of oil is prepared by adding the emulsifier to a triacylglycerol oil. The oil phase may also contain oil-soluble additives such as antioxidants and fragrance. The total emulsifier concentration is 1.5 % by weight. The oil phase is then gently mixed. The continuous phase may be pure water or an aqueous solution containing water-soluble additives such as glycerol, preservatives and buffers. A water-soluble active compound, such as glycerol as a moisturiser, may then be added to the aqueous phase; consequently, an oil-soluble compound such as 13-hydroxy-9,11-octadecadienoic acid (13-HODE) is added to the oil phase. Hydrocortisone, an anti-inflammatory drug which is insoluble in both water and oil, may be dispersed in either the aqueous phase or the oil phase. Alternatively, the drug may also be added to the final cream in an extemporaneous preparation. If necessary, the pH of the aqueous phase is adjusted. The oil phase as well as the aqueous phase are preheated to 70°C and then the oil phase is added to the aqueous phase under high-shear mixing. The pre-emulsion is then subjected to homogenisation at 200 psi. After cooling, the cream is transferred to suitable containers.

The invention also refers to the use of a topical formulation of the invention, wherein the incorporated compound is a moisturising compound for the preparation of a medicament for prophylaxis or treatment of atopic dermatitis.

Formulations, that is creams and lotions, having the following, preferred compositions can be prepared accordingly:

Topical cream base giving an incorporated substance a prolonged effect, comprising in % by weight

Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

Topical formulation having a prolonged moisturising effect, comprising in % by weight

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Glycerol	1.0-5.0 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

Topical formulation having a prolonged anti-inflammatory effect, comprising in % by weight

Hydrocortisone	0.5-1.5 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

Topical formulation having a prolonged anti-inflammatory effect, comprising in % by weight

Betamethasone	0.01-0.5 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

Topical formulation having a prolonged anti-psoriatic effect, comprising in % by weight

13-hydroxy-linoleic acid	0.001-0.1 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

Different topical formulations with various non-polar oils as the cream base were formulated as described in Examples 1-7.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Typical batch sizes are 0.5 to 1 kg. All concentrations are expressed in percent by weight.

EXAMPLES OF FORMULATIONS

Example 1. Moisturising cream

Oil phase:			
CPL®-Soybean oil	20.0	%	Oily material
Cetostearyl alcohol	7.0	%	Thickener
Glyceryl monostearate/citrate	2.0	%	Thickener
Emulsifier:			
CPL®-Galactolipid	1.5	%	
Aqueous phase:			
Glycerol	2.0	%	Moisturiser
Methyl-p-hydroxybenzoate	0.54	%	Preservative
Propyl-p-hydroxybenzoate	0.06	%	Preservative
Water	ad 100	%	

The oil and CPL®-Galactolipid were mixed in a beaker and then stirred with a magnetic stirrer until the galactolipid material had dispersed, that is for 30-60 min. The aqueous phase was mixed in another beaker and stirred with a magnetic stirrer. When the oil phase was homogeneous glyceryl monostearate/ citrate and cetostearyl alcohol were added. The oil phase and the aqueous phase were both heated to 65-70°C while stirring. The warm oil phase was added to the warm aqueous phase during high-shear mixing (Polytron PT-MR 3000). After addition of the oil phase the pre-emulsification (high-shear mixing) continued for 2 minutes at 15,000 rpm. The pre-emulsion was then homogenised 2 times at 200 psi in an Ultrasonic homogeniser (Branson Minisonic 4). The cream was allowed to cool in a water bath.

Example 2. Moisturising lotion

Oil phase:			
CPL®-Evening Primrose oil	12.0	%	Oily material
Cetostearyl alcohol	2.0	%	Thickener
Glyceryl monostearate/citrate	2.0	%	Thickener
Ascorbyl palmitate	0.02	%	Antioxidant

Emulsifier:

Padagis Ex. 1029
IPR Petition - USP 11,311,482

CPL®-Galactolipid	1.0 %	
Aqueous phase:		
Glycerol	2.0 %	Moisturiser
Methyl-p-hydroxybenzoate	0.54%	Preservative
Propyl-p-hydroxybenzoate	0.06%	Preservative
Fragrance	0.1 %	
Water	ad 100 %	

The lotion was prepared in the same way as the cream in Example 1, that is CPL®-Evening Primrose Oil, CPL®-Galactolipid and ascorbyl palmitate were mixed in a beaker and stirred until the galactolipid material had dispersed properly, that is for 30-60 minutes. The rest of the ingredients was added to the oil phase which was then heated to 70°C. The aqueous phase was prepared in another beaker and heated to 70°C. The oil phase was added to the aqueous phase during high-shear mixing. After addition of the oil phase the high-shear mixing, that is pre-emulsification, continued for 2 min at 15,000 rpm. The pre-emulsion was homogenized twice at 200 psi in an Ultrasonic homogeniser (Branson Minisonic 4). The lotion was allowed to cool in a water bath. The fragrance was added to the cool, that is 35°C, lotion.

Example 3. Moisturising cream

Oil phase:		
CPL®-Evening Primrose oil	20.0 %	Oily material
Cetostearyl alcohol	7.0 %	Thickener
Glyceryl monostearate/citrate	2.0 %	Thickener
Ascorbyl palmitate	0.02%	Antioxidant
Emulsifier:		
Galactolec™	3.0 %	
Aqueous phase:		
Glycerol	2.0 %	Moisturiser
Methyl-p-hydroxybenzoate	0.63%	Preservative
Propyl-p-hydroxybenzoate	0.07%	Preservative
Water	ad 100 %	

The cream was prepared as described in Example 1.

The cream had the following appearance in the microscope. Small regular to irregular droplets of uniform size evenly distributed in the sample. The average droplet size, estimated by comparison with a ruler installed in the microscope, was

Padagis Ex. 1029
IPR Petition - USP 11,311,482

found to be in the range of 5-10 μm.

Example 4. Cream base

Oil phase:		
Olive oil	20.0 %	Oily material
Cetostearyl alcohol	7.0 %	Thickener
Glyceryl monostearate	2.0 %	Thickener
Emulsifier:		
CPL®-Galactolipid	1.0 %	
Aqueous phase:		
Methyl-p-hydroxybenzoate	0.54 %	Preservative
Propyl-p-hydroxybenzoate	0.06 %	Preservative
Tri-sodium citrate dihydrate	0.035%	pH-modifier
Citric acid (aq.)	q.s. pH 3.5	pH-modifier
Water	ad 100 %	

The cream was prepared as described in Example 1.

Example 5. Cream base

Oil phase:		
Medium-chain triglyceride oil	10.0 %	Oily material
Cetostearyl alcohol	7.0 %	Thickener
Glyceryl monostearate	2.0 %	Thickener
Emulsifier:		
CPL®-Galactolipid	1.0 %	
Aqueous phase:		
Methyl-p-hydroxybenzoate	0.18 %	Preservative
Propyl-p-hydroxybenzoate	0.02 %	Preservative
Water	ad 100 %	

The cream was prepared as described in Example 1.

Example 6. Anti-inflammatory cream

Oil phase:		
Hydrocortisone	1.0 %	Active substance
CPL®-Evening Primrose oil	20.0 %	Oily material
Cetostearyl alcohol	7.0 %	Thickener
Glyceryl monostearate	2.0 %	Thickener
Ascorbyl palmitate	0.02 %	Antioxidant
Emulsifier:		
CPL®-Galactolipid	1.5 %	
Aqueous phase:		
Glycerol	2.0 %	Moisturiser
Methyl-p-hydroxybenzoate	0.63 %	Preservative

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Propyl-p-hydroxybenzoate	0.07 %	Preservative
Water	ad 100 %	

Hydrocortisone was added to the mixture of oil and galactolipid. Otherwise the cream was prepared as described in Example 1.

Example 7. Anti-inflammatory cream

Oil phase:		
Betamethasone, dipropionate	0.05 %	Active substance
CPL®-Evening Primrose oil	20.0 %	Oily material
Cetostearyl alcohol	7.0 %	Thickener
Glyceryl monostearate	2.0 %	Thickener
Ascorbyl palmitate	0.02 %	Antioxidant
Emulsifier:		
CPL®-Galactolipid	1.5 %	
Aqueous phase:		
Glycerol	2.0 %	Moisturiser
Methyl-p-hydroxybenzoate	0.63 %	Preservative
Propyl-p-hydroxybenzoate	0.07 %	Preservative
Water	ad 100 %	

A comparable cream is obtained if betamethasone, dipropionate 0.05 % is replaced by betamethasone, valerate 0.1 %.

Example 8. Anti-psoriatic cream

Oil phase:		
13-HODE	0.01 %	Active substance
CPL®-Evening Primrose oil	20.0 %	Oily material
Cetostearyl alcohol	7.0 %	Thickener
Glyceryl monostearate	2.0 %	Thickener
Ascorbyl palmitate	0.02 %	Antioxidant
Emulsifier:		
CPL®-Galactolipid	1.5 %	
Aqueous phase:		
Methyl-p-hydroxybenzoate	0.63 %	Preservative
Propyl-p-hydroxybenzoate	0.07 %	Preservative
Water	ad 100 %	

A small amount, about 5 %, of the oil mixture was added to 13-HODE (13-hydroxy-linoleic acid, from Scotia Pharmaceuticals Ltd, Carlisle). This mixture was not heated like the rest of the oil phase and was added separately during the pre-emulsification

Padagis Ex. 1029
IPR Petition - USP 11,311,482

step. Otherwise the cream was prepared as in Example 1.

EXPERIMENTAL TESTS

Tests of skin smoothing and moisturising properties.

The aim of the studies was to evaluate the moisturising and smoothing properties of creams of the invention after use twice daily for 14 days. Twenty healthy female volunteers aged 18 to 60 years were studied.

The test creams had the following compositions:

	Cream A	Cream B	Cream C
Oil phase:			
CPL®-Evening Primrose oil	20.0 %	20.0 %	20.0 %
Cetostearyl alcohol	7.0 %	7.0 %	7.0 %
Ascorbyl palmitate	0.02 %	0.02 %	0.02 %
Emulsifier:			
CPL®-Galactolipid	0.75 %	0.75 %	1.5 %
Aqueous phase:			
Glycerol	-	2.0 %	2.0 %
Methyl-p-hydroxybenzoate	0.54 %	0.54 %	0.63 %
Propyl-p-hydroxybenzoate	0.06 %	0.06 %	0.07 %
Water	ad 100 %	ad 100 %	ad 100 %

All creams were prepared in the following way: The CPL®-Evening Primrose oil, CPL®-Galactolipid and ascorbyl palmitate were mixed in a beaker and then stirred with a magnetic stirrer until the galactolipid was completely dispersed, that is for 30-60 min. The aqueous phase was mixed in another beaker and stirred with a magnetic stirrer. When the oil phase was homogeneous, cetostearyl alcohol was added. The oil phase and the aqueous phase were both heated to 55°C while stirring. The warm oil phase was added to the warm aqueous phase during high-shear mixing (Polytron PT-MR 3000). After addition of the oil phase the pre-emulsification continued for 2 min at 15,000 rpm. The pre-emulsion was then homogenised 6 times at 200 psi in an Ultrasonic homogeniser (Branson Minisonic 4). The cream was allowed to cool in a water bath.

On the first day of the study the subjects were instructed as to the proper manner of application of the products. The creams were then applied by the subjects at home

Padagis Ex. 1029
IPR Petition - USP 11,311,482

once in the morning and once in the evening as part of the daily body care routine.

An amount approximating the usual applied amount of skin care cream (one fingertip full, approximately 0.2 ml) was taken from the respective container, applied to the test fields noted on the container and rubbed in with the finger. The test fields were not marked during the application period. In order to locate the test fields, the inside of the forearm was optically divided into thirds. The middle third was defined as the lower test field and the upper third as the upper test field. An area the width of two fingers was left free between the two test fields on the underarm. A field on the inside of the upper arm served as the upper test field. The subjects were given a stencil to simplify locating the boundary between the lower and middle field on each arm.

The subjects were instructed that the finger used to apply the creams had to be carefully cleaned with a dry cloth between applications to avoid mixing of the test preparations.

Skin moisture was assessed using a device for determining the capacitance of the skin surface (Corneometer CM 820, Courage & Khazaka, Cologne). The capacity of a conductor (the more or less moist stratum corneum on the skin surface) to store an electric charge is recorded using this method. The instrument probe was held onto the skin without pressing for a brief, defined interval. Five measurements were made per test field. The mean of the five measurements was recorded on-line.

Following the measurement of skin moisture, a negative replica of the skin was made using 2-component silicone rubber impression material (Xantopren® L, Fa. Bayer Dental, Leverkusen, Germany). The subjects laid the stretched but relaxed arms on special arm rests with the inner surface facing upwards. A surface of approximately 8 x 8 cm in the centre of the test fields was thinly covered with the impression mass mixed with hardener. Approximately 3 min were required for setting. The replicas were peeled off after 8 min. Labels were pressed into the lower edge of the hardening mass. These serve for

Padagis Ex. 1029
IPR Petition - USP 11,311,482

identification as well as marking of the alignment.

The surface of the silicone replicas was scanned using a Hommel-Tester T2000 (Hommelwerke, Schwenningen, Germany). The path and speed of scanning were controlled over the software. The surface was characterised by the roughness parameter $R_{z(DIN)}$. Each replica was measured in a star-shaped fashion in 12 directions (30° angles).

Skin moisture was measured and replicas taken immediately before the first application of treatments (baseline) and on study days 15, 16 and 17. The measurements on day 15 were performed 12 to 16 hours after the last application. The measurements on day 16 and 17 were performed 36 to 40 h and 60 to 64 h, respectively, after the last application. The silicone replicas were made directly following the corneometer measurements. The results are presented in Table 1 and 2.

Cream A did not lead to any improvement at all in skin moisture. The incorporation of an active moisturising agent (glycerol) in Cream B resulted in a clearly demonstrated moisturising effect as expected. Unexpectedly though, the effect was also long lasting.

Table 1. Skin moisturisation.

	Comparison	Moisturisation
Cream A (no active)	day 0 vs. day 15	-1.3 %
	day 0 vs. day 16	-0.9 %
Cream B (glycerol)	day 0 vs. day 15	+6.3 %**
	day 0 vs. day 16	+7.3 %**
Cream C (glycerol)	day 0 vs. day 15	+16.9 %**
	day 0 vs. day 16	+12.7 %**
	day 0 vs. day 17	+6.6 %**

*= p<0.1 ** = p<0.05

Table 2. Skin roughness.

	Comparison	Smoothing
Cream C (glycerol)	day 0 vs. day 15	+6.3 %*
	day 0 vs. day 16	+6.6 %**
	day 0 vs. day 17	+3.3 %*

*= p<0.1 ** = p<0.05

The sustained effect found for Cream B was even more pronounced for Cream C which contained a higher content of

Padagis Ex. 1029
IPR Petition - USP 11,311,482

the galactolipid based emulsifier. Conventional creams containing glycerol have not been reported to exhibit any sustained moisturising effect at all. The results presented in Table 1 and 2 clearly and surprisingly demonstrate a moisturising as well as a smoothing effect which last for at least three days after the last application.

The test of skin smoothing and moisturising properties of creams was repeated with slightly different cream compositions. The test creams had the following compositions:

	Cream D
Oil phase:	
CPL®-Evening Primrose oil	20.0 %
Cetostearyl alcohol	7.0 %
Glyceryl stearate	2.0 %
Ascorbyl palmitate	0.02 %
Emulsifier:	
CPL®-Galactolipid	1.5 %
Aqueous phase:	
Glycerol	2.0 %
Methyl-p-hydroxybenzoate	0.63 %
Propyl-p-hydroxybenzoate	0.07 %
Water	ad 100 %

In creams E, F and G the CPL® - Evening primrose oil was replaced by the same amount, i.e. 20 % of soybean oil, MCT oil and liquid paraffin oil, respectively. All other ingredients and the amounts of each were as in cream D.

Obviously the prolonged moisturising effect is dependent of the choice of oil as shown in Table 3 below. However, all four creams based on the oil-in-water emulsion type, described in the present invention, have a general ability of prolonging the moisturising effect compared to commercially available creams.

Table 3. Skin moisturisation

	Comparison	Moisturisation
Cream D	day 0 vs. day 15	+8.4 %**
(Evening primrose oil)	day 0 vs. day 16	+10.9 %**
	day 0 vs. day 17	+6.0 %**

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Cream E (Soybean oil)	day 0 vs. day 15	+6.7 %**
	day 0 vs. day 16	+4.3 %
	day 0 vs. day 17	+1.7 %
Cream F (MCT oil)	day 0 vs. day 15	+8.8 %**
	day 0 vs. day 16	+6.3 %**
	day 0 vs. day 17	+5.8 %*
Cream G (Liquid paraffin oil)	day 0 vs. day 15	+7.2 %**
	day 0 vs. day 16	+6.5 %**
	day 0 vs. day 17	+2.4 %

* = p<0.1 ** = p<0.05

A consumer test

Thirty human volunteers participated in a consumer test of cream D described above. All subjects were regular users of emollients and moisturisers; eighteen subjects because of having atopic dry skin and twelve subjects because of necessary frequent exposure to detergents and water, e.g. during work at hospitals.

All subjects received one tube containing 100 ml of the cream and a questionnaire to fill in prior to, during and after having used the cream for two days.

The questionnaire was divided into six parts. The first part covered the background, sex, date of birth, the reason for and the frequency of using emollients etc. Parts two, three, four and five covered questions related to: the immediate reaction, 5-10 minutes later, after washing of hands, and after two days of using the cream, respectively. Part six covered "Further comments". In parts two, three, four and five, the question raised was, "To what extent do you agree with the following statements?" The extent of agreement could be given a score between 0 and 10, where 0 meant "No, not at all" and a score of 10 meant "Yes, definitely". For practical reasons the score results were grouped together according to the following:

0-2: No, not at all

3-7: Yes, to a certain degree

8-10: Yes, definitely

The moisturising effect was found to be more long lasting

Padagis Ex. 1029
IPR Petition - USP 11,311,482

than what is normally experienced with this type of products. It is also clear from the results presented in Table 4 that washing the skin is not detrimental to the effect, which is normally the case when using emollients and moisturisers. It makes it much easier to keep the skin smooth and supple and to avoid dryness. The cream was not found to be irritating to dry and sensitive skin. It seems to be very well tolerated also by persons with atopic dry skin.

Table 4.

To what extent do you agree with the following statements?

Statement / Extent of agreement	No. of subjects giving the score 0-2	3-7	8-10
Immediate reaction			
"The cream is easily absorbed into the skin"	3	13	14
"The cream is greasy on my skin"	10	14	5
"The odour of the cream is unpleasant"	22	7	1
"The cream irritates the skin"	30	0	0
"The skin feels smooth and supple"	1	4	25
5-10 minutes later			
"The cream is greasy on my skin"	24	4	2
"The odour of the cream is unpleasant"	22	5	1
"The skin feels smooth and supple"	0	6	24
"The skin is dry"	25	4	1
After washing of hands (with soap and water)			
"The skin still feels smooth and supple"	4	5	21
"The skin is dry again"	23	2	5
After two days of using the cream			
"I like the cream"	1	7	20
"The effect of the cream is long lasting"	4	8	16

A pilot study on children having atopic dry skin

The study was performed at two Swedish hospitals by dermatologists specialised in the field of atopic dermatitis. Twenty children were treated for two months with cream D described above. The age of the children varied between one and twelve years and they were all having widespread atopic dry skin, regularly developing into periods of acute atopic dermatitis. The dermatitis was treated in the normal way, i.e.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

with glucocorticoids of varying potencies. Treatment with cream D was started at a stage with no acute dermatitis and the cream was applied only once daily at bedtime.

Preliminary results strongly indicate the potential of cream D with respect to its ability to decrease frequency as well as seriousness of the periods of atopic dermatitis. Furthermore, the previously necessary amounts of glucocorticosteroids used could be significantly reduced if cream D was used to prevent skin from being dry and sensitive.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

CLAIMS

1. A topical formulation of the oil-in-water emulsion type, in which a variety of pharmaceutical or cosmetic compounds can be incorporated, comprising an oily material, an emulsifier and an aqueous phase, wherein the emulsifier is a glycolipid based material, and which after application on the skin gives a prolonged local effect of the incorporated compound.

2. A topical formulation according to claim 1, comprising 0.1-50 % by weight oily material and 0.5-20 % by weight galactolipid emulsifier.

3. Use of a topical formulation of the oil-in-water type comprising an oily material, an aqueous phase and an emulsifier, wherein the emulsifier is a galactolipid material, as a carrier for providing a prolonged effect of an incorporated active substance.

4. Use according to claim 3, wherein the topical formulation comprises 0.1-50 % by weight oily material, preferably 1-40 %, and 0.5-20 % by weight emulsifier.

5. Use according to claim 3 or 4, wherein the galactolipid material consists of at least 50 % by weight digalactosyl-diacylglycerols and a remainder of other polar lipids, preferably in an amount of 1.0-5.0 % by weight.

6. Use according to any of claims 3-5, wherein the galactolipid material consists of 50-70 % by weight digalactosyldiacyl-glycerols and 30-50 % other polar lipids.

7. Use according to claim 3 or 4, wherein the galactolipid material is a fractionated oat oil which contains 10-90 % by weight polar lipids and a remainder of non-polar lipids, preferably in an amount of 2.0-10 % by weight.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

8. Use according to any of claims 3, 4 and 7, wherein the galactolipid material is a fractionated oat oil which contains 40-60 % by weight polar lipids and a remainder of non-polar lipids.

9. Use according to any of claims 3-8, wherein the active substance is a pharmacologically active substance.

10. Use according to any of claims 3-8, wherein the active substance is a cosmetological substance.

11. Use according to any of claims 3-8, wherein the active substance is a moisturiser.

12. Topical cream base giving an incorporated substance a sustained effect, comprising in % by weight

Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

13. Topical formulation having a prolonged moisturising effect, comprising in % by weight

Glycerol	1.0-5.0 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

Padagis Ex. 1029
IPR Petition - USP 11,311,482

14. Topical formulation having a prolonged anti-inflammatory effect, comprising in % by weight

Hydrocortisone	0.5-1.5 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

15. Topical formulation having a prolonged anti-inflammatory effect, comprising in % by weight

Betamethasone	0.01-0.5 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

16. Topical formulation having a prolonged anti-psoriatic effect, comprising in % by weight

13-hydroxy-linoleic acid	0.001-0.1 %
Oily material	10.0-30.0 %
Galactolipid emulsifier	0.5-5 %
Thickener	2.0-10.0 %
Preservative	0.1-1.0 %
Water	ad 100 %

17. Use of a topical formulation according to claim 1 or 2, wherein the incorporated compound is a moisturising compound for the preparation of a medicament for prophylaxis or treatment of atopic dermatitis.

18. Use of a topical formulation according to claim 1 or 2, wherein the compound is a corticosteroid for the preparation of a medicament for treatment of skin inflammation.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00347

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/107, A61K 7/00, A61K 47/00
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)

IPC6: A61K

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

SE,DK,FI,NO classes as above

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

WPI, EPODOC, EMBASE, MEDLINE, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9520943 A1 (KARLSHAMNS LIPIDTEKNIK AB), 10 August 1995 (10.08.95), page 4, line 20 - page 7, line 11, claims ---	1-15
X	EP 0647443 A1 (L'OREAL), 12 April 1995 (12.04.95), claims --- ---	1-4,9-11

☐ 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" erlier 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
16 June 1999	03 -07- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson/EÖ Telephone No. +46 8 782 25 00

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Padagis Ex. 1029
IPR Petition - USP 11,311,482

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00347

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 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. ☒ Claims Nos.: 3-8 (partly), 9
because they relate to subject matter not required to be searched by this Authority, namely:

see next page

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:

Box II **Observations where unity of invention is lacking (Continuation of item 2 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 fee, this Authority did not invite payment of any additional fee.
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.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July1992)

Padagis Ex. 1029
IPR Petition - USP 11,311,482

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/00347

Remark: Claims 3-8 (partly) 9 are directed to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/ composition.

Form PCT/ISA/210 (extra sheet) (July1992)

Padagis Ex. 1029
IPR Petition - USP 11,311,482

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/06/99

International application No.
PCT/SE 99/00347

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Form PCT/ISA/210 (patent family annex) (July 1992)

Padagis Ex. 1029
IPR Petition - USP 11,311,482

INTERNATIONAL SEARCH REPORT

Information on patent family members

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International application No.
PCT/SE 99/00347

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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Padagis Ex. 1029
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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: TOPICAL GEL DELIVERY SYSTEM

(57) Abstract: A composition is provided that has a viscosity of less than about 15,000 cP and a pH of about 3.0 to 9.0 for treating a skin disorder in a human subject. The composition consists essentially of (a) a therapeutically-effective amount of at least one compound useful for treating such disorder, (b) a pharmaceutically-acceptable, lightly cross-linked polyacrylic acid polymer compatible with the compound, (c) optionally a water miscible solvent, (d) optionally a preservative, (e) optionally an oil phase component and suitable surfactant, and (f) water. The composition is useful for treating an inflammatory skin disorder, acne, or rosacea. The low viscosity composition has an advantage of being administered more accurately when combined with a container that administers the composition as drops.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

TOPICAL GEL DELIVERY SYSTEM

BACKGROUND OF THE INVENTION

FIELD OF INVENTION

This invention relates to a composition for treating a skin disorder in a human, and a method of administering and preparing such composition.

BACKGROUND

Skin disorders are a common problem in childhood, adolescence and adulthood. Skin disorders can include, for example, acne, inflammatory diseases such as atopic eczema, or rosacea.

Acne vulgaris is a follicular disease characterized by pilosebaceous inflammations such as comedones, papules, pustules, cysts and nodules. Chiefly a disease of adolescence (and often a cause of emotional distress), acne originates endogenously and stems for multifactorial influences. Major progressive factors in the development acne include hyperkeratosis of the follicular epithelium, increased sebum production, and proliferation of *Propionibacterium acnes*. These factors are primarily responsible for hyperkeratosis of the follicle lining, including retention of keratin and sebum, as well as the free fatty acid by-products of *P.acnes* metabolization which can lead to inflamed acne papules and pustules.

Although acne may also be influenced by exogeneous and hormonal factors, research has been centered around eliminating *P.acnes*, the most common cause of inflammation. To date, the pathogenesis of acne is not fully understood, and there is currently no cure for the disease. Many systemic and topical medications, such as tetracycline, have been used to manage and control acne. None, however, is universally successful.

Acne treatment is typified by "polypharmacy", whereby physicians employee simultaneous treatment with a variety of modalities. The search for improved acne treatments has been widespread and continuous during the past several decades. Enhanced cosmetic properties to encourage user compliance, the use of topical therapies in place of systemic drugs to reduce toxicity and side effects, and the introduction of new drugs and formulations represent the forefront of acne treatment advances.

The first use of a topical antibiotic, erythromycin, for the treatment of acne was reported by Fulton (Fulton, J.E. Jr. and Pablo, G. *Topical antibacterial therapy for acne.*

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Study of the family of erythomycins. Arch. Dermatol. 110:83-86, 1974). Topical administration of these potent agents has the advantage of reduced side effects, particularly those caused by systemic drug effects, e.g., nausea, gastrointestinal upset, diarrhea, and vaginal yeast overgrowth.

Lincomycin antibiotics have been employed in the topical treatment of acne (U.S. Patent No. 3,969,516). Lincomycin was commercialized by Upjohn Co. (now Pharmacia & Upjohn) as Cleocin T Solution, Gel, Lotion and Pledgets. Cleocin T Gel was an improvement over Cleocin T Solution because of the elimination of alcohol and the ease of application to the facial skin for the treatment of acne. This gel is based on carbomer 934, NF.

Atopic dermatitis is a polygenic disease with an inherited predelection and strongly influenced by environmental factors. The condition affects infants, children, adolescents and adults and is allergic in nature. The distribution is symmetrical, typically involving the face, neck and flexural areas. Atopic dermatitis is chronic, relapsing and usually pruritic. Topical treatment frequently includes topical corticosteroids, such as desonide, hydrocortisone valerate, fluocinolone acetonide, triamcinolone acetonide, betamethasone valerate, hydrocortisone butyrate, halobetasol propionate, betamethasone dipropionate, clobetasol propionate, difloransone diacetate, fluticasone propionate, budesonide or the like.

Rosacea is a chronic inflammatory eruption of the nose, face and other flushing areas of the skin. The disease is most common in middle aged women and is characterized by erythema, papules, pustules, telangiectasia and enlarged sebaceous glands. The cause etiology is not totally clear; however vasomotor lability and menopause are predisposing factors. The organism Demodex folliculorum is found frequently in the contents of inflamed pustular follicles, and has a possible role in this skin disorder. Treatments include topical metronidazole and oral tetracycline type antibiotics.

SUMMARY OF THE INVENTION

One aspect of this invention is a composition having a pH of about 3.0 to about 9.0 and a viscosity of less than about 15,000 centipoise (cP) for treating a skin disorder in a human subject. The composition comprises (a) a therapeutically-effective amount of at least one compound useful for treating such disorder, (b) a pharmaceutically-acceptable polyacrylic acid polymer compatible with the compound, (c) optionally a water miscible solvent, (d) optionally a preservative, (e) optionally an oil phase and surfactant, and (f) water.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Another aspect of the invention is a composition described above in combination with a container that accurately administers a portion of the composition for topical administration to a patient.

Another aspect of the invention is a composition described above in combination with labeling instructions for use in treating the skin disorder.

Still another aspect of the invention is a method for treating a skin disorder in a human subject, which method comprises administering a composition described above to an affected area of the subject's skin having such disorder in an amount and for a period of time sufficient to improve the skin disorder.

Still another aspect of the invention is a method for preparing a composition of this invention by combining water with a therapeutically-effective amount of a suitable compound and the polymer and optionally a water-miscible solvent and preservative. If a lotion is desired an oil phase is formed for integration with the aqueous phase.

Other aspects of the invention may be apparent upon further reading the specification and claims of the patent application.

