polyethylene oxide; polyethylene glycol; inorganic calcium salts; silicic acid; polymethacrylates; waxes; water; alcohol; *etc.*; and combinations thereof.

[000255] Exemplary preservatives may include, but are not limited to, antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and/or other preservatives. Exemplary antioxidants include, but are not limited to, alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and/or sodium sulfite. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA), citric acid monohydrate, disodium edetate, dipotassium edetate, edetic acid, fumaric acid, malic acid, phosphoric acid, sodium edetate, tartaric acid, and/or trisodium edetate. Exemplary antimicrobial preservatives include, but are not limited to, benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate,

propylene glycol, and/or thimerosal. Exemplary antifungal preservatives include, but are not limited to, butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and/or sorbic acid. Exemplary alcohol preservatives include, but are not limited to, ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and/or phenylethyl alcohol. Exemplary acidic preservatives include, but are not limited to, vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and/or phytic acid. Other preservatives include, but are not limited to, tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, GLYDANT PLUS®, PHENONIP®, methylparaben, GERMALL®115, GERMABEN®II, NEOLONE™, KATHON™, and/or EUXYL®.

[000256] Exemplary buffering agents include, but are not limited to, citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, *etc.*, and/or combinations thereof.

[000257] Exemplary lubricating agents include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, *etc.*, and combinations thereof.

[000258] Exemplary oils include, but are not limited to, almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl

myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macadamia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, medium-chain triglycerides (*e.g.*, 1349 oil), and/or combinations thereof.

[000259] Dosage forms for topical and/or transdermal administration of a composition may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, deodorants, and/or patches. Generally, an active ingredient is admixed (*e.g.*, under sterile conditions) with at least one pharmaceutically acceptable excipient and/or any needed preservatives and/or buffers as may be required. Additionally, the present invention contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms may be prepared, for example, by dissolving and/or dispensing the compound in the proper medium. Alternatively or additionally, the rate may be controlled by either providing a rate controlling membrane and/or by dispersing the compound in a polymer matrix and/or gel.

[000260] Those of ordinary skill in the art will appreciate that compositions in accordance with the invention that achieve transdermal administration of a therapeutic agent (*e.g.*, botulinum toxin) may be incorporated into a device such as, for example, a patch. A variety of transdermal patch structures are known in the art; those of ordinary skill will appreciate that nanoparticle compositions may readily be incorporated into any of a variety of such structures. In some embodiments, a transdermal patch may further comprise a plurality of needles extending from one side of the patch that is applied to the skin, wherein needles extend from the patch to project through the stratum corneum of the skin. In some embodiments, needles do not rupture a blood vessel.

[000261] In some embodiments, a transdermal patch includes an adhesive. Some examples of adhesive patches are well known (for example, see U.S. Design Patent 296,006; and U.S. Patents 6,010,715; 5,591,767; 5,008,110; 5,683,712; 5,948,433; and 5,965,154; all of which are incorporated herein by reference). Adhesive patches are generally characterized as having an adhesive layer, which will be applied to a patient's skin, a depot or reservoir for

holding a pharmaceutical agent, and an exterior surface that prevents leakage of the pharmaceutical from the depot. The exterior surface of a patch is typically non-adhesive.

[000262] In accordance with the present invention, a therapeutic agent (*e.g.*, botulinum toxin) is incorporated into the patch so that it remains stable for extended periods of time. For example, a therapeutic agent may be present in a nanoparticle composition. Alternatively or additionally, a therapeutic agent may be incorporated into a polymeric matrix that stabilizes the agent, and permits the agent to diffuse from the matrix and the patch. A therapeutic agent may also be incorporated into the adhesive layer of the patch so that once the patch is applied to the skin, the agent may diffuse through the skin. In some embodiments, an adhesive layer may be heat-activated where temperatures of about 37 ºC cause the adhesive to slowly liquefy so that the agent diffuses through the skin. The adhesive may remain tacky when stored at less than 37 ºC, and once applied to the skin, the adhesive loses its tackiness as it liquefies. Administration of the therapeutic agent is complete once the patch no longer adheres to the skin.

[000263] In some embodiments, a therapeutic agent (*e.g.*, botulinum toxin) can be provided in a depot in the patch so that pressure applied to the patch causes the therapeutic agent to be directed out of the patch (optionally through needles) and through the stratum corneum.

[000264] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions may be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes may be used in the classical mantoux method of intradermal administration.

[000265] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in

oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions. Topically-administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient may be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[000266] Those of ordinary skill in the art will appreciate that a transdermal patch is but one example of a device with which nanoparticle compositions may be administered. To give but a few other examples, a device may be employed that allows the composition to be applied without first applying the composition to one's fingers, which may lead to undesirable paralysis of the fingers. Suitable devices include gloves, spatulas, swabs, syringes without needles, and adhesive patches. Use of spatulas, swabs, or the like may require the device to be inserted into a container containing the composition. Using syringes may be accomplished by filling the syringe with the composition. A composition may then be topically spread by spatulas or swabs, or may be expelled from the syringes onto the patient's skin.

[000267] In many embodiments, it may be desirable to limit delivery of a therapeutic agent (*e.g.*, botulinum toxin) to only an intended delivery area. In some embodiments, such limited delivery may be accomplished by utilizing a nanoparticle composition in an application device that permits application of the composition to a target site on the skin without applying the composition to non-target site areas of the skin. Clearly, a transdermal patch may be utilized to this end. Alternatively or additionally, if a therapeutic agent is to be applied topically to only a selected area, other areas may be covered or pre-treated or otherwise protected from exposure.

[000268] General considerations in the formulation and/or manufacture of pharmaceutical agents may be found, for example, in *Remington: The Science and Practice of Pharmacy* 21st ed., Lippincott Williams & Wilkins, 2005 (incorporated herein by reference).

Treatment Applications of Nanoparticle Compositions

[000269] As described herein, the present invention provides treatment of conditions or disorders associated with the dermal level of the skin, including, but not limited to, acne, hyperhidrosis, bromhidrosis, chromhidrosis, rosacea, hair loss, psoriasis, actinic keratosis, eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*), excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*), Raynaud's phenomenon, lupus erythematosus, hyperpigmentation disorders (*e.g.*, melasma, *etc.*), hypopigmentation disorders (*e.g.*, vitiligo,

etc.), skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*) and/or dermal infection (*e.g.*, fungal infection, herpes simplex virus infection, human papillomavirus infection, fungal infection, *etc.*) via transdermal administration of one or more therapeutic agents (*e.g.*, botulinum toxin) to a subject in the context of a nanoparticle composition. Such delivery is useful in a variety of contexts, including in particular certain cosmetic and medical applications. Certain such applications are discussed in more detail below.

The Dermis

[000270] In some embodiments, the present invention provides methods of treating conditions, diseases, and/or disorders that involve the layer of the skin called the "dermis." In general, the dermis is the layer of skin beneath the epidermis that contains connective tissue and cushions the body from stress and strain. The dermis is tightly connected to the epidermis by a basement membrane and harbors nerve endings that provide the sense of touch and heat. The dermis contains hair follicles, sweat glands, sebaceous glands, apocrine glands, lymphatic vessels and blood vessels. Blood vessels in the dermis provide nourishment and waste removal to its own cells as well as to the Stratum basale of the epidermis.

[000271] The dermis is structurally divided into two areas: a superficial area adjacent to the epidermis, called the papillary region, and a deep thicker area known as the reticular region. The papillary region comprises loose areolar connective tissue. It is named for its fingerlike projections (called papillae) that extend toward the epidermis. Papillae provide the dermis with a "bumpy" surface that interdigitates with the epidermis, strengthening the connection between the two layers of skin. Also located within the reticular region are the roots of the hair, sebaceous glands, sweat glands, receptors, nails, and blood vessels.

[000272] The dermis comprises sebaceous glands, which secrete an oily substance called sebum that comprises lipids and debris of dead fat-producing cells. Sebum typically comprises about 25% wax monoesters, about 41% triglycerides, about 16% free fatty acids, and about 12% squalene. In sebaceous glands, sebum is produced within specialized cells and is released as these cells burst; sebaceous glands are thus classified as holocrine glands. Sebum acts to protect and waterproof hair and skin, and keeps them from becoming dry, brittle, and cracked. It can also inhibit the growth of microorganisms on skin. Sebum itself is odorless, but its bacterial breakdown can produce odors. Sebum is one cause of some people experiencing "oily" hair or skin if not washed for several days. Sebum is also found in earwax.

[000273] The dermis comprises two different types of sweat glands: apocrine sweat glands and merocrine sweat glands. Both gland types contain myoepithelial cells, specialized epithelial cells located between the gland cells and the underlying basal lamina. Myoepithelial cell contractions squeeze the gland and discharge any accumulated secretions. The secretory activities of gland cells and the contractions of myoepithelial cells are controlled by both the autonomic nervous system and by circulating hormones.

[000274] Apocrine sweat glands develop during the early- to mid-puberty ages within the age range of 13 to 15, and release more than normal amounts of sweat for approximately a month, regulating and releasing normal amounts of sweat after a certain period of time. These glands produce sweat that contains organic molecules (lipids and proteins) and pheromones. Mainly present on the face, in the armpits, and around the genital area, their activity is the main cause of sweat odor, due to the bacteria that break down the organic compounds in the sweat.

[000275] The name apocrine sweat gland is archaic; these glands are no longer believed to secrete their products by an apocrine mechanism in which the apical portion of the cell is sloughed off with secretory products inside. Rather, apocrine sweat glands secrete in a merocrine fashion: membrane-bound vesicles bind to the plasma membrane of secretory cells and release products by exocytosis with no net loss of the plasma membrane. These glands are still called apocrine sweat glands to distinguish them from the merocrine (eccrine) sweat glands.

[000276] Merocrine sweat glands (eccrine sweat glands) are far more numerous and widely distributed than apocrine sweat glands is the merocrine sweat glands. The adult integument contains around 3 million merocrine glands. They are smaller than apocrine sweat glands, and they do not extend as far into the dermis. Palms and soles have the highest numbers; estimates are that the palm of the hand has about 500 glands per square centimeter (3000 glands per square inch). Merocrine sweat glands are coiled tubular glands that discharge their secretions directly onto the surface of the skin.

[000277] The dermis comprises hair follicles, which are attached to sebaceous glands. Also attached to the follicle is a tiny bundle of muscle fiber ("arrector pili") that is responsible for causing the follicle lissis to become more perpendicular to the surface of the skin, and causing the follicle to protrude slightly above the surrounding skin (piloerection), resulting in goose bumps.

[000278] Hair follicles are structures that support hair growth by packing old cells together. At the base of a hair follicle is a large structure that is called the papilla, which is made up

mainly of connective tissue and a capillary loop. Around the papilla is the hair matrix, a collection of epithelial cells often interspersed with melanocytes. Cell division in the hair matrix is responsible for the cells that will form the major structures of the hair fiber and the inner root sheath. The papilla is usually ovoid or pear shaped with the matrix wrapped completely around it except for a short stalk-like connection to the surrounding connective tissue that provides access for the capillary. The root sheath is composed of an external root sheath ("Henle's layer"), a middle layer ("Huxley's layer"), and an internal cuticle that is continuous with the outermost layer of the hair fiber. The hair fiber is composed of a cuticle that is continuous with the root sheath, an intermediate cortex, and an inner medulla.

[000279] Hair grows in cycles of various phases: anagen (growth phase), catagen (involuting or regressing phase), and telogen (quiescent phase). Each phase has several morphologically and histologically distinguishable sub-phases. Prior to the start of cycling is a phase of follicular morphogenesis, and there is also a shedding phase ("exogen") in which a hair exits the follicle. Typically up to 90% of the hair follicles are in anagen phase while, 10–14% are in telogen and 1–2% in catagen. The cycle's length varies on different parts of the body. For example, the cycle for eyebrows takes around 4 months, while the cycle for the scalp takes 3 to 4 years to finish. Growth cycles are controlled by a chemical signal like epidermal growth factor

[000280] Botulinum toxin A (BTXA) has become a widely used drug in cosmetic dermatology. Adverse effects of BTXA observed with cosmetic use can have a significant impact on patient health and appearance and can deter patient use and/or repeat use. Currently, BTXA is administered by medical personnel and in a clinical setting both because BTXA is administered by injection, which requires trained personnel, and because the major tools for preventing adverse effects from BTXA are knowledge and skill. Use of correct injection techniques is mandatory since most unwanted effects are caused by incorrect technique. Knowledge of human anatomy, (*i.e.*, for example, facial and extrafacial muscles, location and depth of glands, *etc.*), is important for physicians to select the optimal dose, time and technique.

[000281] The most common adverse effects of current procedures for administering BTXA are pain and hematoma. When BTXA solution is administered by injection to the periocular region, eyelid and brow ptosis are common adverse effects. Adverse effects such as pain, hematoma, ecchymosis, and bruising may also occur in the upper and lower face and at extrafacial sites. Other possible adverse effects include, but are not limited to, headache and possible interaction with concomitant medications. Suggestions have been made to avoid the

most unwanted adverse effects by implementing the proper techniques of dilution, storage, and injection, as well as the careful exclusion of patients with any contraindications. Pain, hematoma, ecchymosis, and bruising can be prevented by cooling the skin before and after BTXA injection. Upper lid ptosis may be partly corrected using apraclonidine or phenylephrine eyedrops (Wollina *et al.*, 2005, *Am. J. Clin. Dermatol.*, 6:141; incorporated herein by reference). However, significant adverse effects remain with current strategies.

[000282] By contrast, the present invention provides methods and compositions for safely and effectively administering therapeutic agents, such as botulinum toxins, in a manner that minimizes adverse side effects. In some embodiments, topical administration of a therapeutic agent reduces unwanted side effects by about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99%, or about 100% relative to non-topical administration (*e.g.*, injection, oral administration, *etc.*) of the same therapeutic agent. For example, in some embodiments, topical administration of a therapeutic agent (*e.g.*, botulinum toxin) reduces pain, bruising, ecchymosis, and/or hematoma by about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99%, or about 100% relative to injection of the same therapeutic agent.

[000283] In some embodiments, topical administration of a therapeutic agent reduces unwanted systemic effects by about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99%, or about 100% relative to non-topical administration (*e.g.*, injection, oral administration, *etc.*) of the same therapeutic agent. In some embodiments, topical administration of a therapeutic agent reduces undesirable blood levels by about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99%, or about 100% relative to non-topical administration (*e.g.*, injection, oral administration, *etc.*) of the same therapeutic agent. For example, in specific embodiments, topical administration of botulinum toxin reduces the incidence and/or severity of botulism by about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99%, or about 100% relative to injection of botulinum toxin. In specific embodiments, topical administration of botulinum toxin reduces delivery of the therapeutic agent to the bloodstream by about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99%, or about 100% relative to injection of botulinum toxin.

[000284] In some embodiments, topical administration of a therapeutic agent reduces damage to underlying nervous tissue (*e.g.*, neuronal paralysis) by about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99%, or about 100% relative to non-topical administration (*e.g.*, injection, oral administration, *etc.*) of the same

therapeutic agent. In some embodiments, topical administration of a therapeutic agent reduces unwanted effects on muscles (*e.g.*, muscle paralysis) by about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99%, or about 100% relative to non-topical administration (*e.g.*, injection, oral administration, *etc.*) of the same therapeutic agent.

[000285] In some embodiments, the present invention provides methods and compositions for specific delivery of therapeutic agents to dermal structures. In some embodiments, therapeutic agents are specifically delivered to dermal structures without significant delivery to subdermal structures. In some embodiments, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, greater than about 99%, greater than about 99.5%, or about 100% of a therapeutic agent administered to the skin of a subject is delivered specifically to the dermis. In some embodiments, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, less than about 1%, less than about 0.5%, or less than about 0.1% of a therapeutic agent administered to the skin of a subject is delivered to subdermal structures.

[000286] In some embodiments, specific delivery to dermal structures is achieved through application of a dose of therapeutically active agent that is lower than a dose per area used to achieve delivery to subdermal structures. For example, in some embodiments, a volume of nanoparticle composition is applied to a larger surface area; in some embodiments, a nanoparticle composition containing a reduced amount of therapeutic agent per unit volume of composition is utilized; in some embodiments, penetration of the therapeutic agent and/or the nanoparticle composition into the skin is reduced (*e.g.*, through combination with penetration inhibitors and/or adjustment of nanoparticle composition characteristics such as particle size, component ratios, component identity, *etc.*, and combinations thereof). In some embodiments, the lower dose is at least about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 10-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 100-fold, or greater than about 100-fold lower than a dose per area used to achieve delivery to subdermal structures.

[000287] In some embodiments, the present invention contemplates method of administration of therapeutic agents as a topically and/or locally delivered composition comprising a nanoparticle composition such as a nanoemulsion (*e.g.*, microfluidized nanoemulsion). In some embodiments, the composition is formulated as a cream, ointment,

oil, foam, spray, lotion, liquid, powder, thickening lotion, or gel. Formulations comprising nanoparticle compositions can contain water and also any cosmetically acceptable solvent, in particular, monoalcohols, such as alkanols having 1 to 8 carbon atoms (like ethanol, isopropanol, benzyl alcohol and phenylethyl alcohol), polyalcohols, such as alkylene glycols (like glycerine, ethylene glycol and propylene glycol), and glycol ethers, such as mono-, di-, and tri-ethylene glycol monoalkyl ethers, for example, ethylene glycol monomethyl ether and diethylene glycol monomethyl ether, used singly or in a mixture. Such components can be present, for example, in proportions of up to as much as 70% by weight, relative to the weight of the total composition.

[000288] Formulations including nanoparticle compositions may contain at least one filler, for example, in order to obtain a matte product, which may be especially desired for individuals with greasy skin. The term "filler" means any particle that is solid at room temperature and atmospheric pressure, used alone or in combination, which does not react chemically with the various ingredients of the composition and which are insoluble in these ingredients, even when these ingredients are brought to a temperature above room temperature and especially to their softening point or to their melting point. Such inert fillers typically have melting points at least higher than 170 °C, higher than 180 ºC, higher than 190 ºC, or higher than 200 °C.

[000289] Fillers may be absorbent or nonabsorbent, *i.e.*, capable in particular of absorbing the oils of the composition and also the biological substances secreted by the skin. In some embodiments, fillers are particulate and have an apparent diameter ranging from 0.01 μm to 150 μm, from 0.5 μm to 120 μm, or from 1 μm to 80 μm. An apparent diameter corresponds to the diameter of the circle in which the elementary particle is inscribed along its smallest dimension (thickness for lamellae).

[000290] Pharmaceutical compositions are described in further detail in the section entitled "Pharmaceutical Compositions."

Acne Vulgaris

[000291] In some embodiments, nanoparticle compositions may comprise at least one therapeutic agent that is useful for treating acne vulgaris (commonly referred to as "acne"), a skin disease caused by changes in the pilosebaceous units (*i.e.*, skin structures comprising a hair follicle and its associated sebaceous gland). In some embodiments, acne is inflammatory. In some embodiments, acne is noninflammatory. While not life-threatening, acne vulgaris can cause significant problems for affected individuals. Depending on its severity and other factors, recalcitrant acne can be psychologically debilitating, and can

impose significant financial and emotional costs on those whom it afflicts. Despite some recent successes in acne therapy, treatment failures are still common, especially in adult women. While many adults "outgrow" this disease, there are some who continue to be afflicted during much of adulthood, despite continued medical advances. Unfortunately, the most potent acne medication in current use is administered systemically via a treatment that is teratogenic, an important issue for many women. There is an unfilled need for a more localized and effective treatment for acne, one with minimal side effects.

[000292] In general, acne develops as a result of blockages in follicles. The pathology centers on the pilosebaceous units, comprising a sebaceous gland, a follicle (*i.e.*, pore), and a vellus hair. Among the first events leading to acne are hyperkeratinization and formation of a plug of keratin and sebum (a "microcomedo"), obstructing the upper region of a follicle. Enlargement of sebaceous glands and an increase in sebum production occur with increased androgen production at adrenarche. A microcomedo may enlarge to form an open comedo (a "blackhead") or closed comedo (a "whitehead"). In these conditions the naturally occurring largely commensual bacteria *Propionibacterium acnes* can cause inflammation, leading to inflammatory lesions (papules, infected pustules, or nodules) in the dermis around the microcomedo or comedo, which results in redness and may result in scarring or hyperpigmentation.

[000293] Adolescence is marked by an increase in levels of circulating androgens, particularly dehydroepiandrosterone sulfate (DHEAS). Increased androgen levels are thought to cause sebaceous glands to enlarge and to increase sebum production. While most acne patients have normal hormone levels, there are reasons to conclude that increased sebum production plays a role in acne. For example, there may be a correlation between the rate of sebum production and the severity of acne. In addition, acne patients typically produce sebum that is deficient in linoleic acid, which is a potential cause of abnormal keratinization and follicular obstruction.

[000294] In response to increased sebum levels, *Propionibacterium acnes*, a relatively slow growing, typically aerotolerant anaerobic gram positive, diphtheroid bacterium, often colonizes the sebaceous follicles. *P. acnes* exacerbates acne by acting as a chemo-attractant for neutrophils. Neutrophils ingest *P. acnes*, and in doing so release various hydrolytic enzymes that damage the follicular wall. Released follicular contents then invade the dermis and cause an inflammatory reaction, manifesting as pustules, erythematous papules, or nodules. In a separate route, *P. acnes* can hydrolyze triglycerides to free fatty acids, which

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also increase inflammation and follicular obstruction. *P. acnes* may also activate the complement components of the immune system, which can also lead to follicular obstruction.

[000295] Follicles are lined with squamous epithelium, a layer of cells that is contiguous with the skin surface. In an acne-prone individual, the shedding of cells from this lining is often impeded, perhaps due to an increased level of intercellular adhesion that promotes the retention of cells. Retained cells can obstruct follicles, resulting in comedones. Such inhibited shedding may be related to abnormalities in epidermal differentiation and/or to abnormal sebum composition (*e.g.*, a deficiency in linoleic acid). It has also been demonstrated that increased sebum levels can irritate keratinocytes, causing the release of interleukin-1, which in turn can cause follicular hyperkeratinization. In general, each of these acne-causing routes, which are not mutually exclusive, is associated with follicular obstruction.

[000296] Several factors are known to be linked to acne, including, but not limited to, family and/or genetic history (see, *e.g.*, Ballanger *et al.*, 2006, *Dermatology*, 212:145-149; incorporated herein by reference); hormonal activity (*e.g.*, menstrual cycles, puberty, *etc.*); stress (*e.g.*, through increased output of hormones from the adrenal glands); hyperactive sebaceous glands; accumulation of dead skin cells; bacteria in the pores (*e.g.*, *P. acnes*); skin irritation or scratching; use of anabolic steroids; use of medications containing halogens (*e.g.*, iodides, chlorides, bromides), lithium, barbiturates, or androgens; exposure to certain chemical compounds (*e.g.*, dioxins such as chlorinated dioxins); exposure to testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone sulfate (DHEAS), and/or insulin-like growth factor 1 (IGF-I); diet including milk and/or high levels of carbohydrate; low levels of vitamins A and/or E; poor hygiene; or any combinations thereof.

[000297] In some embodiments, acne treatments work via one or more of the following mechanisms: (1) normalizing shedding into the pore to prevent blockage; (2) killing *P. acnes*; (3) having antinflammatory activity; and/or (4) manipulating hormone levels.

[000298] The present invention provides methods of treating acne comprising topical administration of a nanoparticle composition comprising at least one therapeutic agent to a subject suffering from, susceptible to, and/or displaying symptoms of acne. In some embodiments, such a nanoparticle composition is administered locally to an affected site (*e.g.*, face, neck, back, arms, chest, *etc.*). In some embodiments, nanoparticle compositions for treatment of acne are formulated into a cream, lotion, gel, sunscreen, *etc.* Further considerations for formulation and administration are described in further detail in the sections entitled "Pharmaceutical Compositions" and "Administration."

[000299] In some embodiments, botulinum toxin (*e.g.*, administered in the context of a nanoparticle composition) can be utilized to treat acne. Injected botulinum toxin has been reported to alleviate the appearance of acne. For example, see U.S. Patent 7,226,605 (incorporated herein by reference). However, as discussed herein, there are numerous negative side effects associated with botulinum toxin injection. The present invention contemplates administration of a botulinum nanoparticle composition such as a botulinum toxin nanoemulsion (*e.g.*, a microfluidized botulinum toxin nanoemulsion) to a patient exhibiting symptoms of acne.