SPECIFIC DESCRIPTION

This invention provides a novel topical gel or lotion delivery system for the treatment of skin diseases, particularly acne vulgaris. One unique aspect of the system is the use of a polymeric material that provides a gel material that has a very low viscosity but which is cosmetically elegant and aids in the administration process by providing a pourable composition that flows through a dropper tip easily.

The Composition

One aspect of this invention is a composition having a pH of about 3 to about 9 and a viscosity of less than about 15,000 cP for treating a skin disorder in a human subject. The composition comprises a therapeutically-effective amount of at least one compound useful for treating such disorder, a pharmaceutically-acceptable, lightly cross-linked polyacrylic acid polymer compatible with the therapeutically-effective compound, optionally a water miscible solvent, optionally a preservative, and water. The composition may include a solution of the active compound or a suspension. A lotion will also include a pharmaceutically-acceptable oil phase emulsified with one or more surfactants.

The composition is useful to treat skin disorders, *e.g.* acne, rosacea, or inflammatory skin diseases such as atopic dermatitis. The composition will include an active agent that will be one compound alone or two or more compounds in combination.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

The active agent can be an antibiotic, a corticosteroid, a retinoid, an anti-inflammatory imidazole, a non-steroidal anti-inflammatory agent (NSAID), or a combination.

An antibiotic is generally viewed as a drug that inhibits the growth of an unwanted microorganism. Representative examples of topical antibiotics include lincomycins, (*e.g.* clindamycin), erythromycin, minocycline, and tetracycline, and the pharmaceutically-acceptable salts, esters, or prodrugs thereof. Preferred is clindamycin phosphate.

A "retinoid" is a keratolytic drug related to retinoic acid and generally includes chemical entities such as retinol and its esters and closely related naturally-occurring derivatives and structurally-related synthetic analogs. This includes, for example, retinol, retinal, tretinoin (all-trans retinoic acid), isotretinoin, adapalene (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid), and the like. Of these, tretinoin is preferred.

Generally, a topical corticosteroid is a compound that is a structural modification of hydrocortisone (also known as cortisol) and that shows topical anti-inflammatory activity. Representative examples include those set forth in Table 65-1 at page 1575 of "Goodman & Gilman's The Pharmacological Basis of Therapeutics," Eighth Edition, McGraw-Hill, Inc. (1993). Specific, non-limiting examples of topical cortiocosteroids include those mentioned in the "background" section of this application. Preferred corticosteroids, when used as a single active agent, include diflorasone diactetate, desonide, fluticasone propionate, halobetasol priopionate, or budesonide. Halobetasol propionate or desonide is most preferred when used as a single active ingredient.

Nonsteroidal anti-inflammatory agents (NSAIDs) are compounds that suppress the inflammatory response when topically applied by inhibiting prostaglandin synthesis or by other mechanisms of action. Examples may be found in Goodman and Gilman, *Ibid.* Representative examples include ibuprofen, indomethacin, diclofenac, and naproxen and their salts. Preferred is diclofenac.

An anti-inflammatory imidazole is an imidazole compound that suppresses a topical inflammatory response. Metronidazole is a representative imidazole compound suitable for this invention.

In describing the details of the composition, the numerical ranges given herein are those amounts that provide the functional results in the composition. Thus, the ranges are generally introduced with the term "about" to indicate a certain flexibility in the range, *i.e.* ±10% or less at the lower and upper numerical ranges given.

As mentioned, the active agent may be present alone or in combination. For example, a topical antibiotic, such as clindamycin phosphate, may be combined with a

Padagis Ex. 1029
IPR Petition - USP 11,311,482

topical corticosteroid. Where a formulation is designed primarily for application to the facial area, to treat acne for example, it is preferred to combine an antibiotic (e.g. clindamycin phosphate) with a less potent corticosteroid, such as desonide, hydrocortisone valerate, fluocinolone acetonide, hydrocortisone butyrate, or triamcinolone acetonide. The topical antibiotic can also be combined with a retinoid, *e.g.* clindamycin phosphate and tretinoin or adapalene.

The composition of the invention will include a polymeric material that will be present in an amount sufficient to bring the viscosity of the composition to a level of not more than about 15,000 cP, preferably between about 100 and about 12,000, and more preferably between about 300 and about 10,000. The viscosity is determined at room temperature (20-25°C) using a Brookfield viscometer model DV-I+, spindle #27 at 12 revolutions per minute (rpm). If the measured viscosity is less than 4,000 cP, spindle #21 should be used instead of #27. By keeping the viscosity below about 15,000 cP, the advantages of more appealing cosmetic characteristics and ease of accurate application through improved flow and pourability are achieved.

The polymers that have been found to be particularly useful in the composition of the present invention are lightly cross-linked polyacrylic acid polymers which are available from B.F. Goodrich under the tradename CARBOPOL®. They are generically referred to as carbomers. The CARBOPOL polymers are hydrophilic polymers based on a polyacrylic acid structure. For use in the present invention the lightly cross-linked polymers include CARBOPOL 910, 941,971, and 981 and CARBOPOL ETD 2050.

Either CARBOPOL 941 or 981 is particularly valuable for the present invention because the viscosity of a gel based on CARBOPOL 941 or 981 is low relative to its concentration. This feature is the result of the low level of cross-linking within the polymer structure in a neutralized aqueous system. In contrast polyacrylic acid polymers which display a high level of cross-linking, such as CARBOPOL 980 or 974P, produce gels with higher viscosity at comparable concentrations.

A 0.5% solution of either CARBOPOL 941 or 981 at pH 7.5 has a viscosity measurement of from 4,000 to 11,000 cP (Brookfield viscometer at 20 rpm) compared to a viscosity measurement of from 40,000 to 60,000 cP for a comparable 0.5% solution of either CARBOPOL 940 or 980 (reference: B.F. Goodrich Product Guide, Bulletin 2).

This lower-level viscosity feature of the lightly cross-linked polyacrylic acid polymers, e.g. CARBOPOL 941 and 981, offers two advantages to the composition of the present invention. A gel made from one of these lightly cross-linked polymers provides

better skin feel and lubricity than a gel of comparable viscosity made from a highly cross-linked polymer. Second, a low viscosity gel can be administered very accurately by a dropper or drip-type dispenser as compared to other commercial products which are thicker gels that do not provide as accurate an application.

CARBOPOL 941 NF resin and its cosolvent polymerized alternative, CARBOPOL 981 NF resin, provide permanent emulsions and suspensions at low viscosities. The gels produced with these resins have excellent clarity. In ionic systems, they perform better than most of the other CARBOPOL resins and at concentrations below 1.5% in solvent systems. The polymers are available from B.F. Goodrich Specialty Chemicals, 9911 Brecksville Road, Cleveland, OH 44414-3247.

CARBOPOL resins are polymers of acrylic acid crosslinked with polyalkenyl ethers or divinyl glycol. The polymers are flocculated powders of primary particles averaging about 0.2 micron in diameter. The flocculated powders are agglomerates that average 2 to 7 microns as determined by Coulter Counter. These agglomerates cannot be broken down into the primary particle once produced.

Each primary particle can be viewed as a network structure of polymer chains interconnected by crosslinks. Without the crosslinks, the primary particle would be a collection of linear polymer chains intertwined but not chemically bonded. These linear polymers are soluble in a polar solvent, such as water. They swell in water up to 1000 times their original volume (and ten times their original diameter) to form a gel, especially when exposed to a pH environment above about 4-6. Since the pK_a of these polymers is 6.0±0.5, the carboxylate groups on the polymer backbone ionize, resulting in repulsion between the negative particles, which adds to the swelling of the polymer. Highly crosslinked polymers of this type do not dissolve in water, rather they form gels by forming homogeneous dispersions.

The glass transition temperature of CARBOPOL resin is 105°C (221° F) in powder form. However, the glass transition temperature drops dramatically as the resin comes into contact with water. The polymer chains start gyrating and the radius of gyration becomes bigger and bigger. Macroscopically, this phenomenon manifests itself as swelling.

The aqueous composition of the invention, will optionally include a water miscible solvent and a preservative. The water miscible solvent (i.e. a cosolvent) will be present if needed, to assist in dissolving the active agent. The cosolvent may be a single component or a mixture. Examples include those that are miscible with water such as ethanol,

Padagis Ex. 1029
IPR Petition - USP 11,311,482

propylene glycol, glycerin, polyethylene glycol 400, and the like. Certain water-miscible solvents, such as glycerin or propylene glycol, also add beneficial humectant properties to the composition. Drug delivery and penetration into the skin can be modified by the water-miscible cosolvent composition.

The preservative useful in the composition is material that aids in ensuring a stable composition and/or prevents growth of bacteria. Thus, a preservative may be one or more of an antioxidant, a chelator, an antibacterial, or the like. Suitable preservatives include methylparaben, butylparaben, propylparaben, benzyl alcohol, sorbic acid, imidurea, thimerisal, propyl gallate, BHA, BHT, citric acid, disodium edetate, and the like. Another optional additive is a fragrance. Generally, this will be present in a trace amount only and has no effect on the functioning of the composition.

A preferred composition, particularly for the treatment of acne, will exhibit a pH of about 3 to 9, preferably about 4 to 7, and most preferably at about 5 to 6. Thus, the composition may also include a pH-adjusting agent as needed at a level to adjust the pH to the desired range. Such agents include many pharmaceutically-acceptable organic or inorganic bases, e.g., sodium hydroxide and tromethamine. The pH chosen will depend in part on the pH tolerance of the active agent chosen for the composition. The examples provide guidance for certain compounds and suitable pH values for the compositions.

Another aspect of this invention is an emollient embodiment, *i.e.*, a fluid emulsion or lotion. This aspect of this invention is a composition having an internal oil phase dispersed with the aid of at least one surfactant, e.g. an emulsifier, in water. Suitable surfactants are well known in the art and include those referred to as anionic and nonionic agents. These are described in Remington: The Science and Practice of Pharmacy, Nineteenth Edition, Vol. 1 at p. 251. Representative surfactants include polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, sorbitan laurate, sorbitan oleate, sorbitan stearate, polyoxyethylene stearate, sodium laureth sulfate, and laureth-10. Oil phase components include those that are commonly used in the art such as mineral oil, petrolatum, stearyl alcohol, cetyl alcohol, isopropyl myristate, diisopropyl adipate, stearic acid, white wax, and the like.

The following Table sets forth operational and preferred ranges of the various components for a gel composition having an active ingredient, which may be a single compound or a combination of two or more compounds. The term surfactant means one or more surfactants, which includes wetting agents and emulsifiers.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

TABLE A

Component	% w/w		
	Operational	Preferred	More Preferred
Active ingredient	0.005-10.0	0.01-5.0	0.05-2.0
Polyacrylic Polymer Acid	0.05-3.0	0.05-1.0	0.1-0.5
Cosolvent	0.0-70.0	0.0-40.0	0.0-25.0
Preservative	0.0-3.0	0.01-1.0	0.05-0.25
Surfactant*	0.0-8.0	0.0-5.0	0.0-3.5
Oil phase*	0.0-50.0	0.0-25.0	0.0-15.0
Water	QSAD 100	QSAD 100	QSAD 100
Base	QS pH	QS pH	QS pH

* Present for lotion

The following Table B sets forth the operational, preferred, and more preferred concentrations of representative active ingredients that can beneficially be used in practicing our invention, whether alone or in combination. The exact amount will be readily determined by one of ordinary skill by referencing standard texts such as the Physicians Desk Reference or Goodman and Gilmann's referred to hereinbefore.

TABLE B

Component	% w/w		
	Operational	Preferred	More Preferred
Antibiotic	0.1-5.0	0.5-2.0	0.5-1.0
Corticosteroid	0.005-2.5	0.01-1.0	0.05-0.1
Retinoid	0.005-0.5	0.05-0.1	0.025-0.05
Imidazole	0.1-5.0	0.5-2.0	0.75-1.0
NSAID	0.1-3.0	0.2-2.0	0.2-1.0

To make an emulsion (*i.e.*, lotion) form of our invention as broadly set forth in Table A, the surfactant and oil phase component are included in the composition. The following table illustrates the manner in which the composition is modified to form a lotion.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

TABLE C

Component	% w/w		
	Operational	Preferred	More Preferred
Surfactant	0.1-8.0	0.5-5.0	1.0-3.5
Oil phase	1.0-50.0	2.5-25.0	5.0-15.0

The preferred formula of the composition would either be preservative-free or have a decreased level of preservatives as compared to material that is commercially available. This is important because the presence of preservatives in a composition can result in irritation or allergic reaction of the skin. Reducing the possibility of skin irritation or allergic reaction in a composition provides a better product. Regarding compositions that contain clindamycin phosphate, the leading product is Cleocin T Gel. It is a clear viscous gel that tests have shown is not as well accepted as the less viscous material of the invention made with a more lightly cross-linked polymer. By controlling the viscosity of the gel at a low level it can be accurately dispensed from a clear plastic squeeze bottle rather than from an ointment tube. The advantage is two-fold. One is accurate dosage control by using a reduced orifice tip and improved product presentation for marketing. In addition, tests have shown that the less viscous material is cosmetically more elegant and will result more regular use.

In preparing a composition of this invention general formulation techniques known in the art of pharmaceutical science will be used. See, for example, Remington: The Science and Practice of Pharmacy, Nineteenth Edition, Mack Publishing Company (1995). Preparation of specific formulations may be found in the examples.

To prepare a gel with two active ingredients where one is suspended and the other is dissolved, first add the insoluble active to a water-miscible ingredient, or a portion of the water with a surfactant, to disperse. Separately, dissolve the other active and any other preservative ingredients in the purified water. Disperse the gelling agent in the aqueous solution with appropriate stirring. Then add the dispersion of the first active ingredient to the gel and mix well to blend. Last, add a pH adjusting agent to adjust the pH to the desired range. The preparation of a gel when both active ingredients are dissolved is similar, varying only in the first step. First, add the active with lower aqueous solubility to a solvent, blend of solvents, or water. Mix to dissolve. Separately, dissolve the other active and any preservative ingredients in the purified water. Disperse the gelling agent in the aqueous solution with appropriate stirring. Then add the solution of the first active to

Padagis Ex. 1029
IPR Petition - USP 11,311,482

the gel and mix well to blend. Last, add a neutralizing agent to adjust the pH to the desired range.

For a combination of an antibiotic e.g. clindamycin phosphate with a retinoid, such as tretinoin, three formulation approaches can be applied to a composition of the invention: 1) an aqueous gel, formed from a lightly crosslinked carbomer gelling agent, with the clindamycin phosphate dissolved and the tretinoin suspended; 2) an oil-in-water emulsion with the clindamycin phosphate dissolved in the water thickened with a lightly cross-linked carbomer gelling agent and the tretinoin dissolved in an internal liquid oil phase; and 3) a solution consisting of water and water-miscible organic solvents with the clindamycin phosphate and tretinoin both dissolved.

The following compositions are given as representative as the types of compositions useful in this invention.

Where the composition contains an antibiotic alone, for example clyndamycin phosphate, the composition has a pH of about 4 to 7 and contains

(a) about 0.5% to 2.0% w/w clindamycin phosphate,

(b) about 0.1% to 0.4% w/w of the polymer,

(c) the base to adjust pH,

(d) about 15.0% to 25.0% w/w of a water miscible solvent,

(e) less than about 0.2% w/w of a preservative, and

(g) QSAD purified water to 100% w/w.

Preferably such a composition has a pH of about 5 to 6 and contains

(a) 1.0 to 1.5% w/w clindamycin phosphate,

(b) 0.2% w/w of the polymer,

(c) the base to adjust pH,

(d) 15.0% w/w propylene glycol and 5.0% w/w polyethylene glycol 400,

(e) 0.1 – 0.15% w/w methylparaben, and

(g) QSAD purified water to 100% w/w.

A gel composition where the antibiotic in clindamycin phosphate and the retinoid is tretinoin may contain

(a) (i) about 0.5% to about 2.0% w/w clyndanycin phosphate, and

(ii) about 0.01% to about 0.05% w/w tretinoin;

(b) about 0.1% to about 0.5% w/w of the polymer;

(c) the base to adjust pH;

(d) about 10% to about 30% w/w of a water-miscible solvent;

Padagis Ex. 1029
IPR Petition - USP 11,311,482

(e) less than about 0.2% of a preservative; and

(g) QSAD purified water 100% w/w.

A lotion composition of clindamycin phosphate and tretinoin usefully will contain

(a) (i) about 0.5% to about 2.0% w/w clyndanycin phosphate and

(ii) about 0.01% to about 0.05% w/w tretinoin;

(b) about 0.1% to about 0.5% w/w0 of the polymer;

(c) the base to adjust pH;

(d) about 5% to about 30% w/w of a water-miscible solvent;

(e) less than about 0.2% of a preservative;

(f) an oil phase in combination with at least one surfactant to form an emulsion; and

(g) QSAD purified water 100% w/w.

Treatment

Another aspect of the invention is a method for treating a skin disorder in a human, which method comprises administering a composition to an affected area of the subject's skin having such disorder in an amount and for a period of time sufficient to improve the skin disorder, wherein the composition is described in this patent application. Preferably, the composition is administered once a day over the treatment period. Depending on the patient's improvement, the treatment may extend for less than a week to two months or more. The progress of improvement may be monitored by the patient or by a physician.

The skin disorders which are treatable with the composition of the invention include acne vulgaris, rosacea, and various inflammatory conditions including atopic dermatitis. A discussion of these conditions may be found in the Merck Manual. For example, acne vulgaris is an inflammatory disease affecting hair follicles and sebaceous glands. Lesions are most common on the face, but the neck, chest, upper back, and shoulders may also be affected.

The affected area of the subject's skin can be anywhere on the body in which the skin disorder exists. The amount of composition and period of administration time sufficient to improve the skin disorder will be dependent on the subject and skin condition. Generally, a sufficient amount will be squeezed from a dropper tip of a squeeze bottle or an eye dropper onto the area affected and rubbed gently into the skin. Usually, no more than a few drops will be needed to apply to an affected area.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Article of Manufacture

Another aspect of the invention is an article of manufacture that comprises a composition for treating a skin disorder as described above in a suitable container, preferably in a dropper bottle, in combination with labeling instructions. The dropper bottle can be made of any material, for example, glass, rigid plastic, or flexible plastic. Other means of administration are an eyedropper, or tube with a suitable small orifice size, such as an extended tip tube.

The composition of this invention may be, for example, filled and packaged into a plastic squeeze bottle (*i.e.*, 42 g). A suitable container-closure system for the package presentation for the composition described in Table D.

TABLE D

NOMINAL SIZE	OVERFLOW CAPACITY	MATERIAL DESCRIPTION	MANUFACTURER
1 oz	46 cc	• Natural cylinder, round polypropylene bottle, 15/415 finish, Wheaton B-21411 • White low density polyethylene 15 mm dropper tip plug, Wheaton B-11048 • White polypropylene extended tip closure, Wheaton B-15044	Wheaton Plastic Products 1101 Wheaton Avenue Milville, NJ 08332

The labeling instructions can come in the form of a pamphlet, a label applied to or associated with the packaging of the article of manufacture.

The labeling instructions provide for administering a composition of the invention to an affected area of a subject's skin having a skin disorder, in an amount and for a period of time sufficient to improve the skin disorder. Printed labeling instructions are functionally related to the composition of the invention inasmuch as such labeling instructions describe a method to treat a skin disorder. The labeling instructions are an important aspect of the invention in that before a composition can be approved for any particular use, it must be approved for marketing by the United States Food and Drug Administration. Part of that process includes providing a label that will accompany the pharmaceutical composition which is ultimately sold. While the label will include a definition of the composition and such other items such as the clinical pharmacology, mechanism of action, drug resistance, pharmacokinetics, absorption, bioavailability, contraindications and the like, it will also provide the necessary dosage, administration and usage. Thus, the combination of the composition with the dropper bottle with

Padagis Ex. 1029
IPR Petition - USP 11,311,482

appropriate treatment instructions is important for the proper usage of the drug once it gets on the market. Such treatment instructions will describe the usage in accordance with the method of treatment set forth herein before.

Having now generally described this invention, the same will be better understood by reference to certain specific examples which are included herein for purposes of illustration only and are not intended to be limiting of the invention or any embodiment thereof, unless so specified.

In the following examples, the viscosity is determined at room temperature (20-25°C) using a Brookfield viscometer model DV-I+, spindle #27 at 12 revolutions per minute (rpm). If the measured viscosity is less than 4,000 cP, spindle #21 should be used instead of #27.

EXAMPLES

EXAMPLE I

This example sets forth a pourable gel composition of this invention. The procedure set forth in steps a-f produces a composition according to Table I. The composition is referred to as "Clindagel." An application to designate Clindagel as a trademark has been filed.

TABLE I

COMPONENT	% W/W
Clindamycin phosphate, USP (equivalent to 1% clindamycin)	1.19
Methylparaben	0.15
CARBOPOL® 941 (or 981)	0.20
Propylene glycol	15.0
Polyethylene glycol 400	5.0
Sodium hydroxide (10% solution)	QS pH 5.3 to 5.7
Purified water	QSAD 100.00

The viscosity of this composition is about 1,000 cP.

a. Weigh approximately 90% of the purified water into a stainless steel kettle. Add the propylene glycol and polyethylene glycol 400. Stir with propeller mixer.

b. At room temperature add methylparaben to step a) with continued stirring. Mix until dissolved.

c. While continuing to mix, add clindamycin phosphate to step b). Mix until dissolved.

d. While continuing to mix, add CARBOPOL® 981 or 941 slowly to step c), avoiding clumping. Mix vigorously at room temperature until a uniform and lump-free dispersion is achieved.

e. While mixing, add sufficient sodium hydroxide, 10% solution, to achieve a pH of 5.3 to 5.7. Mix until uniform.

f. Add the remaining water to make 100% and mix until uniform.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

EXAMPLE II

This example shows the composition of a commercially available product containing clindamycin phosphate. The product is sold by Pharmacia as Cleocin T® Gel. The components and amounts were analyzed to be as follows:

TABLE II

COMPONENT	% W/W
Clindamycin phosphate	1.19
Carbomer 934 P	0.8
Propylene glycol	4.9
Polyethylene glycol 400	10.2
Sodium hydroxide	QS pH 5.4
Methylparaben	0.3
Allantoin	0.2
Purified water	QSAD 100

The viscosity of this composition is about 20,000 cP.

EXAMPLE III

Comparison of Clindagel and Cleocin-T® Gel

This example provides clinical data showing the advantages of a composition of the invention as compared to a known commercial composition.

A multi-center investigator-blind clinical trial was conducted comparing a composition of this invention (see Example I) Clindagel, once daily, and Cleocin-T® Gel (see Example II), twice daily (according to manufacturer's directions), in acne vulgaris. Three hundred and twenty four patients, half in each group, were treated for up to 12 weeks. The investigator was "blinded" in that she/he did not know which treatment the patient used before the investigator evaluated the condition of the patient's acne.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Evaluations included inflammatory lesion count, total lesion count, physician's global assessment and skin-related side effects. Papules and pustules were considered inflammatory lesions. Total acne lesions included open and closed comedones in addition to inflammatory lesions. The physician's global severity assessment was based on a nine-point scale. At study end (12 weeks or last evaluation) it was concluded that Clindagel used once a day was equal in effectiveness to Cleocin-T® used twice daily and Clindagel had significantly fewer side effects. The data on lesion counts are summarized in Table III.

Table III: Improvement in Acne Lesions at Endpoint: Clindagel™ Once Daily vs. Cleocin-T Gel Twice Daily.

ACNE LESIONS	Clindagel™ Once Daily	Cleocin-T® Gel Twice Daily	95% Confidence Lower Bound
	Percent Change from Baseline (standard deviation)		
Inflammatory	-50.90 (2.62)	-50.02 (2.62)	0.897
Total	-37.27 (2.44)	-39.52 (2.44)	0.801

The physician's global assessment is summarized in Table IV.

Table IV: Summary of Number of Patients with a Two-Category Improvement from Baseline in the 9-Point Physician's Global Severity Assessment at Endpoint

PHYSICIAN'S GLOBAL Assessment	Clindagel™ Once Daily	Cleocin-T® Gel Twice Daily	95% Confidence Lower Bound
	Number of Patients		
Improved by 2 categories	84	84	0.833
Same or Worsened	72	73	
TOTAL	156	157	

The frequency of dermal side effects from Clindagel™ once daily and from Cleocin-T® twice daily are tabulated in Table V.

Table V: Summary Results of Frequency of Adverse Events Comparing Clindagel™ Once Daily and from Cleocin-T® Twice Daily.

Category	ADVERSE EVENTS		Fisher's Exact Test
	Clindagel™ Once Daily	**Cleocin-T® Gel Twice Daily**	
Number of patients in safety evaluation	168	165	
Number of patients with at least one skin/appendage disorder reported	2	13	0.003
Frequency of local adverse reactions	1.2%	7.9%	

EXAMPLE IV

This example sets forth the results of a user preference test (with vehicles, not actives) comprising a composition of this invention is shown in Example I (with CARBOPOL® 981) with the commercially available composition of Example II, (with Carbomer 934 P). Table VI sets forth the formulation compositions.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

The study was conducted amongst a normal subject patient population of 10 in order to evaluate the functional and cosmetic attributes using a half-face, paired, and symmetrical design.

Table VI

Component	**% w/w**	
Vehicle Formulae:	**Clindagel**	**Cleocin-T Gel**
Carbomer 934P	—	0.8
Carbomer 981	0.2	—
Propylene glycol	15.0	4.9
Polyethylene glycol 400	5.0	10.2
Sodium hydroxide	qs to pH 5.5	qs to pH 5.4
Methylparaben	0.15	0.3
Allantoin	—	0.2
Purified water	QSAD 100	QSAD 100

Test articles (gel vehicles) were identified by blinded identification code, thereby preventing test subject from knowing the identity of the test articles being applied. Each test pair involved test articles L vs. R, which were used on the left and right sides of the face respectively. The test articles assigned to L and R codes were varied so that each test article was randomly evaluated on R and L test locations and by order of application.

The subjects were equally balanced for sex. The mean age of the population was 34 years old within an age range of 25-44 years.

The following attributes were assessed during and after application: spreadability, feel/texture during application, ease of application, ability to rub the gel into the skin, drying time on the skin, skin feel after application, overall cosmetic preference, and usability of the product. Each gel was evaluated for its functional and cosmetic attributes on a scale of 1-6, with 1 being *Unacceptable* and 6 being *Excellent.*

Of the nine subjects with a preference for one of the test articles, 67% preferred Clindagel vehicle over Cleocin-T vehicle. The degree of preference of Clindagel over Cleocin-T was judged "moderate" to "great" in 100% of those tested. The data are tabulated in Table VII.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Table VII. Vehicle Preference By Subject

Subject	1	2	3	4	5	6	7	8	9	10	TOTAL
Age	26	39	44	42	25	28	42	35	33	26	
Sex	F	F	M	M	F	F	M	F	M	M	
Cleocin-T							P	P	P	NP	3
Clindagel	P	P	P	P	P	P				NP	6

P = Preferred NP = No Preference F = Female M = Male

There was a significantly higher score for Clindagel vehicle than for Cleocin-T gel vehicle in four of the specific attributes, and no significant difference in two of those attributes (Table VIII). Clindagel vehicle scored marks of "Very Good" in three of the six attribute categories and marks of "Good" in three other. Cleocin-T gel vehicle scored marks of "Very Good" in one category, "Good" in four categories and "Fair" in one category.

Table VIII. Frequency of Higher Score of Clindagel Vehicle and Cleocin-T Gel Vehicle

	Frequency of Higher Score (%)		No Preference
Functional and Cosmetic Attribute:	**CLINDAGEL**	**CLEOCIN-T**	
Spreadability	30%	30%	40%
Feel/texture during application	50%	30%	20%
Ease of application	20%	30%	50%
Ability to rub gel into skin	50%	20%	30%
Length of drying time	70%	20%	10%
Skin feel after application	50%	30%	20%

Forty percent of test subjects commented independently that the Clindagel vehicle was "runny" or "waterey" upon application. This was also reflected in the "Ease of Application" attribute, where Cleocin-T had a slightly higher score. 50% of test subjects commented independently on their face feeling "sticky" after application of the Cleocin-T vehicle. 80% of test subjects indicated that they would use the Clindagel vehicle as a facial medication product. Only 30% of those tested indicated that they would use Cleocin-T vehicle as a facial medication product.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

EXAMPLE V

Stability Study of Clindagel™ with Clindaymycin Phosphate as Active Ingredient

This example provides laboratory data showing stability of Clindagel (Example I) for at least 18 months at 25°C. Clindagel was tested for the stability of the active ingredient, clindamycin phosphate, over time at controlled room temperature (i.e., 25°C and 60% relative humidity). A stability-indicating, high performance liquid chromatography assay was used to assess remaining clindamycin phosphate potency, expressed as clynamycin, during the experiment. Based on the data shown in Table IX, Clindagel is projected to have a commercial shelf life of about 24 months.

The estimated shelf life was calculated from the 95% confidence interval around the least squares fit to the available data. The projected shelf life is the time at which the drug potency reaches 90% of label claim (as allowed by the USP). The software used for the statistical analysis is named "SLIMStat+" and is sold by Metrics, Inc., P.O. Box 4035, Greenville, NC 27836, phone 252-752-3800.

Table IX: Room Temperature Stability Assessment of Clindamycin Potency in Clindagel™, 1%.

	Percent Clindamycin by Weight					
	Initial	1 month	2 months	6 months	12 months	18 months
Clindamycin Phosphate Assay	1.028	1.017	1.009	1.004	0.983	0.959

EXAMPLE VI

Clindamycin Phosphate-Tretinoin Combination Composition

Section 1

This section of this example describes two gel compositions of the invention in which the active ingredients are clindamycin phosphate and tretinoin.

Two pourable gel compositions containing a combination of clindamycin phosphate and tretinoin were made according to the invention. In Formulation A, the gel had a pH of about 5.5 and a viscosity of about 6100 cP. In Formulation B, the gel exhibited a pH of about 4.7 and a viscosity of about 6,000 cP. See quantitative formulae in Table X. This example illustrates the utility of our invention in the preparation of physically and chemically stable gel formulations.