[000300] In some embodiments, nanoparticle compositions may comprise any therapeutic agent that is useful for treatment of acne, including all therapeutic agents for acne listed in the section entitled "*Therapeutic Agents*." In some embodiments, such agents include, but are not limited to, cleansers or soaps; topical bactericidals (*e.g.*, benzoyl peroxide, triclosan, chlorhexidine gluconate, *etc.*); topical antibiotics (*e.g.*, externally-applied erythromycin, clindamycin, tetracycline, *etc.*); oral antibiotics (*e.g.*, erythromycin, tetracycline, oxytetracycline, doxycycline, minocycline, lymecycline, trimethoprim, *etc.*); hormonal treatments (*e.g.*, estrogen/progestogen oral contraceptives, low dose spironolactone, cortisone, *etc.*); topical retinoids (*e.g.*, tretinoin [RETIN-A®], adapalene [DIFFERIN®], tazarotene [TAZORAC®], retinol, isotretinoin, *etc.*); oral retinoids (*e.g.*, isotretinoin [ACCUTANE®, AMNESTEEM™, SOTRET™, CLARAVIS™]); herbs (*e.g.*, aloe vera; aruna, haldi [turmeric], papaya, *etc.*); azelaic acid; anti-inflammatory agents (*e.g.*, naproxen, ibuprofen, rofecoxib [Tehrani and Dharmalingam, 2004, *Indian J. Dermatol. Venereol. Leprol.*, 70:345-348; incorporated herein by reference], *etc.*); nicotinamide [vitamin B3]; tea tree oil [melaleuca oil]; rofecoxib; zinc (Dreno *et al.*, 1989, *Acta Derm. Venereol.*, 69:541-3; and Dreno *et al.*, 2001, *Dermatology*, 203:135-40; both of which are incorporated herein by reference); and/or combinations thereof; as described in further detail in the section entitled "*Therapeutic Agents*."

[000301] It will be appreciated that nanoparticle compositions in accordance with the present invention can be employed in combination therapies. In some embodiments, the present invention encompasses "therapeutic cocktails" comprising nanoparticle compositions. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. In some embodiments, pharmaceutical compositions comprising one or more nanoparticle compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired

pharmaceutical agents and/or procedures. In some embodiments, nanoparticle compositions themselves may comprise one or more additional therapeutic agents, as described herein.

[000302] The particular combination of therapies to employ in a combination regimen will generally take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, a nanoparticle composition may be administered concurrently with another agent that is useful for treating a disorder associated with the dermal level of the skin, *etc.*), or they may achieve different effects (for example, a nanoparticle composition may be administered concurrently with another agent that is useful for alleviating any adverse side effects of the nanoparticle composition). In some embodiments, compositions in accordance with the invention are administered with a second therapeutic agent that is approved by the U.S. Food and Drug Administration (FDA).

[000303] By "in combination with," it is not intended to imply that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the invention. In some embodiments, therapeutic agents utilized in combination are administered together in a single composition. In some embodiments, therapeutic agents utilized in combination are administered separately in different compositions. Compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. Additionally, the invention encompasses the delivery of nanoparticle compositions in combination with agents that may improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body.

[000304] In general, it is expected that agents utilized in combination will be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, levels utilized in combination will be lower than those utilized individually.

[000305] Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of acne, such as the agents described above. Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with procedures that are used to treat the symptoms and/or causes of acne. In some embodiments, such procedures include, but are not limited to, phototherapy (*e.g.*, alternating blue and red light); photodynamic therapy (*e.g.*, intense blue/violet light); laser

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treatment (*e.g.*, to burn away the follicle sac from which the hair grows; to burn away the sebaceous gland which produces the oil; and/or to induce formation of oxygen in the bacteria, killing them); local heating; and/or combinations thereof.

[000306] In some embodiments, nanoparticle compositions comprising therapeutic agents useful for treatment of acne may be administered to a subject in combination with phototherapy for treatment of acne. It is known in the art that short-term improvement of acne can be achieved with sunlight, but studies have shown that sunlight worsens acne long-term. More recently, visible light has been successfully employed to treat acne (*i.e.*, "phototherapy") – in particular, intense violet light (405 nm – 420 nm) generated by purpose-built fluorescent lighting, dichroic bulbs, LEDs, and/or lasers. Used twice weekly, this has been shown to reduce the number of acne lesions by about 64% (Kawada *et al.*, 2002, *J. Dermatol. Sci.*, 30:129-35; incorporated herein by reference) and is even more effective when applied daily. Without wishing to be bound by any one theory, a porphyrin (Coproporphyrin III) produced within *P. acnes* generates free radicals when irradiated by 420 nm and shorter wavelengths of light (Kjeldstad, 1984, *Z. Naturforsch [C]*, 39:300-2; incorporated herein by reference). Particularly when applied over several days, these free radicals ultimately kill bacteria (Ashkenazi *et al.*, 2003, *FEMS Immunol. Med. Microbiol.*, 35:17-24; incorporated herein by reference). Since porphyrins are not otherwise present in skin, and no ultraviolet (UV) light is employed, it appears to be safe, and has been licensed by the U.S. FDA. The treatment apparently works even better if used with red visible light (about 660 nm), resulting in a 76% reduction of lesions after 3 months of daily treatment for 80% of the patients (Papageorgiou *et al.*, 2000, *Br. J. Dermatol.*, 142:973-8; incorporated herein by reference). Unlike most of other treatments, few negative side effects are typically experienced, and development of bacterial resistance to the treatment seems very unlikely. After treatment, clearance can be longer lived than is typical with topical or oral antibiotic treatments (*e.g.*, may be up to several months).

[000307] In some embodiments, nanoparticle compositions comprising therapeutic agents useful for treatment of acne may be administered to a subject in combination with photodynamic therapy for treatment of acne. There is some evidence that intense blue/violet light (405 nm – 425 nm) can decrease the number of inflammatory acne lesion by 60% – 70% in 4 weeks of therapy, particularly when *P. acnes* is pretreated with delta-aminolevulinic acid (ALA), which increases the production of porphyrins.

[000308] In some embodiments, nanoparticle compositions comprising therapeutic agents useful for treatment of acne may be administered to a subject in combination with laser

treatment for treatment of acne. Laser surgery has been in use for some time to reduce the scars left behind by acne, but research has been done on lasers for prevention of acne formation itself. In general, laser is used to burn away the follicle sac from which the hair grows, to burn away the sebaceous gland which produces the oil, and/or to induce formation of oxygen in the bacteria, thereby killing them.

[000309] In some embodiments, nanoparticle compositions comprising therapeutic agents useful for treatment of acne may be administered to a subject in combination with local heating for treatment of acne. In some cases, local heating may be used to kill bacteria in a developing pimple, thereby expediting healing.

[000310] In some embodiments, the present invention involves administration of at least one therapeutic agent in a nanoparticle composition in an amount sufficient to achieve a reduction in the severity and/or prevalence of acne of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the severity and/or prevalence of acne of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the severity and/or prevalence of acne of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Hyperhidrosis

[000311] Hyperhidrosis is a medical condition in which a person sweats excessively and unpredictably. People with hyperhidrosis can sweat even when the temperature is cool, and when they are at rest. Sweating helps the body stay cool and is perfectly natural. People sweat more in warm temperatures, when they exercise, or in response to situations that make them nervous, angry, embarrassed, or afraid. Uncontrollable sweating can lead to significant discomfort, both physical and emotional.

[000312] Hyperhidrosis occurs without normal sweat triggers, and refers to the condition characterized by perspiration in excess of that required for regulation of body temperature. Those with hyperhidrosis appear to have overactive sweat glands. Hyperhidrosis can either be generalized or localized to specific parts of the body. Hands, feet, axillae, forehead, and

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the groin area are among the most active regions of perspiration due to the relatively high concentration of sweat glands; however, any part of the body may be affected. Excessive sweating that affects hands, feet, and armpits and has no other identifiable cause is referred to as "primary" or "focal hyperhidrosis." Primary hyperhidrosis affects 2% – 3% of the population, yet less than 40% of patients with this condition seek medical advice. There may be a genetic component involved in primary hyperhidrosis. One theory is that hyperhidrosis results from an overactive sympathetic nervous system. Primary hyperhidrosis is found to start during adolescence or even before.

[000313] If sweating occurs as a result of another medical condition, it is called secondary hyperhidrosis. Sweating may be all over one's body, or it may be localized to one area. Secondary hyperhidrosis can start at any point in life. For some, it can seem to come on unexpectedly. Conditions that cause secondary hyperhidrosis include but are not limited to, acromegaly, hyperthyroidism, glucose control disorders (including diabetes), pheochromocytoma, carcinoid syndrome, cancer, tuberculosis, infections, menopause, spinal cord injury, stroke, thyroid gland disorder, pituitary gland disorder, gout, mercury poisoning, Parkinson's disease, heart disease, lung disease, certain medications, substance abuse, or anxiety conditions.

[000314] Hyperhidrosis can be categorized as "palmar" (*i.e.*, excessive sweating of the hands), "axillary" (*i.e.*, excessive sweating of the armpits), "plantar" (*i.e.*, excessive sweating of the feet), "facial" (*i.e.*, excessive sweating of the face), "cranial" (*i.e.*, excessive sweating of the head, especially noted around the hairline), or "general" (*i.e.*, overall excessive sweating).

[000315] The present invention provides methods of treating hyperhidrosis comprising topical administration of a nanoparticle composition comprising at least one therapeutic agent to a subject suffering from, susceptible to, and/or displaying symptoms of hyperhidrosis. In some embodiments, such a nanoparticle composition is administered locally to an affected site (*e.g.*, axillae, hands, feet, *etc.*). In some embodiments, nanoparticle compositions for treatment of hyperhidrosis are formulated into a cream, lotion, gel, sunscreen, *etc.* In some embodiments, nanoparticle compositions for treatment of hyperhidrosis are formulated into a deodorant and/or antiperspirant (*e.g.*, as a roll-on, solid stick, gel, cream, aerosol, *etc.*). Further considerations for formulation and administration are described in further detail in the sections entitled "Pharmaceutical Compositions" and "Administration."

[000316] In some embodiments, botulinum toxin (*e.g.*, administered in the context of a nanoparticle composition) can be utilized to treat hyperhidrosis. Botulinum toxin type A

(BOTOX®) was approved by the FDA in 2004 for the treatment of severe underarm sweating (*i.e.*, primary axillary hyperhidrosis). Small doses of purified botulinum toxin injected into the underarm temporarily block the nerves that stimulate sweating. Side effects include included injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety. BOTOX® used for sweating of the palms can cause mild, but temporary, weakness and intense pain.

[000317] In some embodiments, the present invention contemplates administration of a botulinum nanoparticle composition such as a botulinum toxin nanoemulsion (*e.g.*, microfluidized botulinum toxin nanoemulsion) to a patient exhibiting symptoms of hyperhidrosis.

[000318] In some embodiments, nanoparticle compositions may comprise any therapeutic agent that is useful for treatment of hyperhidrosis, including all therapeutic agents for hyperhidrosis listed in the section entitled "*Therapeutic Agents*." In some embodiments, such agents include, but are not limited to, antiperspirants (*e.g.*, aluminum chloride, aluminum chlorohydrate, aluminum-zirconium compounds, aluminum zirconium tetrachlorohydrex gly, aluminum zirconium trichlorohydrex gly, ammonium alum, *etc.*); oral medication (*e.g.*, diphenhydramine hydrochloride, hydroxyzine, glycopyrrolate, *etc.*); anticholinergic drugs (*e.g.*, oxybutynin, glycopyrrolate, propantheline bromide, benztropine, *etc.*); beta-blockers; antidepressants; anxiolytics; talc and/or baby powder; and/or combinations thereof; as described in further detail in the section entitled "*Therapeutic Agents*."

[000319] It will be appreciated that nanoparticle compositions in accordance with the present invention can be employed in combination therapies, as described above for the treatment of acne. Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of hyperhidrosis, such as those described above. Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with procedures that are used to treat the symptoms and/or causes of hyperhidrosis. In some embodiments, such procedures include, but are not limited to, surgery (*e.g.*, endoscopic thoracic sympathectomy, lumbar sympathectomy, sweat gland suction, percutaneous sympathectomy, *etc.*); iontophoresis; weight loss; relaxation and/or meditation; hypnosis; use of shoe inserts; and/or combinations thereof.

[000320] In some embodiments, nanoparticle compositions comprising therapeutic agents may be administered to a subject in combination with endoscopic thoracic sympathectomy (ETS) for treatment of hyperhidrosis. In ETS procedures, select sympathetic nerves or nerve

ganglia in the chest are either excised, cut, burned, or clamped. The procedure causes relief of excessive hand sweating in about 85% – 95% of patients. However, compensatory sweating is seen in about 20% to 80% of patients. While ETS can be helpful to treat axillary hyperhidrosis, palmar hyperhidrosis patients frequently have better results.

[000321] In some embodiments, nanoparticle compositions comprising therapeutic agents may be administered to a subject in combination with lumbar sympathectomy for treatment of hyperhidrosis. Lumbar sympathectomy can be useful for patients for whom endoscopic thoracic sympathectomy did not relieve their excessive plantar sweating. With this procedure, the sympathetic chain in the lumbar region is being clipped or divided in order to relieve the severe or excessive feet sweating. The success rate is about 90%.

[000322] In some embodiments, nanoparticle compositions comprising therapeutic agents may be administered to a subject in combination with sweat gland suction for treatment of hyperhidrosis. Sweat gland suction is a technique adapted and modified from liposuction (Bieniek *et al.*, 2005, *Acta dermatovenerologica Croatica : ADC / Hrvatsko dermatolosko drustvo*, 13:212-8; incorporated herein by reference). Approximately 30% of the sweat glands are removed with a proportionate reduction in sweat.

[000323] In some embodiments, nanoparticle compositions comprising therapeutic agents may be administered to a subject in combination with iontophoresis for treatment of hyperhidrosis. Iontophoresis was originally described in the 1950s, and its exact mode of action remains elusive to date (Kreyden, 2004, *J. Cosmetic Dermatol.*, 3:211-4; incorporated herein by reference). An affected area is placed in a device that has two pails of water with a conductor in each one. The hand or foot acts like a conductor between the positively- and negatively-charged pails. As the low current passes through the area, the minerals in the water clog the sweat glands, limiting the amount of sweat released. The device is usually used for the hands and feet, but there has been a device created for the axillae area and for the stump region of amputees.

[000324] In some embodiments, nanoparticle compositions comprising therapeutic agents may be administered to a subject in combination with percutaneous sympathectomy for treatment of hyperhidrosis. Percutaneous sympathectomy is a minimally invasive procedure in which nerves are blocked by injection of phenol (Wang *et al.*, 2001, *Neurosurgery*, 49:628-34; incorporated herein by reference).

[000325] In some embodiments, nanoparticle compositions comprising therapeutic agents may be administered to a subject in combination with weight loss for treatment of

hyperhidrosis. Hyperhidrosis can be aggravated by obesity, so for some patients, weight loss can help alleviate the symptoms of hyperhidrosis.

[000326] In some embodiments, nanoparticle compositions comprising therapeutic agents may be administered to a subject in combination with relaxation, meditation, and/or hypnosis for treatment of hyperhidrosis. Hypnosis has been used with some success in improving the process of administering injections for the treatment of hyperhidrosis (Maillard *et al.*, 2007, *Annales de dermatologie et de vénéréologie*, 134:653-4; incorporated herein by reference).

[000327] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a sweat reduction of at least about 25%; in some embodiments in an amount sufficient to achieve a sweat reduction of at least about 30%; in some embodiments in an amount sufficient to achieve a sweat reduction of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Bromhidrosis

[000328] Bromhidrosis (also called osmidrosis, ozochrotia, body odor, and B.O.) is the smell of bacteria growing on a body. Bacteria multiply rapidly in the presence of sweat, but sweat itself is almost completely odorless. Body odor is associated with the hair, feet, groin, anus, skin in general, armpits, genitals, pubic hair, and mouth.

[000329] Apocrine bromhidrosis is the most prevalent form, whereas eccrine bromhidrosis is less common. Several factors contribute to the pathogenesis of apocrine bromhidrosis. Bacterial decomposition of apocrine secretion yields ammonia and short-chain fatty acids, with their characteristic strong odors. The most abundant of these acids is (E)-3-methyl-2-hexanoic acid (E-3M2H), which is brought to the skin surface bound by 2 apocrine secretion odor-binding proteins (ASOB1 and ASOB2). One of these binding proteins, ASOB2, has been identified as apolipoprotein D (apoD), a known member of the lipocalin family of carrier proteins.

[000330] Axillary bacterial florae have been shown to produce the distinctive axillary odor by transforming nonodiferous precursors in sweat to more odiferous volatile acids. The most common of these are E-3M2H and (RS)-3-hydroxy-3-methlyhexanoic acid (HMHA), which are released through the action of a specific zinc-dependent *N*-alpha-acyl-glutamine aminoacylase (*N*-AGA) from *Corynebacterium* species. This aminoacylase has recently been demonstrated to also release other odiferous acids from glutamine conjugates in sweat, which may be the basis of individual body odor.

[000331] In certain circumstances, eccrine secretion, which is typically odorless, assumes an offensive aroma and causes eccrine bromhidrosis. When eccrine sweat softens keratin, bacterial degradation of the keratin yields a foul smell. Ingestion of some foods, including garlic, onion, curry, alcohol, certain drugs (*e.g.*, penicillin, bromides), and toxins may cause eccrine bromhidrosis. Eccrine bromhidrosis may result from underlying metabolic or endogenous causes.

[000332] The role of excessive eccrine secretion, or hyperhidrosis, in the pathogenesis of bromhidrosis is unclear. Hyperhidrosis may promote the spread of apocrine sweat and contribute further to bromhidrosis by creating a moist environment, one ripe for bacterial overgrowth. Conversely, eccrine hyperhidrosis may cause a decrease in odor because the eccrine sweat flushes away the more odiferous apocrine sweat.

[000333] The present invention provides methods of treating bromhidrosis comprising topical administration of a nanoparticle composition to a subject suffering from, susceptible to, and/or displaying symptoms of bromhidrosis. In some embodiments, a therapeutic agent in the context of a nanoparticle composition is administered locally to an affected site (*e.g.*, axillae, *etc.*). In some embodiments, nanoparticle compositions for treatment of bromhidrosis are formulated into a cream, lotion, gel, sunscreen, deodorant, *etc.* Further considerations for formulation and administration are described in further detail in the sections entitled "Pharmaceutical Compositions" and "Administration."

[000334] Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of bromhidrosis, as described above for the treatment of bromhidrosis, including all therapeutic agents for bromhidrosis listed in the section entitled "*Therapeutic Agents*." In some embodiments, such agents include perfumes; deodorants; antiperspirants; and/or combinations thereof.

[000335] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount

sufficient to achieve an odor reduction of at least about 25%; in some embodiments in an amount sufficient to achieve an odor reduction of at least about 30%; in some embodiments in an amount sufficient to achieve an odor reduction of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Chromhidrosis

[000336] Chromhidrosis is a rare condition characterized by the secretion of colored sweat. It is caused by the deposition of lipofuscin in the sweat glands. Approximately 10% of people without the disease have colored sweat that is regarded as acceptable and within the normal range. Usually chromhidrosis affects the apocrine glands, mainly on the face and underarms. Lipofuscin pigment is produced in the apocrine gland, and its various oxidative states account for the characteristic yellow, green, blue, or black secretions observed in apocrine chromhidrosis. Chromhidrosis of the eccrine glands is rare, occurring mainly after the ingestion of certain dyes or drugs. Pseudochromhidrosis occurs when clear eccrine sweat becomes colored on the surface of the skin as a result of extrinsic dyes, paints, or chromogenic bacteria.

[000337] The present invention provides methods of treating chromhidrosis comprising topical administration of a nanoparticle composition to a subject suffering from, susceptible to, and/or displaying symptoms of chromhidrosis. In some embodiments, a therapeutic agent in the context of a nanoparticle composition is administered locally to an affected site (*e.g.*, axillae, *etc.*). In some embodiments, botulinum nanoparticle compositions for treatment of chromhidrosis are formulated into a cream, lotion, gel, sunscreen, deodorant, *etc.* Further considerations for formulation and administration are described in further detail in the sections entitled "Pharmaceutical Compositions" and "Administration."

[000338] Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of chromhidrosis, as described above for the treatment of chromhidrosis, including all therapeutic agents for chromhidrosis listed in the section entitled

"*Therapeutic Agents*." In some embodiments, such agents include perfumes; deodorants; antiperspirants; and/or combinations thereof.

[000339] In some embodiments, the present invention involves administration of one or more therapeutic agents (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a reduction in the degree and/or prevalence of colored sweat of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of colored sweat of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of colored sweat of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Rosacea

[000340] Rosacea is a condition that is estimated to affect over 45 million people worldwide. Rosacea affects both sexes, but is almost three times more common in women, and has a peak age of onset between 30 and 60. It begins as erythema (*i.e.*, flushing and redness) on the central face and across the cheeks, nose, and/or forehead but can also less commonly affect the neck and chest. As rosacea progresses, other symptoms can develop such as one or more of semi-permanent erythema, telangiectasia (*i.e.*, dilation of superficial blood vessels on the face), red domed papules and pustules, red gritty eyes, burning and stinging sensations, and/or rhinophyma (*i.e.*, a red lobulated nose).

[000341] There are four main subtypes of rosacea. "Erythematotelangiectatic rosacea" is characterized by permanent redness with a tendency to flush and blush easily. It is also common to have small blood vessels visible near the surface of the skin (*i.e.*, telangiectasias) and/or burning or itching sensations. "Papulopustular rosacea" is characterized by some permanent redness with papules and/or pustules, which typically last 1 to 4 days. This subtype is commonly confused with acne. "Phymatous rosacea" is most commonly associated with rhinophyma, an enlargement of the nose. Symptoms include thickening skin, irregular surface nodularities, and enlargement. Phymatous rosacea can also affect the chin

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(gnatophyma), forehead (metophyma), cheeks, eyelids (blepharophyma), and/or ears (otophyma) (see, *e.g.*, Jansen and Plewig, 1998, *Facial Plast. Surg.*, 14:241; incorporated herein by reference). Small blood vessels visible near the surface of the skin (*i.e.*, telangiectasias) may be present. "Ocular rosacea" is characterized by red, dry, irritated eyes and/or eyelids. Other symptoms may include foreign body sensations, itching, and/or burning.

[000342] Rosacea can be triggered by a variety of stimuli. Triggers that cause episodes of flushing and blushing play a part in the development of rosacea, such as exposure to temperature extremes, strenuous exercise, heat from sunlight, severe sunburn, stress, anxiety, cold wind, and/or moving to a warm or hot environment from a cold one. Some foods and drinks can trigger flushing, such as alcohol, foods and beverages containing caffeine (*e.g.*, hot tea, coffee), foods high in histamines, and spicy foods. Certain medications and topical irritants can quickly progress rosacea (*e.g.*, steroids, benzoyl peroxide, isotretinoin.)

[000343] The present invention provides methods of treating rosacea comprising topical administration of a nanoparticle composition comprising at least one therapeutic agent to a subject suffering from, susceptible to, and/or displaying symptoms of rosacea. In some embodiments, a therapeutic agent in the context of a nanoparticle composition is administered locally to an affected site (*e.g.*, cheeks, nose, forehead, ears, neck, chest, *etc.*). In some embodiments, nanoparticle compositions for treatment of rosacea are formulated into a cream, lotion, gel, sunscreen, *etc.* Further considerations for formulation and administration are described in further detail in the sections entitled "Pharmaceutical Compositions" and "Administration."

[000344] In some embodiments, different subtypes of rosacea are treated differently from other subtypes of rosacea (Cohen and Tiemstra, 2002, *J. Am. Board Fam. Pract.*, 15:214; incorporated herein by reference). In some embodiments, different subtypes of rosacea are not treated differently from other subtypes of rosacea.

[000345] In some embodiments, nanoparticle compositions may comprise any therapeutic agent that is useful for treatment of rosacea, including all therapeutic agents for rosacea listed in the section entitled "*Therapeutic Agents*." In some embodiments, such agents include, but are not limited to, oral antibiotics (*e.g.*, tetracycline, doxycycline, minocycline, metronidazole, macrolide antibiotics, *etc.*). In some embodiments, oral antibiotics may be administered at anti-inflammatory doses (*e.g.*, about 40 mg/day) or at higher doses. In some embodiments, agents for combination therapy may include oral isotretinoin. In some embodiments, agents for combination therapy may include topical antibiotics (*e.g.*,

metronidazole, clindamycin, erythromycin, *etc.*); topical azelaic acid (*e.g.*, FINACEA™, AZELEX™, FINEVIN®, SKINOREN, *etc.*); topical sulfacetamide; topical sulfur; topical calcineurin inhibitor (*e.g.*, tacrolimus, pimecrolimus, *etc.*); topical benzoyl peroxide; topical permethrin; a combination of plant-sourced methylsulfonylmethane (MSM) and Silymarin; and/or combinations thereof. Any combination of the foregoing may be utilized, and such therapeutic agents are described in further detail in the section entitled "*Therapeutic Agents*."

[000346] It will be appreciated that nanoparticle compositions in accordance with the present invention can be employed in combination therapies, as described above for the treatment of acne. Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of rosacea, such as those described above. Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with procedures that are used to treat the symptoms and/or causes of rosacea. In some embodiments, such procedures include, but are not limited to, use of a gentle skin cleansing regimen using non-irritating cleansers; protecting skin from the sun by covering skin with clothing; applying sunscreen to exposed skin; dermatological vascular laser (single wavelength); intense pulsed light (broad spectrum); carbon dioxide lasers; low level light therapies; and/or combinations thereof.

[000347] Rosacea may be treated via dermatological vascular laser (single wavelength) and/or intense pulsed light (broad spectrum) (Angermeier, 1999, *J. Cutan. Laser Ther.*, 1:95; incorporated herein by reference). These methods use light to penetrate the epidermis to target the capillaries in the dermis. Light is absorbed by oxy-hemoglobin, thereby causing capillary walls to heat up to 70 ºC, damaging them, which causes them to be absorbed by the body's natural defense mechanism. These methods may be successful for eliminating redness altogether, though additional periodic treatments might be necessary to remove newly-formed capillaries. Alternatively or additionally, a 595 nm long pulse-duration pulsed-dye laser may be useful for the treatment of rosacea (Kligman and Bernstein, 2008, *Lasers Surg. Med.*, 40:233; incorporated herein by reference).

[000348] Alternatively or additionally, carbon dioxide lasers can be used to remove excess tissue caused by phymatous rosacea. Carbon dioxide lasers emit a wavelength that is absorbed directly by the skin. The laser beam can be focused into a thin beam and used as a scalpel or defocused and used to vaporize tissue.

[000349] In some embodiments, rosacea can be treated using low level light therapies.

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[000350] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of rosacea of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of rosacea of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of rosacea of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Hair Loss

[000351] Baldness involves the state of lacking hair where it often grows, especially on the head. The most common form of baldness is a progressive hair thinning condition called androgenic alopecia or "male pattern baldness" that occurs in adult male humans and other species. The amount and patterns of baldness can vary greatly; it ranges from male and female "pattern alopecia" (androgenic alopecia, also called androgenetic alopecia or alopecia androgenetica); "alopecia areata," which involves the loss of some of the hair from the head; "alopecia totalis," which involves the loss of all head hair; to the most extreme form, "alopecia universalis," which involves the loss of all hair from the head and the body.

[000352] In some embodiments, nanoparticle compositions may comprise any therapeutic agent that is useful for treatment of hair loss, including all therapeutic agents for hair loss listed in the section entitled "*Therapeutic Agents*." In some embodiments, such agents include, but are not limited to, aza-steroids, such as finasteride (PROPECIA®; PROSCAR®; *etc.*) or dutasteride (AVODART®); topically applied minoxidil, a vasodilator (ROGAINE®); antiandrogens (*e.g.*, ketoconazole, fluconazole, spironolactone, *etc.*); saw palmetto; caffeine; copper peptides; nitroxide spin labels TEMPO and TEMPOL; unsaturated fatty acids (*e.g.*, gamma linolenic acid); hedgehog agonists; azelaic acid and zinc in combination; Chinese knotweed; pumpkin seed; spironolactone; tretinoin; zinc; stinging nettle; and/or combinations

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thereof. Any combination of the foregoing may be utilized, and such therapeutic agents are described in further detail in the section entitled "*Therapeutic Agents*."

[000353] It will be appreciated that nanoparticle compositions in accordance with the present invention can be employed in combination therapies, as described above for the treatment of acne. Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of hair loss, such as those described above. Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with procedures that are used to treat the symptoms and/or causes of hair loss. In some embodiments, such procedures include, but are not limited to, hair transplantation; healthy diet and exercise; hair multiplication; scalp massage; low-level laser therapy; and/or electrotrichogenesis.

[000354] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hair loss of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hair loss of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hair loss of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Psoriasis

[000355] Psoriasis is a disorder which affects the skin and joints. It commonly causes red scaly patches to appear on the skin. The scaly patches caused by psoriasis, called "psoriatic plaques," are areas of inflammation and excessive skin production. Skin rapidly accumulates at these sites and takes a silvery-white appearance. Plaques frequently occur on the skin of the elbows and knees, but can affect any area including the scalp and genitals. Psoriasis is hypothesized to be immune-mediated and is not contagious.

[000356] Psoriasis is a chronic recurring condition which varies in severity from minor localized patches to complete body coverage. Fingernails and toenails are frequently affected ("psoriatic nail dystrophy"). Psoriasis can also cause inflammation of the joints, which is known as "psoriatic arthritis." Ten to fifteen percent of people with psoriasis have psoriatic arthritis.

[000357] The cause of psoriasis is not known, but it is believed to have a genetic component. Several factors are thought to aggravate psoriasis, including stress, excessive alcohol consumption, and smoking. Individuals with psoriasis may suffer from depression and loss of self-esteem. As such, quality of life is an important factor in evaluating the severity of the disease.

[000358] In some embodiments, nanoparticle compositions may comprise any therapeutic agent that is useful for treatment of psoriasis, including all therapeutic agents for psoriasis listed in the section entitled "*Therapeutic Agents*." In some embodiments, such agents include, but are not limited to, coal tar; dithranol (anthralin); a corticosteroid such as desoximetasone (TOPICORT®); a vitamin D3 analog (*e.g.*, calcipotriol); a retinoid; argan oil; topical administration of psoralen with exposure to ultraviolet A light (PUVA); milk thistle; methotrexate; cyclosporine; the antimetabolite tioguanine; hydroxyurea; sulfasalazine; mycophenolate mofetil; azathioprine; tacrolimus; and/or antibody-based therapeutics (*e.g.*, alefacept [AMEVIEVE®], etanercept [EMBREL®], infliximab [REMICADE®], *etc.*). Any combination of the foregoing may be utilized, and additional such therapeutic agents are described in further detail in the section entitled "*Therapeutic Agents*."

[000359] It will be appreciated that nanoparticle compositions in accordance with the present invention can be employed in combination therapies, as described above for the treatment of acne. Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of psoriasis, such as those described above. Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with procedures that are used to treat the symptoms and/or causes of psoriasis. In some embodiments, such procedures include, but are not limited to, phototherapy and/or photochemotherapy.

[000360] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of psoriasis of at least about 25%; in some embodiments in an amount sufficient to achieve a

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reduction in the degree and/or prevalence of one or more symptoms of psoriasis of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of psoriasis of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Dermal Infections

[000361] In some embodiments, a therapeutic agent is useful for treating dermal infections (*e.g.*, bacterial, viral, and/or fungal infections). In some embodiments, one or more therapeutic agents in the context of nanoparticle compositions may be used to treat a condition or disorder associated with bacterial infection of the dermis, including, but not limited to, impetigo, folliculitis, furunculosis, carbunculosis, hidradenitis suppurativa (*i.e.*, bacterial infection of sweat glands and/or hair follicles), skin abscesses, cat scratch disease, cellulitis, erysipelas, ecthyma, necrotizing fasciitis, erythrasma, pitted keratolysis, trichomycosis axillaris, staphylococcal scalded skin syndrome, acute paronychia, and/or combinations thereof.

[000362] In some embodiments, conditions or disorders associated with bacterial infection of the dermis may be caused by or correlated with infection by one or more of *Staphylococcus aureus*, *Streptococcus pyogenes*, group B and C streptococci, anaerobic bacteria (*e.g.*, *Clostridium* species), *Corynebacterium* species (*e.g.*, *Corynebacterium minutissimum*, *Corynebacterium tenuis*, *etc.*), *Dermatophilus congolensis*, and/or combinations thereof.

[000363] In some embodiments, therapeutic agents useful for treatment of conditions or disorders associated with bacterial infection of the dermis include, but are not limited to, antibiotics (*e.g.*, penicillin, dicloxacillin, cephalexin, erythromycin, clindamycin, gentamicin, *etc.*), topical antibiotics (*e.g.* clindamycin, erythromycin, mupirocin *etc.*), topical mixture of bacitracin and polymyxin (*e.g.*, NEOSPORIN®, POLYSPORIN®), topical fusidic acid cream, and combinations thereof.

[000364] In some embodiments, one or more therapeutic agents in the context of nanoparticle compositions may be used to treat a condition or disorder associated with viral infection of the dermis, including, but not limited to, herpes labialis, genital herpes, shingles, molluscum contagiosum, warts, and/or combinations thereof.

[000365] In some embodiments, conditions or disorders associated with viral infection of the dermis may be caused by or correlated with infection by one or more of herpes simplex virus type 1, herpes simplex type 2, varicella-zoster virus, human papillomavirus, poxvirus, and/or combinations thereof.

[000366] Therapeutic agents useful for treatment of conditions or disorders associated with dermal infection include all therapeutic agents for dermal infection listed in the section entitled "*Therapeutic Agents*."

[000367] In some embodiments, therapeutic agents useful for treatment of conditions or disorders associated with viral infection of the dermis include, but are not limited to, antiviral therapeutics (*e.g.*, acyclovir, famciclovir, valacyclovir, *etc.*), topical treatments (*e.g.*, trichloroacetic acid, salicylic acid, podophyllin, canthacur, imiquimod cream, *etc.*), and/or combinations thereof.

[000368] In some embodiments, one or more therapeutic agents in the context of nanoparticle compositions may be used to treat a condition or disorder associated with fungal infection of the dermis, including, but not limited to, dermatophytosis, tinea pedis ("athlete's foot"), candidal intertrigo, thrush, paronychia, angular cheilitis, candidal vulvovaginitis, balanitis, tinea versicolor, chronic paronychia, and/or combinations thereof.

[000369] In some embodiments, conditions or disorders associated with fungal infection of the dermis may be caused by or correlated with infection by one or more of *Trichophyton* species (*e.g.*, *Trichophyton rubrum*), *Microsporum* species, *Epidermophyton* species, *Candida* species (*e.g.*, *Candida albicans*), and/or *Pityrosporum ovale*, and/or combinations thereof.

[000370] In some embodiments, therapeutic agents useful for treatment of conditions or disorders associated with fungal infection of the dermis include, but are not limited to, topical therapeutics (*e.g.*, terbinafine [LAMISIL®], clotrimazole [LOTRIMIN®, MYCELEX®], or econazole [SPECTAZOLE®], selenium sulfide shampoo, ketoconazole shampoo, *etc.*), oral therapeutics (*e.g.*, itraconazole [SPORANOX®], terbinafine, *etc.*), and/or combinations thereof.

[000371] Any combination of the foregoing may be utilized, and additional such therapeutic agents are described in further detail in the section entitled "*Therapeutic Agents*."

[000372] It will be appreciated that nanoparticle compositions in accordance with the present invention can be employed in combination therapies, as described above for the treatment of acne. Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of dermal infection, such as those described above. Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with procedures that are used to treat the symptoms and/or causes of dermal infection. In some embodiments, such procedures include, but are not limited to, surgical removal of affected skin, amputation, *etc.*

[000373] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of dermal infection of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of dermal infection of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of dermal infection of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Actinic Keratosis

[000374] In some embodiments, a therapeutic agent is useful for treating actinic keratosis. Actinic keratosis (also called "solar keratosis," or "AK") is a premalignant condition of thick, scaly, or crusty patches of skin. It is most common in fair-skinned people who are frequently exposed to the sun. When skin is exposed to the sun constantly, thick, scaly, or crusty bumps appear. The scaly or crusty part of the bump is dry and rough. A growth starts out as flat scaly areas, and later grows into a tough, wart-like area.

[000375] An actinic keratosis site commonly ranges between 2 mm and 6 mm in size, and can be dark or light, tan, pink, red, a combination of all these, or have the same pigment as

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the surrounding skin. It may appear on any sun-exposed area, such as the face, ears, neck, scalp, chest, backs of hands, forearms, or lips.

[000376] In some embodiments, therapeutic agents useful for treatment of conditions or disorders associated with actinic keratosis include, but are not limited to, 5-fluorouracil, imiquimod, diclofenac, crocodile oil, and/or combinations thereof. Any combination of the foregoing may be utilized, and additional such therapeutic agents are described in further detail in the section entitled "*Therapeutic Agents*."

[000377] It will be appreciated that nanoparticle compositions in accordance with the present invention can be employed in combination therapies, as described above for the treatment of actinic keratosis. Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of actinic keratosis, such as those described above. Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with procedures that are used to treat the symptoms and/or causes of actinic keratosis. In some embodiments, such procedures include, but are not limited to, cryosurgery, photodynamic therapy, laser treatment, electrocautery, surgery, *etc.*

[000378] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of actinic keratosis of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of actinic keratosis of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of actinic keratosis of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

[000379] The present invention provides methods of treating bromhidrosis comprising topical administration of a nanoparticle composition to a subject suffering from, susceptible

to, and/or displaying symptoms of actinic keratosis. In some embodiments, a therapeutic agent in the context of a nanoparticle composition is administered locally to an affected site (*e.g.*, axillae, *etc.*). In some embodiments, nanoparticle compositions for treatment of actinic keratosis are formulated into a cream, lotion, gel, sunscreen, deodorant, *etc.* Further considerations for formulation and administration are described in further detail in the sections entitled "Pharmaceutical Compositions" and "Administration."

Eczematous Dermatitis

[000380] Eczematous dermatitis is a skin condition characterized by local inflammatory reactions that are erythematous with indistinct margins. In the acute phase, lesions may exhibit edema, vesiculation, oozing, and in some cases bullae. Most chronic lesions are dry and scaly and may exhibit secondary lichenification. These lesions frequently get secondary bacterial infections, which may also cause crusting. These lesions are frequently pruritic. Sometimes, this condition may be secondary to exposure to an allergen.

[000381] Atopic dermatitis is a more generalized form of eczematous dermatatitis which typically involves many areas of the skin and intense prurititis. This condition is often associated with a personal or family history of asthma, hay fever, or other allergies. Lesions are frequently distributed on the antecubital andpopliteal fosse, and on the wrist and neck. Eczematous dermatitis and atopic dermatitis are also known in the art as "eczema."

[000382] Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of eczematous dermatitis, as described above for the treatment of eczematous dermatitis. In some embodiments, such agents include botulinum toxin, glucocorticosteroids, coal tar, calcineurin inhibitors (*e.g.*, tacrolimus, pimecrolimus, *etc.*), antihistamines (*e.g.*, diphenhydramine, *etc.*), cyclosporine, interferon, omalizumab, rituximab, mycophenolate mofetil, AMG 157, JNJ-26113100, CD 2027, SUN13834, S-777469, GW842470X, TS022, roflumilast, calcipotriol, pitrakinra, and/or combinations thereof.

[000383] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of eczematous dermatitis of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of eczematous dermatitis of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of eczematous dermatitis

of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Excess Sebum-Producing Disorders

[000384] Excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*) are disorders affecting the areas of the skin that are rich in sebum glands, which typically include the scalp, face, and/or trunk. Patients with these conditions typically have scaly, flaky, erythematous, and often pruritic skin. Involvement of the scalp can result in hair loss. In some cases, the skin is also oily.

[000385] Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of excess sebum-producing disorders, as described above for the treatment of excess sebum-producing disorders. In some embodiments, such agents include botulinum toxin, salicylic acid, azelaic acid, selnium sulfide, imidazoles (*e.g.*, ketoconazole, miconazole, fluconazole, econazole, bifonazole, climazole, ciclopirox, ciclopiroxolamine, *etc.*), itraconazole, terbinafine, zinc pyrithione, benzoyl peroxide, coal tar, juniper tar, glucocorticosteroids (*e.g.*, hydrocortisone, *etc.*), metronidazole, lithium, calcineurin inhibitors (*e.g.*, tacrolimus, pimecrolimus, *etc.*), Vitamin D3, isotretinoin, and/or combinations thereof.

[000386] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of excess sebum production of at least about 25%; in some embodiments in an amount excess sebum production to achieve a reduction in the degree and/or prevalence of one or more symptoms of excess sebum production of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of excess sebum production of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about

49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Raynaud's Phenomenon

[000387] Raynaud's phenomenon is a vasospastic condition of the fingers and toes. Typically in response to cold or emotional stress, the skin of the fingers become discolored (white, blue, and/or red, often in this sequence) and painful. Severe Raynaud's can result in necrosis of the skin and ultimately the fingers and/or toes, resulting in "auto-amputation." Nails of Raynaud's patients may become brittle. This condition is frequently associated with connective tissue diseases such as scleroderma and/or rheumatoid arthritis.

[000388] Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of Raynaud's phenomenon, as described above for the treatment of Raynaud's phenomenon. In some embodiments, such agents include calcium channel blockers (*e.g.*, nifedipine, *etc.*), alpha blockers (*e.g.*, hydralazine, *etc.*), nitroglycerin, angiotensin II receptor antagonists (*e.g.*, losartan, *etc.*), selective serotonin reuptake inhibitors (*e.g.*, fluoxetine, *etc.*), glyceryl trinitrate, tadalafil, *Ginkgo biloba* extract, SLx-2101, St. John's Wort, fasudil, cilostazol, iloprost, relaxin, treprostinil diethanolamine, sildenafil, atorvastatin, imatinib mesylate, treprostinil diethanolamine, and/or combinations thereof.

[000389] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of Raynaud's phenomenon of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of Raynaud's phenomenon of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of Raynaud's phenomenon of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about

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65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Lupus Erthythematosus

[000390] Lupus erthythematosus is an autoimmune condition that may involve the skin as well as disease of multiple organ systems, including the brain and nervous system, kidneys, liver, and/or blood vessels. A lupus rash often involves the malar region of the face and is described as a "butterfly rash". Some patients exhibit thick, red, scaly patches of skin referred to as discoid lupus. Hair loss can also be a manifestation of the disease. Mouth, nasal and vaginal ulcers are also possible.

[000391] Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of lupus erthythematosus, as described above for the treatment of lupus erthythematosus. In some embodiments, such agents include nonsteriodal anti-inflammatory medications (*e.g.*, ibuprofen, *etc.*), aspirin, antimalarial drugs (*e.g.*, chloroquine, hydroxychloroquine, *etc.*), corticosteroids (*e.g.*, hydroxycortisone, *etc.*), immunosuprresive medications (*e.g.*, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, methotrexate, therapeutic antibodies, *etc.*), and/or combinations thereof.

[000392] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of lupus erthythematosus of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of lupus erthythematosus of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of lupus erthythematosus of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about

81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Hyperpigmentation Disorders

[000393] Hyperpigmentation disorders (*e.g.*, melasma, *etc.*) are disorders that result in focal or generalized abnormal darkening of the skin. Hyperpigmentation is often due to skin damage due to sun exposure, medications, and/or inflammation (including inflammation due to acne vulgaris). Melasma is a condition of dark, irregular patches of skin found most usually on the upper cheek, nose, lips, upper lip, and/or forehead. Melasma is often associated with pregnancy.

[000394] Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of hyperpigmentation disorders, as described above for the treatment of hyperpigmentation disorders. In some embodiments, such agents include botulinum toxin, phenols (*e.g.*, hydroxyquinone, mequinol, *etc.*), retinoids (*e.g.*, tretinoin, isotretinoin, *etc.*), alpha-hydroxy acids (*e.g.*, glycolic acid, salicyclic acid, azelaic acid, *etc.*) and/or combinations thereof.

[000395] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hyperpigmentation disorders of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hyperpigmentation disorders of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hyperpigmentation disorders of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Hypopigmentation Disorders

[000396] Hypopigmentation disorders (*e.g.*, vitiligo, etc.) are characterized by focal and/or generalized abnormal lightening of the skin. Vitiligo is characterized by a chronic focal loss of skin pigment and hence lightening of the skin. When skin lesions occur, they are most prominent on the face, hands and wrists. Depigmentation is particularly noticeable around body orifices, such as the mouth, eyes, nostrils, genitalia, and/or umbilicus.

[000397] Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of hypopigmentation disorders, as described above for the treatment of hypopigmentation disorders. In some embodiments, such agents include botulinum toxin, corticosteriods, calcineurin inhibitors (*e.g.*, tacrolimus, pimecrolimus, *etc.*), calcipotriol, psoralen, and/or combinations thereof.

[000398] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hypopigmentation disorders of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hypopigmentation disorders of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hypopigmentation disorders of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Skin Cancer

[000399] Skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*) is a malignant growth of skin tissue, often resulting in a visible tumor. Skin cancer may exhibit skin growths, changes in the skin that do not heal, ulceration of the skin, discolored skin, and/or changes to existing moles, such as the appearance of irregular edges to the mole and/or or an enlargement of the mole. Basal cell carcinoma usually looks like a raised, smooth, pearly bump on the sun-exposed skin of the head, neck, and/or shoulders. Occasionally,

small blood vessels can be seen within these tumors. Crusting and bleeding in the center of these tumors are frequently exhibited. Squamous cell carcinoma is commonly a red, scaling, thickened patch on sun-exposed skin. Ulceration and bleeding may be exhibited and when untreated, this form of skin cancer may develop into a large mass.

[000400] Pharmaceutical compositions in accordance with the present invention may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of skin cancer, as described above for the treatment of skin cancer. In some embodiments, such agents useful for treatment of squamous cell skin carcinoma include botulinum toxin, 5-aminolevulinic acid, 5-fluorouracil, acitretin, afamelanotide, API 31510, API 31510, cetuximab, dasatinib, eflornithine, erlotinib, GDC-0449, efitinib, HPPH, imiquinod, methyl aminolevulinate, PEG-interferon alfa-2a, PEP005, silicon phthalocyanine 4, tazarotene, tretinoin, verteporfin, and/or combinations thereof. In some embodiments, such agents useful for treatment of basal cell skin carcinoma include botulinum toxin, 5-aminolevulinic acid, 5-fluorouracil, acitretin, afamelanotide, API 31510, API 31510, cetuximab, dasatinib, eflornithine, erlotinib, GDC-0449, gefitinib, HPPH, imiquinod, methyl aminolevulinate, PEG-interferon alfa-2a, PEP005, silicon phthalocyanine 4, tazarotene, Tretinoin, verteporfin, and/or combinations thereof.

[000401] In some embodiments, the present invention involves administration of at least one therapeutic agent (*e.g.*, botulinum toxin) in a nanoparticle composition, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of skin cancer of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of skin cancer of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of skin cancer of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

Kits

[000402] In some embodiments, the present invention provides pharmaceutical packs or kits including nanoparticle compositions antigens according to the present invention. In certain embodiments, pharmaceutical packs or kits include preparations or pharmaceutical compositions containing nanoparticle compositions in one or more containers filled with optionally one or more additional ingredients of pharmaceutical compositions in accordance with the invention. In certain embodiments, the pharmaceutical pack or kit includes an additional approved therapeutic agent (*e.g.*, benzoyl peroxide for treatment of acne; aluminum compounds for treatment of hyperhidrosis; *etc.*) for use in combination therapies. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceutical products, which notice reflects approval by the agency of manufacture, use, or sale for human administration.

[000403] Kits are provided that include therapeutic reagents. As but one non-limiting example, nanoparticle compositions can be provided as topical formulations and administered as therapy. Pharmaceutical doses or instructions therefor may be provided in a kit for administration to an individual suffering from or at risk for conditions or disorders associated with the dermal level of the skin, including, but not limited to, acne, hyperhidrosis, bromhidrosis, chromhidrosis, rosacea, hair loss, actinic keratosis, psoriasis, eczematous dermatitis (*e.g.*, atopic dermatitis, *etc.*), excess sebum-producing disorders (*e.g.*, seborrhea, seborrheic dermatitis, *etc.*), Raynaud's phenomenon, lupus erythematosus, hyperpigmentation disorders (*e.g.*, melasma, *etc.*), hypopigmentation disorders (*e.g.*, vitiligo, *etc.*), skin cancer (*e.g.*, squamous cell skin carcinoma, basal cell skin carcinoma, *etc.*) and/or dermal infection (*e.g.*, fungal infection, herpes simplex virus infection, human papillomavirus infection, *etc.*).

[000404] In some embodiments, a kit may comprise (i) a nanoparticle composition; and (ii) at least one pharmaceutically acceptable excipient; and optionally (iii) at least one syringe, spatula, swab for administration to skin; and (iv) instructions for use.

[000405] The representative examples that follow are intended to help illustrate the invention, and are not intended to, nor should they be construed to, limit the scope of the invention. Indeed, various modifications of the invention and many further embodiments thereof, in addition to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including the examples which follow and the references to the scientific and patent literature cited herein. The following

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examples contain information, exemplification and guidance, which can be adapted to the practice of this invention in its various embodiments and the equivalents thereof.

Exemplification

[000406] The following examples are only intended to provide illustrations of specific embodiments contemplated by the present invention. The examples are not intended in any way to be limiting.

Example 1: Botulinum Nanoemulsion Formulation

[000407] This example presents one embodiment of nanoemulsion prepared by microfluidization comprising botulinum toxin (*i.e.*, for example, botulinum toxin type A, whether complexed or isolated).

[000408] A preparation for microfluidization was made as follows:

1. 5 g of soybean oil and 5 g of Tween 80 were mixed, heating as needed (typically not required) to emulsify the mixture.
2. 100 Units of botulinum toxin type A, was added to 100 mL of deionized/distilled water and stirred until evenly mixed.
3. Step 1 preparation was added to Step 2 preparation and stirred until evenly mixed.
4. Preparation was homogenized for 1 minute (see resulting particle distributions in Table 1 and Figure 1)
5. Single-pass microfluidization procedure at 21,000 psi was performed using a Microfluidizer® Processor.

[000409] The resulting nanoemulsion was evaluated for particle size using the Malvern Nano S particle sizer capable of sizing particles between about 0.6 nm and 6,000 nm. The botulinum nanoemulsion preparation had two particle size peaks having an average particle size of about 95 nm (Table 2 and Figure 2).