20.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Table X: Quantitative compositions of two combination Clindamycin Phosphate/Tretinoin gel formulations:

Component	A % w/w	B % w/w
Tretinoin	0.025	0.025
Clindamycin Phosphate	1.21	1.21
Propyl Gallate	---	0.02
BHA	0.02	---
Citric Acid	---	0.05
Disodium Edetate	0.05	0.05
Polysorbate 80	5.0	0.08
Propylene Glycol	5.0	---
PEG 400	20.0	---
Glycerin	---	10.0
Methylparaben	0.1	0.15
CARBOPOL 981	0.5	0.5
Tromethamine (10% in water)	QS to pH 5.5	QS to pH 4.5
Purified Water	QSAD 100	QSAD 100

Method of preparation: Formula A

a. Combine the propylene glycol, polyethylene glycol 400, and polysorbate 80. Add the tretinoin and stir to dissolve.

b. In a separate container dissolve the disodium edetate, methylparaben, and butylated hydroxyanisole in the purified water.

c. Add the clindamycin phosphate to the aqueous solution of step b and stir to dissolve.

d. Disperse the CARBOPOL 981 into the aqueous solution with high-speed stirring.

e. Add the tretinoin drug phase to the aqueous CARBOPOL dispersion with stirring and then add the tromethamine and mix to form a homogeneous gel.

Method of preparation of Formula B

a. Combine the glycerin and polysorbate 80. Add the tretinoin and stir to wet and disperse.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

b. In a separate container dissolve the propyl gallate, citric acid, disodium edetate, methylparaben, and butylated hydroxyanisole in the purified water.

c. Add the clindamycin phosphate to the aqueous solution of step b and stir to dissolve.

d. Disperse the CARBOPOL 981 into the aqueous solution with high-speed stirring.

e. Add the tretinoin drug phase to the aqueous CARBOPOL dispersion with stirring and then add the tromethamine and mix to form a homogeneous gel.

Section 2

This Section of this example describes two additional compositions that are slight modifications of Formulas A and B, wherein the preservatives have been changed or adjusted. The formulas are given below. C is similar to A, and D is similar to B.

TABLE XI

Component	C % w/w	D % w/w
Clindamycin Phosphate	1.24	1.24
Tretinoin	0.025	0.025
Propyl Gallate	—	0.02
BHA	0.02	—
Citric Acid	—	0.05
Disodium Edetate	0.05	0.05
Methylparaben	—	0.15
Propylparaben	—	0.03
Benzyl Alcohol	1	—
Polysorbate 80	5	0.08
Propylene Glycol	5	—
PEG 400	20	—
Glycerin	—	10
Tromethamine (10%)	qs to pH 5.5	qs to pH 4.5
CARBOPOL 981	0.5	0.5
Purified Water	qsad 100	qsad 100

In making formula C, the 0.1% methylparaben preservative in Formula A was replaced with 1.0% benzyl alcohol. In Formula D, 0.03% propylparaben was added as an additional preservative (because the combination of methylparaben and propylparaben is sometimes a better preservative system). Methods of preparation:

22.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

- Formula C is prepared similarly to Formula A, except that methylparaben would be omitted from step "b," and the benzyl alcohol would be added to step "a."
- Formula D is prepared similarly to Formula B; propylparaben would be added to step "b."

The Formula C gel has a pH about 5.5 and a viscosity about 9000 cP. The Formula D gel has a pH about 4.6 and a viscosity about 4100 cP.

EXAMPLE VII

Assessment of Chemical Stability of Tretinoin in Formulations A and B from Example VI.

This example provides laboratory data showing the stability of tretinoin in two compositions of the invention under accelerated test conditions.

Tretinoin is known to be relatively unstable, therefore, the chemical stability of these combination formulations was assessed in a 12-week accelerated stability study. The gels were packaged in amber glass vials, 8 grams each, and stored at 40°C. High performance liquid chromatography assays were performed initially and at 2, 4, and 12 weeks using the method for tretinoin cream (USP 24, page 1684). Both compositions were found to retain their potency in this accelerated study. Table XII summarizes the chemical stability results.

Table XII: Accelerated Temperature (40°C) Stability Assessment of Tretinoin Potency in Formulations A and B, Example VI.

	TIME IN WEEKS			
Tretinoin Concentration (% w/w)	**0**	**2**	**4**	**12**
Formula A	0.0210	0.0228	0.0236	0.0231
Formula B	0.0236	0.0231	0.0234	0.0234

Padagis Ex. 1029
IPR Petition - USP 11,311,482

EXAMPLE VIII

Composition of Combination Gel Formulation

This example teaches how to modify a known commercial composition of Example II to include tretinoin.

A combination gel formulation of tretinoin 0.025%, and clindamycin 1% was made by spatulating tretinoin powder and propyl gallate (an antioxidant to retard oxidative loss of tretinoin) into Cleocin®T gel (Example II). The quantitative formula is shown in Table XIII.

TABLE XIII

Component	Amount
Tretinoin	0.0074g
Propyl Gallate	0.0145g
Cleocin®T gel	28.0000g
TOTAL	28.0219g

The tretinoin and propyl gallate were accurately weighed, placed on a glass plate, and incorporated into the Cleocin®T gel with a spatula. During spatulation, the product was protected from light. The resulting product was a smooth, clear light yellow gel with a pH of 5.7 and a viscosity of about 20,000 cP.

EXAMPLE IX

Physical Stability Studies of the Compositions of Example VI (Formula A) and Example VIII

This example compares a composition of the invention (Example VI, Formula A) with a modified commercial composition (Example VIII) with regards to crystal growth.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

The physical stability of Example VI, Formula A and Example VIII, was assessed over a 4-week period at 5°C, 40°C and 50°C. The stability evaluation was based on careful physical examination for description at initial, 2 week and 4 week times. At study end, microscopic examination was performed to check for precipitation of tretinoin and crystal growth. As illustrated in the data summary below (Table XIV), the modified commercial formulation, Cleocin®T gel, was physically unstable compared to a composition of the invention, Example VI (Formula A).

Table XIV

	Description: Clear Light Yellow Gel		
Example VI (Formula A)	**Initial**	**2 weeks**	**4 weeks**
5°C	Clear	Clear	Clear – no crystals
40°C	Clear	Clear	Clear – no crystals
50°C	Clear	Clear	Clear – no crystals
Example VIII	**Initial**	**2 weeks**	**4 weeks**
5°C	Clear	Hazy	Hazy – Crystals to 1200 microns
40°C	Clear	Translucent	Hazy – Crystals to 1200 microns
50°C	Clear	Translucent	Hazy – Crystals to 1200 microns

Padagis Ex. 1029
IPR Petition - USP 11,311,482

EXAMPLE X

This example sets forth a lotion composition of this invention comprising two active ingredients: an antibiotic, i.e., clindamycin phosphate, and a retinoid, i.e., tretinoin. The components for this lotion are set forth in Table XIV.

Table XIV

Component	% w/w
Clindamycin Phosphate	1.21
Tretinoin	0.025
Stearyl Alcohol	5.00
Diisopropyl Adipate	6.00
PEG 40 Stearate (Myrj 52)	2.00
Sorbitan Stearate (Span 60)	2.00
Butylated Hydroxytoluene	0.02
Propylene Glycol	5.00
Methylparaben	0.15
Propylparaben	0.03
Citric Acid	0.05
Disodium Edetate	0.10
CARBOPOL 981	0.10
Tromethamine (10%)	qs pH 5.5
Purified Water	qsad 100

The viscosity of this composition is about 7,000 cP.

Method of preparation:

a. Combine the propylene glycol and purified water. Add the methylparaben, propylparaben, citric acid, and disodium edetate and stir to dissolve.

b. Add the clindamycin phosphate to step "a" and stir to dissolve.

c. Add the Carpobol 981 to step "b" and stir to form a homogeneous dispersion.

d. Warm step "c" water phase to between 60°C and 70°C.

e. Combine the stearyl alcohol, PEG 40 stearate, sorbitan stearate, and butylated hydroxytoluene and warm to melt at between 60°C to 70°C.

f. Add the tretinoin to the diisopropyl adipate and stir to dissolve.

g. With high-speed stirring add step "e" oil phase and step "f" drug phase sequentially to step "d" water phase and mix well.

h. Cool emulsion with continued stirring.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

i. Add the tromethamine solution and stir to form a homogeneous emulsion. Cool to room temperature with continued stirring.

EXAMPLE XI

This example sets forth a pourable gel composition of this invention which gel contains a corticosteroid. Such formulation is suitable for treating inflammatory skin conditions such as atopic dermatitis.

Table XV

Component	% by weight
Halobetasol propionate, micronized	0.05
Docusate sodium	0.10
CARBOPOL® 981	0.3
Propylene glycol	12
Methylparaben	0.1
Propylparaben	0.02
Tromethamine	QS pH 6.5
Purified water	QSAD 100.00

The viscosity of this composition is about 6200 cP.

a. Dissolve the methylparaben and propylparaben in the propylene glycol at room temperature using a propeller mixer.

b. Weigh 70% of the formula weight of purified water and slowly add the solution from step "a" while mixing with propeller mixer.

c. While continuing to mix, add CARBOPOL® 981 slowly to step "b." Mix at room temperature until a smooth and uniform dispersion is produced.

d. To 10% of the formula weight of water add the docusate sodium and mix until fully dissolved. To facilitate dissolution the mixture may be warmed to 40-50°C, and then cooled to room temperature when dissolution is complete.

e. Disperse the micronized halobetasol propionate in step "d" with a propeller mixer or preferably a homogenizer of the rotor-stator type.

f. Add step "e" to step "c" using propeller mixer to uniformly disperse the drug material.

g. Dissolve the tromethamine in 10 times its weight in purified water. While mixing, use the tromethamine solution to adjust the pH and thicken the gel. Continue incremental additions until a pH of about 6.5 is attained.

h. Add water to make 100% of the batch size and mix until homogeneous with a propeller-type mixer.

EXAMPLE XII

This example sets forth yet another pourable gel composition of this invention. The formulation contains metronidazole for topical application to the skin areas affected, for example, with rosacea.

Table XVI

Component	% by weight
Metronidazole	0.75
Methylparaben	0.12
Propylparaben	0.03
CARBOPOL® 981	0.25
Glycerin	5.00
Trolamine	QS pH 8
Purified Water	QSAD 100

The viscosity of this composition is about 4700 cP.

a. Weigh 90% of the formula weight of purified water, metronidazole, glycerin, methyl-paraben and propylparaben into a suitable stainless steel container. Mix vigorously at room temperature until all components are dissolved. A propeller-type mixer is particularly suitable.

b. While continuing to mix, slowly add the CARBOPOL®. Mix until a lump-free dispersion is attained.

c. Mix the trolamine with an equal part of purified water. Use this solution to adjust the pH to about 8 with incremental additions while mixing.

d. Add the balance of the purified water to make 100% and mix until a homogeneous gel is produced.

EXAMPLE XIII

This example sets forth a pourable gel composition of this invention which gel contains a NSAID agent.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Table XVII

Component	% by weight
Naproxen	1.00
Octoxynol 9	0.10
CARBOPOL® 981	0.30
Propylene glycol	5.00
Glycerin	5.00
Benzyl alcohol	1.00
Sodium hydroxide, 10% solution	QS pH 3.0 to 3.5
Purified water	QSAD 100.00

The viscosity of this composition is about 4200 cP.

a. Mix the benzyl alcohol, glycerin and propylene glycol together at room temperature using a propeller mixer.

b. Weigh 70% of the formula weight of purified water and slowly add the solution from step "a" while mixing with propeller mixer.

c. While continuing to mix, add CARBOPOL® 981 slowly to step "b." Mix at room temperature until a smooth and uniform dispersion is produced.

d. To 2-5% of the formula weight of water add the octoxynol 9 and mix until fully dissolved.

e. Disperse the naproxen in step "d" with a propeller mixer or a homogenizer.

f. Add step "e" to step "c" using propeller mixer to uniformly disperse the drug material.

g. While mixing, use the sodium hydroxide solution to adjust the pH. Continue incremental additions until a pH of 3.0 to 3.5 is attained.

g. Add water to make 100% of the batch size and mix until homogeneous with a propeller-type mixer.

EXAMPLE XIV

This example sets forth a pourable gel composition of this invention. The procedure set forth in steps a-f produces a composition according to Table I. The composition is designed to be used on sensitive skin and contains clindamycin phosphate as the active ingredient.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Table XVIII

COMPONENT	% W/W
Clindamycin phosphate, USP (equivalent to 1% clindamycin)	1.19
Methylparaben	0.15
CARBOPOL® 941 (or 981)	0.20
Polyethylene glycol 400	5.0
Sodium hydroxide (10% solution)	QS pH 5.3 to 5.7
Purified water	QSAD 100.00

The viscosity of this composition is about 1,000 cP.

a. Weigh approximately 90% of the purified water into a stainless steel kettle. Add the polyethylene glycol 400. Stir with propeller mixer.

b. At room temperature add methylparaben to step a) with continued stirring. Mix until dissolved.

c. While continuing to mix, add clindamycin phosphate to step b). Mix until dissolved.

d. While continuing to mix, add CARBOPOL® 981 or 941 slowly to step c), avoiding clumping. Mix vigorously at room temperature until a uniform and lump-free dispersion is achieved.

e. While mixing, add sufficient sodium hydroxide, 10% solution, to achieve a pH of 5.3 to 5.7. Mix until uniform.

f. Add the remaining water to make 100% and mix until uniform.

EXAMPLE XV

This example sets forth a pourable gel composition of this invention which gel contains a corticosteroid (desonide) as the sole active ingredient. Such formulation is suitable for treating inflammatory skin conditions such as atopic dermatitis.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Table XIX

Component	% by weight
Desonide, micronized	0.05
Docusate sodium	0.10
CARBOPOL® 981	0.3
Propylene glycol	5.0
Methylparaben	0.2
Propylparaben	0.3
Tromethamine	QS pH 5.5
Purified water	QSAD 100.00

The viscosity of this composition is about 6200 cP.

a. Dissolve the methylparaben and propylparaben in the propylene glycol at room temperature using a propeller mixer.

b. Weigh 70% of the formula weight of purified water and slowly add the solution from step "a" while mixing with propeller mixer.

c. While continuing to mix, add CARBOPOL® 981 slowly to step "b." Mix at room temperature until a smooth and uniform dispersion is produced.

d. To 10% of the formula weight of water add the docusate sodium and mix until fully dissolved. To facilitate dissolution the mixture may be warmed to 40-50°C, and then cooled to room temperature when dissolution is complete.

e. Disperse the micronized desonide in step "d" with a propeller mixer or preferably a homogenizer of the rotor-stator type.

f. Add step "e" to step "c" using propeller mixer to uniformly disperse the drug material.

g. Dissolve the tromethamine in 10 times its weight in purified water. While mixing, use the tromethamine solution to adjust the pH and thicken the gel. Continue incremental additions until a pH of about 5.5 is attained.

h. Add water to make 100% of the batch size and mix until homogeneous with a propeller-type mixer.

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

31.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

The subject matter claimed is:

1. A composition having a pH of about 3 to about 9 and a viscosity of less than about 15,000 cP for treating a skin disorder in a human subject, which composition consists essentially of

(a) a therapeutically-effective amount of at least one compound useful for treating such disorder,

(b) a pharmaceutically-acceptable, lightly cross-linked polyacrylic acid polymer compatible with the compound,

(c) a pharmaceutically-acceptable base to adjust pH,

(d) optionally a water miscible solvent,

(e) optionally a preservative,

(f) optionally at least one surfactant alone or in combination with an oil phase, and

(g) water.

2. The composition of Claim 1, wherein the compound is an antibiotic, imidazole, retinoid, corticosteroid, or a non-steroidal anti-inflammatory drug (NSAID).

3. The composition of Claim 2, wherein the compound is an antibiotic alone or in combination with a corticosteroid or a retinoid.

4. The composition of Claim 3, wherein the compound is an antibiotic alone.

5. The composition of Claim 4, wherein the antibiotic is clindamycin phosphate.

6. The composition of Claim 5 having a pH of about 4.0 to 7.0, which composition consists essentially of

(a) about 0.5% to 2.0% w/w clindamycin phosphate,

(b) about 0.1% to 0.4% w/w of the polymer,

(c) the base to adjust pH,

(d) about 15.0% to 25.0% w/w of a water miscible solvent,

(e) less than about 0.2% w/w of a preservative, and

(g) QSAD purified water to 100% w/w.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

7. The composition of Claim 6, wherein the water miscible solvent of part (d) is present at an amount of about 3.0% to 10.0% w/w.

8. The composition of Claim 6 having a pH of about 5.0 to 6.0, which composition consists essentially of:

(a) about 1.0 to 1.5% w/w clindamycin phosphate,

(b) about 0.2% w/w of the polymer,

(c) the base to adjust pH,

(d) about 5.0% w/w polyethylene glycol 400,

(e) about 0.1 – 0.15% w/w methylparaben, and

(g) QSAD purified water to 100% w/w.

9. The composition of Claim 6 having a pH of about 5.0 to 6.0, which composition consists essentially of:

(a) about 1.0 to 1.5% w/w clindamycin phosphate,

(b) about 0.2% w/w of the polymer,

(c) the base to adjust pH,

(d) about 5.0% w/w polyethylene glycol 400,

(e) about 0.1 – 0.15% w/w methylparaben, and

(g) QSAD purified water to 100% w/w.

10. The composition of Claim 3, wherein an antibiotic is combined with a corticosteroid, the antibiotic is clindamycin phosphate, and the corticosteroid is desonide, hydrocortisone valerate, fluocenolone acetinide, hydrocortisone butyrate, ortriamcinolone acetonide.

11. The composition of Claim 3, wherein an antibiotic is combined with a retinoid, the antibiotic is clindamycin phosphate, and the retinoid is tretinoin.

12. The composition of Claim 11 having a pH of about 4 to 7, which composition is a gel consisting essentially of

(a) (i) about 0.5% to about 2.0% w/w clindamycin phosphate, and

Padagis Ex. 1029
IPR Petition - USP 11,311,482

(ii) about 0.01% to about 0.05% w/w tretinoin;

(b) about 0.1% to about 0.5% w/w of the polymer;

(c) the base to adjust pH;

(d) about 10% to about 30% w/w of a water-miscible solvent;

(e) less than about 0.2% of a preservative; and

(g) QSAD purified water 100% w/w.

13. The composition of Claim 11 having a pH of about 5 to 6, which composition is a lotion consisting essentially of

(a) (i) about 0.5% to about 2.0% w/w clindamycin phosphate and

(ii) about 0.01% to about 0.05% w/w tretinoin;

(b) about 0.1% to about 0.5% w/w of the polymer;

(c) the base to adjust pH;

(d) about 5% to about 30% w/w of a water-miscible solvent;

(e) less than about 0.2% of a preservative; and

(f) an oil phase in combination with at least one surfactant to form an emulsion; and

(g) QSAD purified water 100% w/w.

14. The composition of Claim 1, wherein the compound is a non-steroidal anti-inflammatory drug.

15. The composition of Claim 14, wherein the compound is naproxen or diclofenac or a pharmaceutically-acceptable salt thereof.

16. The composition of Claim 2, having a corticosteroid as the sole active agent.

17. The composition of Claim 16, wherein the corticosteroid is diflorasone diacetate, desonide, fluticasone propionate, halobetasol propionate, or budesonide.

18. The composition of Claim 17, wherein the corticosteroid is halobetasol propionate.

19. The composition of Claim 17, wherein the corticosteroid is desonide.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

20. The composition of Claim 19 having a pH of about 4.0 to 7.0, which composition consists essentially of

(a) about 0.01% to 0.1% w/w desonide,

(b) about 0.1% to 0.4% w/w of the polymer,

(d) about 3.0% to 10% w/w of a water miscible solvent,

(e) less than about 0.25% w/w of a preservative, and

(g) QSAD purified water to 100% w/w.

21. The composition of Claim 19 having a pH of about 5.0 to 6.0, which composition consists essentially of:

(a) about 0.025 to 0.05% w/w desonide,

(b) about 0.3% w/w of the polymer,

(c) the base to adjust pH,

(d) about 5% w/w propylene glycol,

(e) about 0.2 – 0.25% w/w methylparaben and propylparaben, and

(g) QSAD purified water to 100% w/w.

22. The composition of Claim 1 in combination with a container that accurately administers a portion of the composition for topical administration to a patient.

23. The composition of Claim 22 in combination with labeling instructions for use in treating the skin disorder.

24. A method for treating a skin disorder in a human subject, which method comprises topically administering a composition having a pH of about 3 to about 9 and a viscosity of less than about 15,000 cP to an affected area of the subject's skin having such disorder in an amount and for a period of time sufficient to improve the skin disorder, wherein the composition consists essentially of

Padagis Ex. 1029
IPR Petition - USP 11,311,482

(a) a therapeutically-effective amount of at least one compound useful for treating such disorder,

(b) a pharmaceutically-acceptable lightly cross-linked polyacrylic acid polymer compatible with the pharmaceutical active material,

(c) a pharmaceutically-acceptable base to adjust pH

(d) optionally a water miscible solvent,

(e) optionally a preservative,

(f) optionally an oil phase in combination with a surfactant, and

(g) water.

25. A method of preparing a composition having a viscosity of less than about 15,000 cP and a pH of about 3 to 9 useful for treating a skin disorder in a human subject, which method comprises

(a) combining water with a therapeutically-effective amount of at least one compound useful for treating such disorder and a pharmaceutically-acceptable, lightly cross-linked polyacrylic acid polymer compatible with the compound,

(b) adjusting the pH to about 3 to 9, and

(c) optionally combining a water-miscible solvent, a preservative, and at least one surfactant alone or in combination with an oil phase component to form the composition.

26. The method of Claim 25, wherein the compound is an antibiotic, imidazole, retinoid, corticosteroid, or a nonsteroidal anti-inflammatory drug (NSAID).

27. The method of Claim 26, wherein the compound is an antibiotic alone or in combination with a corticosteroid or a retinoid.

28. The method of Claim 27, wherein the compound is an antibiotic alone.

29. The method of Claim 28, wherein the antibiotic is clindamycin phosphate.

30. The method of Claim 29, wherein the composition has a pH of about 4 to 7, and consists essentially of

Padagis Ex. 1029
IPR Petition - USP 11,311,482

(a) about 0.5% to 2.0% w/w clindamycin phosphate,

(b) about 0.1% to 0.4% w/w of the polymer,

(c) the base to adjust pH,

(d) about 15.0% to 25.0% w/w of a water miscible solvent,

(e) less than about 0.2% w/w of a preservative, and

(g) QSAD purified water to 100% w/w.

31. The method of Claim 30, wherein the water miscible solvent of part (d) is present in an amount of about 3.0% to 10.0% w/w.

32. The method of Claim 30, wherein the composition has a pH of about 5 to 6, and consists essentially of:

(a) 1.0 to 1.5% w/w clindamycin phosphate,

(b) 0.2% w/w of the polymer,

(c) the base to adjust pH,

(d) 15.0% w/w propylene glycol and 5.0% w/w polyethylene glycol 400

(e) 0.1 – 0.15% w/w methylparaben, and

(g) QSAD purified water to 100% w/w.

33. The method of Claim 6 having a pH of about 5.0 to 6.0, wherein the composition consists essentially of:

(a) about 1.0 to 1.5% w/w clindamycin phosphate,

(b) about 0.2% w/w of the polymer,

(c) the base to adjust pH,

(d) about 5.0% w/w polyethylene glycol 400

(e) about 0.1 – 0.15% w/w methylparaben, and

(g) QSAD purified water to 100% w/w.

34. The method of Claim 27, wherein the antibiotic is combined with a corticosteroid, the antibiotic is clindamycin phosphate, and the corticosteroid is desonide, hydrocortisone valerate, fluocenolone acetinide, hydrocortisone butyrate, or triamcinolone acetonide.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

35. The method of Claim 27, wherein the antibiotic is combined with a retinoid, the antibiotic is clindamycin phosphate, and the retinoid is tretinoin.

36. The method of Claim 35, wherein the composition is a gel having a pH of about 4 to 7 and consists essentially of

(a) (i) about 0.5% to about 2.0% w/w clindamycin phosphate, and
(ii) about 0.01% to about 0.05% w/w tretinoin;
(b) about 0.1% to about 0.5% w/w of the polymer;
(c) the base to adjust pH;
(d) about 10% to about 30% w/w of a water-miscible solvent;
(e) less than about 0.2% of a preservative; and
(g) QSAD purified water 100% w/w.

37. The method of Claim 35, wherein the composition is a lotion having a pH of about 5 to 6 and consists essentially of

(a) (i) about 0.5% to about 2.0% w/w clindamycin phosphate and
(ii) about 0.01% to about 0.05% w/w tretinoin;
(b) about 0.1% to about 0.5% w/w of the polymer;
(c) the base to adjust pH;
(d) about 5% to about 30% w/w of a water-miscible solvent;
(e) less than about 0.2% of a preservative; and
(f) an oil phase in combination with at least one surfactant to form an emulsion; and
(g) QSAD purified water 100% w/w.

38. The method of Claim 26, wherein the compound is a NSAID.

39. The method of Claim 38, wherein the compound is naproxen or diclofenac or a pharmaceutically-acceptable salt thereof.

40. The method of Claim 26, wherein the composition has a corticosteroid as the sole active agent.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

41. The method of Claim 40, wherein the corticosteroid is diflorasone diacetate, desonide, fluticasone propionate, halobetasol propionate, or budesonide.

42. The method of Claim 41, wherein the corticosteroid is halobetasol propionate.

43. The method of Claim 41, wherein the corticosteroid is desonide.

44. The method of Claim 43, wherein the composition exhibits having a pH of about 4.0 to 7.0 and consists essentially of

(a) about 0.01% to 0.1% w/w desonide,

(b) about 0.1% to 0.4% w/w of the polymer,

(d) about 3.0% to 10% w/w of a water miscible solvent,

(e) less than about 0.25% w/w of a preservative, and

(g) QSAD purified water to 100% w/w.

45. The method of Claim 43, wherein the composition exhibits having a pH of about 5.0 to 6.0 and consists essentially of

(a) about 0.025 to 0.05% w/w desonide,

(b) about 0.3% w/w of the polymer,

(c) the base to adjust pH,

(d) about 5% w/w propylene glycol,

(e) about 0.2 – 0.25% w/w methylparaben and propylparaben, and

(g) QSAD purified water to 100% w/w.

46. The method of Claim 25, which method further comprises placing the composition in a container from which drops are accurately administered for topical administration to a patient.

47. The method of Claim 46, which method further comprises combining the container with labeling instructions for use in treating the skin disorder.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

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B. FIELDS SEARCHED

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NONE

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

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 6,106,848 A (PREUILH et al) 22 August 2000 (22.08.2000), abstract, Columns 1-5, Examples 1-2.	1-47

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

*	Special categories of cited documents:	"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
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Padagis Ex. 1029
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(54) Title: COMPOSITIONS AND METHODS FOR DERMAL DELIVERY OF DRUGS

(57) Abstract: The present invention is drawn to adhesive formulations, methods of drug delivery, and solidified layers for dermal delivery of a drug. The formulation can include a drug, a solvent vehicle, and at least one solidifying agent. The solvent vehicle can have a volatile solvent system including at least one volatile solvent, and a non-volatile solvent system including at least one non-volatile solvent. The formulation can be formulated to contain at least two volatile solvents, at least two non-volatile solvents, or at least two solidifying agents. The formulation can have a viscosity suitable for application to a skin surface prior to evaporation of the volatile solvents system. When applied to the skin, the formulation can form a solidified layer after at least a portion of the volatile solvent system is evaporated.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

COMPOSITIONS AND METHODS FOR DERMAL DELIVERY OF DRUGS

FIELD OF THE INVENTION

The present invention relates generally to systems developed for dermal delivery of drugs. More particularly, the present invention relates to formulations including at least two non-volatile solvents, wherein the formulation as a whole has a viscosity suitable for application as a layer to a skin surface, and which forms a sustained drug-delivering adhesive solidified layer on the skin.

BACKGROUND OF THE INVENTION

Traditional dermal drug delivery systems can generally be classified into two forms: semisolid formulations and dermal patch dosage forms. Semisolid formulations are available in a few different forms, including ointments, creams, foams, pastes, gels, or lotions and are applied topically to the skin. Dermal (including transdermal) patch dosage forms also are available in a few different forms, including matrix patch configurations and liquid reservoir patch configurations. In a matrix patch, the active drug is mixed in an adhesive that is coated on a backing film. The drug-laced adhesive layer is typically directly applied onto the skin and serves both as means for affixing the patch to the skin and as a reservoir or vehicle for facilitating delivery of the drug. Conversely, in a liquid reservoir patch, the drug is typically incorporated into a solvent system which is held by a thin bag, which can be a thin flexible container. The thin bag can include a permeable or semi-permeable membrane surface that is coated with an adhesive for affixing the membrane to the skin. The membrane is often referred to as a rate limiting membrane (although it may not actually be rate

Padagis Ex. 1029
IPR Petition - USP 11,311,482

limiting in the delivery process in all cases) and can control transport of the drug from within the thin bag to the skin for dermal delivery.

While patches and semisolid formulations are widely used to deliver drugs into and through the skin, they both have significant limitations. For example, most semisolid formulations usually contain solvent(s), such as water and ethanol, which are volatile and thus evaporate shortly after application. The evaporation of such solvents can cause a significant decrease or even termination of dermal drug delivery, which may not be desirable in many cases. Additionally, semisolid formulations are often "rubbed into" the skin, which does not necessarily mean the drug formulation is actually delivered into the skin. Instead, this phrase often means that a very thin layer of the drug formulation is applied onto the surface of the skin. Such thin layers of traditional semisolid formulations applied to the skin may not contain sufficient quantity of active drug to achieve sustained delivery over long periods of time. Additionally, traditional semisolid formulations are often subject to unintentional removal due to contact with objects such as clothing, which may compromise the sustained delivery and/or undesirably soil clothing. Drugs present in a semisolid formulation may also be unintentionally delivered to persons who come in contact with a subject undergoing treatment with a topical semisolid formulation.

With respect to matrix patches, in order to be delivered appropriately, a drug should have sufficient solubility in the adhesive, as primarily only dissolved drug contributes to the driving force required for skin permeation. Unfortunately, solubility in adhesives that is too low does not generate adequate skin permeation driving force over sustained period of time. In addition, many ingredients, e.g., liquid solvents and permeation enhancers, which could be used to help dissolve the drug or increase the skin permeability, may not be able to be incorporated into many adhesive matrix systems in sufficient quantities to be effective. For example, at functional levels, most of these materials may adversely alter the wear properties of the adhesive. As such, the selection and allowable quantities of additives, enhancers, excipients, or the like in adhesive-based matrix patches can be limited. To illustrate, for many drugs, optimal transdermal flux can be achieved when the drug is dissolved in certain

Padagis Ex. 1029
IPR Petition - USP 11,311,482

liquid solvent systems, but a thin layer of adhesive in a typical matrix patch often cannot hold enough appropriate drug and/or additives to be therapeutically effective. Further, the properties of the adhesives, such as coherence and tackiness, can also be significantly changed by the presence of liquid solvents or enhancers.

Regarding liquid reservoir patches, even if a drug is compatible with a particular liquid or semisolid solvent system carried by the thin bag of the patch, the solvent system still has to be compatible to the adhesive layer coated on the permeable or semi-permeable membrane; otherwise the drug may be adversely affected by the adhesive layer or the drug/solvent system may reduce the tackiness of the adhesive layer. In addition to these dosage form considerations, reservoir patches are bulkier and usually are more expensive to manufacture than matrix patches.

Another shortcoming of dermal (including transdermal) patches is that they are usually neither stretchable nor flexible, as the backing film (in matrix patches) and the thin fluid bag (in reservoir patches) are typically made of polyethylene or polyester, both of which are relatively non-stretchable materials. If the patch is applied to a skin area that is significantly stretched during body movements, such as a joint, separation between the patch and skin may occur thereby compromising the delivery of the drug. In addition, a patch present on a skin surface may hinder the expansion of the skin during body movements and cause discomfort. For these additional reasons, patches are not ideal dosage forms for skin areas subject to expansion, flexing and stretching during body movements.

In view of the shortcomings of many of the current delivery systems, it would be desirable to provide systems, formulations, and/or methods that can i) provide sustained drug delivery over long periods of time; ii) are not vulnerable to unintentional removal by contact with clothing, other objects, or people for the duration of the application time; iii) can be applied to a skin area subject to stretching and expansion without causing discomfort or poor contact to skin; and/or iv) can be easily removed after application and use.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

SUMMARY OF THE INVENTION

Although film-forming technologies have been used in cosmetic and pharmaceutical preparations, typically, the solvents used in such systems evaporate shortly after application, and thus, are not optimal for sustained-release applications. In accordance with this, it has been recognized that the use of multiple non-volatile solvents, multiple volatile solvents, and/or multiple solidifying agents in the formulation can often optimize sustained drug delivery.

In accordance with this, it would be advantageous to provide dermal delivery formulations, systems, and/or methods in the form of adhesive compositions or formulations having a viscosity suitable for application to the skin surface and which form a drug-delivering solidified layer on the skin that is optionally peelable or otherwise easily removable after use. As such, an adhesive formulation for dermal delivery of a drug can comprise a drug, a solvent vehicle, and at least one solidifying agent. The solvent vehicle can comprise a volatile solvent system including at least one volatile solvent and a non-volatile solvent system including at least one non-volatile solvents. The at least two non-volatile solvents of the non-volatile solvent system can facilitate transdermal delivery of the drug at a therapeutically effective rate over a sustained period of time, even after the non-volatile solvent system is substantially evaporated from the solidified layer. The formulation can have viscosity suitable for application to the skin surface prior to evaporation of at least one volatile solvent, and can further be formulated such that when applied to the skin surface, the formulation forms a solidified layer after at least a portion of the volatile solvent system is evaporated. Sustained drug delivery from the solidified layer can also occur. The formulation is formulated such that it has at least two volatile solvents, at least two non-volatile solvents, at least two solidifying agents, or combinations thereof.

In an alternative embodiment, a method of dermally delivering a drug can comprise applying an adhesive formulation to a skin surface of a subject. The formulation be any formulation as set forth above. Other steps include solidifying the formulation to form a solidified layer on the skin surface by at

Padagis Ex. 1029
IPR Petition - USP 11,311,482

least partial evaporation of the volatile solvent system, and dermally delivering the drug from the solidified layer to the skin surface at therapeutically effective rates over a sustained period of time.

In another embodiment, a solidified layer for delivering a drug can comprise a drug, a non-volatile solvent system including at least one non-volatile solvents, wherein the non-volatile solvent system is capable of facilitating the delivery of the drug at therapeutically effective rates over a sustained period of time, and at least one solidifying agent. In one embodiment, the solidified layer can be stretchable by 5% in one direction without cracking, breaking, or separating from a skin surface to which the layer is applied. The formulation is formulated such that it has at least two non-volatile solvents, at least two solidifying agents, or combinations thereof.

Additional features and advantages of the invention will be apparent from the following detailed description and figures which illustrate, by way of example, features of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graphical representation of cumulative amount of testosterone delivered across a biological membrane *in vitro* over time from a solidified adhesive formulation and a marketed product (AndroGel) in accordance with embodiments of the present invention.

FIG. 2 is a graphical representation of the cumulative amount of acyclovir delivered transdermally over time from two separate formulations in accordance with embodiments of the present invention compared to the marketed product Zovirax cream.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT(S)

Before particular embodiments of the present invention are disclosed and described, it is to be understood that this invention is not limited to the particular process and materials disclosed herein as such may vary to some degree. It is

Padagis Ex. 1029
IPR Petition - USP 11,311,482

also to be understood that the terminology used herein is used for the purpose of describing particular embodiments only and is not intended to be limiting, as the scope of the present invention will be defined only by the appended claims and equivalents thereof.

In describing and claiming the present invention, the following terminology will be used.

The singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a drug" includes reference to one or more of such compositions.

"Skin" is defined to include human skin (intact, diseased, ulcerous, or broken), finger and toe nail surfaces, and mucosal surfaces that are usually at least partially exposed to air such as lips, genital and anal mucosa, and nasal and oral mucosa.

The term "drug(s)" refers to any bioactive agent that is applied to, into, or through the skin which is applied for achieving a therapeutic affect. This includes compositions that are traditionally identified as drugs, as well other bioactive agents that are not always considered to be "drugs" in the classic sense, e.g., peroxides, humectants, emollients, etc., but which can provide a therapeutic effect for certain conditions. When referring generally to a "drug," it is understood that there are various forms of a given drug, and those various forms are expressly included. In accordance with this, various drug forms include polymorphs, salts, hydrates, solvates, and cocrystals. For some drugs, one physical form of a drug may possess better physical-chemical properties making it more amenable for getting to, into, or through the skin, and this particular form is defined as the "physical form favorable for dermal delivery." For example the steady state flux of diclofenac sodium from flux enabling non-volatile solvents is much higher than the steady state flux of diclofenac acid from the same flux enabling non-volatile solvents. It is therefore desirable to evaluate the flux of the physical forms of a drug from non-volatile solvents to select a desirable physical form/non-volatile solvent combination.

The phrases "dermal drug delivery" or "dermal delivery of drug(s)" shall include both transdermal and topical drug delivery, and includes the delivery of

Padagis Ex. 1029
IPR Petition - USP 11,311,482

drug(s) to, through, or into the skin. "Transdermal delivery" of drug can be targeted to skin tissues just under the skin, regional tissues or organs under the skin, systemic circulation, and/or the central nervous system. "Topical delivery" includes delivery of a drug to a skin tissue, and subsequent absorption into deeper tissues that may occur.

The term "flux" such as in the context of "dermal flux" or "transdermal flux," respectively, refers to the quantity of the drug permeated into or across skin per unit area per unit time. A typical unit of flux is microgram per square centimeter per hour. One way to measure flux is to place the formulation on a known skin area of a human volunteer and measure how much drug can permeate into or across skin within certain time constraints. Various methods (*in vivo* methods) might be used for the measurements as well. The method described in Example 1 or other similar method (*in vitro* methods) can also be used to measure flux. Although an *in vitro* method uses human epidermal membrane obtained from a cadaver, or freshly separated skin tissue from hairless mice rather than measure drug flux across the skin using human volunteers, it is generally accepted by those skilled in the art that results from a properly designed and executed *in vitro* test can be used to estimate or predict the results of an *in vivo* test with reasonable reliability. Therefore, "flux" values referenced herein can mean that measured by either *in vivo* or *in vitro* methods.

The term "flux-enabling" with respect to the non-volatile solvent system (or solidified layer including the same) refers to a non-volatile solvent system (including one or more non-volatile solvents) selected or formulated specifically to be able to provide therapeutically effective flux for a particular drug(s). For topically or regionally delivered drugs, a flux enabling non-volatile solvent system is defined as a non-volatile solvent system which, alone without the help of any other ingredients, is capable of delivering therapeutic effective levels of the drug across, onto or into the subject's skin when the non-volatile solvent system is saturated with the drug. For systemically targeted drugs, a flux enabling non-volatile solvent system is a non-volatile solvent system that can provide therapeutically effective daily doses over 24 hours when the non-volatile solvent system is saturated with the drug and is in full contact with the subject's

Padagis Ex. 1029
IPR Petition - USP 11,311,482

skin with no more than 500 cm^2 contact area. Preferably, the contact area for the non-volatile solvent system is no more than 100 cm^2. Testing using this saturated drug-in-solvent state can be used to measure the maximum flux-generating ability of a non-volatile solvent system. To determine flux, the drug solvent mixture needs to be kept on the skin for a clinically effective amount of time. In reality, it may be difficult to keep a liquid solvent on the skin of a human volunteer for an extended period of time. Therefore, an alternative method to determine whether a solvent system is "flux-enabling" is to measure the *in vitro* drug permeation across the hairless mouse skin or human cadaver skin using the apparatus and method described in Example 1. This and similar methods are commonly used by those skilled in the art to evaluate permeability and feasibility of formulations. Alternatively, whether a non-volatile solvent system is flux-enabling can be tested on the skin of a live human subject with means to maintain the non-volatile solvent system with saturated drug on the skin, and such means may not be practical for a product. For example, the non-volatile solvent system with saturated drug can be soaked into an absorbent fabric material which is then applied on the skin and covered with a protective membrane. Such a system is not practical as a pharmaceutical product, but is appropriate for testing whether a non-volatile solvent system has the intrinsic ability to provide effective drug flux, or whether it is flux-enabling.

It is also noted that once the formulation forms a solidified layer, the solidified layer can also be "flux enabling" for the drug while some of the non-volatile solvents remain in the solidified layer, even after the volatile solvents (including water) have been substantially evaporated.

The phrase "effective amount," "therapeutically effective amount," "therapeutically effective rate(s)," or the like, as it relates to a drug, refers to sufficient amounts or delivery rates of a drug which achieves any appreciable level of therapeutic results in treating a condition for which the drug is being delivered. It is understood that "appreciable level of therapeutic results" may or may not meet any government agencies' efficacy standards for approving the commercialization of a product. It is understood that various biological factors may affect the ability of a substance to perform its intended task. Therefore, an

Padagis Ex. 1029
IPR Petition - USP 11,311,482

"effective amount," "therapeutically effective amount," or "therapeutically effective rate(s)" may be dependent in some instances on such biological factors to some degree. However, for each drug, there is usually a consensus among those skilled in the art on the range of doses or fluxes that are sufficient in most subjects. Further, while the achievement of therapeutic effects may be measured by a physician or other qualified medical personnel using evaluations known in the art, it is recognized that individual variation and response to treatments may make the achievement of therapeutic effects a subjective decision. The determination of a therapeutically effective amount or delivery rate is well within the ordinary skill in the art of pharmaceutical sciences and medicine.

"Therapeutically effective flux" is defined as the permeation flux of the selected drug that delivers sufficient amount of drug into or across the skin to be clinically beneficial in that some of the patient population can obtain some degree of benefit from the drug flux. It does not necessarily mean that most of the patient population can obtain some degree of benefit or the benefit is high enough to be deemed "effective" by relevant government agencies or the medical profession. More specifically, for drugs that target skin or regional tissues or organs close to the skin surface (such as joints, certain muscles, or tissues/organs that are at least partially within 5 cm of the skin surface), "therapeutically effective flux" refers to the drug flux that can deliver a sufficient amount of the drug into the target tissues within a clinically reasonable amount of time. For drugs that target the systemic circulation, "therapeutically effective flux" refers to drug flux that, via clinically reasonable skin contact area, can deliver sufficient amounts of the selected drug to generate clinically beneficial plasma or blood drug concentrations within a clinically reasonable time. Clinically reasonable skin contact area is defined as a size of skin application area that most subjects would accept. Typically, a skin contact area of 400 cm^2 or less is considered reasonable. Therefore, in order to deliver 4000 mcg of a drug to the systemic circulation via a 400 cm^2 skin contact area over 10 hours, the flux needs to be at least 4000 mcg/400cm^2/10 hour, which equals 1 mcg/cm^2/hr. By this definition, different drugs have different "therapeutically

Padagis Ex. 1029
IPR Petition - USP 11,311,482

effective flux. Therapeutically effective flux may also be different in different subjects and or at different times for even the same subject. However, for each drug, there is usually a consensus among the skilled in the art on the range of doses or fluxes that are sufficient in most subjects at most times.

The following are estimates of flux for some drugs that are therapeutically effective:

Table 1 - *In vitro* steady state flux values of various drugs

Drug	Indication	Estimated Therapeutically effective flux* ($mcg/cm^2/h$)
Ropivacaine**	Neuropathic pain	5
Lidocaine	Neuropathic pain	30
Acyclovir	Herpes simplex virus	3
Ketoprofen	Musculoskeletal pain	16
Diclofenac	Musculoskeletal pain	1
Clobetasol	Dermatitis, psoriasis, eczema	0.05
Betamethasone	Dermatitis, psoriasis, eczema	0.01
Testosterone	Hypogonadal men,	0.8
Testosterone	Hormone treatment for postmenopausal women	0.25
Imiquimod	Warts, basal cell carcinoma	0.92

* Flux determined using an *in vitro* method described in Example 1.
** Estimated flux based on known potency relative to lidocaine.

The therapeutically effective flux values in Table 1 (with the exception of ropivacaine) represent the steady state flux values of marketed products through hairless mouse or human epidermal membrane in an *in vitro* system described in Example 1. These values are meant only to be estimates and to provide a basis of comparison for formulation development and optimization. The therapeutically effective flux for a selected drug could be very different for different diseases to be treated for, different stages of diseases, different individual subjects, etc. It should be noted that the flux listed may be more than therapeutically effective.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

The following examples listed in Table 2 illustrate screening of a non-volatile solvent's flux enabling ability for some of the drugs specifically studied. Experiments were carried out as described in Example 1 below and the results are further discussed in the subsequent Examples 2-9.

Table 2 - *In vitro* steady state flux values of various drugs from non-volatile solvent systems

Drug	Non-Volatile Solvent	Average Flux* ($mcg/cm^2/hr$)
Betamethasone Dipropionate	Oleic acid	0.009 ± 0.003
	Sorbitan Monolaurate	0.03 ± 0.02
Clobetasol Propionate	Propylene Glycol (PG)	0.0038 ± 0.0004
	Light Mineral Oil	0.031 ± 0.003
	Isostearic acid (ISA)	0.019 ± 0.003
Ropivacaine	Glycerol	1.2 ± 0.7
	Mineral Oil	8.9 ± 0.6
Ketoprofen	Polyethylene glycol 400	5 ± 2
	Span 20	15 ± 3
Acyclovir	Polyethylene glycol 400	0
	Isostearic acid + 10% trolamine	2.7 ± 0.6

* Each value represents the mean and st. dev of three determinations.

The *in vitro* steady state flux values in Table 2 from non-volatile solvents show surprising flux-enabling and non flux-enabling solvents. This information can be used to guide formulation development.

The term "plasticizing" in relation to flux-enabling non-volatile solvent(s) is defined as a flux-enabling non-volatile solvent that acts as a plasticizer for the solidifying agent. A "plasticizer" is an agent which is capable of increasing the percentage elongation of the formulation after the volatile solvent system has at least substantially evaporated. Plasticizers also have the capability to reduce the brittleness of solidified formulation by making it more flexible and/or elastic. For example, propylene glycol is a "flux-enabling, plasticizing non-volatile solvent" for the drug ketoprofen with polyvinyl alcohol as the selected solidifying agent. However, propylene glycol in a formulation of ketoprofen with Gantrez S-97 or Avalure UR 405 as solidifying agents does not provide the same plasticizing effect. The combination of propylene glycol and Gantrez S-97 or

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Avalure UR 405 is less compatible and results in less desirable formulation for topical applications. Therefore, whether a given non-volatile solvent is "plasticizing" depends on which solidifying agent(s) is selected.

Different drugs often have different matching flux-enabling non-volatile solvent systems which provide particularly good results. Examples of such are noted in Table 3. Experiments were carried out as described in Example 1 below.

Table 3 - *In vitro* steady state flux values of various drugs from particularly high flux-enabling non-volatile solvent systems

Drug	High flux-enabling non-volatile solvent	Avg. Flux* ($mcg/cm^2/h$)
Ropivacaine	ISA Span 20	11 ± 2 26 ± 8
Ketoprofen	Propylene glycol (PG)	90 ± 50
Acycolvir	ISA + 30% trolamine	7 ± 2
Betamethasone Dipropionate	Propylene Glycol	0.20 ± 0.07
Clobetasol propionate	PG+ISA (Ratio of PG:ISA ranging from 200:1 to 1:1)	0.8 ± 0.2

* Each value represents the mean and st. dev of three determinations.

It should be noted that "flux-enabling non-volatile solvent," "flux-enabling, plasticizing non-volatile solvent," or "high flux-enabling non-volatile solvent" can be a single chemical substance or a mixture of two or more chemical substances. For example, the steady state flux value for clobetasol propionate in Table 3 is a 9:1 for propylene glycol:isostearic acid mixture that generated much higher clobetasol flux than propylene glycol or ISA alone (see Table 2). Therefore, the 9:1 propylene glycol:isostearic acid mixture is a "high flux-enabling non-volatile solvent" but propylene glycol or isostearic acid alone is not.

The term "adhesion" or "adhesive" when referring to a solidified layer herein refers to sufficient adhesion between the solidified layer and the skin so that the layer does not fall off the skin during intended use on most subjects. Thus, "adhesive" or the like when used to describe the solidified layer means

Padagis Ex. 1029
IPR Petition - USP 11,311,482

the solidified layer is adhesive to the skin surface to which the initial formulation layer was originally applied (before the evaporation of the volatile solvent(s)). In one embodiment, it does not mean the solidified layer is adhesive on the opposing side. In addition, it should be noted that whether a solidified layer can adhere to a skin surface for the desired extended period of time partially depends on the condition of the skin surface. For example, excessively sweating or oily skin, or oily substances on the skin surface may make the solidified layer less adhesive to the skin. Therefore, the adhesive solidified layer of the current invention may not be able to maintain perfect contact with the skin surface and deliver the drug over a sustained period of time for every subject under any conditions on the skin surface. A standard is that it maintains good contact with most of the skin surface, e.g. 70% of the total area, over the specified period of time for most subjects under normal conditions of the skin surface and external environment.

The terms "flexible," "elastic," "elasticity," or the like, as used herein refer to sufficient elasticity of the solidified layer so that it is not broken if it is stretched in at least one direction by up to about 5%, and often to about 10% or even greater. For example, a solidified layer that exhibits acceptably elasticity and adhesion to skin can be attached to human skin over a flexible skin location, e.g., elbow, finger, wrist, neck, lower back, lips, knee, etc., and will remain substantially intact on the skin upon stretching of the skin. It should be noted that the solidified layers of the present invention do not necessarily have to have any elasticity in some embodiments.

The term "peelable," when used to describe the solidified layer, means the solidified layer can be lifted from the skin surface in one large piece or several large pieces, as opposed to many small pieces or crumbs.

The term "sustained" relates to therapeutically effective rates of dermal drug delivery for a continuous period of time of at least 30 minutes, and in some embodiments, periods of time of at least about 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, or longer.

The use of the term "substantially" when referring to the evaporation of the volatile solvents means that a majority of the volatile solvents which were

Padagis Ex. 1029
IPR Petition - USP 11,311,482

included in the initial formulation have evaporated. Similarly, when a solidified layer is said to be "substantially devoid" of volatile solvents, including water, the solidified layer has less than 10 wt%, and preferably less than 5 wt%, of the volatile solvents in the solidified layer as a whole.

"Volatile solvent system" can be a single solvent or a mixture of solvents that are volatile, including water and solvents that are more volatile than water. Non-limiting examples of volatile solvents that can be used in the present invention include iso-amyl acetate, denatured alcohol, methanol, ethanol, isopropyl alcohol, water, propanol, C4-C6 hydrocarbons, butane, isobutene, pentane, hexane, acetone, chlorobutanol, ethyl acetate, fluro-chloro-hydrocarbons, turpentine, methyl ethyl ketone, methyl ether, hydrofluorocarbons, ethyl ether, 1,1,1,2 tetrafluorethane 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,3,3,3 hexafluoropropane, and combinations thereof.

"Non-volatile solvent system" in this invention is defined as a mixture of at least two solvents that are each less volatile than water. Similarly, a non-volatile solvent is defined as a solvent that is less volatile than water. The non-volatile solvent system can also contain substances that are solid or liquid at room temperatures, such as pH or ion-pairing agents. After evaporation of the volatile solvent system, most of the non-volatile solvent system should remain in the solidified layer for a period of time sufficient to adequately dermally deliver a given drug to, into, or through the skin of a subject at a sufficient flux for a period of time to provide a therapeutic effect.

The non-volatile solvent system can also serve as a plasticizer of the solidified layer, so that the solidified layer is elastic and flexible. In one embodiment, the non-volatile solvent system provides better plasticizing effects for the solidifying agents than any single non-volatile solvent of the non-volatile solvent system alone. Including multiple non-volatile solvents as part of the non-volatile solvent system can also provide various other benefits. In some cases, a single non-volatile solvent may not provide the formulation with adequate compatibility with other ingredients in the formulation, e.g. volatile solvent system or solidifying agent, and/or the ability to generate therapeutically

Padagis Ex. 1029
IPR Petition - USP 11,311,482

effective flux of the drug. In one aspect of the invention, the non-volatile solvent system provides better compatibility with the solidifying agent than any single non-volatile solvent of the non-volatile solvent system alone. In another aspect of the invention, the non-volatile solvent system provides higher flux than any single non-volatile solvent of the non-volatile solvent system alone. The present invention allows for combinations of two or more non-volatile solvents which together are able to provide both therapeutically effective drug flux while maintaining formulation component compatibility.

The term "solvent vehicle" describes compositions that include both a volatile solvent system and non-volatile solvent system. The volatile solvent system is chosen so as to evaporate from the adhesive formulation quickly to form a solidified layer, and the non-volatile solvent system is formulated or chosen to substantially remain as part of the solidified layer after volatile solvent system evaporation so as to provide continued delivery of the drug. Typically, the drug can be partially or completely dissolved in the solvent vehicle or formulation as a whole. Likewise, the drug can also be partially or completely solubilizable in the non-volatile solvent system once the volatile solvent system is evaporated. Formulations in which the drug is only partially dissolved in the non-volatile solvent system after the evaporation of the volatile solvent system have the potential to maintain longer duration of sustained delivery, as the undissolved drug can dissolve into the non-volatile solvent system as the dissolved drug is being depleted from the solidified layer during drug delivery.

"Adhesive solidifying formulation" or "solidifying formulation" refers to a composition that has a viscosity suitable for application to a skin surface prior to evaporation of its volatile solvent(s), and which can become a solidified layer after evaporation of at least a portion of the volatile solvent(s). The solidified layer, once formed, can be very durable. In one embodiment, once solidified on a skin surface, the formulation can form a peel. The peel can be a soft, coherent solid that can be removed by peeling large pieces from the skin relative to the size of the applied formulation, and often, can be peeled from the skin as a single piece. The application viscosity is typically more viscous than a water-like liquid, but less viscous than a soft solid. Examples of preferred

Padagis Ex. 1029
IPR Petition - USP 11,311,482

viscosities include materials that have consistencies similar to pastes, gels, ointments, and the like, e.g., viscous liquids that flow but are not subject to spilling. Thus, when a composition is said to have a viscosity "suitable for application" to a skin surface, this means the composition has a viscosity that is high enough so that the composition does not substantially run off the skin after being applied to skin, but also has a low enough viscosity so that it can be easily spread onto the skin. A viscosity range that meets this definition can be from about 100 cP to about 3,000,000 cP (centipoises), and more preferably from about 1,000 cP to about 1,000,000 cP.

In some embodiments of the present invention, it may be desirable to add an additional agent or substance to the formulation so as to provide enhanced or increased adhesive characteristics. The additional adhesive agent or substance can be an additional non-volatile solvent or an additional solidifying agent. Non-limiting examples of substances which might be used as additional adhesion enhancing agents include copolymers of methylvinyl ether and maleic anhydride (Gantrez polymers), polyethylene glycol and polyvinyl pyrrolidone, gelatin, low molecular weight polyisobutylene rubber, copolymer of acrylsan alkyl/octylacrylamido (Dermacryl 79), and/or various aliphatic resins and aromatic resins.

The terms "washable," "washing" or "removed by washing" when used with respect to the adhesive formulations of the present invention refers to the ability of the adhesive formulation to be removed by the application of a washing solvent using a normal or medium amount of washing force. The required force to remove the formulations by washing should not cause significant skin irritation or abrasion. Generally, gentle washing force accompanied by the application of an appropriate washing solvent is sufficient to remove the adhesive formulations disclosed herein. The solvents which can be used for removing by washing the formulations of the present invention are numerous, but preferably are chosen from commonly acceptable solvents including the volatile solvents listed herein. Preferred washing solvents do not significantly irritate human skin and are generally available to the average subject. Examples of washing solvents include but are not limited to water, ethanol,

Padagis Ex. 1029
IPR Petition - USP 11,311,482

methanol, isopropyl alcohol, acetone, ethyl acetate, propanol, and combinations thereof. In aspect of the invention the washing solvents can be selected from the group consisting of water, ethanol, isopropyl alcohol and combinations thereof. Surfactants can also be used in some embodiments.

An acceptable length of time with respect to "drying time" refers to the time it takes for the formulation to form a non-messy solidified surface after application on skin under standard skin and ambient conditions, and with standard testing procedure. It is noted that the word "drying time" in this application does not mean the time it takes to completely evaporate off the volatile solvent(s). Instead, it means the time it takes to form the non-messy solidified surface as described above.

"Standard skin" is defined as dry, healthy human skin with a surface temperature of between about 30°C to about 36°C. Standard ambient conditions are defined by the temperature range of from 20°C to 25°C and a relative humidity range of from 20% to 80%. The term "standard skin" in no way limits the types of skin or skin conditions on which the formulations of the present invention can be used. The formulations of the present invention can be used to treat all types of "skin," including undamaged (standard skin), diseased skin, or damaged skin. Although skin conditions having different characteristics can be treated using the formulations of the present invention, the use of the term "standard skin" is used merely as a standard to test the compositions of the varying embodiments of the present invention. As a practical matter, formulations that perform well (e.g., solidify, provide therapeutically effective flux, etc.) on standard skin can also perform well diseased or damaged skin.

The "standard testing procedure" or "standard testing condition" is as follows: To standard skin at standard ambient conditions is applied an approximately 0.1 mm layer of the adhesive solidifying formulation and the drying time is measured. The drying time is defined as the time it takes for the formulation to form a non-messy surface such that the formulation does not lose mass by adhesion to a piece of 100% cotton cloth pressed onto the formulation surface with a pressure of between about 5 and about 10 g/cm^2 for 5 seconds.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

"Solidified layer" describes the solidified or dried layer of an adhesive solidifying formulation after at least a portion of the volatile solvent system has evaporated. The solidified layer remains adhered to the skin, and is preferably capable of maintaining good contact with the subject's skin for substantially the entire duration of application under standard skin and ambient conditions. The solidified layer also preferably exhibits sufficient tensile strength so that it can be peeled off the skin at the end of the application in one piece or several large pieces (as opposed to a layer with weak tensile strength that breaks into many small pieces or crumbles when removed from the skin).

As used herein, a plurality of drugs, compounds, and/or solvents may be presented in a common list for convenience. However, these lists should be construed as though each member of the list is individually identified as a separate and unique member. Thus, no individual member of such list should be construed as a de facto equivalent of any other member of the same list solely based on their presentation in a common group without indications to the contrary.

Concentrations, amounts, and other numerical data may be expressed or presented herein in a range format. It is to be understood that such a range format is used merely for convenience and brevity and thus should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. As an illustration, a numerical range of "about 0.01 to 2.0 mm" should be interpreted to include not only the explicitly recited values of about 0.01 mm to about 2.0 mm, but also include individual values and sub-ranges within the indicated range. Thus, included in this numerical range are individual values such as 0.5, 0.7, and 1.5, and sub-ranges such as from 0.5 to 1.7, 0.7 to 1.5, and from 1.0 to 1.5, etc. This same principle applies to ranges reciting only one numerical value. Furthermore, such an interpretation should apply regardless of the breadth of the range or the characteristics being described.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

With these definitions in mind, the present invention is drawn to an adhesive formulation for dermal delivery of a drug can comprise a drug, a solvent vehicle, and a solidifying agent. The solvent vehicle can comprise a volatile solvent system including at least one volatile solvent and a non-volatile solvent system including at least two non-volatile solvents. The at least two non-volatile solvents of the non-volatile solvent system can facilitate transdermal delivery of the drug at a therapeutically effective rate over a sustained period of time, even after the non-volatile solvent system is substantially evaporated.. The formulation can have viscosity suitable for application to the skin surface prior to evaporation of at least one volatile solvent, and can further be formulated such that when applied to the skin surface, the formulation forms a solidified layer after at least a portion of the volatile solvent system is evaporated. Sustained drug delivery from the solidified layer can also occur.