Table 1: Particle Size Distribution of a Homogenized Botulinum Microemulsion

		Diam. (nm)	% Intensity	Width (nm)
Z-Average: 3391	Peak 1	1512	100	76.6
PDI: 0.341	Peak 2	0	0	0
Intercept: 0.5852	Peak 3	0	0	0

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Table 2: Particle Size Distribution of a Microfluidized Botulinum Nanoemulsion

		Diam. (nm)	% Intensity	Width (nm)
Z-Average: 95.33	Peak 1	134.2	76.49	31.03
PDI: 0.252	Peak 2	44.97	23.51	6.34
Intercept: 0.9659	Peak 3	0	0	0

Example 2: Muscle Relaxant Effect of Transdermal Botulinum Toxin Nanoemulsions

[000410] This example demonstrates the therapeutic efficacy of transdermally applied botulinum nanoemulsions (*i.e.*, for example, a nanoemulsion containing botulinum toxin type A).

[000411] A botulinum nanoemulsion (9.9 U/100 µl), prepared in accordance with methods similar to Example 1 (*e.g.*, as described in co-pending U.S. Patent Application U.S.S.N. 11/607,436, entitled "BOTULINUM NANOEMULSIONS," filed December 1, 2006; incorporated herein by reference), was topically administered to the hind leg gastrocnemius muscle of ten (10) Swiss Webster female mice. A control group of ten (10) Swiss Webster female mice received an identically prepared nanoemulsion except that botulinum toxin was omitted. During the eleven days following treatment, the Digital Abduction Score (DAS) assay was used to determine local muscle weakening efficacy (Aoki, 1999), The DAS values were assigned as follows: (0) flat foot, digit spread same as control leg; (1) flat foot, a difference in the width of digit abduction compared to the control leg or two digits touching and the rest spread completely; (2) flat foot, slight space open at tips of all digits or three digits touching; (3) five digits touching if foot is flat; four digits together if foot is curved; (4) curved foot, all five digits touching. DAS scores of 1-2 were observed for the botulinum toxin nanoemulsion treated group but not in the control group, *i.e.*, the control had a DAS score of 0. Aggravation of the skin (*e.g.*, irritation, redness, *etc.*) was not observed at any time after treatment. The data show that a botulinum toxin nanoemulsion is biologically active upon transdermal administration in a manner similar to conventionally administered botulinum toxin injections.

Example 3: Administration of Botulinum Nanoparticle Composition to a Human Subject to Relieve Wrinkles

[000412] A topical botulinum nanoemulsion was prepared according to a method similar to Example 1 and applied to a person with significant forehead wrinkles to determine if it could be effective in relaxing the muscles in the forehead that generated those wrinkles (in much the same manner that would be expected from the injection of botulinum into those muscles).

Methods

[000413] A botulinum nanoemulsion was made employing steps similar to Example 1 (see, for example, those described in co-pending U.S. Patent Application U.S.S.N. 11/607,436, entitled "BOTULINUM NANOEMULSIONS," filed December 1, 2006; incorporated herein by reference).

[000414] The nanoemulsion was added to an equal volume of skin cream (Base PCCA Vanishing Cream Light) and was vortexed into a uniform cream.

[000415] A patient who had significant horizontal wrinkles over his forehead, representing overactivity of his frontalis muscles, was selected for treatment. This patient had never been treated with a botulinum product or a dermal filler product. The patient was assessed prior to treatment by a board-certified plastic surgeon using a 4-point wrinkle scale, with a score of "1" equal to "no wrinkle" and a score of "4" equal to significant wrinkle. The patient was assessed using this scale when his face was "At Rest" and when he attempted to create maximal wrinkles by contracting his frontalis muscles which was achieved by attempting to maximally elevate his eyebrows ("Maximal Brow Elevation").

[000416] This patient had a score of 4 at rest and 4 on maximal brow elevation. He demonstrated excellent mobility of being able to contract the frontalis muscles. The patient was photographed using a digital SLR camera as well as digital video, both At Rest and when asked to perform a Maximal Brow Elevation (Figure 3A, maximal brow elevation prior to treatment).

[000417] The patient was asked not to use any facial make-up or sun-screen on the day of treatment but wash his face prior to coming to the office with Ivory Soap. When at the office, 0.6 cc of the nanoemulsion cream (as prepared in Example 1) was applied to the patient's forehead over the distribution of his frontalis muscles by the plastic surgeon. The cream was applied to the patient's forehead skin by a pipette and rubbed into the skin by the surgeon using his finger (covered by a plastic glove) until the cream was no longer visible to the surgeon. The patient was observed at the physician's office for three hours. He was asked not to touch his forehead for 12 hours and then to wash it off with Ivory Soap and water. The patient was then observed on follow-up after 1 day and then at 1, 2, 4, 8, and 12 weeks. On

follow-up visits, the patient's wrinkles At Rest and at Maximal Brow Elevation were assessed by the physician. As well, the physician repeated standardized digital still photographs and video.

Results

[000418] By the first week after treatment, the patient was unable to contract his forehead muscles as evidenced by an inability to lift his brow on requested Maximal Brow Elevation (Figure 3B). His wrinkle score was 2 At Rest and 2 on Maximal Brow Elevation. The physician's clinical assessment was that the treatment had induced a complete paralysis of the treated muscles that was equivalent to treatments he had performed on other patients using injections of botulinum toxin in a similar treatment area. The patient had a slight restoration of brow mobility by Week 8 but continued to have a significant reduction in his brow mobility at Week 12 of observation.

[000419] The patient was able to move his other facial muscles under areas of skin not treated and no side-effects were observed by the plastic surgeon, including no changes to the skin immediately after treatment or in any follow-up visit. Likewise, the patient reported no side-effects, including any changes to his skin (*e.g.*, irritation, redness, *etc.*) at any time after treatment.

Conclusion

[000420] In sum, this experiment strongly suggests that the topical botulinum nanoemulsion preparation delivered a significant biological and clinical effect that was assessed by the plastic surgeon to be comparable in clinical efficacy to what would have been expected for following a standard treatment of injected botulinum (in a simple saline solution) for this patient.

Example 4: Botulinum Nanoparticle Compositions for Treatment of Hyperhidrosis

[000421] As already discussed herein, botulinum toxin type A (BOTOX®) was approved by the FDA in 2004 for the treatment of severe underarm sweating (*i.e.*, primary axillary hyperhidrosis). Small doses of purified botulinum toxin injected into the underarm temporarily block the nerves that stimulate sweating. Side effects include injection-site pain and flu-like symptoms. BOTOX® used for sweating of the palms can cause mild, but temporary, weakness and intense pain during and after injection.

[000422] The present invention provides, among other things, improved botulinum toxin therapies for the treatment of hyperhidrosis. Moreover, in demonstrating effective and

efficient transdermal delivery of botulinum toxin for the treatment of hyperhidrosis without unwanted clinical effects associated with such delivery (*e.g.*, one or more of systemic side effects, damage to underlying nervous tissue [*e.g.*, neuronal paralysis], unwanted effects on muscles [*e.g.*, muscle paralysis], undesirable blood levels, flu-like symptoms, *etc.*)., the present invention demonstrates the appropriateness of treating other disorders or conditions associated with sweat or sebaceous glands (*e.g.*, acne, bromhidrosis, chromhidrosis, *etc.*) with botulinum toxin nanoparticle compositions as described herein and/or in United States patent application serial number 11/607,436 (entitled "BOTULINUM NANOEMULSIONS," filed December 1, 2006) (see, for example, Example 5). Furthermore, the data presented herein demonstrate effective and efficient delivery of botulinum toxin to the dermis (which houses the sweat and sebaceous glands). The present invention therefore also demonstrates the usefulness of botulinum nanoparticle compositions as described herein and/or in United States patent application serial number 11/607,436 in the treatment of other disorders and conditions associated with the dermis, or defects therein. For example, as addressed below in Example 6, which describes use of botulinum nanoparticle compositions in the treatment of rosacea.

Materials and Methods

Botulinum toxin nanoparticle composition

[000423] A nanoemulsion containing botulinum toxin type A prepared as described in Example 1 or in co-pending U.S. Patent Application U.S.S.N. 11/607,436, entitled "BOTULINUM NANOEMULSIONS," filed December 1, 2006 was used in the treatment of hyperhidrosis as described in this Example.

Selection of Subjects

[000424] Inclusion criteria include the following: a) diagnosis of primary axillary hyperhidrosis; b) a Hyperhidrosis Disease Severity Score ("HDSS") of 3 or 4; and c) 50 mg of sweat production per axilla in 5 minutes as measured gravimetrically.

Experimental Design

[000425] Three subjects received a topical treatment containing 80 Units of an approved botulinum pharmaceutical formulated in a nanoparticle composition similar to the prior examples.

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Treatment Procedure

[000426] The clinical investigator wiped each axilla of the subject with an alcohol wipe and then wiped dry with cotton gauze. Using a latex-gloved finger, the investigator massaged the topical treatment into the skin of the axilla in the distribution area of the axillary sweat glands. This procedure was completed when there is no topical treatment visible on the surface of the skin. This procedure was employed for the right and left axillary regions.

Study Duration

[000427] Subjects who received the drug treatment were evaluated prior to treatment (Week 0) and at Week 2 following treatment.

Study Visits

[000428] During the first office visit and the Week 2 follow-up visit, the Hyperhidrosis Disease Severity Scale questionnaire ("HDSS questionnaire") was administered to the subjects. This questionnaire is a four point scale, where a score of 1 is the least severe sweating and 4 is most severe sweating. Each subject's sweat production for each axilla was measured using the Gravimetric Sweat Test by placing the subject in a room with relatively constant temperature and humidity, and a) having him or her sit down in a semi-reclining position with the axilla fully exposed and the arm resting comfortably above the head; b) drying the axilla gently with a cotton gauze square; c) using a forceps, placing one filter paper (90 mm diameter) on a balance sensitive to 0.01 mg and recording its weight; d) again using a forceps, placing the measured filter paper on the axilla, covering it with a plastic bag, and taping the edges of the bag against the subject's skin with hypoallergenic tape, forming a seal around the bag; and e) after 5 minutes, gently removing the tape and plastic bag from the subject's axilla and then, using forceps, immediately taking the filter paper from the axilla and placing it onto the scale to record its weight again.

[000429] Finally, the starch-iodine test ("Starch-Iodine Test") was administered to the subject by maintaining the subject in a semi-reclining position, with the axilla fully exposed and the arm resting comfortably above the head and a) drying the axilla with cotton gauze; (b) applying povidine solution with a swab to the axilla to create a thin coat and letting it dry; (c) sprinkling starch powder to the area coated with povidine; (d) having the subject rest in this position for 10 minutes; and (e) photographing the axilla from about 1 foot away, with minimal background in the frame.

Results

Gravimetric Sweat Test

[000430] Baseline Sweat Production Levels

[000431] The three subjects whose results are described below had an average baseline gravimetric sweat production over a five minute period of 368 mg (entry criterion was 50 mg or greater).

Table 3: Gravimetric Sweat Reduction @ 80 Unit/Axilla Dose

	At two weeks
Subject #1	71%
Subject #2	71%
Subject #3	68%

HDSS Assessment

Table 4: HDSS Reduction @ 80 Unit/Axilla Dose

	At two weeks
Subject #1	2.0 points
Subject #2	2.0 point
Subject #3	1.0 point

Minor's Starch-Iodine Test

[000432] Generally, as reflected in the Minor's Starch-Iodine Test, subjects demonstrated a reduction in sweat production across the area of the axilla with the exception of punctate areas (darkened spots) where there was "break-through" sweating. Figure 4a illustrates a subject prior to treatment where the darkened skin areas and sweat demonstrate profuse sweating at rest; Figure 4b illustrates a subject two weeks following treatment demonstrating a profound diminishment of sweating at rest as demonstrated by the minor areas of skin darkening.

Discussion

[000433] The interim results of this study with three subjects studied suggest that botulinum nanoparticle compositions are effective in treating hyperhidrosis without any unwanted side-effects. In particular, the results show efficacy as evaluated by gravimetric sweat

measurement, HDSS assessment, and Minor's starch iodine test. In this three-person study, the average maximal gravimetric sweat measurement reduction with a treatment of 80 Units/axilla was 70% at two weeks. By comparison, injected botulinum toxin (50 Units/axilla) achieved an average response rate of 83% in a large placebo-controlled trial (Naumann, 2001). Also by comparison, placebo rates in published controlled studies have an average of 15% – 25% reduction. The initial response observed herein far exceeded expected placebo rates, and therefore, demonstrated a true treatment response. By clinical observation and questioning of the subjects, none of the subjects had any side-effects, including muscular weakness and flu-like symptoms.

[000434] While the gravimetric sweat test demonstrated substantial objective reductions in sweat production, some subjects had some focal areas of the sweat gland distribution that had "break-through" sweating as reflected in the Minor's starch iodine test. By comparison, this same phenomenon is observed in standard botulinum injection treatment; often the first treatment round does not adequately treat all sweat glands, that then requires a second more focal treatment. The variable subjective response – as measured by the HDSS – is likely being modulated by the degree of the break-through sweat gland phenomenon in an individual subject. A few sub-optimally treated sweat glands may influence a subjective impression of an individual subject despite a substantial overall reduction in sweating.

[000435] In the present example, patients were administered 80 U of botulinum toxin per dose per axilla, and the nanoparticle composition comprising this dose was applied to a surface area that is estimated to be approximately 30 cm^2 to 40 cm^2 (as contrasted with, for example, a surface area of approximately 4 cm^2 for treatment of sub-dermal muscle structures which cause peri-orbital ["Crow's Feet"] wrinkles.)

[000436] In sum, the results of this study suggested that response rates for this topical botulinum treatment are promising when considered in their own right and when compared to either injectable treatments or placebo.

[000437] Moreover, the results of this study demonstrate effective and efficient delivery of botulinum toxin to areas of the skin including sebaceous glands using inventive nanoparticle compositions. The surprising ability to introduce a significant reduction in sweating without unwanted side-effects reveals a degree of success that demonstrates the applicability of this technology to other gland-based disorders and conditions. For example, these results well illustrate the usefulness of botulinum toxin nanoparticle compositions in accordance with the invention in the treatment of disorders or conditions such as acne, bromhidrosis, and/or chromhidrosis. Furthermore, these results demonstrate effective transdermal delivery of

botulinum toxin to the dermis using nanoparticle compositions, and therefore demonstrate usefulness of such compositions in the treatment of disorders and conditions of the dermis such as rosacea.

Example 5: Botulinum Nanoparticle Compositions for Treatment of Acne

Materials and Methods

Selection of Subjects

[000438] Inclusion criteria include a diagnosis of acne.

Experimental Design

[000439] A pre-determined number of subjects (*e.g.*, 2, 4, 8, 10, 12, 14, 16, 18, 20, or more) receives a topical treatment containing a botulinum pharmaceutical in a preparation similar to the prior examples. If no significant adverse events are observed with a starting dose of treatment (*e.g.*, 20, 30, 40, 50, 60, 75, 80, or 100 Units) at a pre-determined endpoint (*e.g.*, 4, 6, 8, 10, or 12 weeks after treatment), a second group of different subjects of a similar size to the first group receives a topical treatment containing a higher dose (*e.g.*, 30, 40, 50, 60, 75, 80, 100, 120, 125, 150, 160, 175, 200, 240, 250, 300, 350, 400, 500, 600, 800, or 1,000 Units) of a botulinum pharmaceutical in a preparation similar to the prior examples. If no significant adverse events are observed with the second group of subjects, a third group of subjects of similar size is treated at a higher dose than the second group of subjects (*e.g.*, 40, 50, 60, 75, 80, 100, 120, 125, 150, 160, 175, 200, 240, 250, 300, 350, 400, 500, 600, 800, or 1,000 Units) using a botulinum pharmaceutical in a preparation similar to the prior examples.

Treatment Procedure

[000440] The clinical investigator wipes a region affected by acne with an alcohol wipe and then wipe dry with cotton gauze. Using a latex-gloved finger, the investigator massages the topical treatment into the skin. This procedure is completed when there is no topical treatment visible on the surface of the skin.

Study Duration

[000441] Subjects are evaluated prior to treatment (Week 0) and 2, 4, 8, 12, and 16 weeks after treatment.

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Study Visits

[000442] During the first office visit and the follow-up office visits, the study investigator evaluates the treatment region for number of open comedomes, closed comedomes, raised lesions, papules, pustules, lesion with erythema, and cysts.

Results

[000443] The study shows that the area of treatment is significantly improved on at least one of the follow-up office observation visits when compared to pre-treatment levels for at least some of the number of open comedomes, closed comedomes, raised lesions, papules, pustules, lesion with erythema, and cysts for treatment with at least one of the dose levels selected for study.

[000444] Based on these results, the investigator concludes that topical botulinum treatment in accordance with the invention is effective in treating acne.

Example 6: Botulinum Nanoparticle Compositions for Treatment of Rosacea

Materials and Methods

Selection of Subjects

[000445] Inclusion criteria includes a diagnosis of rosacea.

Experimental Design

[000446] A pre-determined number of subjects (*e.g.*, 2, 4, 8, 10, 12, 14, 16, 18, 20, or more) receives a topical treatment containing a botulinum pharmaceutical in a preparation similar to the prior examples. If no significant adverse events are observed with a starting dose of treatment (*e.g.*, 20, 30, 40, 50, 60, 75, 80, or 100 Units) at a pre-determined endpoint (*e.g.*, 4, 6, 8, 10, or 12 weeks after treatment), a second group of different subjects of a similar size to the first group receives a topical treatment containing a higher dose (*e.g.*, 30, 40, 50, 60, 75, 80, 100, 120, 125, 150, 160, 175, 200, 240, 250, 300, 350, 400, 500, 600, 800, or 1,000 Units) of a botulinum pharmaceutical in a preparation similar to the prior examples. If no significant adverse events are observed with the second group of subjects, a third group of subjects of similar size is treated at a higher dose than the second group of subjects (*e.g.*, 40, 50, 60, 75, 80, 100, 120, 125, 150, 160, 175, 200, 240, 250, 300, 350, 400, 500, 600, 800, or 1,000 Units) using a botulinum pharmaceutical in a preparation similar to the prior examples.

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Treatment Procedure

[000447] The clinical investigator wipes the surface of the affected skin area with an alcohol wipe and then wipes it dry with cotton gauze. Using a latex-gloved finger, the investigator massages the topical treatment into the skin. This procedure is completed when there is no topical treatment visible on the surface of the skin.

Study Duration

[000448] Subjects are evaluated prior to treatment (Week 0) and 2, 4, 8, 12, and 16 weeks after treatment.

Study Visits

[000449] During the first office visit and the four week follow-up office visit, the study investigator evaluates the treatment region in terms of Investigator Global Assessment (using, for example, a seven point scale with 0 = clear, 1 = minimal, 2 = mild to moderate, 4 = moderate, 5 = moderate to severe, and 6 = severe); Subject Global Self-Assessment (using, for example, a nine point scale from 100% worse to no change to 100% improved as measured in 25% increments); and erythema intensity and teleangiectasis intensity (each using, for example, a four point scale from 1 = none, 2 = mild, 3 = moderate, and 4 = severe).

Results

[000450] The study shows that the area of treatment is significantly improved on at least one of the follow-up office observation visits when compared to pre-treatment levels for at least some of the number of Investigator Global Assessment, Subject Global Self-Assessment, erythema intensity or teleangiectasis intensity for treatment with one or more of the applied strengths of botulinum.

[000451] Based on these results, the investigator concludes that the inventive topical botulinum treatment was effective in treating rosacea.

Example 7: Clindamycin Nanoparticle Compositions for Treatment of Acne

Materials and Methods

Selection of Subjects

[000452] Inclusion criteria includes a diagnosis of acne.

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Experimental Design

[000453] A pre-determined number of subjects, *e.g.*, 2, 4, 8, 10, 12, 14, 16, 18, or 20, receives a topical treatment containing a clindamycin pharmaceutical in a preparation similar to the prior examples. If no significant adverse events are observed with a starting dose of, *e.g.*, 0.05%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, or 1.0% treatment (applied in a pre-determined manner once, twice, or three times per day) at a pre-determined endpoint (*e.g.*, 4, 6, 8, 10, or 12 weeks after treatment), a second group of different subjects of a similar size to the first group receive a topical treatment containing a higher dose, *e.g.*, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.5%, 2.0%, 2.5%, or 5% of a clindamycin pharmaceutical in a preparation similar to the prior examples applied with the same frequency per day as the first group. If no significant adverse events are observed with the second group of subjects, a third group of subjects of similar size is treated at a higher dose than the second group of subjects (*e.g.*, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.5%, 2.0%, 2.5%, 5%) using a clindamycin pharmaceutical in a preparation similar to the prior examples applied with the same frequency per day as the first group.

Treatment Procedure

[000454] After wiping a region affected by acne with soap and water and then drying, the subject massages the topical treatment into the skin at the pre-determined frequency of once, twice or three times per day. This procedure is completed when there is no topical treatment visible on the surface of the skin.

Study Duration

[000455] Subjects are evaluated prior to treatment (Week 0) and 2, 4, 8, 12, and 16 weeks after treatment.

Study Visits

[000456] During the first office visit and the follow-up office visits, the study investigator evaluates the treatment region for number of open comedomes, closed comedomes, raised lesions, papules, pustules, lesion with erythema, and cysts.

Results

[000457] The study shows that the area of treatment is significantly improved compared to pre-treatment levels for at least some of the number of open comedomes, closed comedomes,

raised lesions, papules, pustules, lesion with erythema, and cysts on at least one of the follow-up examination office visits following treatment with one of the dose levels selected of the preparations.

[000458] Based on these results, the investigator concludes that the inventive topical clindamycin treatment was effective in treating acne.

Example 8: Azelaic Acid Nanoparticle Compositions for Treatment of Rosacea

Materials and Methods

Selection of Subjects

[000459] Inclusion criteria includes a diagnosis of rosacea.

Experimental Design

[000460] A pre-determined number of subjects, *e.g.*, 2, 4, 8, 10, 12, 14, 16, 18, or 20, receives a topical treatment containing an azelaic acid pharmaceutical in a preparation similar to the prior examples. If no significant adverse events are observed with a starting dose of, *e.g.*, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, or 10% treatment (applied in a pre-determined manner once, twice, or three times per day) at a pre-determined endpoint (*e.g.*, 4, 6, 8, 10, or 12 weeks after treatment), a second group of different subjects of a similar size to the first group receive a topical treatment containing a higher dose, *e.g.*, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13% 14%, 15%, 20%, 25% of an azelaic acid pharmaceutical in a preparation similar to the prior examples applied with the same frequency per day as the first group. If no significant adverse events are observed with the second group of subjects, a third group of subjects of similar size is treated at a higher dose than the second group of subjects (*e.g.*, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.5%, 2.0%, 2.5%, 5%) using an azelaic acid pharmaceutical in a preparation similar to the prior examples applied with the same frequency per day as the first group.

Treatment Procedure

[000461] After washing the treatment area with soap and water and then drying, the subject massages the topical treatment into the skin at a pre-determined frequency of once, twice or three times per day. This procedure is completed when there is no topical treatment visible on the surface of the skin.

Study Duration

[000462] Subjects are evaluated prior to treatment (Week 0) and 2, 4, 8, 12, and 16 weeks after treatment.

Study Visits

[000463] During the first office visit and the follow-up office visit, the study investigator evaluates the treatment region of the nose in terms of Investigator Global Assessment (using, for example, a seven point scale with 0 = clear, 1 = minimal, 2 = mild to moderate, 4 = moderate, 5 = moderate to severe, and 6 = severe); Subject Global Self-Assessment (using, for example, a nine point scale from 100% worse to no change to 100% improved as measured in 25% increments); and erythema intensity and teleangiectasis intensity (each using, for example, a four point scale from 1 = none, 2 = mild, 3 = moderate, and 4 = severe).

Results

[000464] The study show that the area of treatment is significantly improved compared to pre-treatment levels for at least some of the number of Investigator Global Assessment, Subject Global Self-Assessment, erythema intensity or teleangiectasis intensity on at least one of the follow-up examination visits following treatment with one more of the selected dose levels.

[000465] Based on these results, the investigator concludes that the inventive topical azelaic acid treatment is effective in treating rosacea.

Equivalents and Scope

[000466] The foregoing has been a description of certain non-limiting embodiments in accordance with the invention. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments described herein. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

[000467] In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the

context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention also includes embodiments in which more than one or all of the group members are present in, employed in, or otherwise relevant to a given product or process. Furthermore, it is to be understood that the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, descriptive terms, *etc.*, from one or more of the claims or from relevant portions of the description is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Furthermore, where the claims recite a composition, it is to be understood that methods of using the composition for any of the purposes disclosed herein are included, and methods of making the composition according to any of the methods of making disclosed herein or other methods known in the art are included, unless otherwise indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise. In addition, the invention encompasses compositions made according to any of the methods for preparing compositions disclosed herein.