In an alternative embodiment, a method of dermally delivering a drug can comprise applying an adhesive solidifying formulation to a skin surface of a subject. The formulation can comprise a drug, solvent vehicle, and a solidifying agent. The solvent vehicle can comprise a volatile solvent system including at least one volatile solvent, and a non-volatile solvent system including at least two non-volatile solvents, wherein the non-volatile solvent system facilitates dermal delivery of the drug at a therapeutically effective rate over a sustained period of time. The formulation can have a viscosity suitable for application and adhesion to the skin surface prior to evaporation of the volatile solvent system Other steps include solidifying the formulation to form a solidified layer on the skin surface by at least partial evaporation of the volatile solvent system; and dermally delivering the drug from the solidified layer to the skin surface at therapeutically effective rates over a sustained period of time.

In another embodiment, a solidified layer for delivering a drug can comprise a drug, a non-volatile solvent system including at least two non-volatile solvents, wherein the non-volatile solvent system is capable of facilitating the delivery of the drug at therapeutically effective rates over a sustained period of time, and a solidifying agent. The solidified layer can be stretchable by 5% in at

Padagis Ex. 1029
IPR Petition - USP 11,311,482

least one direction without cracking, breaking, or separating from a skin surface to which the layer is applied.

In another embodiment, an adhesive formulation for dermal delivery of a drug can comprise a drug, a solvent vehicle, and at least two solidifying agents. The solvent vehicle can include a volatile solvent system including at least one volatile solvent, and a non-volatile solvent system including at least one non-volatile solvent wherein the non-volatile solvent system can be flux-enabling for the drug such that the drug can be delivered in therapeutically effective amounts even after most of the volatile solvent(s) is(are) evaporated. The formulation can have a viscosity suitable for application and adhesion to a skin surface prior to evaporation of the volatile solvent system, and can form a solidified layer after at least partial evaporation of the volatile solvent system after skin application. The drug can continue to be dermally delivered after the volatile solvent system is substantially evaporated.

In another embodiment, a method of dermally delivering a drug can comprise applying an adhesive solidifying formulation to a skin surface of a subject. The formulation can include a drug, a solvent vehicle, and at least two solidifying agents. The solvent vehicle can comprise a volatile solvent system including at least one volatile solvent, and a non-volatile solvent system including at least one non-volatile solvent. The formulation can have a viscosity suitable for application and adhesion to the skin surface prior to evaporation of the volatile solvent system. Other steps include solidifying the formulation to form a solidified layer on the skin surface by at least partial evaporation of the volatile solvent system; and dermally delivering the drug from the solidified layer to the skin surface at therapeutically effective rates over a sustained period of time.

In another embodiment, a solidified layer for delivering a drug can comprise a drug, a non-volatile solvent system comprising at least one non-volatile solvent, and at least two polymeric solidifying agents.

In yet another embodiment, a formulation for dermal delivery of a drug can comprise a drug, a solvent vehicle, and a solidifying agent. The solvent vehicle can comprise a volatile solvent system including at least two volatile

Padagis Ex. 1029
IPR Petition - USP 11,311,482

solvents, and a non-volatile solvent system including at least one non-volatile solvent. The formulation has a viscosity suitable for application and adhesion to a skin surface prior to evaporation of the volatile solvent system wherein the non-volatile solvent system can be flux-enabling for the drug such that the drug can be delivered at a therapeutically effective amount even after most of the volatile solvent(s) is(are) evaporated. The formulation applied to the skin surface can form a solidified layer after at least partial evaporation of the volatile solvent system and can further be formulated such that when applied to the skin surface, the formulation forms a solidified layer after at least a portion of the volatile solvents is (are) evaporated, but yet continues to deliver drug after substantially solidifying. Additionally, the drug can continue to be delivered after the volatile solvent system is at least substantially evaporated.

In another embodiment, a method of dermally delivering a drug can comprise applying an adhesive solidifying formulation to a skin surface of a subject. The adhesive formulation can comprise a drug, a solvent vehicle, and a solidifying agent. The solvent vehicle can comprise a volatile solvent system including at least two volatile solvent, and a non-volatile solvent system including at least one non-volatile solvent. The formulation can have a viscosity suitable for application and adhesion to the skin surface prior to evaporation of the volatile solvent system. Other steps include solidifying the formulation to form a solidified layer on the skin surface by at least partial evaporation of the volatile solvent system; and dermally delivering the drug from the solidified layer to the skin surface at therapeutically effective rates over a sustained period of time.

In further detail, the formulations can also contain substances that are solid or liquid at room temperatures, such as pH or ion-pairing agents. After evaporation of the volatile solvent system, most of the non-volatile solvent system should remain in the solidified layer for a period of time sufficient to adequately dermally deliver a given drug to, into, or through the skin of a subject at a sufficient flux for a period of time to provide a therapeutic effect. The non-volatile solvent system can also serve as a plasticizer of the solidified layer, so that the solidified layer is elastic and flexible.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Thus, these embodiments exemplify the present invention which is related to novel formulations, methods, and solidified layers that are typically in the initial form of semi-solids (including creams, gels, pastes, ointments, and other viscous liquids), which can be easily applied onto the skin as a layer, and can quickly (from 15 seconds to about 4 minutes under standard skin and ambient conditions) to moderately quickly (from about 4 to about 15 minutes under standard skin and ambient conditions) change into a solidified layer, e.g., a coherent and soft solid layer which can be peelable, for drug delivery. A solidified layer thus formed is capable of delivering drug to the skin, into the skin, across the skin, etc., at substantially constant rates, over an sustained period of time, e.g., hours to tens of hours, so that most of the active drug is delivered after the solidified layer is formed.

Although a solid layer-forming formulation for dermal drug delivery can use a single solidifying agent, the use of two or more solidifying agents in the formulation herein can provide important advantages. This is because in addition to solidifying the formulations, the solidifying agent(s) in the formulation often impacts component compatibility as well as flexibility and skin adhesiveness of the solidified layer. Sometimes it takes two or more solidified agents to address all these needs. The present invention is related to solidifying formulations that use two or more solidified agents to produce better formulation properties than any single solidifying agent alone within a given formulation could accomplish.

Additionally, the solidified layer typically adheres to the skin, but has a solidified, minimally-adhering, outer surface which is formed relatively soon after application and which does not substantially transfer to or otherwise soil clothing or other objects that a subject is wearing or that the solidified layer may inadvertently contact. The solidified layer can also be formulated such that it is highly flexible and stretchable, and thus capable of maintaining good contact with a skin surface, even if the skin is stretched during body movement, such as at a knee, finger, elbow, or other joints.

In selecting the various components that can be used, e.g., drug, solvent vehicle of volatile solvent system and non-volatile solvent system, solidifying

Padagis Ex. 1029
IPR Petition - USP 11,311,482

agent(s), etc., various considerations can occur. For example, the volatile solvent system can be selected from pharmaceutically or cosmetically acceptable solvents known in the art. In one embodiment of the present invention, the volatile solvent system can include ethanol, isopropyl alcohol, water, dimethyl ether, diethyl ether, butane, propane, isobutene, 1,1, difluoroethane, 1,1,1,2 tetrafluorethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,3,3,3 hexafluoropropane, ethyl acetate, acetone or combinations thereof. In another embodiment of the present invention, the volatile solvent system can include iso-amyl acetate, denatured alcohol, methanol, propanol, isobutene, pentane, hexane, chlorobutanol, turpentine, cytopentasiloxane, cyclomethicone, methyl ethyl ketone, or combinations thereof. The volatile solvent system can include a mixture or combination of any of the volatile solvents set forth in the embodiments above.

In one embodiment, of the present invention the volatile solvent system comprises at least one volatile solvent with a boiling point higher than 20 °C (a liquid volatile solvent) and at least one volatile solvent with a boiling point lower than about 20 °C (gaseous volatile solvents). Boiling points refer to boiling points measured at normal atmospheric pressure. Formulations of the present invention which have both liquid and gas volatile solvents can have significantly shorter drying times than those with only liquid volatile solvents. When a gas volatile solvent is included in the volatile solvent system, it is often the case that concentration of the gas volatile solvent is below the formulations solubility. This allows the formulation to be stored in containers for conventional, un-pressurized semi-solid products. Alternatively, these solvents can be used as propellants for spray-on formulations. Examples of gas volatile solvents which may be used in the present invention include but are not limited to ether, dimethyl ether, diethyl ether, propane, isobutene, diflouroethane, butane, 1,1,1,2 tetraflourethane, 1,1,1,2,3,3,3-heptaflouropropane, and 1,1,1,3,3,3, hexaflouropropane, and combinations thereof.

Additionally, these volatile solvents should be chosen to be compatible with the rest of the formulation. It is desirable to use an appropriate weight percentage of the volatile solvent(s) in the formulation. Too much of the volatile

Padagis Ex. 1029
IPR Petition - USP 11,311,482

solvent system prolongs the drying time. Too little of the volatile solvent system can make it difficult to spread the formulation on the skin. For most formulations, the weight percentage of the volatile solvent(s) can be from about 10 wt% to about 85 wt%, and more preferably from about 20 wt% to about 50 wt%. In one aspect of the invention, the volatile solvent system comprises at least 10 wt% of the formulation. In another embodiment, the volatile solvent system comprises at least about 20 wt% of the formulation.

The volatile solvent system can also be chosen to be compatible with the non-volatile solvent system, solidifying agent, drug, and any other excipients that may be present. For example, polyvinyl alcohol (PVA) is not soluble in ethanol. Therefore, a volatile solvent which will dissolve PVA needs to be formulated in the solidified layer. For instance, water will dissolve PVA and can be utilized as a volatile solvent in a formulation; however, the drying time in such a formulation may be too long to certain applications. Therefore, a second volatile solvent (e.g., ethanol) can be formulated into the formulation to reduce the water content but maintain a sufficient amount of water to keep PVA in solution and thereby reduce the drying time for the formulation.

The volatile solvent system can be chosen to reduce drying time for the formulation. Returning to the PVA example above, the use of water to dissolve the PVA may result in the drying time in such a formulation may be too long to certain applications. Therefore, a second volatile solvent (e.g., ethanol) can be formulated into the formulation to reduce the water content but maintain a sufficient amount of water to keep PVA in solution and thereby reduce the drying time for the formulation.

The volatile solvent can be chosen to improve solubility of a particular drug form utilized in the formulation. For example, ropivacaine HCl is not soluble in non-volatile solvents isostearic acid, triacetin, and Span 20. Therefore, addition of water to the formulation will aid in dissolving the ropivacaine HCl and with addition of a small amount of base to dissolve the remaining drug crystals. Complete dissolution of ropivacaine in the formulation is advantageous to having to avoid suspending the undissolved drug particles in a formulation with a relatively low viscosity that may result in drug settling.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

For a selected drug or a selected solidifying agent, some volatile solvents may be better solvents or more compatible than other volatile solvents. However, some times, the most suitable volatile solvent for a drug is not compatible with a solidifying agent, and vice versa. In some other situations, the most suitable volatile solvent for a drug and a solidifying agent evaporates to slowly resulting in a drying time that is unacceptable for the application. In the above situations, satisfactory compromises may be reached by using a specially formulated volatile solvent systems that contains two or more volatile solvents according to certain ratios (which are often experimentally determined). For example, one solvent can provide acceptable evaporation time, and another volatile solvent provides improved formulation compatibility.

In one embodiment of the present invention, one of the volatile solvents of the volatile solvent system can be less volatile than the other. The less volatile solvent can have better compatibility with the solidifying agent as compared to a more volatile solvent in the solvent system.

In another aspect of the present invention, it can be beneficial to retain or delay the volatilization of the volatile solvent system so that the solidifying formulation can maintain its desirable wear, and drug delivery properties. Such retention can be accomplished by including a volatile solvent retaining substance in the formulation. Volatile solvent retaining substances can include water, hygroscopic substances, honey, glycerol, propylene glycol, and the like.

The non-volatile solvent system can also be chosen or formulated to be compatible with the solidifying agent, the drug, the volatile solvent, and any other ingredients that may be present. For example, the solidifying agent can be chosen so that it is dispersible or soluble in the non-volatile solvent system. Most non-volatile solvent systems and solvent vehicles as a whole will be formulated appropriately after experimentation. For instance, certain drugs have good solubility in poly ethylene glycol (PEG) having a molecular weight of 400 (PEG 400, non-volatile solvent) but poor solubility in glycerol (non-volatile solvent) and water (volatile solvent). However, PEG 400 cannot effectively dissolve poly vinyl alcohol (PVA), and thus, is not very compatible alone with PVA, a solidifying agent. In order to dissolve sufficient amount of an active drug

Padagis Ex. 1029
IPR Petition - USP 11,311,482

and use PVA as a solidifying agent at the same time, a non-solvent system including PEG 400 and glycerol (compatible with PVA) in an appropriate ratio can be formulated, achieving a compatibility compromise. As a further example of compatibility, non-volatile solvent/solidifying agent incompatibility is observed when Span 20 is formulated into a formulation containing PVA. With this combination, Span 20 can separate out of the formulation and form an oily layer on the surface of the solidified layer. Thus, appropriate solidifying agent/non-volatile solvent selections are desirable in developing a viable formulation and compatible combinations. It is not necessary that both the non-volatile solvents of the non-volatile solvent system be compatible with the solidifying agent. In some embodiments one of the non-volatile solvents of the non-volatile solvent system can be present to provide compatibility with the solidifying agent while a second non-volatile solvent can act as the flux enabling non-volatile solvent.

In further detail, the at least two non-volatile solvents that can be used to form non-volatile solvent systems can be selected from a variety of pharmaceutically acceptable liquids. In one embodiment of the present invention, the non-volatile solvent system can include glycerol, propylene glycol, isostearic acid, oleic acid, propylene glycol, trolamine, tromethamine, triacetin, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, butanol, or combinations thereof. In another embodiment the non-volatile solvent system can include benzoic acid, butyl alcohol, dibutyl sebecate, diglycerides, dipropylene glycol, eugenol, fatty acids such as coconut oil, fish oil, palm oil, grape seed oil, isopropyl myristate, mineral oil, oleyl alcohol, vitamin E, triglycerides, sorbitan fatty acid surfactants, triethyl citrate, or combinations thereof. In a further embodiment the non-volatile solvent system can include 1,2,6-hexanetriol, alkyltriols, alkyldiols, acetyl monoglycerides, tocopherol, alkyl dioxolanes, p-propenylanisole, anise oil, apricot oil, dimethyl isosorbide, alkyl glucoside, benzyl alcohol, bees wax, benzyl benzoate, butylene glycol, caprylic/capric triglyceride, caramel, cassia oil, castor oil, cinnamaldehyde, cinnamon oil, clove oil, coconut oil, cocoa butter, cocoglycerides, coriander oil, corn oil, coriander oil, corn syrup, cottonseed oil, cresol, cyclomethicone, diacetin, diacetylated monoglycerides, diethanolamine, dietthylene glycol

Padagis Ex. 1029
IPR Petition - USP 11,311,482

monoethyl ether, diglycerides, ethylene glycol, eucalyptus oil, fat, fatty alcohols, flavors, liquid sugars ginger extract, glycerin, high fructose corn syrup, hydrogenated castor oil, IP palmitate, lemon oil, lime oil, limonene, milk, monoacetin, monoglycerides, nutmeg oil, octyldodecanol, olive alcohol, orange oil, palm oil, peanut oil, PEG vegetable oil, peppermint oil, petrolatum, phenol, pine needle oil, polypropylene glycol, sesame oil, spearmint oil, soybean oil, vegetable oil, vegetable shortening, vinyl acetate, wax, 2-(2-(octadecyloxy)ethoxy)ethanol, benzyl benzoate, butylated hydroxyanisole, candelilla wax, carnauba wax, ceteareth-20, cetyl alcohol, polyglyceryl, dipolyhydroxy stearate, PEG-7 hydrogenated castor oil, diethyl phthalate, diethyl sebacate, dimethicone, dimethyl phthalate, PEG Fatty acid esters such as PEG-stearate, PEG - oleate, PEG- laurate, PEG fatty acid diesters such as PEG-dioleate, PEG- distearate, PEG-castor oil, glyceryl behenate, PEG glycerol fatty acid esters such as PEG glyceryl laurate, PEG glyceryl stearate, PEG glyceryl oleate, hexylene glycerol, lanolin, lauric diethanolamide, lauryl lactate, lauryl sulfate, medronic acid, methacrylic acid, multisterol extract, myristyl alcohol, neutral oil, PEG-octyl phenyl ether, PEG -alkyl ethers such as PEG-cetyl ether, PEG-stearyl ether, PEG- sorbitan fatty acid esters such as PEG-sorbitan diisosterate, PEG-sorbitan monostearate, propylene glycol fatty acid esters such as propylene glycol stearate, propylene glycol, caprylate/caprate, sodium pyrrolidone carboxylate, sorbitol, squalene, stear-o-wet, triglycerides, alkyl aryl polyether alcohols, polyoxyethylene derivatives of sorbitan-ethers, saturated polyglycolyzed C8-C10 glycerides, N-methyl pyrrolidone, honey, polyoxyethylated glycerides, dimethyl sulfoxide, azone and related compounds, dimethylformamide, N-methyl formamaide, fatty acid esters, fatty alcohol ethers, alkyl-amides (N,N-dimethylalkylamides), N-methyl pyrrolidone related compounds, ethyl oleate, polyglycerized fatty acids, glycerol monooleate, glyceryl monomyristate, glycerol esters of fatty acids, silk amino acids, PPG-3 benzyl ether myristate, Di-PPG2 myreth 10-adipate, honeyquat, sodium pyroglutamic acid, abyssinica oil, dimethicone, macadamia nut oil, limnanthes alba seed oil, cetearyl alcohol, PEG-50 shea butter, shea butter, aloe vera juice, phenyl trimethicone, hydrolyzed wheat protein, or combinations thereof. In yet a

Padagis Ex. 1029
IPR Petition - USP 11,311,482

further embodiment, the non-volatile solvent system can include a combination or mixture of non-volatile solvents set forth in any of the above discussed embodiments.

In addition to these and other considerations, the non-volatile solvent system, or at least one of the non-volatile solvents in the non-volatile solvent system can also serve as plasticizer in the adhesive formulation so that when the solidified layer is formed, the layer is flexible, stretchable, and/or otherwise "skin friendly."

Certain volatile and/or nonvolatile solvent(s) that are irritating to the skin may be desirable to use to achieve the desired solubility and/or permeability of the drug. It is also desirable to add compounds that are both capable of preventing or reducing skin irritation and are compatible with the formulation. For example, in a formulation where the volatile solvent is capable of irritating the skin, it would be helpful to use a non-volatile solvent that is capable of reducing skin irritation. Examples of solvents that are known to be capable of preventing or reducing skin irritation include, but are not limited to, glycerin, honey, and propylene glycol.

The feature of two non-volatile solvents in the non-volatile solvent system enhances the ability of the non-volatile solvent to provide therapeutically effective flux, while at the same time providing additional important characteristics which make the solidified formulations superior. As discussed in other areas of the application, non-volatile solvents can provide advantageous benefits such as acting as a plasticizer, improve adhesion, reducing skin irritation, inhibiting phase separation, and the like. In some embodiments it may be desirable to deliver two drugs which do not share a common flux-enabling non-volatile solvent. In such instances at least on of the at least two non-volatile solvents present in the non-volatile solvent system can act to promote the flux of one of the drugs while the other non-volatile solvent promotes the flux of the other drug. In such situations it may be desirable or necessary to include an additional non-volatile solvent which provides some of the other advantageous benefits discussed above.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

The two or more non-volatile solvents of the non-volatile solvent system of the present invention may be such that the non-volatile solvents used independently are not flux-enabling non-volatile solvents for a drug but when formulated together become a flux-enabling non-volatile solvent. One possible reason for these initially non enabling non-volatile solvents to become enabling non-volatile solvents when formulated together may be due to the optimization of the ionization state of the drug to a physical form which has higher flux or the non-volatile solvents act in some other synergistic manner. One further benefit of the mixing of the non-volatile solvents is that it may optimize the pH of the formulation or the skin tissues under the formulation layer to minimize irritation. Examples of suitable combinations of non-volatile solvents that result in an adequate non-volatile solvent system include but are not limited to isostearic acid /trolamine, isostearic acid /diisopropyl amine, oleic acid/trolamine, and propylene glycol /isostearic acid.

The selection of the solidifying agent can also be carried out in consideration of the other components present in the adhesive formulation. The solidifying agent can be selected or formulated to be compatible to the drug and the solvent vehicle (including the volatile solvent(s) and the non-volatile solvent system), as well as to provide desired physical properties to the solidified layer once it is formed. Depending on the drug, solvent vehicle, and/or other components that may be present, the solidifying agent can be selected from a variety of agents. In one embodiment, the solidifying agent can include polyvinyl alcohol with a MW range of 20,000-70,000 (Amresco), esters of polyvinylmethylether/maleic anhydride copolymer (ISP Gantrez ES-425 and Gantrez ES-225) with a MW range of 80,000-160,000, neutral copolymer of butyl methacrylate and methyl methacrylate (Degussa Plastoid B) with a MW range of 120,000-180,000, dimethylaminoethyl methacrylate-butyl methacrylate-methyl methacrylate copolymer (Degussa Eudragit E100) with a MW range of100,000-200,000, ethyl acrylate-methyl methacrylate-trimethylammonioethyl methacrylate chloride copolymer with a MW greater than 5,000 or similar MW to Eudragit RLPO (Degussa), Zein (prolamine) with a MW greater than 5,000 such as Zein with a MW around 35,000 (Freeman industries), pregelatinized starch

Padagis Ex. 1029
IPR Petition - USP 11,311,482

having a MW similar to Instant Pure-Cote B793 (Grain Processing Corporation), ethyl cellulose MW greater than 5,000 or MW similar to Aqualon EC N7, N10, N14, N22, N50 , or N100 (Hercules), fish gelatin having a MW 20,000-250,000 (Norland Products), gelatin, other animal sources with MW greater than 5,000, acrylates/octylacrylamide copolymer MW greater than 5,000 or MW similar to National Starch, Chemical Dermacryl 79, or combinations thereof.

In another embodiment, the solidifying agent can include ethyl cellulose, hydroxy ethyl cellulose, hydroxy methyl cellulose, hydroxy propyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, methyl cellulose, polyether amides, corn starch, pregelatinized corn starch, polyether amides, shellac, polyvinyl pyrrolidone, polyisobutylene rubber, polyvinyl acetate phthalate, or combinations thereof. In a further embodiment, the solidifying agent can include ammonia methacrylate, carrageenan, cellulose acetate phthalate aqueous such as CAPNF from Eastman, carboxy polymethylene, cellulose acetate (microcrystalline), cellulose polymers, divinyl benzene styrene, ethylene vinyl acetate, silicone, guar gum, guar rosin, gluten, casein, calcium caseinate, ammonium caseinate, sodium caseinate, potassium caseinate, methyl acrylate, microcrystalline wax, polyvinyl acetate, PVP ethyl cellulose, acrylate, PEG/PVP, xantham gum, trimethyl siloxysilicate, maleic acid/anhydride colymers, polacrilin, poloxamer, polyethylene oxide, poly glactic acid/poly-l-lactic acid, turpene resin, locust bean gum, acrylic copolymers, polyurethane dispersions, dextrin, polyvinyl alcohol-polyethylene glycol co-polymers, methacrylic acid-ethyl acrylate copolymers such as BASF's Kollicoat polymers, methacrylic acid and methacrylate based polymers such as poly(methacrylic acid), or combinations thereof. In another embodiment, the solidifying agent can include a combination of solidifying agents set forth in the any of the above discussed embodiments. Other polymers may also be suitable as the solidifying agent, depending on the solvent vehicle components, the drug, and the specific functional requirements of the given formulation. Other polymers may also be suitable as the solidifying agent, depending on the solvent vehicle components, the drug, and the specific functional requirements of the given formulation.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

In one embodiment, the non-volatile solvent system and the solidifying agent(s) should be compatible with each other. Compatibility can be defined as i) the solidifying agent does not substantially negatively influence the function of the non-volatile solvent system, except for some reduction of flux; ii) the solidifying agent can hold the non-volatile solvent system in the solidified layer so that substantially no non-volatile solvent oozes out of the layer, and/or iii) the solidified layer formed with the selected non-volatile solvent system and the solidifying agent has acceptable flexibility, rigidity, tensile strength, elasticity, and adhesiveness. The weight ratio of the non-volatile solvent system to the solidifying agent(s) can be from about 0.1:1 to about 10:1. In another aspect, the ratio between the non-volatile solvent system and the solidifying agent can be from about 0.5:1 to about 2:1.

The use of at least two solidifying agents can provide superior peel characteristics. Desirable characteristics can include enhanced elasticity, enhanced skin adhesion, enhanced tensile strength, and the like. In some embodiments, the combination of the at least two solidifying agents can provide a more homogenous formulation with minimal if any phase separation. For example, in one embodiment, polyvinyl alcohol (PVA) can be used as one of the solidifying agents in combination with Gantrez. In that combination, the PVA functions to provide enhanced elasticity while the Gantrez provides enhanced skin adhesion. In another embodiment, a formulation can be made which utilizes Eudgragit E-100 in combination with PVA as the solidifying agent. The formulation has quicker solidifying characteristics and results in a solidified layer with enhanced tensile strength.

The thickness of the formulation layer applied on the skin should also be appropriate for a given formulation and desired drug delivery considerations. If the layer is too thin, the amount of the drug may not be sufficient to support sustained delivery over the desired length of time. If the layer is too thick, it may take too long to form a non-messy outer surface of the solidified layer. If the drug is very potent and the solidified layer has very high tensile strength, a layer as thin as 0.01 mm may be sufficient. If the drug has rather low potency and the solidified layer has low tensile strength, a layer as thick as 2-3 mm may be

Padagis Ex. 1029
IPR Petition - USP 11,311,482

desirable. Thus, for most drugs and formulations, the appropriate thickness can be from about 0.01 mm to about 3 mm, but more typically, from about 0.05 mm to about 1 mm.

The flexibility and stretchability of a solidified layer can be desirable in some applications. In one aspect of the invention, the solidified layer is coherent, flexible, and continuous. Such flexible and coherent nature can greatly enhance the ease of use of the formulation. For instance, certain non-steroidal anti-inflammatory agents (NSAIDs) can be applied directly over joints and muscles for transdermal delivery into joints and muscles. However, skin areas over joints and certain muscle groups are often significantly stretched during body movements. Such movement prevents non-stretchable patches from maintaining good skin contact. Lotions, ointments, creams, gels, foams, pastes, or the like also may not be suitable for use for the reasons cited above. As such, in transdermal delivery of NSAIDs into joints and/or muscles, the solidifying formulations of the present invention can offer unique advantages and benefits. It should be pointed out that although good stretchability can be desirable in some applications. The solidifying formulations of the present invention do not always need to be stretchable, as certain applications of the present invention do not necessarily benefit from this property. For instance, if the formulation is applied on a small facial area overnight for treating acne, a subject would experience minimal discomfort and formulation-skin separation even if the solidified layer is not stretchable, as facial skin usually is not stretched very much during a sleep cycle.

A further feature of a formulation prepared in accordance with embodiments of the present invention is related to drying time. If a formulation dries too quickly, the user may not have sufficient time to spread the formulation into a thin layer on the skin surface before the formulation is solidified, leading to poor skin contact. If the formulation dries too slowly, the subject may have to wait a long time before resuming normal activities (e.g. putting clothing on) that may remove un-solidified formulation. Thus, it is desirable for the drying time to be longer than about 15 seconds but shorter than about 15 minutes, and preferably from about 0.5 minutes to about 5 minutes.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Other benefits of the solidified layers of the present invention include the presence of a physical barrier that can be formed by the material itself. For instance, local anesthetic agents and other agents such as clonidine may be delivered topically for treating pain related to neuropathy, such as diabetic neuropathic pain. Since many of such subjects feel tremendous pain, even when their skin area is only gently touched, the physical barrier of the solidified layer can prevent or minimize pain caused by accidental contact with objects or others.

These and other advantage can be summarized in the following non-limiting list of benefits, as follows. The solidified layers of the present invention can be prepared in an initial form that is easy to apply as a semisolid dosage form. Additionally, upon volatile solvent system evaporation, the resulting solidified layer is relatively thick and can contain much more active drug than a typical layer of traditional cream, gel, lotion, ointment, paste, etc., and further, is not as subject to unintentional removal. Further, as the solidified layer remains adhesive and optionally peelable, easy removal of the solidified layer can occur, usually without the aid of a solvent or surfactant. In some embodiments, the adhesion to skin and elasticity of the material is such that the solidified layer will not separate from the skin upon skin stretching at highly stretchable skin areas, such as over joints and muscles. For example, in one embodiment, the solidified layer can be stretched by 5%, or even 10% or greater, in at least one direction without cracking, breaking, and/or separating form a skin surface to which the solidified layer is applied. Still further, the solidified layer can be formulated to advantageously deliver drug and protect sensitive skin areas without cracking or breaking. Generally, the solidified layers made using the formulations of the present invention can be soft and coherent solids that are peelable from a skin surface as a single piece or as only a few large pieces relative to the application size. In other embodiments, the solidified layer can be removable by use of a solvent, such as water, alcohol, surfactant, or mixture thereof.

As a further note, it is a unique feature of the solidified layers of the present invention that they can keep a substantial amount of the non-volatile

Padagis Ex. 1029
IPR Petition - USP 11,311,482

solvent system, which is optimized for delivering the drug, on the skin surface. This feature can provide unique advantages over existing products. For example, in some semi-solid formulations, upon application to a skin surface the volatile solvents quickly evaporate and the formulation layer solidifies into a hard lacquer-like layer. The drug molecules are immobilized in the hard lacquer layer and are substantially unavailable for delivery into the skin surface. As a result, it is believed that the delivery of the drug is not sustained over a long period of time. In contrast to this type of formulation, the solidified layers formed using the formulations of the present invention keep the drug molecules quite mobile in the non-volatile solvent system which is in contact with the skin surface, thus ensuring sustained delivery.