[000468] Where elements are presented as lists, *e.g.*, in Markush group format, it is to be understood that each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It is also noted that the term "comprising" is intended to be open and permits the inclusion of additional elements or steps. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements, features, steps, *etc.*, certain embodiments or aspects consist, or consist essentially of, such elements, features, steps, *etc.* For purposes of simplicity those embodiments have not been specifically set forth *in haec verba* herein. Thus for each embodiment that comprises one or more elements, features, steps, *etc.*, the invention also provides embodiments that consist or consist essentially of those elements, features, steps, *etc.*

[000469] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and/or the understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value within the stated ranges in different embodiments, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise. It is also to be understood that unless otherwise indicated or otherwise evident from the context and/or the understanding of one of ordinary skill in the art, values expressed as ranges can assume

any subrange within the given range, wherein the endpoints of the subrange are expressed to the same degree of accuracy as the tenth of the unit of the lower limit of the range.

[000470] In addition, it is to be understood that any particular embodiment may be explicitly excluded from any one or more of the claims. Any embodiment, element, feature, application, or aspect of the compositions and/or methods (*e.g.*, any dermal gland disorder, any botulinum toxin, any oil, any surfactant, any dispersion medium, any nanoparticle or composition comprising any nanoparticle, any method of manufacturing nanoparticles, any route or location of administration, any purpose for which a composition is administered, *etc.*), can be excluded from any one or more claims. For purposes of brevity, all of the embodiments in which one or more elements, features, purposes, or aspects are excluded are not set forth explicitly herein.

Claims

We claim:

1. A method comprising steps of:

identifying a patient exhibiting at least one symptom of a disorder associated with the dermal level of the skin; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein the nanoemulsion comprises at least one therapeutic agent.

2. A method comprising steps of:

providing a patient exhibiting at least one symptom of acne; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein the nanoemulsion comprises at least one therapeutic agent.

3. A method comprising steps of:

identifying a patient exhibiting at least one symptom of hyperhidrosis; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein the nanoemulsion comprises at least one therapeutic agent.

4. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of about 50%.

5. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of about 60%.

6. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of about 70%.

7. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of about 75%.

8. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of about 80%.

9. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of about 85%.

10. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of about 90%.

11. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of about 95%.

12. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of about 98%.

13. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of about 99%.

14. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of at least 50%.

15. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of at least 60%.

16. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of at least 70%.

17. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of at least 75%.

18. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of at least 80%.

19. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of at least 85%.

20. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of at least 90%.

21. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of at least 95%.

22. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of at least 98%.

23. The method of claim 3, wherein the nanoemulsion is administered in an amount sufficient to achieve a sweat reduction of at least 99%.

24. A method comprising steps of:

providing a patient exhibiting at least one symptom of bromhidrosis; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

25. A method comprising steps of:

identifying a patient exhibiting at least one symptom of chromhidrosis; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

26. A method comprising steps of:

identifying a patient exhibiting at least one symptom of rosacea; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority

of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

27. A method comprising steps of:

identifying a patient exhibiting at least one symptom of hair loss; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

28. A method comprising steps of:

identifying a patient exhibiting at least one symptom of psoriasis; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

29. A method comprising steps of:

identifying a patient exhibiting at least one symptom of dermal infection; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

30. A method comprising steps of:

identifying a patient exhibiting at least one symptom of actinic keratosis; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

31. A method comprising steps of:

identifying a patient exhibiting at least one symptom of eczematous dermatitis; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

32. A method comprising steps of:

identifying a patient exhibiting at least one symptom of an excess sebum-producing disorder; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

33. A method comprising steps of:

identifying a patient exhibiting at least one symptom of Raynaud's phenomenon; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

34. A method comprising steps of:

identifying a patient exhibiting at least one symptom of lupus erthythematosus; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

35. A method comprising steps of:

identifying a patient exhibiting at least one symptom of a hyperpigmentation disorder; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

36. A method comprising steps of:

identifying a patient exhibiting at least one symptom of a hypopigmentation disorder; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

37. A method comprising steps of:

identifying a patient exhibiting at least one symptom of skin cancer; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

38. A method comprising steps of:

identifying a patient exhibiting at least one symptom of a dermal infection; and

administering a nanoemulsion to the patient's skin so that at least one of the symptoms is reduced,

wherein the nanoemulsion comprises a population of particles, wherein the majority of particles have diameters between approximately 10 and approximately 300 nanometers, and wherein said nanoemulsion comprises at least one therapeutic agent.

39. The method of any one of claims 1 – 38, wherein the nanoemulsion is administered to the patient's skin without significant unwanted side-effects.

40. The method of any one of claims 1 – 38, wherein administration of the nanoemulsion to the patient's skin reduces at least one unwanted side effect by about 50% relative to injection or oral administration of the same therapeutic agent.

41. The method of any one of claims 1 – 38, wherein administration of the nanoemulsion to the patient's skin reduces at least one unwanted side effect by about 60% relative to injection oral administration of the same therapeutic agent.

42. The method of any one of claims 1 – 38, wherein administration of the nanoemulsion to the patient's skin reduces at least one unwanted side effect by about 70% relative to injection oral administration of the same therapeutic agent.

43. The method of any one of claims 1 – 38, wherein administration of the nanoemulsion to the patient's skin reduces at least one unwanted side effect by about 80% relative to injection oral administration of the same therapeutic agent.

44. The method of any one of claims 1 – 38, wherein administration of the nanoemulsion to the patient's skin reduces at least one unwanted side effect by about 90% relative to injection oral administration of the same therapeutic agent.

45. The method of any one of claims 1 – 38, wherein administration of the nanoemulsion to the patient's skin reduces at least one unwanted side effect by about 95% relative to injection oral administration of the same therapeutic agent.

46. The method of any one of claims 40 – 46, wherein the unwanted side effect is selected from the group consisting of bruising, hematoma, pain, ecchymosis, unwanted systemic effects, undesirable blood levels, botulism, damage to underlying nervous tissue, neuronal paralysis, unwanted effects on muscles, muscle paralysis, and flu-like symptoms.

47. The method of any one of claims 1 – 38, wherein the majority of particles have a range of diameters between approximately 10 and approximately 250 nanometers.

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48. The method of any one of claims 1 – 38, wherein the majority of particles have a range of diameters between approximately 10 and approximately 200 nanometers.

49. The method of any one of claims 1 – 38, wherein the majority of particles have a range of diameters between approximately 10 and approximately 150 nanometers.

50. The method of any one of claims 1 – 38, wherein the majority of particles have a range of diameters between approximately 10 and approximately 120 nanometers.

51. The method of any one of claims 1 – 38, wherein the majority of particles have a range of diameters between approximately 10 and approximately 100 nanometers.

52. The method of any one of claims 1 – 38, wherein the majority of particles have a range of diameters between approximately 10 and approximately 50 nanometers.

53. The method of any one of claims 1 – 38, wherein the population of particles is substantially free of particles having a diameter in excess of 300 nm.

54. The method of any one of claims 1 – 38, wherein fewer than 50% of the particles have a diameter in excess of 300 nm.

55. The method of any one of claims 1 – 38, wherein fewer than 25% of the particles have a diameter in excess of 300 nm.

56. The method of any one of claims 1 – 38, wherein fewer than 10% of the particles have a diameter in excess of 300 nm.

57. The method of any one of claims 1 – 38, wherein fewer than 5% of the particles have a diameter in excess of 300 nm.

58. The method of any one of claims 1 – 38, wherein fewer than 1% of the particles have a diameter in excess of 300 nm.

59. The method of any one of claims 1 – 38, wherein the population of particles is substantially free of particles having a diameter in excess of 200 nm.

60. The method of any one of claims 1 – 38, wherein fewer than 50% of the particles have a diameter in excess of 200 nm.

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61. The method of any one of claims 1 – 38, wherein fewer than 25% of the particles have a diameter in excess of 200 nm.

62. The method of any one of claims 1 – 38, wherein fewer than 10% of the particles have a diameter in excess of 200 nm.

63. The method of any one of claims 1 – 38, wherein fewer than 5% of the particles have a diameter in excess of 200 nm.

64. The method of any one of claims 1 – 38, wherein fewer than 1% of the particles have a diameter in excess of 200 nm.

65. The method of any one of claims 1 – 38, wherein the population of particles is substantially free of particles having a diameter in excess of 120 nm.

66. The method of any one of claims 1 – 38, wherein fewer than 50% of the particles have a diameter in excess of 120 nm.

67. The method of any one of claims 1 – 38, wherein fewer than 25% of the particles have a diameter in excess of 120 nm.

68. The method of any one of claims 1 – 38, wherein fewer than 10% of the particles have a diameter in excess of 120 nm.

69. The method of any one of claims 1 – 38, wherein fewer than 5% of the particles have a diameter in excess of 120 nm.

70. The method of any one of claims 1 – 38, wherein fewer than 1% of the particles have a diameter in excess of 120 nm.

71. The method of any one of claims 1 – 38, wherein the difference between the minimum particle diameter and the maximum particle diameter does not exceed approximately 600 nm.

72. The method of any one of claims 1 – 38, wherein the difference between the minimum particle diameter and the maximum particle diameter does not exceed approximately 500 nm.

73. The method of any one of claims 1 – 38, wherein the difference between the minimum particle diameter and the maximum particle diameter does not exceed approximately 400 nm.

74. The method of any one of claims 1 – 38, wherein the difference between the minimum particle diameter and the maximum particle diameter does not exceed approximately 300 nm.

75. The method of any one of claims 1 – 38, wherein the difference between the minimum particle diameter and the maximum particle diameter does not exceed approximately 200 nm.

76. The method of any one of claims 1 – 38, wherein the difference between the minimum particle diameter and the maximum particle diameter does not exceed approximately 100 nm.

77. The method of any one of claims 1 – 38, wherein the difference between the minimum particle diameter and the maximum particle diameter does not exceed approximately 50 nm.

78. The method of any one of claims 1 – 38, wherein the particles have an average diameter of 300 nm.

79. The method of any one of claims 1 – 38, wherein the particles have an average diameter of 200 nm.

80. The method of any one of claims 1 – 38, wherein the particles have an average diameter of 150 nm.

81. The method of any one of claims 1 – 38, wherein the particles have an average diameter of 100 nm

82. The method of any one of claims 1 – 38, wherein the particles have an average diameter of 75 nm.

83. The method of any one of claims 1 – 38, wherein the particles have an average diameter of 50 nm.

84. The method of any one of claims 1 – 38, wherein the particles have an average diameter ranging between 100 – 300 nm.

85. The method of any one of claims 1 – 38, wherein the particles have an average diameter ranging between 50 – 250 nm.

86. The method of any one of claims 1 – 38, wherein the particles have an average diameter ranging between 60 – 200 nm.

87. The method of any one of claims 1 – 38, wherein the particles have an average diameter ranging between 65 – 150 nm.

88. The method of any one of claims 1 – 38, wherein the particles have an average diameter ranging between 70 – 130 nm.

89. The method of any one of claims 1 – 38, wherein the particles have an average diameter ranging between 80 – 110 nm.

90. The method of any one of claims 1 – 38, wherein the particles have an average diameter ranging between 90 – 100 nm.

91. The method of any one of claims 1 – 38, wherein the particles have an average diameter ranging between 10 – 100 nm.

92. The method of any one of claims 1 – 38, wherein the particles have an average diameter ranging between 25 – 100 nm.

93. The method of any one of claims 1 – 38, wherein the particles have an average diameter ranging between 50 – 100 nm.

94. The method of any one of claims 1 – 38, wherein the particles have an average diameter ranging between 75 – 100 nm.

95. The method of any one of claims 1 – 38, wherein the nanoemulsion is substantially free of toxic solvents.

96. The method of any one of claims 1 – 38, wherein the nanoemulsion comprises less than 50% of toxic solvents.

97. The method of any one of claims 1 – 38, wherein the nanoemulsion comprises less than 25% of toxic solvents.

98. The method of any one of claims 1 – 38, wherein the nanoemulsion comprises less than 10% of toxic solvents.

99. The method of any one of claims 1 – 38, wherein the nanoemulsion comprises less than 5% of toxic solvents.

100. The method of any one of claims 1 – 38, wherein the nanoemulsion comprises less than 1% of toxic solvents.

101. The method of any one of claims 1 – 38, wherein the nanoemulsion is stable.

102. The method of any one of claims 1 – 38, wherein the majority of particles are stable for at least 1 day.

103. The method of any one of claims 1 – 38, wherein the majority of particles are stable for at least 2 weeks.

104. The method of any one of claims 1 – 38, wherein the majority of particles are stable for at least 2 months.

105. The method of any one of claims 1 – 38, wherein the majority of particles are stable for at least 5 months.

106. The method of any one of claims 1 – 38, wherein the majority of particles are stable for at least 12 months.

107. The method of any one of claims 1 – 38, wherein the majority of particles are stable for at least 24 months.

108. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by exposure to high shear force.

109. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by exposure to high shear force for less than 10 minutes.

110. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by exposure to high shear force for less than 2 minutes.

111. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by exposure to high shear force for less than 1 minute.

112. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by exposure to high shear force for less than 30 seconds.

113. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by exposure to pressures greater than 3,000 psi.

114. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by exposure to pressures greater than 10,000 psi.

115. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by exposure to pressures greater than 18,000 psi.

116. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by exposure to pressures greater than 24,000 psi.

117. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by exposure to pressures greater than 30,000 psi.

118. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by exposure to pressures greater than 40,000 psi.

119. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by microfluidization.

120. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by microfluidization at a pressure greater than 3,000 psi.

121. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by microfluidization at a pressure greater than 10,000 psi.

122. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by microfluidization at a pressure greater than 18,000 psi.

123. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by microfluidization at a pressure greater than 21,000 psi.

124. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by microfluidization at a pressure greater than 24,000 psi.

125. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by microfluidization at a pressure greater than 30,000 psi.

126. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by microfluidization at a pressure greater than 40,000 psi.

127. The method of any one of claims 119 – 126, wherein the microfluidization is single-pass microfluidization.

128. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by cavitation.

129. The method of any one of claims 1 – 38, wherein the nanoemulsion was generated by high pressure homogenization.

130. The method of any one of claims 1 – 38, wherein the therapeutic agent is botulinum toxin.

131. The method of claim 130, wherein the botulinum toxin is encapsulated within the particles.

132. The method of claim 130, wherein the botulinum toxin is adsorbed on the surface of the particles.

133. The method of claim 130, wherein the botulinum toxin is associated with the particle interface.

134. The method of claim 130, wherein the botulinum toxin is selected from the group comprising type A, type B, type C1, type C2, type D, type E, type F, and type G.

135. The method of claim 130, wherein the botulinum toxin is type A botulinum toxin.

136. The method of claim 130, wherein the botulinum toxin is a botulinum toxin complex.

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137. The method of claim 136, wherein the botulinum toxin complex comprises a non-toxin hemagglutinin protein or a non-toxic non-hemagglutinin protein.

138. The method of claim 130, wherein the botulinum toxin is incorporated within an albumin matrix.

139. The method of claim 138, wherein the albumin is human albumin.

140. The method of claim 130, wherein the botulinum toxin is not incorporated within an albumin matrix.

141. The method of claim 130, wherein the botulinum toxin is a purified botulinum toxin protein or fragment thereof.

142. The method of claim 130, wherein the botulinum toxin is isolated, or substantially isolated, from other proteins.

143. The method of claim 130, wherein the botulinum toxin is isolated, or substantially isolated, from non-toxin proteins.

144. The method of claim 130, wherein the botulinum toxin is isolated from *Clostridium botulinum*.

145. The method of claim 130, wherein the botulinum toxin is chemically synthesized.

146. The method of claim 130, wherein the botulinum toxin is produced recombinantly.

147. The method of claim 130, wherein the botulinum toxin contains at least one mutation relative to the wild-type toxin.

148. The method of claim 130, wherein the botulinum toxin is a fragment of a wild-type toxin.

149. The method of any one of claims 1 – 38, wherein the therapeutic agent is a polypeptide.

150. The method of any one of claims 1 – 38, wherein the therapeutic agent is a nucleic acid.

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151. The method of any one of claims 1 – 38, wherein the therapeutic agent is a lipid.

152. The method of any one of claims 1 – 38, wherein the therapeutic agent is a carbohydrate.

153. The method of any one of claims 1 – 38, wherein the therapeutic agent is a small molecule.

154. The method of any one of claims 1 – 38, wherein the therapeutic agent is selected from the group consisting of botulinum toxin type A, botulinum toxin type B, botulinum toxin type C_1, botulinum toxin type C_2, botulinum toxin type D, botulinum toxin type E, botulinum toxin type F, botulinum toxin type G, a topical bactericidal, benzoyl peroxide, triclosan, chlorhexidine gluconate, an oral antibiotic, a topical antibiotic, tetracycline, doxycycline, minocycline, metronidazole, macrolide antibiotics, penicillin, dicloxacillin, cephalexin, erythromycin, clindamycin, gentamicin, Stiemycin, mupirocin, a hormone, cortisone, a topical retinoid, tretinoin, adapalene, tazarotene, retinol, a natural product with anti-acne activity, aloe vera, aruna, haldi, papaya, tea tree oil, azelaic acid, nicotinamide, an antiperspirant, aluminium chloride, aluminium chlorohydrate, aluminium-zirconium compounds, aluminium zirconium tetrachlorohydrex gly, aluminium zirconium trichlorohydrex gly, ammonium alum, oral isotretinoin, topical sulfacetamide, topical sulfur, topical calcineurin inhibitor, tacrolimus, pimecrolimus, topical permethrin, a combination of plant-sourced Methylsulfonylmethane (MSM) and Silymarin, an aza-steroid, finasteride, dutasteride, minoxidil, an antiandrogen, ketoconazole, fluconazole, spironolactone, saw palmetto, caffeine, copper peptides, nitroxide spin labels TEMPO and TEMPOL, unsaturated fatty acids, gamma linolenic acid, hedgehog agonists, azelaic acid and zinc in combination, Chinese knotweed, pumpkin seed, zinc, stinging nettle, coal tar, dithranol, a corticosteroid, desoximetasone, a vitamin D3 analog, calcipotriol, argan oil, topical psoralen with exposure to ultraviolet A (UVA) light, milk thistle, methotrexate, cyclosporine, tioguanine, hydroxyurea, sulfasalazine, mycophenolate mofetil, azathioprine, tacrolimus, pimecrolimus, alefacept, etanercept, infliximab, rituximab, efalizumab, adalimumab, ustekinumab, topical mixture of bacitracin and polymyxin, topical fusidic acid cream, antiviral therapeutics, acyclovir, famciclovir, valacyclovir, trichloroacetic acid, salicylic acid, podophyllin, canthacur, imiquimod, terbinafine, clotrimazole, econazole, selenium sulfide shampoo,

ketoconazole shampoo, itraconazole, 5-fluorouricil, imiquimod, diclofenac, crocodile oil, and combinations thereof.

155. The method of any one of claims 1 – 38, wherein the therapeutic agent is an antibiotic.

156. The method of any one of claims 1 – 38, wherein the therapeutic agent is an antibody.

157. The method of any one of claims 1 – 38, wherein the therapeutic agent is benzoyl peroxide.

158. The method of any one of claims 1 – 38, wherein the therapeutic agent is isotretinoin.

159. The method of any one of claims 1 – 38, wherein the therapeutic agent is azeliac acid.

160. The method of any one of claims 1 – 38, wherein the nanoemulsion can penetrate skin without altering or changing the skin.

161. The method of any one of claims 1 – 38, wherein the nanoemulsion can penetrate skin without the use of skin permeation enhancers or abrasives.

162. The method of any one of claims 1 – 38, wherein the nanoemulsion can penetrate the top layer of skin without the use of skin permeation enhancers or abrasives.

163. The method of claim 162, wherein the top layer of the skin is the surface of the stratum corneum.

164. The method of claim 162, wherein the top layer of the skin includes dermal pores.

165. The method of claim 162, wherein the top layer of the skin includes dermal glands.

166. The method of any one of claims 1 – 38, wherein the nanoemulsion can penetrate skin without the use of chemical permeation enhancers or abrasives.

167. The method of any one of claims 1 – 38, wherein the nanoemulsion can penetrate skin without the use of mechanical permeation enhancers or abrasives.

168. The method of any one of claims 1 – 38, wherein the particles can penetrate skin without altering or changing the skin.

169. The method of any one of claims 1 – 38, wherein the particles can penetrate skin without the use of skin permeation enhancers or abrasives.

170. The method of any one of claims 1 – 38, wherein the botulinum toxin can penetrate skin without altering or changing the skin.

171. The method of any one of claims 1 – 38, wherein the botulinum toxin can penetrate skin without the use of skin permeation enhancers or abrasives.

172. The method of any one of claims 1 – 38, wherein the nanoemulsion comprises an oil.

173. The method of claim 172, wherein the oil is selected from the group consisting of almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macadamia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, wheat germ, and 1349 oils, and combinations thereof.

174. The method of claim 172, wherein the oil is soybean oil.

175. The method of claim 172, wherein the oil is a medium-chain triglyceride.

176. The method of claim 172, wherein the oil is 1349 oil.

177. The method of claim 172, wherein the oil is selected from the group consisting of butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

178. The method of any one of claims 1 – 38, wherein the nanoemulsion does not have more than one oil.

179. The method of any one of claims 1 – 38, wherein the nanoemulsion comprises a surfactant.

180. The method of claim 179, wherein the surfactant is a nonionic detergent.

181. The method of claim 179, wherein the surfactant is selected from the group consisting of phosphoglycerides; phosphatidylcholines; dipalmitoyl phosphatidylcholine (DPPC); dioleylphosphatidyl ethanolamine (DOPE); dioleyloxypropyltriethylammonium (DOTMA); dioleoylphosphatidylcholine; cholesterol; cholesterol ester; diacylglycerol; diacylglycerolsuccinate; diphosphatidyl glycerol (DPPG); hexanedecanol; fatty alcohols such as polyethylene glycol (PEG); polyoxyethylene-9-lauryl ether; a surface active fatty acid, such as palmitic acid or oleic acid; fatty acids; fatty acid monoglycerides; fatty acid diglycerides; fatty acid amides; sorbitan trioleate (Span 85) glycocholate; sorbitan monolaurate (Span 20); polysorbate 20 (TWEEN®20); polysorbate 60 (TWEEN®60); polysorbate 65 (TWEEN®65); polysorbate 80 (TWEEN®80); polysorbate 85 (TWEEN®85); super-refined polysorbate 20 (SR TWEEN®20); super-refined polysorbate 60 (SR TWEEN®60); super-refined polysorbate 65 (SR TWEEN®65); super-refined polysorbate 80 (SR TWEEN®80); super-refined polysorbate 85 (SR TWEEN®85); polyoxyethylene monostearate; surfactin; a poloxomer; a sorbitan fatty acid ester such as sorbitan trioleate; lecithin; lysolecithin; phosphatidylserine; phosphatidylinositol; sphingomyelin; phosphatidylethanolamine (cephalin); cardiolipin; phosphatidic acid; cerebrosides; dicetylphosphate; dipalmitoylphosphatidylglycerol; stearylamine; dodecylamine; hexadecyl-amine; acetyl palmitate; glycerol ricinoleate; hexadecyl stearate; isopropyl myristate; tyloxapol; poly(ethylene glycol)5000-phosphatidylethanolamine; poly(ethylene glycol)400-monostearate; phospholipids; synthetic and/or natural detergents having high surfactant properties; deoxycholates; cyclodextrins; chaotropic salts; ion pairing agents; and combinations thereof.

182. The method of claim 179, wherein the surfactant is Tween 80.

183. The method of any one of claims 1 – 38, wherein the nanoemulsion does not have more than one surfactant.

184. The method of any one of claims 1 – 38, wherein the nanoemulsion comprises an oil and a surfactant.

185. The method of claim 184, wherein the oil and surfactant are present in a ratio ranging from 0.5 – 2.0.

186. The method of claim 184, wherein the oil and surfactant are present in a ratio ranging from 0.5 – 1.5.

187. The method of claim 184, wherein the oil and surfactant are present in a ratio ranging from 0.5 – 1.0.

188. The method of claim 184, wherein the oil and surfactant are present in a ratio ranging from 1.0 – 2.0.

189. The method of claim 184, wherein the oil and surfactant are present in a ratio ranging from 1.5 – 2.0.

190. The method of claim 184, wherein the percent of oil in the nanoemulsion ranges from 1% – 30%.

191. The method of claim 184, wherein the percent of oil in the nanoemulsion ranges from 1% – 20%.

192. The method of claim 184, wherein the percent of oil in the nanoemulsion ranges from 1% – 10%.

193. The method of claim 184, wherein the percent of oil in the nanoemulsion is approximately 8%.

194. The method of claim 184, wherein the percent of oil in the nanoemulsion is approximately 5%.

195. The method of claim 184, wherein the percent of surfactant in the nanoemulsion ranges from 1% – 30%.

196. The method of claim 184, wherein the percent of surfactant in the nanoemulsion ranges from 1% – 20%.

197. The method of claim 184, wherein the percent of surfactant in the nanoemulsion ranges from 1% – 10%.

198. The method of claim 184, wherein the percent of surfactant in the nanoemulsion is approximately 8%.

199. The method of claim 184, wherein the percent of surfactant in the nanoemulsion is approximately 5%.

200. The method of claim 184, wherein the oil is selected from the group consisting of almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macadamia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, wheat germ, and 1349 oils, and combinations thereof.

201. The method of claim 184, wherein the oil is soybean oil.

202. The method of claim 184, wherein the oil is a medium-chain triglyceride.

203. The method of claim 184, wherein the oil is 1349 oil.

204. The method of claim 184, wherein the oil is selected from the group consisting of butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

205. The method of claim 184, wherein the surfactant is a nonionic detergent.

206. The method of claim 184, wherein the surfactant is selected from the group consisting of phosphoglycerides; phosphatidylcholines; dipalmitoyl phosphatidylcholine (DPPC); dioleylphosphatidyl ethanolamine (DOPE); dioleyloxypropyltriethylammonium (DOTMA); dioleoylphosphatidylcholine; cholesterol; cholesterol ester; diacylglycerol; diacylglycerolsuccinate; diphosphatidyl glycerol (DPPG); hexanedecanol; fatty alcohols such as polyethylene glycol (PEG);

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polyoxyethylene-9-lauryl ether; a surface active fatty acid, such as palmitic acid or oleic acid; fatty acids; fatty acid monoglycerides; fatty acid diglycerides; fatty acid amides; sorbitan trioleate (SPAN®85) glycocholate; sorbitan monolaurate (SPAN®20); polysorbate 20 (TWEEN®20); polysorbate 60 (TWEEN®60); polysorbate 65 (TWEEN®65); polysorbate 80 (TWEEN®80); polysorbate 85 (TWEEN®85); super-refined polysorbate 20 (SR TWEEN®20); super-refined polysorbate 60 (SR TWEEN®60); super-refined polysorbate 65 (SR TWEEN®65); super-refined polysorbate 80 (SR TWEEN®80); super-refined polysorbate 85 (SR TWEEN®85); method polyoxyethylene monostearate; surfactin; a poloxomer; a sorbitan fatty acid ester such as sorbitan trioleate; lecithin; lysolecithin; phosphatidylserine; phosphatidylinositol; sphingomyelin; phosphatidylethanolamine (cephalin); cardiolipin; phosphatidic acid; cerebrosides; dicetylphosphate; dipalmitoylphosphatidylglycerol; stearylamine; dodecylamine; hexadecyl-amine; acetyl palmitate; glycerol ricinoleate; hexadecyl stearate; isopropyl myristate; tyloxapol; poly(ethylene glycol)5000-phosphatidylethanolamine; poly(ethylene glycol)400-monostearate; phospholipids; synthetic and/or natural detergents having high surfactant properties; deoxycholates; cyclodextrins; chaotropic salts; ion pairing agents; and combinations thereof.

207. The method of claim 184, wherein the surfactant is TWEEN®80.

208. The method of any one of claims 1 – 38, wherein the nanoemulsion comprises oily particles which are dispersed within an aqueous dispersion medium.

209. The method of claim 208, wherein the aqueous dispersion medium is selected from the group consisting of water, saline solution, phosphate buffered saline, short chain alcohols, 5% dextrose, Ringer's solution, lactated Ringer's injection, lactated Ringer's plus 5% dextrose injection, acylated Ringer's injection, Normosol-M, Isolyte E, and combinations thereof.

210. The method of claim 208, wherein the aqueous dispersion medium is water.

211. The method of claim 208, wherein the oily particles comprise an oil selected from the group consisting of almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening

primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macadamia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, wheat germ, and 1349 oils, and combinations thereof.

212. The method of claim 208, wherein the oily particles comprise soybean oil.

213. The method of claim 208, wherein the oily particles comprise a medium-chain triglyceride.

214. The method of claim 208, wherein the oily particles comprise 1349 oil.

215. The method of claim 208, wherein the oily particles comprise an oil selected from the group consisting of butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

216. The method of any one of claims 1 – 38, wherein the nanoemulsion comprises aqueous particles which are dispersed within an oily dispersion medium.

217. The method of claim 216, wherein the aqueous particles comprise an aqueous substance selected from the group consisting of water, saline solution, phosphate buffered saline, short chain alcohols, 5% dextrose, Ringer's solution, lactated Ringer's injection, lactated Ringer's plus 5% dextrose injection, acylated Ringer's injection, or Normosol-M, Isolyte E.

218. The method of claim 216, wherein the aqueous particles comprise water.

219. The method of claim 216, wherein the oily dispersion medium is selected from the group consisting of almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macadamia nut,

mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, wheat germ, and 1349 oils, and combinations thereof..

220. The method of claim 216, wherein the oily dispersion medium is soybean oil.

221. The method of claim 216, wherein the oily dispersion medium is a medium-chain triglyceride.

222. The method of claim 216, wherein the oily dispersion medium is 1349oil.

223. The method of claim 216, wherein the oil is selected from the group consisting of butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

224. The method of any one of claims 1 – 38, wherein the nanoemulsion is provided as a pharmaceutical composition comprising the nanoemulsion and at least one pharmaceutically acceptable excipient.

225. The method of claim 224, wherein the composition is selected from the group consisting of a cream, a lotion, a liniment, a gel, an ointment, a spray, a powder, an emollient, an aerosol, and combinations thereof.

226. The method of claim 224, wherein the composition is a cream.

227. The method of claim 224, wherein the composition is a lotion.

228. The method of claim 224, wherein the composition is a liniment.

229. The method of claim 224, wherein the composition is administered transdermally using an adhesive patch.

230. The method of claim 224, wherein the composition is administered transdermally using a spatula.

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231. The method of claim 224, wherein the composition is administered transdermally using a swab.

232. The method of claim 224, wherein the composition is administered transdermally using a syringe without a needle.

233. The method of claim 224, wherein the composition is administered transdermally using a gloved finger.

234. The method of claim 224, wherein the composition is administered transdermally using an unprotected finger.

235. The method of claim 224, wherein the composition is administered transdermally using a deodorant stick

236. The method of claim 224, wherein the composition is administered transdermally using a device that permits application of the composition to a target site on the skin without applying the composition to non-target sites of the skin.

237. The method of claim 224, wherein all of the botulinum toxin permeates the skin.

238. The method of claim 224, wherein at least 99% of the botulinum toxin permeates the skin.

239. The method of claim 224, wherein at least 95% of the botulinum toxin permeates the skin.

240. The method of claim 224, wherein at least 90% of the botulinum toxin permeates the skin.

241. The method of claim 224, wherein at least 75% of the botulinum toxin permeates the skin.

242. The method of claim 224, wherein at least 50% of the botulinum toxin permeates the skin.

243. The method of claim 224, wherein at least 25% of the botulinum toxin permeates the skin.

244. The method of claim 224, wherein at least 10% of the botulinum toxin permeates the skin.

245. The method of claim 224, wherein at least 1% of the botulinum toxin permeates the skin.

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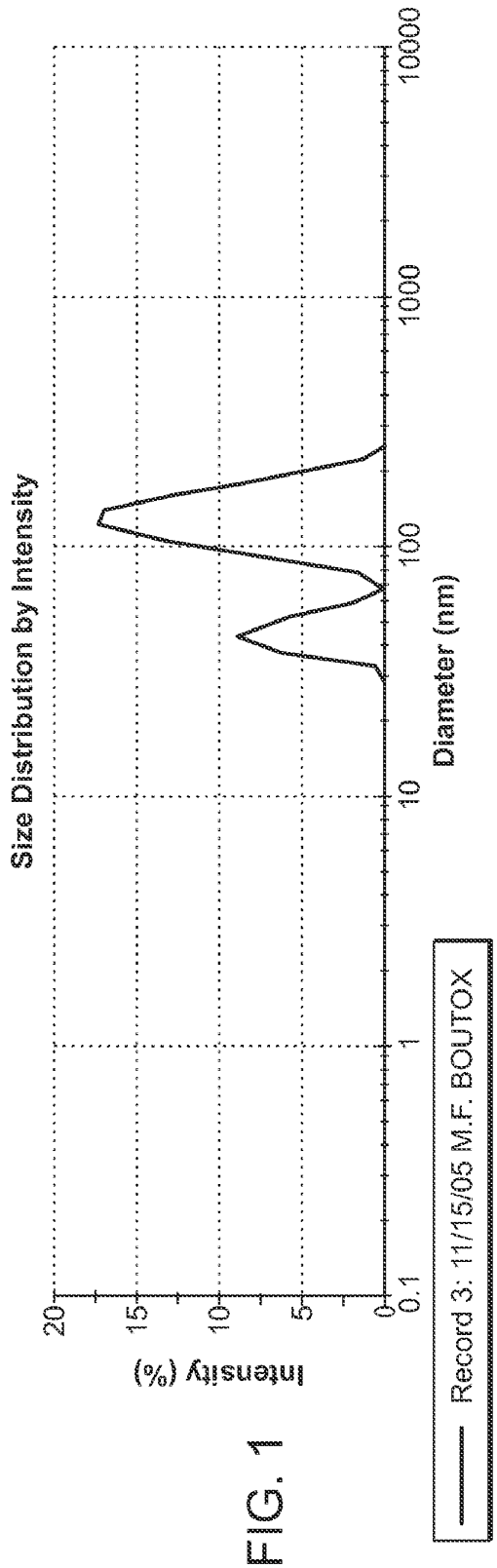

Size Distribution by Intensity
Intensity (%)
Diameter (nm)
Record 3: 11/15/05 M.F. BOUTOX

FIG. 1

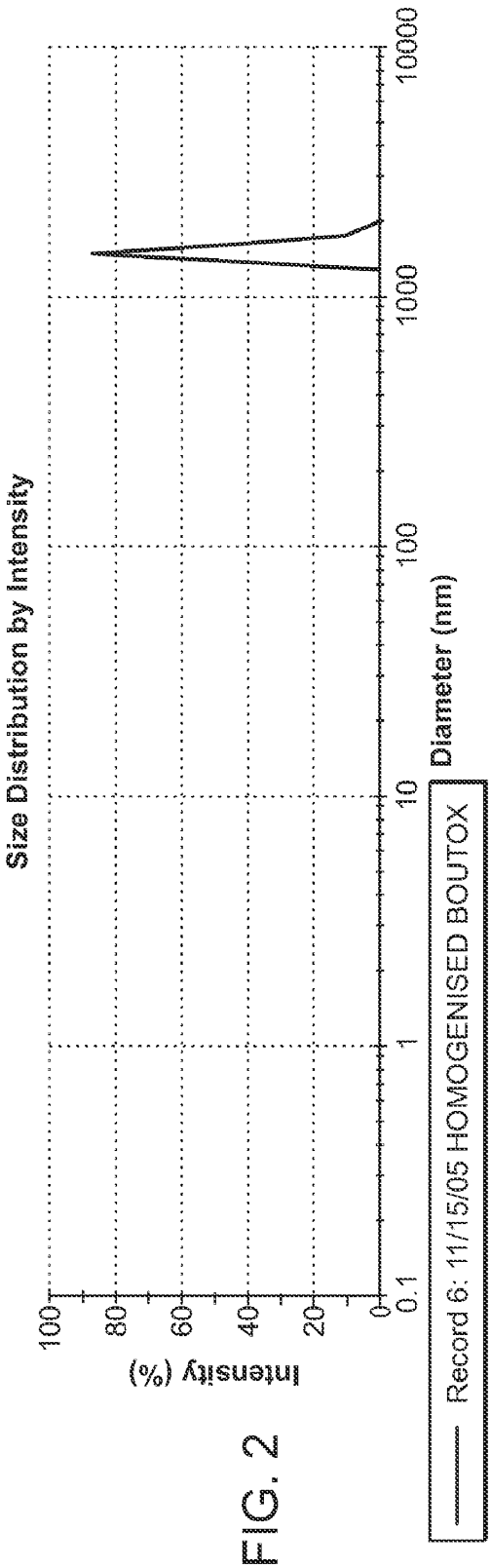

Size Distribution by Intensity
Intensity (%)
Diameter (nm)
Record 6: 11/15/05 HOMOGENISED BOUTOX

FIG. 2

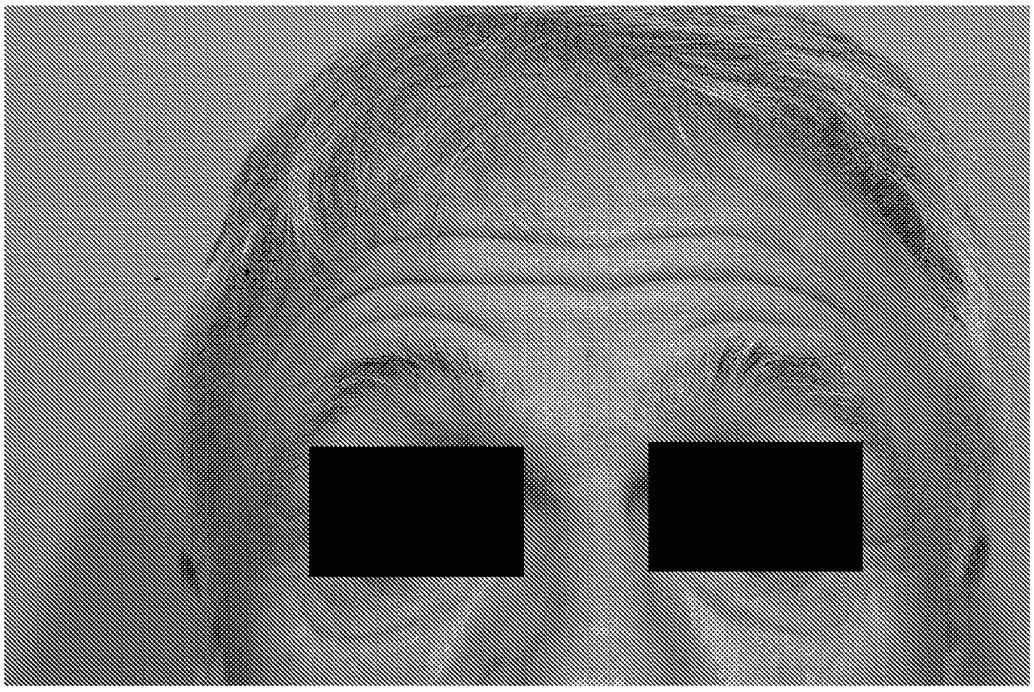


FIG. 3A



FIG. 3B

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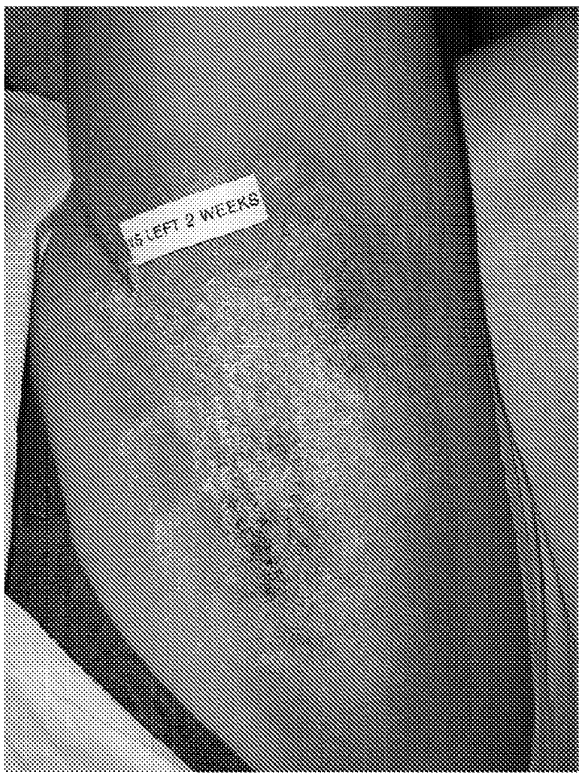


FIG. 4B



FIG. 4A

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/048972

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/51 A61K31/48

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/045107 A (UNIVERSITY OF MASSACHUSETTS) 17 April 2008 (2008-04-17) claims paragraphs [0157], [0160], [0201] - [0204] _____	1,3-23, 39-148, 154, 160-245
X	WO 2005/027872 A (NANOBIO) 31 March 2005 (2005-03-31) claims examples _____ -/--	1, 38-129, 153-155, 160-169, 172-229, 236

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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	Date of mailing of the international search report
23 November 2009	01/12/2009

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/048972

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/036831 A1 (J.R.BAKER) 15 February 2007 (2007-02-15) claims examples	1, 39-129, 153, 160-169, 172-229, 236
X	WO 03/000243 A (UNIVERSITY OF MICHIGAN) 3 January 2003 (2003-01-03) claims	1,2,29, 38-129, 153-155, 157-169, 172-229, 236
X	US 2005/136024 A1 (R.F.STOCKEL) 23 June 2005 (2005-06-23) claims paragraphs [0002], [0003], [0005], [0006], [0009], [0014], [0065]	1,2, 26-32, 35,36, 38-46, 95-101, 153-155, 157-169, 172, 179-185, 198, 205-210, 216-218, 224-229, 236

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/048972

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-245 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/048972

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008045107 A	17-04-2008	AU 2006349377 A1	17-04-2008
		CA 2631927 A1	17-04-2008
		CN 101374498 A	25-02-2009
		EP 1959994 A2	27-08-2008
		JP 2009518307 T	07-05-2009
		KR 20080071615 A	04-08-2008
WO 2005027872 A	31-03-2005	AU 2004273779 A1	31-03-2005
		CA 2528095 A1	31-03-2005
		EP 1633322 A2	15-03-2006
US 2007036831 A1	15-02-2007	CA 2618974 A1	09-02-2007
		EP 1951200 A2	06-08-2008
		JP 2009504805 T	05-02-2009
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		AU 2005201276 A1	14-04-2005
		EP 1411913 A1	28-04-2004
		JP 2005514325 T	19-05-2005
US 2005136024 A1	23-06-2005	US 2007086977 A1	19-04-2007

Form PCT/ISA/210 (patent family annex) (April 2005)

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A61K 9/70 (2006.01) *A61P 17/06* (2006.01)
A61K 31/00 (2006.01) *A61P 17/10* (2006.01)

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2839/DEL/2013 25 September 2013 (25.09.2013) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2015/044857 A1

(54) Title: TOPICAL SPRAY COMPOSITION OF HALOBETASOL

(57) Abstract: The present invention relates to topical spray compositions comprising halobetasol, an emollient, a non-aqueous solvent, and a propellant. It also relates to a process for the preparation of the topical spray compositions. It further relates to a method of treating topical skin condition by administering said topical spray compositions.

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TOPICAL SPRAY COMPOSITION OF HALOBETASOL

Field of the Invention

The present invention relates to topical spray compositions comprising halobetasol, an emollient, a non-aqueous solvent, and a propellant; a process for their preparation; and a method of treating a topical skin condition by administering said topical spray compositions.

Background of the Invention

Many delivery systems, including creams, ointments, lotions, gels, transdermal patches, and sprays, are currently available for the topical application of active ingredients.

Amongst these, semisolid dosage forms such as creams, ointments, lotions, and gels are widely used. However, these are often subject to unintended removal or transfer to other skin surfaces after being applied on the skin. In addition, when a semisolid dosage form is applied on skin, it is typically "rubbed in" which may further irritate the intended site of application. These dosage forms may also cause clogging of pores and therefore block delivery of a suitable quantity of the active ingredient to the skin.

Transdermal patches have fixed shapes and sizes and work best on skin areas that are relatively flat and that do not flex or stretch. However, these comprise an occlusive backing membrane which often results in local skin irritation.

Pharmaceutical sprays exhibit numerous advantages over other known topical delivery systems. These advantages include the ease with which the formulation can be delivered to the areas of the body that are difficult to treat, the possibility of controlling the dose, and the absence of contamination during use. Further, sprays are more suitable when application is required for a large area of skin and therefore result in enhanced patient compliance.

U.S. Patent Nos. 6,126,920 and 7,078,058 disclose betamethasone valerate foamable spray compositions comprising a quick-break foaming agent, an aliphatic alcohol, a fatty alcohol, a surface active agent, buffering agent, water, and a propellant.

U.S. Patent No. 7,645,803 discloses a foamable spray composition comprising a saccharide, a surface active agent, a polymeric agent, a gelling agent, a film-forming agent, water, and a propellant.

U.S. Publication No. 2008/0206155 discloses a non-alcoholic foaming pharmaceutical emulsion composition comprising a steroid, an unctuous emollient, and at least one liquefied or compressed gas propellant.

U.S. Publication No. 2008/0107758 discloses a topical spray composition comprising a corticosteroid, an alcohol, a propellant, and a blend of three or more botanic seed oils that are prepared by a cold press method.

U.S. Patent No. 6,579,512 discloses a topical spray composition comprising clobetasol, an alcohol, isopropyl myristate, and a propellant.

Halobetasol is a high potency corticosteroid. Topical dosage forms of halobetasol, such as creams and ointments, are commercially available under the trade name Ultravate® and have been used for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Although cream and ointment dosage forms of halobetasol have been known for decades, there remains an unmet need for an improved topical composition of halobetasol which overcomes the drawbacks of the available cream and ointment dosage forms and results in better patient compliance.

The present invention teaches topical spray compositions of halobetasol which are non-occlusive, non-irritant, and provide enhanced patient compliance.

Summary of the Invention

The compositions of the present invention are a significant advance over conventional halobetasol compositions, since they allow for the application of halobetasol with no physical contact to the area of application, except by the spray itself.

The present invention relates to non-occlusive, non-irritant, quick drying topical spray compositions of halobetasol. The present invention includes a topical spray composition of halobetasol comprising halobetasol, an emollient, a non-aqueous solvent, and a propellant. It also relates to a process for the preparation of said topical spray composition. It further relates to a method of treating topical skin conditions by administering said topical spray composition.

Detailed Description of the Invention

A first aspect of the present invention provides a topical spray composition of halobetasol comprising halobetasol, an emollient, a non-aqueous solvent, and a propellant.

According to one embodiment of this aspect, there is provided a topical spray composition of halobetasol comprising halobetasol, an emollient, a non-aqueous solvent, and a propellant, wherein the emollient is selected from the group consisting of fatty acid triglycerides, fatty acid esters, and polyhydric alcohols.

According to another embodiment of this aspect, there is provided a topical spray composition of halobetasol comprising halobetasol, an emollient, a non-aqueous solvent, and a propellant, wherein the composition is stable.

A second aspect of the present invention provides a dispensing system for administering a topical spray composition of halobetasol comprising halobetasol, an emollient, a non-aqueous solvent, and a propellant, wherein the dispensing system comprises a container and a valve assembly.

A third aspect of the present invention provides a process for the preparation of a topical spray composition of halobetasol comprising:

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

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

(c) dispensing the solution of step (b) in a dispensing system; and

(d) charging a propellant in the dispensing system of step (c).

A fourth aspect of the present invention provides a method of treating a topical skin condition by administering a topical spray composition of halobetasol comprising halobetasol, an emollient, a non-aqueous solvent, and a propellant.

According to one embodiment of this aspect, there is provided a method of treating a topical skin condition by administering a topical spray composition of halobetasol comprising halobetasol, an emollient, a non-aqueous solvent, and a propellant, wherein the condition is selected from the group consisting of dermatoses, psoriasis, eczema, rosacea,

acne vulgaris, dermatitis, pruritus, seborrhea, skin cancers, inflammation, and combinations thereof.

According to another embodiment of this aspect, there is provided a method of treating a topical skin condition by administering a topical spray composition of halobetasol comprising halobetasol, an emollient, a non-aqueous solvent, and a propellant, wherein the method comprises co-administration of at least one additional drug used to treat topical skin conditions.

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

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

The term "stable", as used herein, means chemical stability 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 three months to the extent necessary for sale and use of composition.

The term "halobetasol", as used herein, includes halobetasol and its salts, polymorphs, hydrates, solvates, prodrugs, chelates, and complexes. The preferred salt of halobetasol is halobetasol propionate. The topical spray composition of the present invention comprises halobetasol in an amount from about 0.01% w/w to about 0.5% w/w of the total composition.

The term "emollient", as used herein, refers to a substance that helps retain skin moisture and also helps control the rate of evaporation and the tackiness of the composition. 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 triglycerides such as mixtures of caprylic and capric triglycerides (*e.g.,* 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 is selected from the group consisting of fatty acid triglycerides, fatty acid esters, and polyhydric alcohols.

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, dimethyl sulfoxide, dimethyl acetamide, lactic acid, glycolic acid, methylene chloride, methyl-ethyl-ketone, ethyl acetate, methylene dimethyl ether, and mixtures thereof. In particular, ethyl alcohol is dehydrated ethyl alcohol.

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, including propane, butane, isobutane, cyclopropane, 1,1,1,2- tetrafluorethane, 1,1,1,2,3,3,3- heptafluoropropane, 1,1- difluoroethane, 1,1,1,3,3,3- hexafluoropropane, and mixtures thereof; fluorocarbon gas; and liquefied petroleum gas.

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

The term "solubilizer" as used herein 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); or combinations thereof.

The term "permeation enhancer" as used herein 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; and combinations thereof.

The term "film-former" as used herein 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; and combinations thereof. These film-formers can partially dissolve on exposure to moisture from the skin or air, resulting in the formation of a porous film. The 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, transcutol, or combinations thereof.

The term "plasticizer" as used herein 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, and 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, and 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, inorganic oxides, inorganic salts of weak acids, and combinations thereof.