Specific examples of applications that can benefit from the systems, formulations, and methods of the present invention are as follows. In one embodiment, a solidified layer including bupivacaine, lidocaine, or ropivacaine, can be formulated for treating diabetic and post herpetic neuralgia. Alternatively, dibucanine and an alpha-2 agonist such as clonidine can be formulated in a solidified layer for treating the same disease. In another embodiment, retinoic acid and benzoyl peroxide can be combined in a solidified layer for treating acne, or alternatively, 1 wt% clindamycin and 5 wt% benzoyl peroxide can be combined in a solidified layer for treating acne. In another embodiment, a retinol solidifying formulation (OTC) can be prepared for treating wrinkles, or a lidocaine solidifying formulation can be prepared for treating back pain. In another embodiment, a zinc oxide solidifying formulation (OTC) can be prepared for treating diaper rash, or an antihistamine solidified layer can be prepared for treating allergic rashes such as poison ivy.

Additional applications include delivering drugs for treating certain skin conditions, e.g., dermatitis, psoriasis, eczema, skin cancer, viral infections such as cold sore, genital herpes, shingles, etc., particularly those that occur over joints or muscles where a transdermal patch may not be practical. For example, solidifying formulations containing imiquimod can be formulated for treating skin cancer, common and genital warts, and actinic keratosis. Solidifying formulations containing antiviral drugs such as acyclovir, penciclovir, famciclovir,

Padagis Ex. 1029
IPR Petition - USP 11,311,482

valacyclovir, steroids, behenyl alcohol can be formulated for treating herpes viral infections such as cold sores on the face and genital areas. Solidifying formulations containing non-steroidal anti-inflammatory drugs (NSAIDs), capsaicin, alpha-2 agonists, and/or nerve growth factors can be formulated for treating soft tissue injury and muscle-skeletal pains such as joint and back pain of various causes. As discussed above, patches over these skin areas typically do not have good contact over sustained period of time, especially for a physically active subject, and may cause discomfort. Likewise, traditional semi-solid formulations such as creams, lotions, ointments, etc., may prematurely stop the delivery of a drug due to the evaporation of solvent and/or unintentional removal of the formulation. The solidified adhesive formulations of the present invention address the shortcomings of both of these types of delivery systems.

A further embodiment involves a formulation containing at least one alpha-2 agonist drug, at least one tricyclic antidepressant agent, and/or at least one local anesthetic drug which is applied topically to treat neuropathic pain. The drugs are gradually released from the formulation to provide pain relief over a sustained period of time. The formulation can become a coherent, soft solid after 2-5 minutes and remains adhered to the skin surface for the length of its application. It is easily removed any time after drying without leaving residual formulation on the skin surface.

Another embodiment involves a formulation containing capsaicin which is applied topically to treat neuropathic pain. The capsaicin is gradually released from the formulation for treating this pain over a sustained period of time. The formulation can become a coherent, soft solid after 2-5 minutes and remains adhered to the skin surface for the length of its application. It is easily removed any time after drying without leaving residual formulation on the skin surface.

Another embodiment involves solidifying formulations containing tazorac for treating stretch marks, wrinkles, sebaceous hyperplasia, seborrheic keratosis. In another embodiment, solidifying formulations containing glycerol can be made so as to provide a protective barrier for fissuring on finger tips.

Still another embodiment can include a formulation containing a drug selected from the local anesthetic class such lidocaine and ropivacaine or the

Padagis Ex. 1029
IPR Petition - USP 11,311,482

like, or NSAID class, such as ketoprofen, piroxicam, diclofenac, indomethacin, or the like, which is applied topically to treat symptoms of back pain, muscle tension, or myofascial pain or a combination thereof. The local anesthetic and/or NSAID is gradually released from the formulation to provide pain relief over a sustained period of time. The formulation can become a coherent, soft solid after about 2-5 minutes and remains adhered to the skin surface for the length of its application. It is easily removed any time after drying without leaving residual formulation on the skin surface.

A similar embodiment can include a formulation containing drugs capsaicin and a local anesthetic drug which is applied topically to the skin to provide pain relief. Another embodiment can include a formulation containing the combination of a local anesthetic and a NSAID. In both of the above embodiments the drugs are gradually released from the formulation to provide pain relief over a sustained period of time. The formulation can become a coherent, soft solid after 2-4 minutes and remains adhered to the skin surface for the length of its application. It is easily removed any time after drying without leaving residual formulation on the skin surface.

In another embodiment, solidifying formulations for the delivery of drugs that treat the causes or symptoms of diseases involving joints and muscles can also benefit from the systems, formulations, and methods of the present invention. Such diseases that may be applicable include, but not limited to, osteoarthritis (OA), rheumatoid arthritis (RA), joint and skeletal pain of various other causes, myofascial pain, muscular pain, and sports injuries. Drugs or drug classes that can be used for such applications include, but are not limited to, non-steroidal anti-inflammatory drugs (NSAIDs) such as ketoprofen and diclofanec, COX-2 selective NSAIDs and agents, COX-3 selective NSAIDs and agents, local anesthetics such as lidocaine, bupivacaine, ropivacaine, and tetracaine, steroids such as dexamethasone.

Delivering drugs for the treatment of acne and other skin conditions can also benefit from principles of the present invention, especially when delivering drugs having low skin permeability. Currently, topical retinoids, peroxides, and antibiotics for treating acne are mostly applied as traditional semisolid gels or

Padagis Ex. 1029
IPR Petition - USP 11,311,482

creams. However, due to the shortcomings as described above, sustained delivery over many hours is unlikely. For example, clindamycin, benzoyl peroxide, and erythromycin may be efficacious only if sufficient quantities are delivered into hair follicles. However, a traditional semisolid formulation, such as the popular acne medicine benzaclin gel, typically loses most of its solvent (water in the case of benzaclin) within a few minutes after the application. This short period of a few minutes likely substantially compromises the sustained delivery of the drug. The formulations of the present invention typically do not have this limitation.

In another embodiment, the delivery of drugs for treating neuropathic pain can also benefit from the methods, systems, and formulations of the present invention. A patch containing a local anesthetic agent, such as Lidoderm™, is widely used for treating neuropathic pain, such as pain caused by post-herpetic neuralgia and diabetes induced neuropathic pain. Due to the limitations of the patch as discussed above, the solidified layers prepared in accordance with the present invention provide some unique benefits, as well as provide a potentially less expensive alternative to the use of a patch. Possible drugs delivered for such applications include, but are not limited to, local anesthetics such as lidocaine, prilocaine, tetracaine, bupivicaine, etidocaine; and other drugs including capsaicin and alpha-2 agonists such as clonidine, dissociative anesthetics such as ketamine, tricyclic antidepressants such as amitriptyline,.

As set forth in part above, the solidifying formulations of the present invention can be formulated to treat a variety of conditions and disease such as musculoskeletal pain, neuropathic pain, alopecia, skin disease including dermatitis and psoriasis as well as skin restoration (cosmetic skin treatment), and infections including viral, bacterial, and fungal infection. As such, the formulations can deliver a wide ranging number and types of drugs and active agents.

In one embodiment, the solidifying formulation can be formulated to include acyclovir, econazole, miconazole, terbinafine, lidocaine, bupivacaine, ropivacaine, and tetracaine, amitriptyline, ketanserin, betamethasone

Padagis Ex. 1029
IPR Petition - USP 11,311,482

dipropionate, triamcinolone acetonide, clindamycin, benzoyl peroxide, tretinoin, Isotretinoin, clobetasol propionate, halobetasol propionate, ketoprofen, piroxicam, diclofenac, indomethacin, imiquimod, salicylic acid, benzoic acid, or combinations thereof

In another embodiment, the formulation can include an antifungal drug such as amorolfine, butenafine, naftifine, terbinafine, fluconazole, itraconazole, ketoconazole, posaconazole, ravuconazole, voriconazole, clotrimazole, butoconazole , econazole, miconazole, oxiconazole, sulconazole, terconazole, tioconazole, caspofungin, micafungin, anidulafingin, amphotericin B, AmB, nystatin, pimaricin, griseofulvin, ciclopirox olamine, haloprogin, tolnaftate, and undecylenate, or combinations thereof.

In another embodiment, the formulation can include an antifungal drug such as acyclovir, penciclovir, famciclovir, valacyclovir, behenyl alcohol, trifluridine, idoxuridine, cidofovir, gancyclovir, podofilox, podophyllotoxin,ribavirin, abacavir, delavirdine, didanosine, efavirenz, lamivudine, nevirapine, stavudine, zalcitabine, zidovudine, amprenavir, indinavir, nelfinavir, ritonavir, saquinavir, amantadine, interferon, oseltamivir, ribavirin, rimantadine, zanamivir, or combinations thereof.

When the formulation is intended to provide antibacterial treatment it can be formulated to include an antibacterial drug such as erythromycin, clindamycin, tetracycline, bacitracin, neomycin, mupirocin, polymyxin B, quinolones such as ciproflaxin, or combinations thereof.

When the formulation is intended to relieve pain, particularly neuropathic pain, the formulation can include a local anesthetic such as lidocaine, bupivacaine, ropivacaine, and tetracaine; an alpha-2 agonists such as clonidine. When the formulation is intended to treat pain associated with inflammation it can be formulated to include an non-steroidal anti-inflammatory drug such as ketoprofen, piroxicam, diclofenac, indomethacin, COX inhibitors general COX inhibitors, COX-2 selective inhibitors, COX-3 selective inhibitors, or combinations thereof

In another embodiment, the formulation can be formulated to treat skin disorders or blemishes by including active agents such as anti-acne drugs such

Padagis Ex. 1029
IPR Petition - USP 11,311,482

as clindamycin and benzoyl peroxide, retinol, vitamin A derivatives such as tazarotene and isotretinoin, cyclosporin, anthralin, vitamin D3, cholecalciferol, calcitriol, calcipotriol, tacalcitol, calcipotriene, or combinations thereof.

In yet another embodiment, the delivery of medication for treating warts and other skin conditions would also benefit from long periods of sustained drug delivery. Examples of anti-wart compounds include but are not limited to:imiquimod, rosiquimod, keratolytic agents: salicylic acid, alpha hydroxy acids, sulfur, rescorcinol, urea, benzoyl peroxide, allantoin, tretinoin, trichloroacetic acid, lactic acid, benzoic acid, or combinations thereof.

A further embodiment involves the use of the solidifying formulations for the delivery of sex steroids including but not limited to progestagens consisting of progesterone, norethindrone, norethindroneacetate, desogestrel, drospirenone, ethynodiol diacetate, norelgestromin, norgestimate, levonorgestrel, dl-norgestrel, cyproterone acetate, dydrogesterone, medroxyprogesterone acetate, chlormadinone acetate, megestrol, promegestone, norethisterone, lynestrenol, gestodene, tibolene, androgens consisting of testosterone, methyl testosterone, oxandrolone, androstenedione, dihydrotestosterone. estrogens consisting of estradiol, ethniyl estradiol, estiol, estrone, conjugated estrogens, esterified estrogens, estropipate, or combinations thereof.

Non-sex steroids can also be delivered using the formulations of the present invention. Examples of such steroids include but are not limited to betamethasone dipropionate, halobetasol propionate, diflorasone diacetate, triamcinolone acetonide, desoximethasone, fluocinonide, halcinonide, mometasone furoate, betamethasone valerate, fluocinonide, fluticasone propionate, triamcinolone acetonide, fluocinolone acetonide, flurandrenolide, desonide, hydrocortisone butyrate, hydrocortisone valerate, alclometasone dipropionate, flumethasone pivolate, hydrocortisone, hydrocortisone acetate, or combinations thereof.

A further embodiment involves controlled delivery of nicotine for treating nicotine dependence among smokers and persons addicted to nicotine.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Formulations of the present invention would be a cost effective way of delivering therapeutic amounts of nicotine transdermally.

Another embodiment involves using the formulation to deliver anti-histamine agents such as diphenhydramine and tripelennamine. These agents would reduce itching by blocking the histamine that causes the itch and also provide relief by providing topical analgesia.

Other drugs which can be delivered using the solidifying formulations of the present invention include but are not limited to tricyclic anti-depressants such as amitriptyline; anticonvulsants such as carbamazepine and alprazolam; N-methyl-D-aspartate (NMDA) antagonists such as ketamine; 5-HT2A receptor antagonists such as ketanserin; and immune modulators such as tacrolimus and picrolimus. Other drugs that can be delivered using the formulations and methods of the current invention include humectants, emollients, and other skin care compounds.

EXAMPLES

The following examples illustrate the embodiments of the invention that are presently best known. However, it is to be understood that the following are only exemplary or illustrative of the application of the principles of the present invention. Numerous modifications and alternative compositions, methods, and systems may be devised by those skilled in the art without departing from the spirit and scope of the present invention. The appended claims are intended to cover such modifications and arrangements. Thus, while the present invention has been described above with particularity, the following examples provide further detail in connection with what are presently deemed to be the most practical and preferred embodiments of the invention.

Example 1

Hairless mouse skin (HMS) or human epidermal membrane (HEM) is used as the model membrane for the *in vitro* flux studies described in herein. Freshly separated epidermis removed from the abdomen of a hairless mouse is mounted carefully between the donor and receiver chambers of a Franz

Padagis Ex. 1029
IPR Petition - USP 11,311,482

diffusion cell. The receiver chamber is filled with pH 7.4 phosphate buffered saline (PBS). The experiment is initiated by placing test formulations on the stratum corneum (SC) of the skin sample. Franz cells are placed in a heating block maintained at 37 °C and the HMS temperature is maintained at 35 °C. At predetermined time intervals, 800 μL aliquots are withdrawn and replaced with fresh PBS solution. Skin flux (μg/cm^2/h) is determined from the steady-state slope of a plot of the cumulative amount of permeation versus time. It is to be noted that human cadaver skin can be used as the model membrane for the *in vitro* flux studies as well. The mounting of the skin and the sampling techniques used as the same as described above for the HMS studies.

Example 2

Human cadaver skin is used as a membrane to select a non-volatile solvent for clobetasol propionate. *In vitro* methodology is described in Example 1. About 200mcL of 0.1% (w/w) solution of clobetasol in various non-volatile solvents is added to the donor compartment of Franz cells. Results obtained after LC analysis are shown in Table 4.

Table 4 - Non volatile solvents for clobetasol propionate

Non-volatile solvent system	Skin Flux* (ng/cm^2/h)
Propylene Glycol	3.8 ± 0.4
Glycerol	7.0 ± 4.1
Light Mineral Oil	31.2 ± 3.4
Isostearic Acid (ISA)	19.4 ± 3.2
Ethyl Oleate	19.4 ± 1.6
Olive Oil	13.6 ± 3.3
Propylene Glycol/ISA (9:1)	764.7 ± 193.9

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 6-28 hours. If the experiment was continued it is anticipated the steady state would continue.

All the neat non-volatile solutions studied have an average flux of less than 40 ng/cm^2/hr over the 30 hour time period. Propylene glycol and glycerol have the lowest permeation for clobetasol propionate. A mixture of propylene

Padagis Ex. 1029
IPR Petition - USP 11,311,482

glycol and isostearic acid at a weight ratio of 9:1 have significantly higher flux than either of the solvents alone or with the other solvents tested. The average flux is 20 times higher than that with light mineral oil which is the best non-mixed solvent. Hence, for clobetasol propionate, propylene glycol/isostearic acid combination is a good candidate for a non-volatile solvent system.

Examples 3-8

Adhesive formulations containing 0.05% (w/w) clobetasol propionate with propylene glycol and isostearic acid as non volatile solutions and various solidifying agents are prepared. The formulations are prepared from the ingredients as shown in Table 5.

Table 5 - Solidifying formulation components

Example	Polymer	Percent Polymer	Percent Ethanol	Percent Propylene Glycol	Percent Isostearic Acid	Percent Water
3	Polyvinyl Alcohol	20	30	19.6	0.4	30
4	Shellac	50	30	19.6	0.4	0
5	Dermacryl 79	65.76	21.16	12.76	0.26	0
6	Eudragit E100	50	30	19.6	0.40	0
7	Eudragit RLPO	50	30	19.6	0.40	0
8	Gantrez S97	14.3	57.1	28	0.6	0

Each of the compositions shown above are studied for flux of clobetasol propionate as shown in Table 6 as follows:

Table 6 - Steady state flux of Clobetasol propionate through human cadaver skin at 35 °C

Formulation	Skin Flux* ($ng/cm^2/h$)
Example 3	87.8 ± 21.4
Example 4	9.7 ± 2.4
Example 5	8.9 ± 0.8
Example 6	3.2 ± 1.7
Example 7	20.2 ± 18.6
Example 8	147.5 ± 38.8

Padagis Ex. 1029
IPR Petition - USP 11,311,482

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 6-28 hours. If the experiment was continued it is anticipated the steady state would continue.

As seen from Table 6 formulation described in Example 3 that contains polyvinyl alcohol as solidifying agent has high flux of clobetasol propionate. Polyvinyl alcohol is known to form stretchable films and it is likely that this formulation will have acceptable wear properties. The toughness of the resulting film can be modified by adding appropriate plasticizers if needed. Tackiness can also be modified by adding appropriate amounts of tackifier or by adding appropriate amounts of another solidifying agent such as Dermacryl 79.

Regarding formulation described in Example 8, a higher percentage of ethanol is needed to dissolve the polymer. However, the solidifying agent used in Example 8 provides the highest flux of clobetasol propionate among the solidifying agents studied. The wear properties of this formulation can be modified by adding appropriate levels of other ingredients including but not limited to plasticizers, tackifiers, non-volatile solvents and or solidifying agents.

Example 9

Formulations of acyclovir in various non-volatile solvent systems are evaluated. Excess acyclovir is present. The permeation of acyclovir from the test formulations through HMS is presented in Table 7 below.

Table 7

Non-volatile solvent system	Skin Flux* (mcg/cm^2/h)
Isostearic acid	0.1 ± 0.09
Isostearic acid + 10% trolamine	2.7 ± 0.6
Isostearic acid + 30% trolamine	7 ± 2
Olive oil	0.3 ± 0.2
Olive oil + 11% trolamine	3 ± 3
Olive oil + 30% trolamine	0.3 ± 0.2
Oleic acid	0.4 ± 0.3
Oleic acid + 10% trolamine	3.7 ± 0.5
Oleic acid + 30% trolamine	14 ± 5
Ethyl oleate	0.2 ± 0.2
Ethyl oleate + 10% trolamine	0.2 ± 0.2

Padagis Ex. 1029
IPR Petition - USP 11,311,482

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

Steady state flux of acyclovir from the above non-volatile solvents are obtained by placing 200 mcL on the stratum corneum side (donor) of hairless mouse skin. The *in vitro* studies are carried out as described in Example 1. The surprising result showed the polyethylene glycol 400, span 80, ethyl oleate, or ethyl oleate plus trolamine are not flux-enabling solvents for acyclovir (e.g., steady state flux values significantly less than the steady state flux of acyclovir in the marketed product noted in Table 2, where the flux was about 3mcg/cm^2/h). However, the combination of isostearic acid and trolamine or oleic acid and increasing amounts of trolamine are flux-enabling solvents for acyclovir. As can be seen, the highest flux was achieved using 30% trolamine with oleic acid as the non-volatile solvent system.

Examples 10-13

Prototype solidifying formulations are prepared as follows. Several acyclovir solidifying formulations are prepared in accordance with embodiments of the present invention in accordance with Table 8, as follows:

Table 8

Example	10	11	12	13
	% by weight			
Ethanol	21	25	28	29.5
Eudragit RL-PO	15	18	20	21.0
Isostearic Acid	31	36	39	42.0
Trolamine	30	18	10	4.7
Acyclovir	3	3	3	2.8

In Examples 10-13, the compositions in Table 6 are prepared as follows. Eudragit RL-PO and ethanol are combined in a glass jar and heated with stirring until the RL-PO is dissolved. The isostearic acid and trolamine is added to the RL-PO/ethanol mixture and the mixture is vigorously stirred. Once a uniform

Padagis Ex. 1029
IPR Petition - USP 11,311,482

mixture is obtained, acyclovir is added to the mixture and the formulation is vigorously mixed.

Examples 14-15

Prototype peel formulations are prepared as follows. Several acyclovir solidifying formulations are prepared in accordance with embodiments of the present invention in accordance with Table 9, as follows:

Table 9

Example	14	15
	% by weight	
Ethanol	26	21
Eudragit RL-PO	44	15
Isostearic Acid	26	31
Diisopropanol Amine	2	--
Neutrol TE Polyol	--	30
Acyclovir	2	3

The compositions of Examples 14 and 15 as shown in Table 8 are prepared as follows. Eudragit RL-PO and ethanol are combined in a glass jar and heated with stirring until the RL-PO is dissolved. The isostearic acid and diisopropanol amine or Neutrol TE Polyol (BASF) is added to the RL-PO/ethanol mixture and the mixture is vigorously stirred. Once a uniform mixture is obtained, acyclovir is added to the mixture and the formulation is vigorously mixed.

Examples 16-17

Prototype solidifying formulations are prepared as follows. Several acyclovir solidifying formulations are prepared in accordance with embodiments of the present invention in accordance with Table 10, as follows:

Table 10

Example	16	17
	% by weight	
Ethanol	59.6	58
EC-N7	19.9	--
EC-N100	--	19
Trolamine	7.6	9
Isostearic Acid	7.7	9
Acyclovir	5.2	5

Padagis Ex. 1029
IPR Petition - USP 11,311,482

In Examples 16-17 the compositions in Table 10 are prepared as follows. Ethyl cellulose ECN7 or ethyl cellulose ECN100 and ethanol are combined in a glass jar and heated with stirring until the solid cellulose is dissolved. The isostearic acid and trolamine is added to the cellulose/ethanol mixture and the mixture is vigorously stirred. Once a uniform mixture is obtained, acyclovir is added to the mixture and the formulation is vigorously mixed.

Example 18

The formulations of Examples 10-17 are tested in a hairless mouse skin (HMS) in vitro model described in Example 1. Table 11 shows data obtained using the experimental process outlined above.

Table 11 – Steady-state flux (J) of Acyclovir through HMS

Formulation	J* ($\mu g/cm^2/h$)	Ratio to Control
Example 10	12 ± 5	6
Example 11	19 ± 1	8
Example 12	8 ± 1	4
Example 13	1 ± 1	0.5
Example 14	0.7 ± 0.3	0.35
Example 15	1 ± 0.9	0.5
Example 16	2 ± 1	1
Example 17	19 ± 7	8
Zovirax Cream	2 ± 0.4	1

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed the steady state flux would extend beyond the 8 hours measured.

The formulations of the invention shown above generally provide for significant penetration of the active ingredient, and further, the formulations of Examples 10-12 and 17 are found to be much greater in permeability than the marketed product Zovirax Cream. The quantity of acyclovir that permeated across the HMS stratum corneum over time for Examples 10, 11, and Zovirax Cream are shown in FIG. 2. Each value shown indicates the mean ± SD of at least three experiments.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Examples 10-13 show the impact of the trolamine to isostearic acid (ISA) ratio on acyclovir flux enhancement. The optimal ISA:trolamine ratio is 1:1 to 2:1 and ratio greater than 4:1 show a significant decrease in the acyclovir skin flux. Additions of diisopropanol amine and Neutrol in place of trolamine (Examples 14 and 15 in the formulation show a significant decrease in acyclovir flux values. This may be due to a specific chemical interaction between trolamine and ISA creating an environment within the formulation which facilitates higher skin flux. Examples 16 and 17 utilize a different solidifying agent to evaluate the impact of the solidifying agent on acyclovir flux. Surprisingly, Example 16 shows a significant decrease in acyclovir skin flux, but Example 17, which differed from Example 16 only by the molecular weight of the solidifying agent, shows no impact on acyclovir skin flux compared to a similar ISA:trolamine ratio in Example 10.

As can be seen from FIG. 2, Examples 10 and 11 show sustained delivery of acyclovir up to 8 hours, it is reasonable to assume based on the drug load and the continued presence of the non volatile solvent that the delivery of acyclovir would continue at the reported flux values for as long as the subject desires to leave the solidifying formulation affixed to the skin.

Examples 19-21

Prototype solidifying formulations are prepared as follows. Several solidifying formulations are prepared in accordance with embodiments of the present invention in accordance with Table 12, as follows:

Table 12

Example	**19**	**20**	**21**
% by weight			
Volatile Solvents			
Ethanol	25	24	43
Water			22
Solidifying agents			
Eudragit RL-PO	18	40	
Polyvinyl Alcohol			14
Non-volatile solvents			
Glycerol		12	14
Propylene Glycol		4	

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Polyethylene glycol			6
Isostearic Acid	36	13	
Trolamine	18	4	
Drug			
Acyclovir	3		
Ropivacaine		3	
Testosterone			1

Solidifying formulations of Examples 19-21 are prepared in the following manner:

- The solidifying agents are dissolved in the volatile solvent (e.g., dissolve polyvinyl alcohol in water, Eudragit polymers in ethanol),
- The non-volatile solvent is mixed with the solidifying agent/volatile solvent mixture.
- The resulting solution is vigorously mixed well for several minutes.
- The drug is then added and the solidifying formulation is mixed again for several minutes.

In all the Examples noted above, the flux-enabling non-volatile solvent/solidifying agent/volatile solvent combination is compatible as evidenced by a homogeneous, single phase system that exhibited appropriate drying time, and provided a stretchable solidified layer and steady state flux for the drug (see Example 22 below).

Example 22

The formulations of the examples are tested in a hairless mouse skin (HMS) or HEM *in vitro* model described in Example 1. Table 13 shows data obtained using the experimental process outlined above.

Table 13 – Steady-state flux (J)

Formulation	J* ($\mu g/cm^2/h$)
Example 19	19 ± 1***
Example 20	32 ± 2***
Example 21	4 ± 1***

Padagis Ex. 1029
IPR Petition - USP 11,311,482

* Skin flux measurements represent the mean and standard deviation of three determinations.

** Data gathered using human epidermal membrane.

***Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

****Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 6-28 hours. If the experiment was continued it is anticipated the steady state would continue.

Acyclovir, ropivacaine, and testosterone have surprisingly higher steady state flux values when the flux-enabling non-volatile solvent is incorporated into the solidifying formulation. It is speculated that the higher flux values may be the result of contributions of the volatile solvent or the solidifying agent impacting the chemical environment (e.g., increasing solubility) of the drug in the solidifying formulation resulting in higher flux values. Conversely, ketoprofen and diclofenac have lower steady state flux values when the enabling non-volatile solvent is incorporated into the solidifying formulation. This could be the result of the volatile solvent system or solidifying agent having the opposite impact on the chemical environment (e.g., decreasing solubility, physical interactions between drug and solidifying formulation) resulting in lower flux values. The steady state flux value for imiquimod is unchanged when comparing the solidifying formulation with the flux-enabling non-volatile solvent flux values.

Example 23

A formulation with the following composition: 10.4% polyvinyl alcohol, 10.4% polyethylene glycol 400, 10.4% polyvinyl pyrrolidone K-90, 10.4% glycerol, 27.1 % water, and 31.3% ethanol was applied onto a human skin surface at an elbow joint and a finger joint, resulting in a thin, transparent, flexible, and stretchable solidified layer. After a few minutes of evaporation of the volatile solvents (ethanol and water), a solidified layer that was peelable was formed. The non-volatile solvent system of polyethylene glycol and glycerol acts a plasticizer in the formulation. The stretchable solidified layer had good

Padagis Ex. 1029
IPR Petition - USP 11,311,482

adhesion to the skin and did not separate from the skin on joints when bent, and could easily be peeled away from the skin.

Examples 24-26

Three formulations similar to the formulation in Example 27 (replacing ropivacaine base with ropivacaine HCl) are applied on the stratum corneum side of freshly separated hairless mouse skin. The *in vitro* flux is determined for each formulation as outlined in Example 1. The formulation compositions are noted in Table 14 below.

Table 14

Example	**24**	**25**	**26**
% by weight			
PVA	15	15	15
Water	23	23	23
Ethylcellulose N-100	11	11	11
Ethanol	33	33	33
Span 20	11		
Polyethylene Glycol 400		11	
Tween 40			11
Tromethamine	4	4	4
Ropivacaine HCl	3	3	3
Avg. Flux* (mcg/cm2/h)	15 ± 1	4.7 ± 0.3	3.4 ± 0.7

* Flux values represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-9 hours. If the experiment was continued it is anticipated the steady state would continue.

Since all three formulations have the exact same compositions of solidifying agent, volatile solvents, and flux-enabling non-volatile solvent. The only difference is which flux-enabling non-volatile solvent is used it is reasonable to conclude that for ropivacaine HCl that Span 20, polyethylene glycol 400, and Tween 40 qualify as flux-enabling non-volatile solvents.

Addition of tromethamine and Span 20 in example 30 produced a flexible coherent solid that was much less brittle than a formulation containing no non-volatile solvents.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Examples 27-31

A solidifying formulation for dermal delivery of imiquimod is prepared which includes a specified amount of imiquimod in an excipient mixture to form an adhesive formulation in accordance with embodiments of the present invention. The solidifying formulations contained the following components:

Table 15 - Imiquimod peelable formulation ingredients

Ingredients*	Example				
	27	28	29	30	31
PVA	12	21.5			
Plastoid B**			22.7	21.1	21
Pemulen TR-2	0.3	0.3			
Water	62.7	34.4	2.8		
Isopropanol			42.5	42.5	41.7
ISA (Isostearic Acid)	19	35.2	9.2	28.2	27.8
Span 20			8.5		
Trolamine	2	3.6	6.1		
Triacetin			4.2	4.2	4.2
Imiquimod	4	5	4	4	5.3

* Ingredients are noted as weight percent.
** Polymer from Degussa

These formulations are applied to HMS skin as described in Example 1, and the imiquimod flux is measured. A summary of the results from in vitro flux studies carried out with the formulations in Examples 27-31 are listed in Table 16.

Table 16 - Steady-state flux of imiquimod through hairless mouse skin from various adhesive formulations at 35 °C

Formulation	Average flux mcg/cm^2/h*	Ratio to Control**
Example 27	0.7 ± 0.09	0.7
Example 28	0.52 ± 0.06	0.6
Example 29	0.40 ± 0.08	0.4
Example 30	0.5 ± 0.1	0.5
Example 31	0.8 ± 0.1	0.9
Aldara (control)	0.92 ± 0.02	

* The flux values represent the mean and SD of three determinations
** Ratio to control calculated by dividing the flux value for each Example by the flux value for Aldara control flux.