In the present invention, the dispensing system comprises a container and a valve assembly.

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), perfluoroethylene-propylene (PFEP), perfluoroalkoxy alkane (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 valve assembly may comprise a valve, a spring, a dip tube, an actuator, and a dust cap. Various types of valves such as continuous spray valves and metering valves can be used. The metered valve dispenses a metered quantity of formulation with each actuation of the actuator. The metered quantity avoids under-dosing or overdosing that may lead to undesirable side effects. A dust cap is fitted onto the container to shield the contents of the container from the outside environment.

The amount of halobetasol depends upon the purpose for which the composition is to be applied. For example, the dosage and frequency of application can vary depending upon the type and severity of the topical condition.

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	52.65
Isopropyl myristate	7.30
Liquefied petroleum gas	40.00

Procedure:

1. Halobetasol propionate is dissolved into a portion of ethyl alcohol while 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, and the container is fitted with a valve assembly.
5. Liquefied petroleum gas is charged into the filled container of step 4.

Example 2

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

Procedure:

1. Halobetasol propionate is dissolved into a portion of ethyl alcohol while 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, and the container is fitted with a valve assembly.
5. Isobutane is charged into the filled container of step 4.

Example 3

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

Procedure:

1. Halobetasol propionate is dissolved into a portion of ethyl alcohol while 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, and the container is fitted with a valve assembly.
5. Butane is charged into the filled container of step 4.

Example 4

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

Procedure:

1. Halobetasol propionate is dissolved into a portion of ethyl alcohol while 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, and the container is fitted with a valve assembly.
5. Propane is charged into the filled container of step 4.

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.
4. The solution of step 3 is filled into an aluminum container with an inert liner, and the container is fitted with a valve assembly.
5. Liquefied petroleum gas is charged into the filled container of step 4.

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 while 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, and the container is fitted with a valve assembly.
5. Isobutane is charged into the filled container of step 4.

Example 7

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 while 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, and the container is fitted with a valve assembly.
5. Isobutane is charged into the filled container of step 4.

Example 8

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

Procedure:

1. Halobetasol propionate is dissolved into a portion of ethyl alcohol while 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, and the container is fitted with a valve assembly.
5. Liquefied petroleum gas is charged into the filled container of step 4.

Example 9

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

Procedure:

1. Halobetasol propionate was dissolved into a portion of ethyl alcohol while 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.
4. The solution of step 3 was filled into an aluminum container with an inert liner, and the container was fitted with a valve assembly.
5. Liquefied petroleum gas was charged into the filled container of step 4.

Example 10

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

Procedure:

1. Halobetasol propionate was dissolved into a portion of ethyl alcohol while 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.
4. The solution of step 3 was filled into an aluminum container with an inert liner, and the container was fitted with a valve assembly.
5. Isobutane was charged into the filled container of step 4.

Example 11

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 was dissolved into a portion of ethyl alcohol while stirring.
2. Crodamol™ GTCC-LQ 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.
4. The solution of step 3 was filled into an aluminum container with an inert liner, and the container was fitted with a valve assembly.
5. Isobutane was charged into the filled container of step 4.

Example 12

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 was dissolved into a portion of ethyl alcohol with stirring.
2. Crodamol™ GTCC-LQ 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.
4. The solution of step 3 was filled into an aluminum container with an inert liner, and the container was fitted with a valve assembly.
5. Liquefied petroleum gas was charged into the filled container of step 4.

We claim:

1. A topical spray composition of halobetasol comprising halobetasol, an emollient, a non-aqueous solvent, and a propellant.

2. The topical spray composition of claim 1, wherein the emollient is selected from the group consisting of fatty acid triglycerides, fatty acid esters, polyhydric alcohols, fatty acids, oils, cyclomethicone, hydrogenated lanolin, waxes, lecithin, or mixtures thereof.

3. The topical spray composition of claim 2, wherein the emollient is selected from the group consisting of fatty acid triglycerides, fatty acid esters, and polyhydric alcohols.

4. The topical spray composition of claim 1, wherein the non-aqueous solvent is 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, dimethyl sulfoxide, dimethyl acetamide, lactic acid, glycolic acid, methylene chloride, methyl-ethyl-ketone, ethyl acetate, methylene dimethyl ether, and mixtures thereof.

5. The topical spray composition of claim 1, wherein the propellant is selected from the group consisting of propane, butane, isobutane, cyclopropane, 1,1,1,2 tetrafluorethane, 1,1,1,2,3,3,3 heptafluoropropane, 1,1, difluoroethane, 1,1,1,3,3,3 hexafluoropropane, fluorocarbon gases, liquefied petroleum gas, and mixtures thereof.

6. The topical spray composition of claim 1, wherein the composition further comprises solubilizers, permeation enhancers, film-formers, plasticizers, antioxidants, pH-adjusting agents, or mixtures thereof.

7. A dispensing system for administering topical spray composition of halobetasol comprising halobetasol, an emollient, a non-aqueous solvent, and a propellant, wherein the dispensing system comprises a container and a valve assembly.

8. A process for the preparation of a topical spray composition of halobetasol, wherein the process comprises the steps of:

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

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

(c) dispensing the solution of step (b) in a dispensing system; and

(d) charging a propellant in the dispensing system of step (c).

9. A method of treating a topical skin condition by administering a topical spray composition of halobetasol comprising halobetasol, an emollient, a non-aqueous solvent, and a propellant.

10. The method of claim 9, wherein the condition is selected from the group consisting of dermatoses, psoriasis, eczema, rosacea, acne vulgaris, dermatitis, pruritus, seborrhea, skin cancers, inflammation, and combinations thereof.

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IPR Petition - USP 11,311,482

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/064745

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/12 A61K9/70 A61K31/00 A61P17/04 A61P17/06
A61P17/10
ADD.
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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/260655 A1 (TAMARKIN DOV [IL] ET AL) 23 October 2008 (2008-10-23) abstract page 12, paragraph 0252-0253 page 23, paragraph 0412 page 31, paragraph 0555 - page 32, paragraph 0597 page 41, paragraph 0647 - page 42, paragraph 0651; example B5 claims 1, 3, 30, 31 -----	1-3,5-9
X	US 2009/136430 A1 (DUGGER HARRY A [US]) 28 May 2009 (2009-05-28) page 1, paragraph 0001 page 4, paragraph 0051 - page 5, paragraph 0068 -----	1-4,7,9, 10

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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	Date of mailing of the international search report
17 October 2014	27/10/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	van de Wetering, P

Form PCT/ISA/210 (second sheet) (April 2005)

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2014/064745

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Form PCT/ISA/210 (patent family annex) (April 2005)

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Electronic Acknowledgement Receipt	
EFS ID:	47173982
Application Number:	16179576
International Application Number:	
Confirmation Number:	1093
Title of Invention:	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES
First Named Inventor/Applicant Name:	Arturo Angel
Customer Number:	112120
Filer:	Eugenia Garrett-Wackowski/Sharleen Lane
Filer Authorized By:	Eugenia Garrett-Wackowski
Attorney Docket Number:	095920-004120US-1240999
Receipt Date:	08-DEC-2022
Filing Date:	02-NOV-2018
Time Stamp:	19:50:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		095920-004120US_IDS.pdf	563309 1079495c0c19388487d0643548584b9dd1bc120c	yes	10

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	Multipart Description/PDF files in .zip description			
	Document Description	**Start**	**End**	
	Transmittal Letter	1	2	
	Information Disclosure Statement (IDS) Form (SB08)	3	10	
Warnings:				
Information:				
2	Foreign Reference	CA1303991.pdf	1452750 8d79c4b9d13277f1eb6cc7acfe305bc154c12b20	no	29
Warnings:				
Information:				
3	Foreign Reference	EP0415766B1.pdf	186146 7321c9beb6d78069573280bc8f06633f7b946904	no	9
Warnings:				
Information:				
4	Foreign Reference	EP2051697A2.pdf	5107459 01764b47676b7d3be614e0c247218db25e60a4c1	no	118
Warnings:				
Information:				
5	Foreign Reference	EP2494959B1.pdf	335145 4ea21ce2a11475b39436f69cb9d56db28af2de7c	no	35
Warnings:				
Information:				
6	Foreign Reference	GB1563638A.pdf	927042 9942f1a991d72d7ac8173ef6fb826865932b01cf	no	11
Warnings:				
Information:				
7	Foreign Reference	GB2050831A.pdf	367233 16ce6a7301a74cdd25848455c46eb658df181658	no	6
Warnings:				

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Information:					
8	Foreign Reference	GB2122087A.pdf	499890 537ccd1a957205756ee8abc2c1b14a97d7c237ba	no	13
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9	Foreign Reference	JP2004-359585A_WithMachTransl.pdf	20291475 36b2419c42a3c6eb3f697a0b873e1fa8f517fbfb	no	19
Warnings:					
Information:					
10	Foreign Reference	JPH06-76328_WithMachTransl.pdf	20937848 aa274b92732f286cb600699dbc53f6b58c3743e7	no	17
Warnings:					
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11	Foreign Reference	JPS63255228_WithEnglAbst.pdf	678953 a44eacd7c73402c52eaf2d33932f9c33569359de	no	10
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Information:					
12	Foreign Reference	WO1998036753A1.pdf	8727230 217f2d59c2e8cf3e14eb8cc927e996b3eff55301	no	22
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13	Foreign Reference	WO1999044585A1.pdf	14628124 7b425aabaaa69726b6612b9ac6a74939a3c19c3e	no	30
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14	Foreign Reference	WO2002011683A1.pdf	20467748 ff16987cb69b51552437c16d3fb6c833a4d4b6f5	no	41
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Information:					

15	Foreign Reference	WO2007100376A2.pdf	5275015 c37df3299716bb1303ecf7e1d4f0e5945be4913e	no	102
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16	Foreign Reference	WO2008038147A2.pdf	5088018 6168fa4b30d595f3bd9c36af6d00a8746125ce6a	no	118
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17	Foreign Reference	WO2008152444A2.pdf	7703824 942bf8c7a45638781fae3774cfb08ec1177d77dc	no	138
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18	Foreign Reference	WO2009063493A2.pdf	2670896 15b3cb2b353d5135a79577abe0bc619a4ce1b917	no	55
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19	Foreign Reference	WO2009084020A2.pdf	8633183 83c4bb06016d7916d038b68b15f95eb6979d88d8	no	26
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20	Foreign Reference	WO2009158687A1.pdf	9575786 f3d2fa0bbe7e6bbf4dc8c0982a1d564a51c7addc	no	162
Warnings:					
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21	Foreign Reference	WO2015044857A1.pdf	671641 fcd7cbb4dddf5561ca8f9d0cc309d82da112d3c0	no	18
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23	Non Patent Literature	103_ClinicalTrialsGov_IDP-118Study2_StudyRecordDetail-StudyResults.pdf	1090770 96d6e41de3cb647389080f5a75eab4ac4574caa	no	8
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24	Non Patent Literature	104_ClinicalTrialsGov_IDP-118Study2_HistoryOfChanges-StudyRecordVersion1.pdf	179671 f6089ff828e5a7149ccbd13a0c819c6d56470b8c	no	3
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Information:					
25	Non Patent Literature	105_ClinicalTrialsGov_IDP-118Study2_HistoryOfChanges-StudyRecordVersion2.pdf	182518 561241af9096df7d1267d236720becd52fc5525a	no	3
Warnings:					
Information:					
26	Non Patent Literature	106_ClinicalTrialsGov_IDP-118Study2_HistoryOfChanges-StudyRecordVersion3.pdf	533212 48360abcbe742c11b68ae7a915dd790725999467	no	4
Warnings:					
Information:					
27	Non Patent Literature	107_ClinicalTrialsGov_IDP-118Study2_HistoryOfChanges-StudyRecordVersion4.pdf	513515 085880b3219f56cba632688ec2070e291ba3e706	no	4
Warnings:					
Information:					
28	Non Patent Literature	108_ClinicalTrialsGov_IDP-118Study2_HistoryOfChanges-StudyRecordVersion5.pdf	526585 1f01ab4bdb3871c9c8fadc23da8b55ead278ade7	no	4
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30	Non Patent Literature	110_ClinicalTrialsGov_IDP-118Study2_HistoryOfChanges-StudyRecordVersion6.pdf	536269 f892fa051716b7051594e2b42c87a701bc662e21	no	4
Warnings:					
Information:					
31	Non Patent Literature	111_ClinicalTrialsGov_IDP-118Study2_HistoryOfChanges-StudyRecordVersion7.pdf	1176586 902e3351cb1f6c778d445090ff163b40ba71e9bd	no	8
Warnings:					
Information:					
32	Non Patent Literature	112_ClinicalTrialsGov_IDP-118Study1_StudyRecordDetails-StudyDetails.pdf	335784 7f0fc3fb1630efc8e00b7802e71dead1bbb8ace9	no	5
Warnings:					
Information:					
33	Non Patent Literature	113_ClinicalTrialsGov_IDP-118Study1_StudyRecordDetail-NoResultsPosted.pdf	83829 85fd328f821f829d6cb4fca9cb64b8cde6fac959	no	2
Warnings:					
Information:					
34	Non Patent Literature	114_ClinicalTrialsGov_IDP-118Study1_StudyRecordDetail-TabularView.pdf	341929 f7117ed16e9bf6eaa39ae2c539ab1cdb91015e01	no	5
Warnings:					
Information:					
35	Non Patent Literature	115_ClinicalTrialsGov_IDP-118Study1_HistoryOfChanges-StudyRecordVersion1.pdf	336855 adff7ece8bb61aa5cee774f11050191c3e18f31a	no	5
Warnings:					
Information:					

36	Non Patent Literature	116_ClinicalTrialsGov_IDP-118Study1_HistoryOfChanges-StudyRecordVersion2.pdf	330655 746b2e9d1342dfc183e65eb0b93fe765439d653f	no	5
Warnings:					
Information:					
37	Non Patent Literature	Afifi.pdf	2329685 452322fe75d17b0ba2813b6dcb1df13e81a06d36	no	7
Warnings:					
Information:					
38	Non Patent Literature	Allergan_Tazorac_Label_2001.pdf	12328812 265d06d48524055f3e8c2c9ad1886a194da0b40e	no	15
Warnings:					
Information:					
39	Non Patent Literature	Allergan_Tazorac_Label_2013.pdf	1749731 58f6f856ff50b40592f1e1f42a99edd80b8a4109	no	14
Warnings:					
Information:					
40	Non Patent Literature	Baid.pdf	2274069 754f0bd40dcfd032dab32686b6bc6baf5f4598a1	no	7
Warnings:					
Information:					
41	Non Patent Literature	Blum.pdf	2034054 01e2315275e22a259f7d73f1a4b65e5f07361397	no	7
Warnings:					
Information:					
42	Non Patent Literature	Bristol-Myers_Ultravate_Cream_Label_2003.pdf	278999 7898448b30d805538fd142d9f9c52e648899d0b8	no	2
Warnings:					
Information:					

43	Non Patent Literature	Bristol-Myers_Ultravate_Ointment_Label_2003.pdf	346352 963220c5f497ff1caaca813c0196e00e14c6587e	no	2
Warnings:					
Information:					
44	Non Patent Literature	Budavari_4625HalobetasolPropionate_MerckIndex_1996.PDF	10687485 23a132bf605cf4e65674aee00c4fde759c7e9270	no	5
Warnings:					
Information:					
45	Non Patent Literature	Carruthers.pdf	698763 2fbac3559af2139d4b81e9eb6c67bf65419f621e	no	2
Warnings:					
Information:					
46	Non Patent Literature	DermikLabs_Psorcon_Label_rev2009.pdf	1078046 c554aff9af48fa73f9193b262d0ddfe0a3659bc7	no	5
Warnings:					
Information:					
47	Non Patent Literature	EFougeraCo_BetamethasoneDipropionateGel_Label.pdf	554407 bb983c99f81128c38fd8a4ebd4e7cb821bd9b2c4	no	6
Warnings:					
Information:					
48	Non Patent Literature	Fang.pdf	2093862 6156fa64598df7992d328723ffb18ffb7db498ab	no	10
Warnings:					
Information:					
49	Non Patent Literature	Feldman.pdf	3120801 fc92b81cabd0e2c9c5bbe46e71b8318d246d9eea	no	18
Warnings:					
Information:					

50	Non Patent Literature	GaldermaLabs_Clobex_Label_2003.pdf	3231953 5923590d3c77266658f063baec6df74bd858a966	no	22
Warnings:					
Information:					
51	Non Patent Literature	Gao.pdf	754407 5f05fbd11f997977808ebcc4f3757f01278410e0	no	5
Warnings:					
Information:					
52	Non Patent Literature	GlaxoWellcome_Temovate_E_Label.pdf	675095 00c50a4874c2088a61bdd6ffa894c3ef37e6464c	no	2
Warnings:					
Information:					
53	Non Patent Literature	Gollnick.pdf	908984 46f0652e8c424944fc1c5bfd581410d968e851f5	no	6
Warnings:					
Information:					
54	Non Patent Literature	Harding.pdf	840506 816c18940d56e3eb6b27d4ed019046341a4abf05	no	10
Warnings:					
Information:					
55	Non Patent Literature	Hu.pdf	1511345 6ec9c05c2e2f4052bb6b8ca090ef33870ad9976b	no	5
Warnings:					
Information:					
56	Non Patent Literature	Ismail.pdf	1208903 fc22f5a763e8a54758d05c21bed0141bcd6e0cfb	no	14
Warnings:					
Information:					

57	Non Patent Literature	Kaidbey.pdf	530355 9ec6af8fe70206c98241ccce8be4d3353248 5f46	no	4
Warnings:					
Information:					
58	Non Patent Literature	Koo.pdf	648907 120c4e9890d8c1764ae756c0050ce677df2 b3743	no	6
Warnings:					
Information:					
59	Non Patent Literature	Krueger.pdf	682180 b3f0c0d97f512f889b4b4fdc0f5ba1f449ba8 808	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	193254510		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on December 8, 2022.

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Sharleen Lane/
Sharleen Lane

PATENT
Attorney Docket No.: 095920-004120US-1240999
Client Ref. No.: DOW-P05877-2-C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Arturo Angel *et al.*

Application No.: 16/179,576

Filed: November 2, 2018

For: TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

Customer No.: 112120

Confirmation No.: 1093

Examiner: Kathrien Ann Hartsfield

Art Unit: 1627

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

The references cited on attached form PTO/SB/08A are being called to the attention of the Examiner. In accordance with the provisions of 37 CFR §1.98(a)(2), copies of any cited U.S. Patents and U.S. Patent Application Publications are not provided. Copies of the remaining cited references are provided.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

The Commissioner is authorized to charge the fee set forth in §1.17(p) to the firm's credit card for consideration of this paper. The Commissioner is authorized to charge any additional fee due to Deposit Account No. 20-1430.

Respectfully submitted,

/Eugenia Garrett-Wackowski/
Eugenia Garrett-Wackowski
Registration No. 37,330

KILPATRICK TOWNSEND & STOCKTON LLP

Attachment

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/179,576	Filing Date 11/02/2018	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

	(Column 1)	(Column 2)			
FOR	NUMBER FILED	NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	12/08/2022	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 8	Minus	** 20	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $480 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	SLIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/TONYA Q MCBRIDE/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/179,576	11/02/2018	Arturo Angel	095920-004120US-1240999	1093

112120 7590 06/08/2022

Bausch Health / Kilpatrick Townsend & Stockton LLP
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

EXAMINER
CRUZ, KATHRIEN ANN

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
06/08/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

KTSDocketing2@kilpatrick.foundationip.com
ipefiling@kilpatricktownsend.com

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 16/179,576	Applicant(s) Angel et al.	
	Examiner KATHRIEN A CRUZ	Art Unit 1627	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 5/13/2022.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1,6-10,12 and 27 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1,6-10,12 and 27 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 5/13/2022.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Claims 1, 6-10, 12 and 27 is pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/13/2022 has been entered.

Action Summary

Claims 1, 6-10, 12 and 27-28 are rejected under 35 U.S.C. 103 as being unpatentable over Tazaorac (Highlights of Prescribing Information, LABEL (fda.gov), 12/2013) and Angel et al (WO2012/087443 published 06/28/2012) both are of record is maintained with modification due to applicants amendment of claims.

Claims 1 rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter is withdrawn.

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Claims 1, 6-10, 12 and 27-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,426,787 is maintained.

Claims 1, 6-10, 12 and 27-28 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,251,895 is maintained.

Claims 1, 6-10, 12 and 27-28 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13-40 of copending Application No. 16/179,561 is maintained with modification.

Response to Arguments

Applicants argues that the office should consider all rebuttal arguments and evidence present by applicants. This assertion has been considered and the arguments has evidence has been considered but was found not be persuasive as previously stated and again asserted below.

Applicants again argue that Dr. Dow explains that he would not expect to achieve effective delivery of tazarotene from a composition formulated for delivery of halobetasol propionate. This argument has been fully considered but has not been found persuasive the formulation for delivery as applicants assert is the very same formulation as instant claimed. Therefore, it would have been obvious to substitute tazarotene in same formulation. Additionally, Tazarotene is a member of the acetylenic class of

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retinoids. Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1%; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate. it would have been obvious to substitute tazarotene instead of halobetasol propionate because both agents are known in the art to treat skin disorder and the composition for delivery (as applicants assert) is the same, thus taken the cited art, it would have been obvious to administer tazarotene with diethyl sebacate, sorbitol solution, methyl and propyl paraben because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl and propyl paraben are useful for enhancing the solubility, chemical stability and penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary

Applicants assert unexpected results (e.g. surprising properties) in which Dr. Dow that a skilled artisan would not expect the surprising advantages of the claimed lotion composition. This argument has been fully considered but has not been found persuasive. Additionally, in looking at table 6 in which applicants assert unexpected results; applicants compare Tazorac® to composition A. First, the specification does not disclose all of the ingredients disclosed in Tazorac®. Second, Compound A has ingredients not disclosed in Tazaorac. Inactive ingredients may play part in the bioavailability and results of compartment of compound A and Tazorac® . Therefore, this is not a true comparison. In order to properly compare, all of ingredients with the

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same concentration and the only difference is the concentration of tazarotene (0.045 versus 0.1%). Therefore, applicants has not established unexpected results.

Applicants argue that there is has not been a prima case of obviousness established by the Office. This argument has been fully considered but has not been found persuasive. Tazaorac teaches (tazarotene) Cream, 0.05% and 0.1% is for topical use and contains the active ingredient, tazarotene. Each gram of TAZORAC® Cream, 0.05% and 0.1% contains 0.5 and 1 mg of tazarotene, respectively in a white cream base to treat psoriasis and acne. Tazarotene is a member of the acetylenic class of retinoids. Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1%; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate (in which this formulation is a oil-in-water formulation, it is noted that the difference between a lotion and cream is the amount of water within each, both are oil-in-water compositions). Angel teach the efficacy of the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulation for enhancing the solubility, chemical stability and penetration properties, Oil-in-water cream and lotion emulsions are encompassed within the teachings of Angel (page 19). Angel teaches that the concentration of the esters in the liquid oil component is at least 30% of the concentration of the liquid oil component (claim 10). Angel teaches that the dicarboxylic acid ester is diethyl sebacate in a concentration of 2.10 % (example 4 and claim 16). Angel teaches sorbitol solution, 70% at a concentration of 10.7%, methyl

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paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60% (table 4). Angel teaches a pH of 4.0 – 6.0. It would have been obvious to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben to the oil-in-water cream of tazarotene of Tazaorac in view of Angel. One would have been motivated to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl and propyl paraben are useful for enhancing the solubility, chemical stability and penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary.

Previous Rejection with modifications due to applicant's amendment of claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having

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ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 6-10, 12 and 27 are rejected under 35 U.S.C. 103 as being unpatentable over Tazaorac (Highlights of Prescribing Information, LABEL (fda.gov), 12/2013) and Angel et al (WO2012/087443 published 06/28/2012) both are of record.

Tazaorac teaches (tazarotene) Cream, 0.05% and 0.1% is for topical use and contains the active ingredient, tazarotene. Each gram of TAZORAC® Cream, 0.05% and 0.1% contains 0.5 and 1 mg of tazarotene, respectively in a white cream base to treat psoriasis and acne. Tazarotene is a member of the acetylenic class of retinoids. Tazorac teaches that the cream contains the following inactive ingredients: benzyl alcohol 1%; carbomer 1342 (type A); carbomer homopolymer type B; edetate disodium; medium chain triglycerides; mineral oil; purified water; sodium hydroxide; sodium thiosulfate; and sorbitan monooleate (in which this formulation is a oil-in-water formulation, it is noted that the difference between a lotion and cream is the amount of water within each, both are oil-in-water compositions). (11, under Description).

Tazaorac does not disclose diethyl sebacate, sorbitol solution, methyl and propyl paraben nor the concentrations of the inactive agents. Tazaorac does not disclose the pH.