Regarding the formulation described in Examples 27 and 28, water is used as the volatile solvent, and the ISA, trolamine mixture is used as the non-volatile

Padagis Ex. 1029
IPR Petition - USP 11,311,482

solvent system. Through experimentation, it is determined that ISA and Span 20 provide the appropriate solubility for the drug, however, these non-volatile solvents are hydrophobic and not compatible with the volatile solvent system used to dissolve the solidifying agent PVA. An emulsifier Pemulen TR-2 was used to emulsify the non-volatile solvents into the water phase. Further, in this embodiment, ISA and trolamine act as a plasticizer in the peelable formulation after the water (volatile solvent) has evaporated. The steady state flux of formulation Examples 27 and 28 demonstrate the importance of the amount of non-volatile solvent in added to the formulation in dictating the flux-generating power of the entire formulation. Formulation Examples 29-31 utilize a different solidifying agent which is compatible in a non-aqueous volatile solvent system (isopropanol). The selection of non-volatile solvent system ISA/triacetin or ISA/Span 20/trolamine/triacetin combination showed no change in the in vitro flux. The increase in vitro flux is shown to be influenced by an increase in the amount of imiquimod present in the formulation. At imiquimod levels above 4% the drug is saturated in the solidifying formulation. The increase in vitro flux as a function of increased drug addition (Examples 30 and 31) may be due to the increased solubility of drug in the solidified formulation once the volatile solvent is evaporated off.

Example 29 demonstrated comparable imiquimod flux to the other formulation Examples, but the importance of the non-volatile solvent system and solidifying agent compatibility necessitated the removal of trolamine because this non-volatile solvent negatively influenced the function of the Plastoid B polymer.

Example 32-35

A solidifying formulation for dermal delivery of imiquimod is prepared which includes a specified amount of imiquimod in an excipient mixture to form an adhesive formulation in accordance with embodiments of the present invention. The solidifying formulations contained the following components:

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Table 17 - Imiquimod formulation ingredients

Ingredients*	Example			
	32	33	34	35
PVA	10.1			
Plastoid B**		17.5		
Eudragit RL PO			16.2	24.8
Pemulen TR-2	0.3			
Water	52.9			
Isopropanol		35.1		
Ethanol			32.4	38.6
ISA (Isostearic Acid)	16.8	23.4	23.1	27.6
Salicylic Acid	15.2	16.4	16.2	
Trolamine	1.7			
Triacetin		3.5	3.5	4.1
Imiquimod	3.0	4.1	4.0	4.8

* Ingredients are noted as weight percent.
** Polymer from Degussa

These formulations are applied to HMS skin as described in Example 1, and the imiquimod flux is measured. A summary of the results from in vitro flux studies carried out with the formulations in Examples 32-35 are listed in Table 18.

Table 18 - Steady-state flux of Imiquimod through hairless mouse skin from various adhesive formulations at 35 °C

Formulation	Average flux mcg/cm^2/h*	Ratio to Control**
Example 32	1 ± 1	1.1
Example 33	4.5 ± 0.4	5
Example 34	3.8 ± 0.5	4.2
Example 35	0.8 ± 0.2	0.9
Aldara	0.9 ± 0.02	1

* The flux values represent the mean and SD of three determinations
** Ratio to control calculated by dividing the flux value for each Example by the flux value for Aldara control flux.

In vitro flux of Examples 32-35 is substantially increased compared to the Aldara control. The reason for the improved in vitro flux values is attributed to the addition of salicylic acid. Improved in vitro flux of imiquimod in Examples 32-35 is thought to be due to an ion pair interaction between imiquimod and

Padagis Ex. 1029
IPR Petition - USP 11,311,482

salicylic acid. The ion pair mechanism is thought that the lipophilicity of the counter ion (salicylic acid) improves the flux of imiquimod across the stratum corneum because it makes imiquimod less 'comfortable' in the formulation. Comparison of the flux of Examples 32-34 show that the selection of the polymer and/or volatile solvents will impact the flux of imiquimod. Example 32 contains PVA and water, one or both of these elements may contribute to an unfavorable medium in which the ion pair can form resulting in a negligible increase in imiquimod flux versus the Aldara control.

Example 36

To demonstrate the ability of the solidified formulations to reduce the transepidermal water loss (TEWL) the following experiment was conducted.

A placebo PVA formulation was applied to the top of the hand and the TEWL was measured on a site immediately adjacent to the solidified layer and on top of the solidified layer. The TEWL measurement of the site covered by the solidified layer was 33% lower than the untreated skin site.

Placebo Plastoid B formulation similar to the formulation described in Example 5 was applied to the top of the hand and the TEWL was measured on a side immediately adjacent to the solidified layer and on top of the solidified layer. The TEWL measurement on the site covered by the solidified layer was 30% lower than the untreated skin site.

Examples 37-38

A solidifying formulation for dermal delivery of ropivacaine is prepared which includes a specified amount of ropivacaine in an excipient mixture to form an adhesive formulation in accordance with embodiments of the present invention. The solidifying formulations contained the following components:

Table 19 Ropivacaine formulation ingredients.

Ingredients*	Examples	
	37	38
Eudragit RL-100	39.6%	39.6%
Ethanol	23.7%	23.6%
ISA (Isostearic Acid)	13.5%	13.5%

Padagis Ex. 1029
IPR Petition - USP 11,311,482

PG (Propylene Glycol)	7.9%	4.0%
Trolamine	4.0%	4.0%
Glycerol	7.9%	11.9%
Ropivacaine	3.4%	3.4%

* Ingredients are noted as weight percent.

These formulations are applied to HMS skin as described in Example 1, and the ropivacaine flux is measured. A summary of the results from in vitro flux studies carried out with the formulations in Examples 37 and 38 is listed in Table 20.

Table 20 - Steady-state flux of Ropivacaine through hairless mouse skin from various adhesive formulations at 35 °C

Formulation	Average flux mcg/cm^2/h*
Example 37	36 ± 5
Example 38	32 ± 2

* The flux values represent the mean and SD of three determinations

Regarding the formulation described in Examples 37 and 38, ethanol is used as the volatile solvent, and the ISA, glycerol, trolamine, and PG mixture is used as the non-volatile solvent system. Through experimentation, it is determined that ISA and propylene glycol used together to provide the appropriate solubility for the drug, while being compatible with the Eudragit RL-100 solidifying agent. Further, in this embodiment, ISA, PG and glycerol serve as a plasticizer in the peelable formulation after the ethanol (volatile solvent) has evaporated. The steady state flux of ropivacaine from formulation Examples 37 and 38 demonstrate the importance of the non-volatile solvent in dictating the flux-generating power of the entire formulation.

Example 39

A formulation for dermal delivery of lidocaine is prepared which includes a saturated amount of lidocaine in an excipient mixture to form an adhesive formulation in accordance with embodiments of the present invention. The solidifying formulation is prepared from the ingredients as shown in Table 26.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Table 21 - Lidocaine formulation components

Ingredients*	Example 39
PVA	11.7
Eudgragit E-100**	11.7
PVP-K90	5.8
Glycerol	8.8
PEG-400	8.8
Water	23.8
Ethanol	23.8
Lidocaine	5.6

*Ingredients are noted as weight percent.
** from Rohm & Haas.

Table 22 Steady-state flux of Lidocaine through hairless mouse skin from various adhesive formulations at 35 °C

Formulation	Average flux mcg/cm^2/h*
Example 39	47 ± 3

The adhesive formulation of lidocaine formulation in the present example has similar physical properties to the formulations in examples noted above. The transdermal flux across hairless mouse skin is acceptable and steady-state delivery is maintained over 8 hours.

Examples 40-43

A formulation for dermal delivery of amitriptyline and a combination of amitripyline and ketamine is prepared which includes an excipient mixture to form an adhesive formulation in accordance with embodiments of the present invention. The solidifying formulation is prepared from the ingredients as shown in Table 23.

Table 23 - Amitriptyline and Amitriptyline/Ketamine formulation components.

Ingredients*	Example 40	41	42	43
Isopropanol	50.3	48.6	50.8	49.8
Water	2.7	2.6	2.7	2.7
Isostearic Acid	6.2	6.1	6.3	6.2
Triisopropanolamine	7.5	7.3	7.5	7.4
Triacetin	2.9	2.8	2.9	2.8

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Span 20	5.7	5.5	5.8	5.6
Plastoid B**	21.7	21.1	22	21.5
Amitriptyline	2	4		
Ketamine	1	2	2	4

*Ingredients are noted as weight percent.
** from DeGussa.

The ingredients listed above are combined according to the following procedure. The drug(s), water, and triisopropanolamine are combined in a glass jar and mixed until the drug is dissolved. Then the isostearic acid, triacetin, Span 20, and isopropanol are added to the formulation and mixed well. The polymer Plastoid B is added last and heated to about 60 ^{0}C until the Plastoid B is completely dissolved. Once the polymer solution cooled to room temperature, the formulation is stirred vigorously for 2-3 minutes.

The formulations in Table 10 are applied to HMS according to Example 1, and the flux of amitriptyline and/or ketamine was measured. The results are summarized in Table 24:

Table 24 - Steady-state flux of Amitriptyline and Amitriptyline/Ketamine through hairless mouse skin from various adhesive formulations at 35 °C

Formulation	Average amitriptyline flux mcg/cm^2/h*	Average ketamine flux mcg/cm^2/h*
Example 40	3 ± 1	15 ± 4
Example 41	7.6 ± 0.2	38 ± 6
Example 42	3 ± 1	
Example 43	8.2 ± 0.7	

The non-volatile solvent systems in the adhesive formulations of amitriptyline and amitriptyline/ketamine were found to exhibit the best compatibility when triacetin was used as the plastizing solvent. For example, when propylene glycol was used in place of triacetin the examples noted above the formulation turned into a soft solid in the storage container in about 12 hours. Replacing propylene glycol with trolamine resulted in a clear, flowable formulation with viscosity low enough so that is can be spread on a skin surface..

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Examples 44-47

A formulation for dermal delivery of ropivacaine is prepared which includes an excipient mixture to form an adhesive formulation in accordance with embodiments of the present invention. The solidifying formulation is prepared from the ingredients as shown in Table 25.

Table 25 - Ropivacaine HCl formulation components.

Ingredients*	Example			
	44	45	46	47
Ropivacaine HCl	0.31	0.31	0.31	0.31
Isopropanol	2	2	2.2	2
Water	0.125	0.125	0.125	0.125
Isostearic Acid	0.36	0.66	0.41	0
Triisopropanolamine	0.31	0.34	0.34	0.34
Triacetin	0.17	0.19	0	0.19
Span 20	0.34	0	0.37	0.66
Plastoid B**	1	1	1	1

*Ingredients are noted as parts by weight.
** from Degussa.

The ingredients listed above are combined according to the following procedure. The ropivacaine HCl, water, and triisopropanolamine are combined in a glass jar and mixed until the drug is dissolved. Then the isostearic acid, triacetin, Span 20, and isopropanol are added to the formulation and mixed well. The polymer Plastoid B is added last and heated to about 60 ^{0}C until the Plastoid B is completely dissolved. Once the polymer solution cooled to room temperature, the formulation is stirred vigorously for 2-3 minutes.

The formulations in Table 25 are applied to HMS according to Example 1, and the flux of ropivacaine was measured. The results are summarized in Table 26:

Table 26 - Steady-state flux of Ropivacaine HCl through hairless mouse skin from various adhesive formulations at 35 °C

Formulation	Average flux mcg/cm^2/h*
Example 44	56 ± 2
Example 45	39 ± 6
Example 46	31 ± 6
Example 47	37 ± 9

Padagis Ex. 1029
IPR Petition - USP 11,311,482

The flux in each of Examples 44-47 shows the importance of the triacetin, isostearic acid, Span 20 combination in the formulation. In Examples 45-47 formulations were made without Span 20, triacetin, and isostearic acid respectively. The in vitro flux of ropivacaine was impacted. The synergistic combination of the flux-enabling non volatile solvent system is important in obtaining the maximum in vitro flux of ropivacaine.

Example 48

This formulation has the following ingredients in the indicated weight parts:

Table 27

PVA	Water	Ethyl cellulose N-7 (Aqualon)	Dermacryl 79 (National Starch)	Ethanol	Isostearic Acid (ISA)	Glycerol	Ropivacaine
1	1.5	0.25	0.35	0.85	0.8	0.35	0.3

In this formulation, polyvinyl alcohol (USP grade, from Amresco) is a solidifying agent, ethyl cellulose and Dermacryl 79 are auxiliary solidifying agents. Isostearic acid and glycerol form the non-volatile solvent system while ethanol and water form the volatile solvent system. Ropivacaine is the drug.

Procedures of making the formulation:

1. Ropvicaine is mixed with ISA.
2. Ethyl cellulose and Dermacryl 79 are dissolved in ethanol.
3. PVA is dissolved in water at temperature of about 60-70 C.
4. All of the above mixtures are combined together in one container and glycerol is added and the whole mixture is mixed well.

The resulting formulation is a viscous fluid. When a layer of about 0.1 mm thick is applied on skin, a non-tacky surface is formed in less than 2 minutes.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Examples 49-50

Anti-fungal solidifying formulations are prepared and a qualitative assessment of the solidified layer's flexibility and viscosity are evaluated. The formulation components are presented in Table 28 below.

Table 28

Example	**49**	**50**
Components	Parts by Weight	
Eudragit RL-PO	3.8	4.2
Isostearic Acid	2	2.2
Ethanol	5.3	3.8
Neutrol TE Polyol	1	1
Econazole	0.09	0.1

The solidifying formulation in Example 49 has a low viscosity that was lower than may be desirable for application on a nail or skin surface. The time to form a solidified layer with this formulation is longer than the desired drying time. The formulation in Example 50 had an increase in the amount of solidifying agent (Eudgragit RL-PO) and decrease in amount of ethanol, which improves the viscosity and drying time. Example 50 has a viscosity suitable for application and an improved drying time.

Example 51

A solidifying formulation was prepared in accordance with Table 29, as follows:

Table 29 - Solidifying formulation for sex steroids

Ingredient	% by weight
Ethanol	43
Water	22
Polyvinyl Alcohol	14
Glycerol	14
Polyethylene Glycol	6
Testosterone	1

The ingredients of Table 29 were combined as follows:

- The solidifying agent is dissolved in the volatile solvent (i.e. dissolve polyvinyl alcohol in water).

- The flux enabling non-volatile solvent is mixed with the solidifying agent/volatile solvent mixture.
- The resulting solution is vigorously mixed well for several minutes.
- Drug is then added and the solidifying formulation is mixed again for several minutes.

Example 52

The formulation prepared in Example 51 was tested for Skin Flux, as set forth in Table 30 below.

Table 30 - Peel-forming formulation for sex steroids

System	Skin Flux* ($mcg/cm^2/h$)
Example 51	4 ± 1
AndroGel	6 ± 2

*Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

AndroGel, currently marked product, is applied directly on the hairless mouse skin and the flux determinations are made as outlined in Example 1. The steady state flux data is shown in FIG 1. It should be noted, the steady-state flux value reported in Table 3 is determined using the linear region between 2-6 hours. As can be seen from FIG. 1, the *in vitro* flux of testosterone from AndroGel substantially decreases beyond 6 hours. This may be due in part to the evaporation of the volatile solvent which may act as the main vehicle for delivery. The formulation in Example 51 will deliver a steady-state amount of testosterone for at least 9 hours.

Example 53

A stretchable adhesive formulation for transdermal delivery of ketoprofen (which is suitable for delivery via skin for treating inflammation or pain of joints and muscles) is prepared which includes saturated amount of ketoprofen in an

Padagis Ex. 1029
IPR Petition - USP 11,311,482

excipient mixture (more ketoprofen than that can be dissolved in the excipient mixture) to form an adhesive formulation, some of which is prepared in accordance with embodiments of the present invention. The excipient mixture, which is a viscous and transparent fluid, is prepared using the ingredients as shown in Table 31.

Table 31 - Ketoprofen formulation components

Ingredients*	Example 53
PVA (Polyvinyl Alcohol)	10.4
PEG-400 (Polyethylene Glycol)	10.4
PVP-K90 (Polyvinyl Pyrrolidone)	10.4
Glycerol	10.4
Water	27.1
Ethanol	31.3
Ketoprofen	saturated

* Ingredients are noted as % by weight.

The compositions of Example 53 were studied for flux of ketoprofen, as shown in Table 32, as follows:

Table 32 - Steady-state flux of Ketoprofen through hairless mouse skin from the adhesive formulation of Example 52 at 35 °C

Formulation	Average flux mcg/cm^2/h*
Example 53	8 ± 3

* Skin flux measurement represents the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed the steady state flux would extend beyond the 8 hours measured.

Regarding formulation described in Example 53, ethanol and water formed the volatile solvent system, while a 1:1 mixture of glycerol and PEG 400 formed the non-volatile solvent system. Through experimentation, it is determined that PEG 400 is a slightly better solvent than glycerol for ketoprofen, while glycerol is much more compatible with PVA than PEG 400. Thus, the non-volatile solvent system of glycerol and PEG 400 are used together to provide a non-volatile solvent system for the drug, while being reasonably compatible with PVA. In

Padagis Ex. 1029
IPR Petition - USP 11,311,482

additional detail with respect to the formulation in Example 53, PVA and PVP act as the solidifying agents. Further, in this embodiment, glycerol and PEG 400 also serve as plasticizers in the adhesive formulation formed after the evaporation of the volatile solvents. Without the presence of glycerol and PEG 400, a solidified layer formed by PVA and PVP alone would be rigid and non-stretchable.

Example 54

A formulation similar to the formulation of Example 53 composition (with no ketoprofen) is applied onto a human skin surface at an elbow joint and a finger joint, resulting in a thin, transparent, flexible, and stretchable solidified layer. After a few minutes of evaporation of the volatile solvents (ethanol and water), a solidified layer is formed. The stretchable solidified layer has good adhesion to the skin and does not separate from the skin on joints when bent, and can easily be peeled away from the skin.

Example 55

A stretchable adhesive formulation for transdermal delivery of ketoprofen (which is suitable for delivery via skin on joints and muscles) is prepared which includes saturated amount of ketoprofen in an excipient mixture (more ketoprofen than that can be dissolved in the excipient mixture) to form an adhesive formulation, some of which are prepared in accordance with embodiments of the present invention. The excipient mixture, which is a viscous and transparent fluid, is prepared using the ingredients as shown in Table 33.

Table 33

Ingredients*	FORMULATIONS		
	A	B	C
PVA (Celvol 502 MW 10,000)	24.4		
PVA (Amresco MW 31,000-50,000)		24.4	
PVA (Celvol 523 MW 125,000)			41.7
Water	33.4	33.4	58.3
Ethanol	8.9	8.9	
PG	17.8	17.8	
Glycerol	11.1	11.1	
Gantrez ES 425	4.4	4.4	

* Ingredients are noted in weight percent.

Formulations A and B are prepared in the following manner:

- PVA (solidifying agent) is dissolved in water.
- The flux adequate non-volatile solvent (glycerol, PG) is mixed together with the solidifying agent/volatile solvent mixture.
- Then ethanol, and Gantrez ES 425 is added to the mixture.
- The resulting solution is vigorously mixed for several minutes.

Preparation of the PVA in water solution in Formulation C was not feasible for this molecular weight of PVA at the percentages noted. Formulation C demonstrates that the correct polymer molecular weight for PVA is important to obtain the desired formulation properties.

Formulations A and B are placed on the skin of human volunteers. After a period of several hours, long enough for the volatile solvent to evaporate, the solidified layers were removed by the volunteers and the peelability properties were evaluated. In all instances the volunteers reported that formulation example A could not be removed in one or two pieces, but was removed in numerous small pieces. Formulation example B removed in one or two pieces. The brittle nature of formulation A is attributed to the lower molecular weight PVA sample (Celvol). Low molecular weight PVA does not possess the same cohesive strength as higher molecular weight PVA material (Amresco) due to the reduced size of the polymer chain leading to a reduction in the degree of cross linking and physical interactions between individual PVA polymer chains. The reduced PVA chain interactions lead to a weakened solidified layer that is

Padagis Ex. 1029
IPR Petition - USP 11,311,482

unable to withstand the mechanical forces the solidified layer is subjected to upon removal.

Example 56-57

A stretchable adhesive formulation for transdermal delivery of ketoprofen (which is suitable for delivery via skin on joints and muscles) was evaluated which includes a placebo excipient mixture which will form an adhesive formulation, some of which are prepared in accordance with embodiments of the present invention. The excipient mixture, which is a viscous and transparent fluid, is prepared using the ingredients as shown in Table 34.

Table 34

Ingredients*	Examples	
	56	57
PVA (Amresco MW 31,000-50,000)	20.41	21.28
Water	30.61	27.66
Ethanol	20.41	21.28
PG	20.41	21.28
Glycerol	6.12	6.38
Gantrez S97	2.04	2.13

* Ingredients are noted in weight percent.

Solidifying formulations in Examples 56 and 57 are prepared in the following manner:

- PVA (solidifying agent) is dissolved in water.
- The flux adequate non-volatile solvent (glycerol, PG) is mixed together with the solidifying agent/volatile solvent mixture.
- Then ethanol, and Gantrez S97 is added to the mixture.
- The resulting solution is vigorously mixed for several minutes.

Formulations above were applied on the forearms of study volunteers and the drying time was assessed by placing a piece of cotton to the application site and then applying a 5 gram weight on the cotton. The cotton and weight was removed after 5 seconds. This procedure was started approximately 3 - 4 minutes after application and at 10 to 60 second intervals thereafter until the cotton was removed without lifting the solidified layer from the skin or leaving residue behind. The time when this observation is made is defined as the

drying time for the solidifying formulation. The results of the study are summarized in Table 35 below.

Table 35

Example	Drying Time (min)
56	7.0
57	6.5

The amount of water in the formulation did not significantly influence the time for the formulation to dry. However, it was noted during the study that the formulation was difficult to expel from the sample tube. After approximately 4 weeks after the formulation in Examples 56 and 57 were made the sample tubes were retrieved and were evaluated for ease of dispensing the formulation. It was noted that the formulation was impossible to expel from the tube. Interpolymer complexation between Gantrez S-97 and PVA through electrostatic interactions, hydrophobic interactions, hydrogen bonding, or Van der Waals interactions is hypothesized to be the reason(s) for the observed thickening. Moreover, the extent of this interaction may be dependent on the stoichiometric ratio of the two polymers.

Example 58-61

A stretchable adhesive formulation for transdermal delivery of ketoprofen (which is suitable for delivery via skin on joints and muscles) was evaluated which includes an excipient mixture which will form an adhesive formulation, some of which are prepared in accordance with embodiments of the present invention. The excipient mixture, which is a viscous and transparent fluid, is prepared using the ingredients as shown in Table 36.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Table 36

Ingredients*	Examples			
	58	59	60	61
PVA (Amresco MW 31,000-50,000)	22.1	24.4	22.1	21.1
Water	26.6	29.2	30.9	33.8
Ethanol	12.6	4.2	8.4	8.2
Butanol	0.4	0.5	0.4	0.4
PG	19.9	21.9	17.7	16.9
Glycerol	8.8	9.7	11	10.6
Gantrez ES 425	4.6	5.1	4.4	4.0
Ketoprofen	5.0	5.0	5.1	5.0

* Ingredients are noted in weight percent.

Solidifying formulations in Examples 58-61 are prepared in the following manner:

- PVA (solidifying agent) is dissolved in water.
- The flux adequate non-volatile solvent (glycerol, PG) is mixed together with the solidifying agent/volatile solvent mixture.
- Then ethanol, and Gantrez ES 425 is added to the mixture.
- The resulting solution is vigorously mixed for several minutes.
- After mixing, ketoprofen is added and the final mixture is vigorously mixed again for several minutes.

Formulations noted above were placed in laminate packaging tubes and stored at 25 C/60% RH and 40 C/ 75% RH conditions until pulled for testing. Physical testing was performed on each formulation. Examples 57-59 have been studied the longest and the resulting viscosity increase necessitated the desire to study the viscosity of Example 60. Table 37 summarizes the data generated on each formulation.

Table 37

Example Storage Cond.	Viscosity* cPs					
	T=0	2 weeks	4 weeks	8 weeks	12 weeks	16 weeks
58 25 C/60% RH	96000	670000	>2500000	Not measured		
58 40 C/75% RH	96000	500000	587500	2320000		
59 25 C/60% RH	168500	204500	251000	>2500000		

Padagis Ex. 1029
IPR Petition - USP 11,311,482

59 40 C/75% RH	168500	215000	217500	>2500000		
60 25 C/60% RH	23000	--	25000	36250	76250	57500
60 40 C/75% RH	23000	--	31000	40000	243500	164500
61 25 C/60% RH	11250	13750				
61 40 C/75% RH	11250	17500				

* Viscosity measured using a RVDV 1+ viscometer at 0.5 rpm.

Examples 58 and 59 had the lowest water content of the four formulations and within 4 weeks of storage attained high viscosity values. The only difference between Examples 58 and 59 is the amount of ethanol in the formulations. It was hypothesized that reducing the level of ethanol may reduce the physical thickening of the formulation due to an incompatibility between the PVA and ethanol. The viscosity data show that the higher ethanol formulation (Example 58) had lower initial viscosity, but over the 4 weeks storage the viscosity of both Examples 58 and 59 attained viscosity values that were too high for a viable formulation. Another hypothesis for the formulation thickening is that PVA is not compatible in high concentrations when dissolved in water. Additional formulations with higher water content were prepared to determine if an optimal water amount would keep the formulation from thickening up over time. Example 60 viscosity after 16 weeks has not reached the viscosity values of the initial viscosity values of Examples 58 and 59.

Placebo versions of the formulations above were applied on study volunteers and the drying time was assessed by placing a piece of cotton to the application site and then applying a 5 gram weight on the cotton. The cotton and weight was removed after 5 seconds. This procedure was started approximately 3 – 4 minutes after application and at 10 to 60 second intervals thereafter until the cotton was removed without lifting the solidified layer or leaving residue behind. The results of the study are summarized in Table 38 below.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Table 38

Example	Drying Time (min)*
58	4 min 49 sec
59	5 min 41 sec
60	4 min 27 sec
61	5 min 1 sec

* average dry time value from 12 study subjects.

The presence of ethanol as a second volatile solvent appears to significantly reduce the time to dry. In data not shown a local anesthetic formulation containing only water as the volatile solvent and a ratio of water to PVA of 2:1 has a drying time of >15 minutes. Optimizing the ratio and the presence of an additional volatile solvent in formulations containing water significantly reduce the drying time. It is hypothesized that the additional volatile solvent, in this case ethanol, will hydrogen bond with the water and water will escape with the ethanol when evaporating off the skin thereby forming a solidified layer.

Example 62-63

A stretchable adhesive formulation for transdermal delivery of ketoprofen (which is suitable for delivery via skin for treating inflammation or pain of joints and muscles) is prepared which includes ketoprofen in an excipient mixture to form an adhesive formulation, some of which is prepared in accordance with embodiments of the present invention. The solidifying formulation is prepared from the ingredients as shown in Table 39.

Table 39 - Ketoprofen solidifying formulation components

Ingredients*	Example 62	Example 63
PVA	22.1	18.9
Water	30.9	37.9
Fumed Silicia		3.0
Glycerol	11.1	9.5
Propylene glycol	17.7	15.2
Gantrez ES-425	4.4	3.8
Ethanol	8.8	7.6
Ketoprofen	5.0	4.2

*Ingredients are noted as weight percent.

Table 40 - Steady-state flux of ketoprofen through hairless mouse skin from an adhesive solidifying formulations at 35 °C

Formulation	Average flux mcg/cm^2/h*
Example 62	25 ± 6
Example 63	27 ± 2

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed the steady state flux would extend beyond the 8 hours measured.

Example 64-66

Placebo formulations containing Gantrez ES 425 as an adhesive polymer were prepared for wear studies by volunteers. The formulations are shown as examples in Table 41. All the formulations have polyvinyl alcohol as a solidifying agent to provide tensile strength to the solidifying formulation. The amount of propylene glycol in the formulations was decreased from 19.6% (w/w) to 8.7% (w/w), and the amount of glycerol was increased by the same amount to keep the total non-volatile ratio constant. Keeping the non-volatile ratio constant is important as it determines the drying time and the duration of delivery. The placebo formulations are worn on the palms of hand and percentage adherence of the solidified layer formed after evaporation of volatile solvents was observed after 5-6 hours.

Table 41: Placebo formulations (%w/w ingredients)

Ingredient	Example 64	Example 65	Example 66
Polyvinyl Alcohol	21.7%	21.7%	21.7%
Water	32.6%	32.6%	32.6%
Glycerol	8.7%	13.0%	19.6%
Propylene Glycol	19.6%	15.2%	8.7%
Gantrez ES 425	4.3%	4.3%	4.3%
Oleic acid	4.3%	4.3%	4.3%
Ethanol	8.7%	8.7%	8.7%

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Wear study results on 3 volunteers show that 70-80% of solidified layer as described in Example 64 stayed on palms after a duration of 5-6 hours. However, greater than 90% of solidified layer as shown in Example 66 stayed on palms of the volunteers. These examples demonstrate that glycerol is a better plasticizer that propylene glycol for the polyvinyl alcohol polymer. It also shows that the ratio of non-volatile solvent is critical in selecting the formulation for treatment of hand dermatitis.

Examples 67-68

Adhesive formulations containing 0.05% (w/w) clobetasol propionate and 0.15% (w/w) clobetasol propionate with polyvinyl alcohol as solidifying polymer are prepared for in-vitro flux evaluation. Propylene glycol and oleic acid are the non volatile solvents selected for facilitation of clobetasol propionate delivery. As shown in Example 66, glycerol is added as the non volatile solvent for its plasticizing properties. Ratios of ingredients used in the two formulations are shown in Table 42.