Angel teach the efficacy of the dicarboxylic acid ester (DCAE) diethyl sebacate and light mineral oil based formulation for enhancing the solubility, chemical stability and penetration properties, Oil-in-water cream and lotion emulsions are encompassed within the teachings of Angel (page 19). Angel teaches that the agent in a formulation containing a liquid oil component that includes a dicarboxylic acid ester and/or a

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monocarboxylic acid ester (page 6). Angel teaches the components of the aqueous phase and of the oil phase may be separately combined and mixed until homogenous solutions are obtained and then the aqueous solution and the oil solution may be combined and mixed, such as by shear mixing, to form the formulation. The oil phase may be added to the water phase, or the water phase may be added to the oil phase. The phases may be combined and mixed, such as at elevated temperatures of 50-90°C or at room temperature, that is between 20-30°C, or at a temperature between room temperature and the elevated temperatures (page 12). Angel teaches that with high speed rotor-stator mixing, the oil phase containing the drug is added to the aqueous phase. Mixing is continued until a homogeneous emulsion is obtained. Anger teaches that the thickening agent is miscible or soluble in an aqueous fluid. Examples of suitable thickening agents include acacia, alginic acid, bentonite, carbomers, also known as carboxy vinyl polymers, such as sold under the tradename Carbopol® (page 10 bridging page 11). Angel further teaches that in a manufacturing vessel, purified water and disodium edetate dihydrate are combined a d the mixture is agitated until a clear solution is achieved. Sorbitol, methylparaben, and propylparaben are then added to the mixture. The mixture is continuously mixed and is heated to approximately 75°C. The mixture is agitated until a solution is obtained. The mixture is then removed from the heat source and allowed to cool to below 40°C with continued mixing. With continuous propeller agitation Carbopol 981 at a concentration of 0.6% and Pemulen™ (polymeric emulsifier) at a concentration of 0.4% are added to the mixture and fully dispersed. (page 20). Angel teaches that the concentration of the esters in the liquid oil component is at least 30% of the concentration of the liquid oil component (claim 10). Angel

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teaches that the dicarboxylic acid ester is diethyl sebacate in a concentration of 2.10 % (example 4 and claim 16). Angel teaches sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60% (table 4). Angel teaches a pH of 4.0 – 6.0 (table 4). Angel exemplify a 0.01 %wt. a formulation comprising the dermatological carrier of light mineral oil and diethyl sebecate and purified water, q.s ad (page 20). Regarding the limitation of claims 1, 8, 31-32, Angel teaches the claimed amounts of diethyl sebecate (2.97% wt.), the claimed amount of light mineral oil (8.03% wt.), the claimed amount of carbomer copolymer type B (Pemulen TR-1 0.40% wt.; see Table 3, page 20 of instant specification defines Pemulen TR-1 as a carbomer copolymer type B) and claimed amount of carbomer homopolymer type A found within the instant claims (carbopol 981, 0.6% wt., see Table 3, page 20 of instant specification defines carbomer 981 as a carbomer homopolymer type A).

It would have been obvious to employ diethyl sebacate, sorbitol solution, methyl, propyl paraben, water, carbopol® and Pemulen ™ to the oil-in-water with an oil phase and aqueous phase in a cream of tazarotene of Tazaorac in view of Angel. One would have been motivated to employ diethyl sebacate, sorbitol solution, methyl and propyl paraben and purified water q.s. ad because it is known that topically administered in a diethyl sebacate, sorbitol solution, methyl, propyl paraben, water and Pemulen ™ are useful in topical administration for enhancing the solubility, chemical stability and

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penetration properties as disclosed by Angel with a reasonable expectation of success absence evidence to the contrary.

One of ordinary skill in the art of preparing a topical lotion and cream emulsions consisting of tazarotene would have found it prima facie obvious to administer the concentration of tazarotene in the emulsion of Tazaorac in order to arrive at the instantly claimed emulsion. Tazaorac teaches the concentration of tazaotene of 0.05% and 0.1% contains 0.5 and 1 mg respectively. The amounts of active agents to be used, the pharmaceutical forms, e.g., tablets, etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Lab. Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997); Smith v. Nichols, 88 U.S. 112, 118-19 (1874) (a change in form, proportions, or degree "will not sustain a patent"); In re Williams, 36 F.2d 436, 438 (CCPA 1929) ("It is a settled principle of law that a mere carrying forward of an original patented conception involving only change of form, proportions, or degree, or the substitution of equivalents doing the same thing as the original invention, by substantially the same means, is not such an invention as will sustain a patent, even though the changes of the kind may produce better results than prior inventions."). See also KSR Int' l Co. v. Teleflex Inc., 550 U.S. 398, 416 (2007) (identifying "the need for caution in granting a patent based on the combination of elements found in the prior art."). Therefore, the ordinary artisan would have been motivated to optimize the

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workable ranges disclosed by Tazaorac, with the reasonable expectation of making formulations which possess improved solubility and pharmaceutical properties such as high bioavailability and prolonged effect. Furthermore, it is obvious to vary and/or optimize the amount of tazarotene provided in the composition, according to the guidance provided by Tazaorac, to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With regards to the of concentrations of sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, is diethyl sebacate in a concentration of 2.10 % (the combination of mineral oil and diethyl sebacate is 11.8%), sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60%, Carbopol® at a concentration of 0.6% and Pemulen™ (polymeric emulsifier) at a concentration of 0.4% as disclosed by Angel. The amounts of active agents to be used, the pharmaceutical forms, e.g., tablets, etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Lab. Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d

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1362 (Fed. Cir. 1997); Smith v. Nichols, 88 U.S. 112, 118-19 (1874) (a change in form, proportions, or degree "will not sustain a patent"); In re Williams, 36 F.2d 436, 438 (CCPA 1929) ("It is a settled principle of law that a mere carrying forward of an original patented conception involving only change of form, proportions, or degree, or the substitution of equivalents doing the same thing as the original invention, by substantially the same means, is not such an invention as will sustain a patent, even though the changes of the kind may produce better results than prior inventions."). See also KSR Int' l Co. v. Teleflex Inc., 550 U.S. 398, 416 (2007) (identifying "the need for caution in granting a patent based on the combination of elements found in the prior art."). Therefore, the ordinary artisan would have been motivated to optimize the workable ranges disclosed by Tazaorac and Angel, with the reasonable expectation of making formulations which possess improved solubility and pharmaceutical properties such as high bioavailability and prolonged effect. Furthermore, it is obvious to vary and/or optimize the amount of sorbitol solution, 70% at a concentration of 10.7%, methyl paraben at a concentration of 0.17% and propyl paraben at a concentration of 0.03%, mineral oil at a concentration of 9.70%, sorbitan monooleat at a concentration of 0.10%, edetate disodium, dihydrate at a concentration of 0.05%, Carbopol at a concentration of 0.60%, Pemulen™ (polymeric emulsifier) at a concentration of 0.4% provided in the composition, according to the guidance provided by Tazaorac and Angel, to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges

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by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

With respect to the art rejection above, it is noted that the reference does not teach that the composition can be used in the manner instantly claimed, treating acne. However, the intended use of the claimed composition does not patentably distinguish the composition, per se, because such undisclosed use is inherent in the reference composition. In order to be limiting, the intended use must create a structural difference between the claimed composition and the prior art composition. If the prior art structure is capable of performing the intended use, then it meets the claim. The logic flows from MPEP 2115:

- "A claim is only limited by positively recited elements. Thus, "[i]nclusion of the material or article worked upon by a structure being claimed does not impart patentability to the claims." *In re Otto*, 312 F.2d 937, 136 USPQ 458, 459 (CCPA 1963); see also *In re Young*, 75 F.2d 996, 25 USPQ 69 (CCPA 1935);
- "the manner or method in which such machine is to be utilized is not germane to the issue of patentability of the machine itself." See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

An intended use will not limit the scope of the claim because it merely defines a context in which the invention operates. (*Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003)). Moreover "the patentability of apparatus or composition claims depends on the claimed structure, not

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on the use or purpose of that structure." (*Catalina Mktg. Int'l, v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002). Additionally, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. (See MPEP 707.07(f) and 2141.02 I; *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and MPEP 2111.02 II; *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951)).

In the instant case, the intended use does not create a structural difference and the body of the claim does not depend on the intended use for completeness but rather can stand alone. Consequently, the intended use is not limiting.

For these reasons, the claimed subject matter is deemed to fail to be patentably distinguishable over the state of the art as represented by the cited reference. The claims are therefore, properly rejected under 35 U.S.C. 103.In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

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Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file

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provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1, 6-10, 12 and 27 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,426,787. Although the claims at issue are not identical, they are not patentably distinct from each other because both application recite the administration of tazarotene to treat acne. The difference between the instant application and the '787 patent is that the '787 also recites halobetasol, however the instant claims do not preclude a combination therapy to treat acne. Thus, the instant application and the '787 patent possess significant overlapping scopes of invention.

Claims 1, 6-10, 12 and 27 is rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 10,251,895. Although the claims at issue are not identical, they are not patentably distinct from each

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other because both application recite the administration of tazarotene to treat acne. The difference between the instant application and the '895 patent is that the '895 also recites halobetasol, however the instant claims do not preclude a combination therapy to treat acne. Thus, the instant application and the '895 patent possess significant overlapping scopes of invention.

Claims with modification due to applicants amendment of claims. is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 13-40 of copending Application No. 16/179,561. Although the claims at issue are not identical, they are not patentably distinct from each other because both the instant claims and the '561 application recite a composition (tazarotene) for the treatment of acne. Taken that both applications disclose the same compound (tazarotene) to treat acne, one of ordinary skills in the art would recognize that both application possess significant overlapping scopes of invention with a reasonable expectation of success.

Claims 1, 6-10, 12 and 27 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-13 of copending Application No. 17/719278 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because both applications are drawn to a topical pharmaceutical composition comprising tazarotenic in a concentration of 0.045. This difference is that in the '278 application the inactive ingredients are in dependent claims rather in one claim as in the present application. However, both application have overlapping scopes of inventions.

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This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

Claims 1, 6-10, 12 and 27 is rejected.

No claims are allowed.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHRIEN A. CRUZ whose telephone number is (571)270-5238. The examiner can normally be reached on Monday - Thursday 8-6pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kortney L. Klinkel can be reached on (571) 270-5239. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KATHRIEN A CRUZ/
Primary Examiner, Art Unit 1627

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IPR Petition - USP 11,311,482

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/179,576	Angel et al.
	Examiner	Art Unit
	KATHRIEN A CRUZ	1627

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner
A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10	08/05/2020	kc
A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10	02/23/2021	kc
A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10	06/07/2021	kc
A61K31/4436 OR A61K47/06 OR A61K47/14 OR A61K47/32 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61P17/00 OR A61P17/10	06/03/2022	kc

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/179,576	Angel et al.
	Examiner	Art Unit
	KATHRIEN A CRUZ	1627

Search Notes		
Search Notes	**Date**	**Examiner**
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	03/15/2019	KC
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	10/23/2019	kc
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	02/24/2020	kc
EAST (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB)	08/05/2020	kc
P2E2 SEARCH (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB, FIT)	02/23/2021	kc
INVENTOR	02/23/2021	kc
P2E2 SEARCH (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB, FIT)	06/07/2021	kc
INVENTOR	06/07/2021	kc
P2E2 SEARCH (US-PGPUB, USPAT, USOCR, FPRS, EPO, JPO, DERWENT, IBM_TDB, FIT)	06/03/2022	kc
INVENTOR	06/03/2022	kc

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/179,576
	Filing Date	November 2, 2018
	First Named Inventor	Arturo Angel
	Art Unit	1627
	Examiner Name	Kathrien Ann Cruz
	Attorney Docket Number	095920-004120US-1240999

U.S. PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code [1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code [1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
/K.A.C/	1.	Allergan, Inc. "Drug Approval Package", Medical Review(s) on Tazorac™ cream, part 1, Sept 25, 2000, 32 pages.	
/K.A.C/	2.	Allergan, Inc. "Tazarotene Cream Package Insert", version 1.0, October 16, 2000, 12 pages.	

EXAMINER SIGNATURE

Examiner Signature	/KATHRIEN A CRUZ/	Date Considered	06/03/2022	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	0	"il in water" SAME lotion	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/02/22 04:51 PM
L2	2	"20140336161"	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/02/22 06:07 PM
L3	3	"20190133943".pn.	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/02/23 03:23 PM
L4	567473	L3 OR ((A61K31/4436 OR A61K47/14 OR A61K47/34 OR A61K47/44 OR A61K9/0014 OR A61K9/06 OR A61K9/107 OR A61K47/06 OR A61K47/32 OR A61P17/00 OR A61P17/10).cpc.)	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/02/23 03:27 PM
L5	5309	L4 AND tazarotene	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/02/23 03:28 PM
L6	279	L5 AND "diethyl sebacate"	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/02/23 03:28 PM
L7	189	L6 AND "mineral oil"	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/02/23 03:29 PM
L8	119	L7 AND "sorbitan monooleate"	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/02/23 03:29 PM
L9	40	L8 AND @py<2015	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT;	OR	ON	ON	2021/02/23 03:29 PM

			IBM_TDB)				
L10	190	L3 OR (("ARTURO A".ine. OR "ARTURO; ANGEL".ine. OR "CHOI YOON E".ine. OR "JEON MIN SEO".ine. OR "KIM SOK".ine. OR "PARK YUN HWAN".ine. OR "PILLAI R".ine. OR "PILLAI; RADHAKRISHNAN".ine .))	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/02/23 03:30 PM
L11	24	L10 AND tazarotene	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2021/02/23 03:30 PM
L12	30	L11	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/06/03 01:18 PM
L13	41	L9	(US-PGPUB; USPAT; USOCR; FIT (CN, FR, WO); FPRS; EPO; JPO; DERWENT; IBM_TDB)	OR	ON	ON	2022/06/03 01:18 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Electronic Acknowledgement Receipt

EFS ID:	45714074
Application Number:	16179576
International Application Number:	
Confirmation Number:	1093
Title of Invention:	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES
First Named Inventor/Applicant Name:	Arturo Angel
Customer Number:	112120
Filer:	Eugenia Garrett-Wackowski/Sharleen Lane
Filer Authorized By:	Eugenia Garrett-Wackowski
Attorney Docket Number:	095920-004120US-1240999
Receipt Date:	13-MAY-2022
Filing Date:	02-NOV-2018
Time Stamp:	20:45:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	Allergan_TazaroteneCreamPackageInsert_10-16-2000_12pages.pdf	1690625 ab3db4225055a9276b09c7a2fd0dc5a44a0fa7cb	no	12
Warnings:					

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Information:	
Total Files Size (in bytes):	1690625

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	16179576	Filing Date	2018-11-02	Docket Number (if applicable)	095920-004120US-1240999	Art Unit	1627
First Named Inventor	Arturo Angel			Examiner Name	Kathrien Cruz		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☑ Enclosed

☑ Amendment/Reply

☑ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☑ Other Petition for 3-mo extension of time.

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☑ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 201430

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

✓ Patent Practitioner Signature

Applicant Signature

PTO/SB/30EFS (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Signature of Registered U.S. Patent Practitioner			
Signature	/Eugenia Garrett-Wackowski/	Date (YYYY-MM-DD)	2022-05-13
Name	Eugenia Garrett-Wackowski	Registration Number	37330

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/22 (10-20)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 095920-004120US-1240999
Application Number 16/179,576	Filed November 2, 2018
For TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES	
Art Unit 1627	Examiner Kathrien Ann Cruz

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	Micro Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$220	$110	$55	$_____
☐ Two months (37 CFR 1.17(a)(2))	$640	$320	$160	$_____
☒ Three months (37 CFR 1.17(a)(3))	$1,480	$740	$370	$1,480
☐ Four months (37 CFR 1.17(a)(4))	$2,320	$1,160	$580	$_____
☐ Five months (37 CFR 1.17(a)(5))	$3,160	$1,580	$790	$_____

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 20-1430.

☒ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71 Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 37,330

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____

/Eugenia Garrett-Wackowski/	May 13, 2022
Signature	Date
Eugenia Garrett-Wackowski	(925) 472-5000
Typed or printed name	Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on May 13, 2022.

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Sharleen Lane/
Sharleen Lane

PATENT
Attorney Docket No.: 095920-004120US-1240999
Client Ref. No.: DOW-P05877-2-C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Arturo Angel *et al.*

Application No.: 16/179,576

Filed: November 2, 2018

For: TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

Customer No.: 112120

Confirmation No.: 1093

Examiner: Kathrien Ann Cruz

Art Unit: 1627

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

The references cited on attached form PTO/SB/08A are being called to the attention of the Examiner. In accordance with the provisions of 37 CFR §1.98(a)(2), copies of the cited references are provided.

It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

As provided for by 37 CFR §1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no

Padagis Ex. 1029
IPR Petition - USP 11,311,482

representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

This Information Disclosure Statement is being filed concurrently with the filing of a Request for Continued Examination under 37 CFR §1.114. Therefore, under 37 CFR §1.97(b)(4), Applicant believes that no fee is required for submission of this statement. However, if any fees are due for the submission of this Information Disclosure Statement, please deduct those fees from Deposit Account No. 20-1430.

Respectfully submitted,

/Eugenia Garrett-Wackowski/

Eugenia Garrett-Wackowski
Registration No. 37,330

KILPATRICK TOWNSEND & STOCKTON LLP

76020286V.1

Attachment

Padagis Ex. 1029
IPR Petition - USP 11,311,482

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16/179,576
	Filing Date	November 2, 2018
	First Named Inventor	Arturo Angel
	Art Unit	1627
	Examiner Name	Kathrien Ann Cruz
	Attorney Docket Number	095920-004120US-1240999

U.S. PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code [1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

U.S. PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code [1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages, Columns, Lines where Relevant Passages or Relevant Figures Appear	T[5]

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1.	Allergan, Inc. "Drug Approval Package", Medical Review(s) on Tazorac™ cream, part 1, Sept 25, 2000, 32 pages.	
	2.	Allergan, Inc. "Tazarotene Cream Package Insert", version 1.0, October 16, 2000, 12 pages.	

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Electronic Patent Application Fee Transmittal	
Application Number:	16179576
Filing Date:	02-Nov-2018
Title of Invention:	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES
First Named Inventor/Applicant Name:	Arturo Angel
Filer:	Eugenia Garrett-Wackowski/Sharleen Lane
Attorney Docket Number:	095920-004120US-1240999

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	1253	1	1480	1480
Miscellaneous:				
RCE- 1ST REQUEST	1801	1	1360	1360
		Total in USD ($)		**2840**

Electronic Acknowledgement Receipt	
EFS ID:	45714053
Application Number:	16179576
International Application Number:	
Confirmation Number:	1093
Title of Invention:	TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES
First Named Inventor/Applicant Name:	Arturo Angel
Customer Number:	112120
Filer:	Eugenia Garrett-Wackowski/Sharleen Lane
Filer Authorized By:	Eugenia Garrett-Wackowski
Attorney Docket Number:	095920-004120US-1240999
Receipt Date:	13-MAY-2022
Filing Date:	02-NOV-2018
Time Stamp:	20:36:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$2840
RAM confirmation Number	E20225CK37494748
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

Padagis Ex. 1029
IPR Petition - USP 11,311,482

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		095920-004120US_AMDAF.pdf	321199 967873bf760c76b478b128acabf4310f1728321e	yes	10
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment Submitted/Entered with Filing of Continued Prosecution Application (CPA)/Request for Continued Examination(RCE)		1	1	
	Claims		2	3	
	Applicant Arguments/Remarks Made in an Amendment		4	10	
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	095920-004120US_RCE.PDF	1351849 a7059d88bcaf232de7211ebf95d3f33277199f2e	no	3
Warnings:					
Information:					
3	Extension of Time	095920-004120US_EOT.pdf	178123 a429d910a49524f6b3f12ea2b85aca6bfe4fa28f	no	1
Warnings:					
Information:					
4		095920-004120US_IDS.pdf	233669 3997fe8a74ae5ed8803f32b73ab90eb885038b6a	yes	3
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	2	

Padagis Ex. 1029
IPR Petition - USP 11,311,482

	Information Disclosure Statement (IDS) Form (SB08)		3	3	
Warnings:					
Information:					
5	Non Patent Literature	Allergan_DrugApprovalPackage_Tazorac_MedicalReview_Part1_09-25-2000_32pages.pdf	1492707 caa7d0e8d16777ac6057e0e9c49ff96931734e7d	no	32
Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	40994 186a4e0e337ac6f258939ca3a713b7edf010de80	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3618541		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on May 13, 2022.

KILPATRICK TOWNSEND & STOCKTON LLP

By: /Sharleen Lane/
Sharleen Lane

PATENT
Attorney Docket No.: 095920-004120US-1240999
Client Ref. No.: DOW-P05877-2-C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Arturo Angel *et al.*

Application No.: 16/179,576

Filed: November 2, 2018

For: TOPICAL COMPOSITIONS AND METHODS FOR TREATING SKIN DISEASES

Customer No.: 112120

Confirmation No.: 1093

Examiner: Kathrien Ann Cruz

Art Unit: 1627

AMENDMENT / RESPONSE TO OFFICE ACTION

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Final Office Action mailed June 11, 2021, please enter the following amendments and consider the following remarks:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

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AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings of claims in the application.

Listing of Claims:

1. (Currently amended) A topical pharmaceutical composition for treating ~~a skin disease~~ acne, comprising:

a sole active pharmaceutical ingredient consisting of tazarotene at a concentration of 0.045 percent by weight of the composition;

wherein said composition is an oil-in-water emulsion lotion comprising an oil phase and an aqueous phase,

wherein the oil phase comprises a dicarboxylic acid ester and a mineral oil,

wherein the aqueous phase comprises water and a carbomer homopolymer,

wherein the composition further comprises a polymeric emulsifier, and

wherein the tazarotene is in solution in the oil phase.

2-5. (Canceled)

6. (Previously presented) The topical pharmaceutical composition of claim 1, wherein:

the dicarboxylic acid ester and the mineral oil are present in a total amount of 10-12 percent by weight of the composition,

the carbomer homopolymer is present in an amount of 0.5-0.7 percent by weight of the composition, and

the polymeric emulsifier is present in an amount of 0.3-0.5 percent by weight of the composition.

7. (Previously presented) The topical pharmaceutical composition of claim 1, wherein the dicarboxylic acid ester in the oil phase of the emulsion is diethyl sebacate.

8. (Previously presented) The topical pharmaceutical composition of claim 1, wherein the composition further comprises sorbitol solution, 70%.

9. (Previously presented) The topical pharmaceutical composition of claim 8, wherein the sorbitol solution, 70%, is present in an amount of 10-11 percent by weight of the composition.

10. (Previously presented) The topical pharmaceutical composition of claim 1, wherein the oil phase comprises diethyl sebacate and light mineral oil.

11. (Canceled)

12. (Original) The topical pharmaceutical composition of claim 1, having a pH of about 4 to about 6.

13-26. (Canceled)

27. (Previously presented) The topical composition of claim 1 consisting essentially of:

0.045 weight % tazarotene;
2.5 -3.5 weight % diethyl sebacate;
7.5-8.5 weight % light mineral oil;
0.05-0.2 weight % sorbitan monooleate;
10-11 weight % sorbitol solution, 70%;
0.1-0.2 weight % methylparaben;
0.02-0.04 weight % propylparaben;
0.03-0.06 weight % edetate disodium dihydrate;
0.3-0.05 weight % carbomer polymer type B;
0.5-0.7 weight % carbomer homopolymer type A;
sodium hydroxide, q.s. to pH 5.5 ±0.5; and
purified water, q.s. to 100 weight %.

28. (Canceled)

REMARKS

Upon entry of the present amendment, claims 1, 6-10, 12, and 27 will be pending in this application. Claim 1 is amended and claim 28 is canceled without disclaimer or prejudice to future prosecution. No new matter is added. Based on the following remarks, Applicant respectfully requests reconsideration and allowance of the pending claims.

I. Amendments to the Claims

Claim 1 is amended to recite that the composition is for treatment of acne. Support for the amendment can be found, for example, in the specification at page 2, paragraph [0005]. The amendment introduces no new matter, and Applicant respectfully requests that the amendment be entered.

II. Rejection of Claims under 35 U.S.C. § 112

Claim 1 is rejected under 35 U.S.C. § 112(b) as allegedly indefinite. Applicant respectfully traverses the rejection.

The Examiner alleges that claim 1 is rendered indefinite due to multiple recitations of the term "comprising." The Examiner points to MPEP § 2173.05(h)(I) in an effort to support the allegation ("If a Markush grouping requires a material selected from an open list of alternatives (e.g., "comprising" or "comprises" the recited alternatives), the claim should generally be rejected under 35 U.S.C. § 112(b) as indefinite because it is unclear what other alternatives are intended to be encompassed by the claim.")

Applicant respectfully submits that this section of the MPEP does *not* apply to pending claim 1. MPEP § 2173.05 specifically refers to the recitation of alternative limitations in Markush claims. *None* of the limitations noted by the Examiner are alternatives that may be substituted for one another.

The claimed composition contains an oil phase which, in turn, contains a dicarboxylic acid ester and a mineral oil. Likewise, the claimed composition *also* contains an aqueous phase which contains water and a carbomer homopolymer. Finally, the composition *also* contains a polymeric emulsifier. These components are *not* alternatives that may be substituted with each other. The limitations are *not* Markush groupings, and the holding cited by the Examiner does