Table 42: Clobetasol Propionate solidifying formulations*

Ingredient	Example 67	Example 68
Polyvinyl Alcohol	22.7%	22.7%
Water	34.1%	34.0%
Glycerol	17.3%	17.2%
Propylene Glycol	7.7%	7.7%
Gantrez ES 425	4.5%	4.5%
Oleic acid	4.5%	4.5%
Ethanol	9.1%	9.1%
Clobetasol Propionate	0.05%	0.15%

* Numbers do not add to 100% because of rounding in the second decimal.

Both of the compositions shown above are studied for flux of clobetasol propionate on cadaver skin from three donors. The permeation results are as shown in Table 43. Commercial clobetasol ointment (0.05% w/w) was used as a control formulation.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Table 43 - Steady state flux of clobetasol propionate through human cadaver skin at 35 °C

Skin Donor	Control J* (ng/ cm^2/h)	Example 67 J* (ng/ cm^2/h)	Example 68 J* (ng/ cm^2/h)
Donor 1	22.4 ± 2.1	8.8 ± 1.9	29.2 ± 8.2
Donor 2	20.0 ± 2.5	7.6 ± 2.5	18.5 ± 6.4
Donor 3	35.0 ± 4.7	19.3 ± 5.9	24.8 ± 7.7
Mean +/- SD (n=3 donors)	25.8 ± 7.5	11.9 ± 6.5	24.2 ± 8.0

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported are determined from the linear region of the cumulative amount versus time plots. The linear region are observed to be between 6-28 hours. If the experiment is continued, it is anticipated the steady state would continue.

As seen from Table 43 formulation described in Example 67 that contained polyvinyl alcohol as a solidifying agent and 0.05% clobetasol propionate had 46% flux of clobetasol propionate when compared to the control formulation. Increasing the clobetasol propionate concentration drug concentration to 0.15% (w/w) increased the steady state flux and the flux values were 94% of the control formulation. It is expected that longer duration of application with the solidifying formulation would increase cumulative delivery in-vivo resulting in effective treatment of dermatitis.

Example 69

Adhesive formulations containing 0.05% (w/w) clobetasol propionate with gelatin as solidifying agent are prepared for in-vitro flux evaluation. Propylene glycol, isostearic acid, and oleic acid are used as non-volatile solvents to facilitate delivery of clobetasol. Talc is added as a filler to reduce the drying time the formulation. Ratio of ingredients used in the formulation is shown in Table 44.

Table 44: Clobetasol Propionate formulations*

Ingredient	Example 69
Fish Gelatin	29.4%
Water	22.0%
Ethanol	14.7%
Propylene Glycol	17.6%
Isostearic acid	2.2%
Oleic acid	2.2%
Talc	11.8%
Clobetasol Propionate	0.05%

* Numbers do not add to 100% because of rounding in the second decimal.

Unlike the polyvinyl based formulations shown in previous examples, the fish gelatin based formulation shown in Example 44 is a water washable formulation and can be easily removed by subjects suffering from hand dermatitis. Steady state flux across human cadaver skin from 3 donors with formulation as described in Example 69 is compared to the commercial clobetasol ointment. The permeation results are shown in Table 45.

Table 45 - Steady state flux of clobetasol propionate through human cadaver skin at 35 °C

Skin Donor	Control J* (ng/ cm^2/h)	Example 69 J* (ng/ cm^2/h)
Donor 1	39.2 ± 9.2	46.1 ± 14.3
Donor 2	35.6 ± 2.1	52.9 ± 22.3
Donor 3	35.6 ± 5.7	79.7 ± 18.4
Mean +/- SD (n=3 donors)	36.8 ± 5.8	59.6 ± 22.3

*Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported are determined from the linear region of the cumulative amount versus time

plots. The linear region are observed to be between 6-28 hours. If the experiment is continued, it is anticipated the steady state would continue.

As seen from Table 45, formulation described in Example 69 has 62% higher steady state flux when compared to the commercial ointment. Higher steady state flux would result is expected to reduce inflammation in difficult to treat dermatitis and psoriasis cases.

Example 70

Adhesive formulations containing 0.05% (w/w) clobetasol propionate with gelatin as solidifying polymer are prepared for in-vitro flux evaluation. Propylene glycol, and isostearic acid are used as non-volatile solvents to facilitate delivery of clobetasol. Fumed silica is added as a filler to reduce the drying time the formulation. Ratio of ingredients used in the formulation is shown in Table 46.

Table 46: Clobetasol Propionate formulations*

Ingredient	Example 70
Fish Gelatin	32.2%
Water	24.2%
Ethanol	16.1%
Propylene Glycol	19.3%
Isostearic acid	4.8%
Fumed Silica	3.2%
Clobetasol Propionate	0.05%

* Numbers do not add to 100% because of rounding in the second decimal.

The fish gelatin based formulation shown in Example 70 is a water washable formulation and can be easily removed by subjects suffering from hand dermatitis. Steady state flux across human cadaver skin from 4 donors with formulation as described in Example 70 is compared to the commercial clobetasol ointment. The permeation results are shown in Table 47.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Table 47 - Steady state flux of clobetasol propionate through human cadaver skin at 35 °C

Skin Donor	Control J* (ng/ cm^2/h)	Example 70 J* (ng/ cm^2/h)
Donor 1	28.2 ± 7.8	20.7 ± 12.8
Donor 2	30.1 ± 14.9	30.6 ± 13.8
Donor 3	36.2 ± 6.2	93.4 ± 7.5
Donor 4	33.6 ± 3.9	101.4 ± 8.5
Mean +/- SD (n=3 donors)	32.0 ± 8.5	61.5 ± 38.9

*Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported are determined from the linear region of the cumulative amount versus time plots. The linear region are observed to be between 6-28 hours. If the experiment is continued, it is anticipated the steady state would continue.

As seen from Table 47, on an average, formulation described in Example 70 has at-least similar or better steady state flux when to compared to the steady state flux with the commercial ointment. Unlike talc used in Example 69, fumed silica had a low density and is expected to have a less potential to separate from the formulation.

Examples 71-73

Solidifying formulations for dermal delivery of ropivacaine HCl are prepared which include excipient mixtures in accordance with embodiments of the present invention. The formulations are prepared from the ingredients as shown in Table 48.

Table 48 - Ropivacaine HCl solidifying formulation components.

Ingredients*	Example		
	71	72	73
Ropivacaine HCl	6.9	6.5	6.6
Isopropanol	50.7	45.8	45.9
Water	5.5	5.2	5.2
Isostearic Acid	6.3	6.6	6.6
Triethylamine			3.0
Diisopropanolamine		3.9	
Cetyl alcohol		3.3	3.9
Triacetin	2.9	2.6	2.6
Span 20	5.8	5.2	5.2
Plastoid B**	21.9	20.9	21.0

*Ingredients are noted as weight percent.
** from Degussa.

The ingredients listed above are combined according to the following procedure. The ropivacaine HCl, water, and the amine base (triethylamine or diisopropanolamine) are combined in a glass jar and mixed until the drug is dissolved. Then the isostearic acid, triacetin, Span 20, and cetyl alcohol (Examples 72 and 73) or isopropanol (Example 71) is added to the formulation and mixed well. The polymer Plastoid B is added last and heated to about 60 ^{0}C until the Plastoid B is completely dissolved. Once the polymer solution cooled to room temperature, the formulation is stirred vigorously for 2-3 minutes.

The formulations in Table 48 are applied to HMS according to Example 1, and the flux of ropivacaine was measured. The results are summarized in Table 49:

Table 49 - Steady-state flux of ropivacaine hcl through hairless mouse skin from various adhesive solidifying formulations at 35 °C

Formulation	Average flux mcg/cm^2/h*
71	96 ± 14
72	61 ± 2
73	70 ± 7

Example 74

A prototype peel is prepared in accordance with Table 50 as follows:

Table 50

Example	74
	% by weight
Plastoid B	21.3
Isopropyl Alcohol	48.4
Water	2.5
Isostearic Acid	18.2
Trolamine	6.6
Acyclovir	3.0

The formulation was prepared by mixing Plastoid B in isopropyl alcohol until the polymer dissolved, then the remaining components were added and the mixture vigorously stirred until a uniform mixture was obtained.

Example 74 illustrates the necessity of an appropriate selection of a non-volatile solvent and a solidifying agent. After mixing the formulation of Example 74 together, the formulation turned from a flowable solution into two distinct layers: a soft solid and a liquid layer. The formulation in this state is not spreadable on the skin surface. An incompatibility between trolamine and the Plastoid B polymer is suggested because of the hydrophilic nature of the trolamine and the hydrophobic nature of the polymer resulted in the trolamine being squeezed out of the formulation.

Examples 75-77

Prototype peel formulations are prepared as follows. Several peel formulations are prepared in accordance with embodiments of the present invention in accordance with Table 51, as follows:

Table 51

Example	75	76	77
Volatile Solvents			
Ethanol	21	18.5	43
Water	32	28	22
Solidifying agents			
Eudragit E-100		18.5	
Polyvinyl Alcohol	21	18.5	14
Non-volatile solvents			
Glycerol			14
Propylene Glycol	21		
Polyethylene Glycol			6
Span 20		11	
Drug			
Ketoprofen	5		
Diclofenac Na		5.5	
Testosterone			1

Peel formulations of Examples 75-77 are prepared in the following manner:

- The solidifying agents are dissolved in the volatile solvent (e.g., dissolve polyvinyl alcohol in water, Eudragit polymers in ethanol),
- The non-volatile solvent is mixed with the solidifying agent/volatile solvent mixture.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

- The resulting solution is vigorously mixed well for several minutes.
- The drug is then added and the peel formulation is mixed again for several minutes.

In all the Examples noted above, the flux-enabling non-volatile solvent/solidifying agent/volatile solvent combination is compatible as evidenced by a homogeneous, single phase system that exhibited appropriate drying time, and provided a stretchable peel and steady state flux for the drug (see Example 78 below).

The use of a volatile solvent system of water and ethanol at the percentages in Examples 75-77 is an attempt to achieve a balance between drying time and compatibility with the other ingredients (namely PVA in these examples) in the formulations. Addition of ethanol is thought to reduce the drying time for the formulation due to ethanol/water interactions resulting in an increased evaporation rate of the volatile solvents, and enough water is present to ensure compatibility of PVA in the formulations. This is an example of using a two-member solvent system to successfully achieve an acceptable compromise between compatibility with the solidifying agent and the drying time.

Example 78

The formulations of the Examples are tested in a hairless mouse skin (HMS) or human epidermal membrane (HEM) *in vitro* model described in Example 1. Table 52 shows data obtained using the experimental process outlined above.

Table 52 – Steady-state flux (J)

Formulation	J* ($\mu g/cm^2/h$)
Example 75	35 ± 20***
Example 76**	5 ± 2****
Example 77	4 ± 1***

* Skin flux measurements represent the mean and standard deviation of three determinations.

** Data gathered using human epidermal membrane.

***Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was

Padagis Ex. 1029
IPR Petition - USP 11,311,482

observed to be between 4-8 hours. If experimental conditions allowed, the steady-state delivery would likely continue well beyond 8 hours.

****Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 6-28 hours. If the experiment was continued it is anticipated the steady state would continue.

In all cases in Table 52, the flux enabling non-volatile solvents in the formulation resulted in therapeutically effective flux for each of the formulations studied.

Example 79

A placebo formulation with the following composition: 10.4% polyvinyl alcohol, 10.4% polyethylene glycol 400, 10.4% polyvinyl pyrrolidone K-90, 10.4% glycerol, 27.1 % water, and 31.3% ethanol was applied onto a human skin surface at an elbow joint and a finger joint, resulting in a thin, transparent, flexible, and stretchable film. After a few minutes of evaporation of the volatile solvents (ethanol and water), a solidified layer that was peelable was formed. The stretchable solidified layer had good adhesion to the skin and did not separate from the skin on joints when bent, and could easily be peeled away from the skin.

Examples 80-82

Prototype peels are prepared as follows. Several acyclovir peel formulations are prepared in accordance with embodiments of the present invention in accordance with Table 53 as follows:

Table 53

Example	**80**	**81**	**82**
	% by weight		
Plastoid B	10	10	
Eudragit RL-100			10
Isopropyl Alcohol	57	57	
Ethanol			57
Water			
Isostearic Acid	9	9	9
Trolamine	9	9	9
Ethylcellulose EC-N7	10		
Ethylcellulose EC-N100		10	10
Acyclovir	5	5	5

Padagis Ex. 1029
IPR Petition - USP 11,311,482

The formulation was prepared by mixing Plastoid B in isopropyl alcohol until the polymer dissolved, then the remaining components were added and the mixture vigorously stirred until a uniform mixture was obtained.

Examples 80 and 81 show the importance of an additional polymer to solve the trolamine/polymer incompatibility. Addition of ethylcellulose (N7 and N100) to the formulation reduced the amount of Plastoid B polymer to a level that is compatible with trolamine. The resulting formulation produced a thickened, easily spreadable formulation. The formulation in Example 82 exhibited precipitation, but the thickening due to addition of the N100 ethylcellulose will prevent the settling of the precipitation.

Example 83

The formulations of Examples 80-72 are tested in a hairless mouse skin (HMS) in vitro model described in Example 1. Table 54 shows data obtained using the experimental process outlined above.

Table 54 – Steady-state flux (J) of Acyclovir through HMS

Formulation	J* ($\mu g/cm^2/h$)	Ratio to Control
Example 80	4.0 ± 0.8	6.7
Example 81	4 ± 1	6.7
Example 82	13 ± 6	21.7
Zovirax Cream	0.6 ± 0.3	1

* Skin flux measurements represent the mean and standard deviation of three determinations. Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 4-8 hours. If experimental conditions allowed the steady state flux would extend beyond the 8 hours measured.

Steady-state flux variations of acyclovir through HMS from various lots of mice are expected. For this reason a control (Zovirax cream) is run with each Example formulation. The ratio to control column in Tables 53 and 54 can be compared to evaluate the improvement of the Example formulation over the control.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

The formulations of the invention shown above generally provide for significant penetration of the active ingredient, and further, the formulations of Examples 80-82 are found to be much greater in permeability than the marketed product Zovirax Cream.

Examples 71-82 show similar in vitro flux increase (based on ratio to control) over the Zovirax control. Addition of ethylcellulose to the formulations in Examples 81-83 may increase the occlusion due to the addition of the hydrophobic polymers.

Examples 84

Prototype peel formulations are prepared as follows. Several peel formulations are prepared in accordance with embodiments of the present invention in accordance with Table 55, as follows:

Table 55

Example	84
	% by weight
Volatile Solvents	
Ethanol	18.5
Water	28
Solidifying agents	
Eudragit E-100	18.5
Polyvinyl Alcohol	18.5
Non-volatile solvents	
Span 20	11
Drug	
Diclofenac Na	5.5

The peel formulation of Example 84 is prepared in the following manner:

- The solidifying agents are dissolved in the volatile solvent (e.g., dissolve polyvinyl alcohol in water, Eudragit polymers in ethanol),
- The non-volatile solvent is mixed with the solidifying agents/volatile solvent mixture.
- The resulting solution is vigorously mixed well for several minutes.
- The drug is then added and the peel formulation is mixed again for several minutes.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

In the example noted above, the flux-enabling non-volatile solvent/solidifying agents/volatile solvent combination is compatible as evidenced by a homogeneous, single phase system that exhibited appropriate drying time, and provided a stretchable peel and steady state flux for the drug (see Example 85 below).

Addition of Eudragit E-100 polymer into the formulation in Example 84 increases adhesion to the skin surface prior to the evaporation of its volatile solvent(s). The PVA polymer in the formulation provides a solidified layer with high tensile strength that allows it to remain in one piece on the skin surface during the intended time of application. The combination of these two polymers provides a solidified layer with flexibility and adhesion to the skin that does not separate from the skin (sites include skin covering joints) and can easily be peeled away from the skin

Example 85

The formulations of the Examples are tested in a hairless mouse skin (HMS) or HEM *in vitro* model described in Example 1. Table 56 shows data obtained using the experimental process outlined above.

Table 56 – Steady-state flux (J)

Formulation	J* ($\mu g/cm^2/h$)
Example 85**	5 ± 2***

* Skin flux measurements represent the mean and standard deviation of three determinations.

** Data gathered using human epidermal membrane.

***Flux measurements reported were determined from the linear region of the cumulative amount versus time plots. The linear region was observed to be between 6-28 hours. If the experiment was continued it is anticipated the steady state would continue.

Diclofenac have lower steady state flux values when the enabling non-volatile solvent is incorporated into the peel formulation. This could be the result of the volatile solvent system or the solidifying agents having the opposite impact on the chemical environment (e.g., decreasing solubility, physical interactions between drug and peel formulation) resulting in lower flux values. The steady

state flux value for imiquimod is unchanged when comparing the peel formulation with the flux-enabling non-volatile solvent flux values.

While the invention has been described with reference to certain preferred embodiments, those skilled in the art will appreciate that various modifications, changes, omissions, and substitutions can be made without departing from the spirit of the invention. It is therefore intended that the invention be limited only by the scope of the appended claims.

CLAIMS

What Is Claimed Is:

1. An adhesive solid formulation for dermal delivery of a drug, comprising:

a) a drug;

b) a solvent vehicle, comprising:

i) a volatile solvent system including at least one volatile solvent, and

ii) a non-volatile solvent system including at least one non-volatile solvent, and

c) a solidifying agent,

wherein the formulation has a viscosity suitable for application and adhesion to a skin surface prior to evaporation of the volatile solvent system, wherein the formulation applied to the skin surface forms a solidified layer after at least partial evaporation of the volatile solvent system, and wherein the drug continues to be dermally delivered after the volatile solvent system is at least substantially evaporated,

with the proviso that there are at least two volatile solvents, two non-volatile solvents, or two solidifying agents.

2. A formulation as in claim 1, wherein the non-volatile solvent system acts as a plasticizer for the solidified agent.

3. A formulation as in claim 1, wherein the formulation further comprises an additional agent that is added to increase adhesion of the formulation when applied to a skin surface.

4. A formulation as in claim 3, wherein the additional agent includes a member selected from the group consisting of copolymers of methylvinyl ether and maleic anhydride, polyethylene glycol and polyvinyl pyrrolidone, gelatin, low

Padagis Ex. 1029
IPR Petition - USP 11,311,482

molecular weight polyisobutylene rubber, copolymer of acrylsan alkyl/octylacrylamido, aliphatic resins, aromatic resins, and combinations thereof.

5. A formulation as in claim 1, wherein the volatile solvent system comprises water.

6. A formulation as in claim 1, wherein the solvent vehicle is substantially free of water.

7. A formulation as in claim 1, wherein the formulation includes a first volatile solvent and a second volatile solvent, wherein the first volatile solvent is more volatile than the second volatile solvent, and wherein the second volatile solvent has better compatibility with the solidifying agent than the first volatile solvent.

8. A formulation as in claim 1, wherein the formulation includes a first volatile solvent and a second volatile solvent, wherein the first volatile solvent is more volatile than the second volatile solvent, and wherein the second volatile solvent has better solubility for the drug than the first volatile solvent.

9. A formulation as in claim 1, wherein the formulation has better solubility for the drug than a formulation that contains the same ingredients except only one of the volatile solvents.

10. A formulation as in claim 1, wherein the formulation includes at least two volatile solvents and has better solubility for the solidifying agent than a formulation that contains the same ingredients except only one of the volatile solvents.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

11. A formulation as in claim 1, wherein at least one of the volatile solvents has a boiling point greater than 20 °C and at least one of the volatile solvents having boiling point lower than 20 °C.

12. A formulation as in claim 1, wherein at least one of the volatile solvents is selected from the group consisting of a hydrofluorocarbon, dimethyl ether, diethyl ether, propane, isobutane, difluoroethane, butane, 1,1,1,2 tetrafluorethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,3,3,3 hexafluoropropane, and combinations thereof.

13. A formulation as in claim 1, wherein the volatile solvent system includes at least one solvent more volatile than water, and includes at least one member selected from the group consisting of ethanol, isopropyl alcohol, water, dimethyl ether, diethyl ether, butane, propane, isobutene, 1,1, difluoroethane, 1,1,1,2 tetrafluorethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,3,3,3 hexafluoropropane, ethyl acetate, acetone, and combinations thereof.

14. A formulation as in claim 1, wherein the volatile solvent system includes at least one solvent more volatile than water, and includes at least one member selected from the group consisting of iso-amyl acetate, denatured alcohol, methanol, propanol, isobutene, pentane, hexane, chlorobutanol, turpentine, cytopentasiloxane, cyclomethicone, methyl ethyl ketone, and combinations thereof.

15. A formulation as in claim 1, wherein the non-volatile solvent system includes at least one member selected from the group consisting of glycerol, propylene glycol, isostearic acid, oleic acid, propylene glycol, trolamine, tromethamine, triacetin, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, butanol, and combinations thereof.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

16. A formulation as in claim 1, wherein the volatile solvent system includes at least one member selected from the group consisting of ethanol, isopropyl alcohol, and combinations thereof.

17. A formulation as in claim 1, wherein the non-volatile solvent system includes at least one member selected from the group consisting of benzoic acid, butyl alcohol, dibutyl sebecate, diglycerides, dipropylene glycol, eugenol, fatty acids, isopropyl myristate, mineral oil, oleyl alcohol, vitamin E, triglycerides, sorbitan fatty acid surfactants, triethyl citrate, and combinations thereof.

18. A formulation as in claim 1, wherein the non-volatile solvent system includes at least one member selected from the group consisting of 1,2,6-hexanetriol, alkyltriols, alkyldiols, acetyl monoglycerides, tocopherol, alkyl dioxolanes, p-propenylanisole, anise oil, apricot oil, dimethyl isosorbide, alkyl glucoside, benzyl alcohol, bees wax, benzyl benzoate, butylene glycol, caprylic/capric triglyceride, caramel, cassia oil, castor oil, cinnamaldehyde, cinnamon oil, clove oil, coconut oil, cocoa butter, cocoglycerides, coriander oil, corn oil, coriander oil, corn syrup, cottonseed oil, cresol, cyclomethicone, diacetin, diacetylated monoglycerides, diethanolamine, dietthylene glycol monoethyl ether, diglycerides, ethylene glycol, eucalyptus oil, fat, fatty alcohols, flavors, liquid sugarsm ginger extract, glycerin, high fructose corn syrup, hydrogenated castor oil, IP palmitate, lemon oil, lime oil, limonene, milk, monoacetin, monoglycerides, nutmeg oil, octyldodecanol, olive alcohol, orange oil, palm oil, peanut oil, PEG vegetable oil, peppermint oil, petrolatum, phenol, pine needle oil, polypropylene glycol, sesame oil, spearmint oil, soybean oil, vegetable oil, vegetable shortening, vinyl acetate, wax, 2-(2-(octadecyloxy)ethoxy)ethanol, benzyl benzoate, butylated hydroxyanisole, candelilla wax, carnauba wax, ceteareth-20, cetyl alcohol, polyglyceryl, dipolyhydroxy stearate, PEG-7 hydrogenated castor oil, diethyl phthalate, diethyl sebacate, dimethicone, dimethyl phthalate, PEG fatty acid esters, PEG-stearate, PEG-oleate, PEG laurate, PEG fatty acid diesters, PEG- dioleate, PEG-distearate, PEG-castor oil, glyceryl behenate, PEG glycerol fatty acid

Padagis Ex. 1029
IPR Petition - USP 11,311,482

esters, PEG glyceryl laurate, PEG glyceryl stearate, PEG glyceryl oleate, hexylene glycerol, lanolin, lauric diethanolamide, lauryl lactate, lauryl sulfate, medronic acid, methacrylic acid, multisterol extract, myristyl alcohol, neutral oil, PEG-octyl phenyl ether, PEG-alkyl ethers, PEG-cetyl ether, PEG-stearyl ether, PEG-sorbitan fatty acid esters, PEG-sorbitan diisosterate, PEG-sorbitan monostearate, propylene glycol fatty acid esters, propylene glycol stearate, propylene glycol, caprylate/caprate, sodium pyrrolidone carboxylate, sorbitol, squalene, stear-o-wet, triglycerides, alkyl aryl polyether alcohols, polyoxyethylene derivatives of sorbitan-ethers, saturated polyglycolyzed C8-C10 glycerides, N-methyl pyrrolidone, honey, polyoxyethylated glycerides, dimethyl sulfoxide, azone and related compounds, dimethylformamide, N-methyl formamaide, fatty acid esters, fatty alcohol ethers, alkyl-amides (N,N-dimethylalkylamides), N-methyl pyrrolidone related compounds, ethyl oleate, polyglycerized fatty acids, glycerol monooleate, glyceryl monomyristate, glycerol esters of fatty acids, silk amino acids, PPG-3 benzyl ether myristate, Di-PPG2 myreth 10-adipate, honeyquat, sodium pyroglutamic acid, abyssinica oil, dimethicone, macadamia nut oil, limnanthes alba seed oil, cetearyl alcohol, PEG-50 shea butter, shea butter, aloe vera juice, phenyl trimethicone, hydrolyzed wheat protein, and combinations thereof.

19. A formulation as in claim 1, wherein the solidifying agent includes at least one member selected from the group consisting of polyvinyl alcohol, esters of polyvinylmethylether/maleic anhydride copolymer, neutral copolymers of butyl methacrylate and methyl methacrylate, dimethylaminoethyl methacrylate-butyl methacrylate-methyl methacrylate copolymers, ethyl acrylate-methyl methacrylate-trimethylammonioethyl methacrylate chloride copolymers, prolamine (Zein), pregelatinized starch, ethyl cellulose, fish gelatin, gelatin, acrylates/octylacrylamide copolymers, and combinations thereof.

20. A formulation as in claim 1, wherein the solidifying agent includes at least one member selected from the group consisting of ethyl cellulose, hydroxy ethyl cellulose, hydroxy methyl cellulose, hydroxy propyl cellulose,

Padagis Ex. 1029
IPR Petition - USP 11,311,482

hydroxypropyl methyl cellulose, carboxymethyl cellulose, methyl cellulose, polyether amides, corn starch, pregelatinized corn starch, polyether amides, shellac, polyvinyl pyrrolidone, polyisobutylene rubber, polyvinyl acetate phthalate and combinations thereof.

21. A formulation as in claim 1, wherein the solidifying agent includes at least one member selected from the group consisting of ammonia methacrylate, carrageenan, cellulose acetate phthalate aqueous, carboxy polymethylene, cellulose acetate (microcrystalline), cellulose polymers, divinyl benzene styrene, ethylene vinyl acetate, silicone, guar gum, guar rosin, gluten, casein, calcium caseinate, ammonium caseinate, sodium caseinate, potassium caseinate, methyl acrylate, microcrystalline wax, polyvinyl acetate, PVP ethyl cellulose, acrylate, PEG/PVP, xantham gum, trimethyl siloxysilicate, maleic acid/anhydride colymers, polacrilin, poloxamer, polyethylene oxide, poly glactic acid/poly-l-lactic acid, turpene resin, locust bean gum, acrylic copolymers, polyurethane dispersions, dextrin, polyvinyl alcohol-polyethylene glycol co-polymers, methyacrylic acid-ethyl acrylate copolymers, methacrylic acid and methacrylate based polymers such as poly(methacrylic acid), and combinations thereof.

22. A formulation as in claim 1, wherein the formulation includes at least two solidifying agents which together are capable of generating a higher flux in the solidified layer than either of the solidifying agents alone.

23. A formulation as in claim 1, wherein the formulation includes at least two solidifying agents which together provide enhanced physical stability of the formulation greater than either of the at least two solidifying agents alone.

24. A formulation as in claim 1, wherein the formulation includes at least two solidifying agents and at least one of the at least two solidifying agents is an acrylate/octylacrylamide copolymer or a polymethyl vinyl ether/maleic anhydride copolymer.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

25. A formulation as in claim 1, wherein the drug includes multiple pharmaceutically active agents.

26. A formulation as in claim 1, wherein the drug includes at least one member selected from the group consisting of acyclovir, econazole, miconazole, terbinafine, lidocaine, bupivacaine, ropivacaine, and tetracaine, amitriptyline, ketanserin, betamethasone dipropionate, triamcinolone acetonide, clindamycin, benzoyl peroxide, tretinoin, isotretinoin, clobetasol propionate, halobetasol propionate, ketoprofen, piroxicam, diclofenac, indomethacin, imiquimod, salicylic acid, benzoic acid, and combinations thereof.

27. A formulation as in claim 1, wherein the drug includes at least one member selected from the group consisting of amorolfine, butenafine, naftifine, terbinafine, fluconazole, itraconazole, ketoconazole, posaconazole, ravuconazole, voriconazole, clotrimazole, butoconazole , econazole, miconazole, oxiconazole, sulconazole, terconazole, tioconazole, caspofungin, micafungin, anidulafingin, amphotericin B, AmB, nystatin, pimaricin, griseofulvin, ciclopirox olamine, haloprogin, tolnaftate, undecylenate, penciclovir, famciclovir, valacyclovir, behenyl alcohol, trifluridine, idoxuridine, cidofovir, gancyclovir, podofilox, podophyllotoxin, ribavirin, abacavir, delavirdine, didanosine, efavirenz, lamivudine, nevirapine, stavudine, zalcitabine, zidovudine, amprenavir, indinavir, nelfinavir, ritonavir, saquinavir, amantadine, interferon, oseltamivir, ribavirin, rimantadine, zanamivir, erythromycin, clindamycin, tetracycline, bacitracin, neomycin, mupirocin, polymyxin B, quinolones, ciproflaxin, bupivacaine, alpha-2 agonists, clonidine, amitriptyline, carbamazepine, alprazolam, ketamine, ketanserin, betamethasone dipropionate, halobetasol propionate, diflorasone diacetate, triamcinolone acetonide, desoximethasone, fluocinonide, halcinonide, mometasone furoate, betamethasone valerate, fluocinonide, fluticasone propionate, triamcinolone acetonide, fluocinolone acetonide, flurandrenolide, desonide, hydrocortisone butyrate, hydrocortisone valerate, alclometasone dipropionate, flumethasone

Padagis Ex. 1029
IPR Petition - USP 11,311,482

pivolate, hydrocortisone, hydrocortisone acetate, tacrolimus, picrolimus, tazarotene, isotretinoin, cyclosporin, anthralin, vitamin D3, cholecalciferol, calcitriol, calcipotriol, tacalcitol, calcipotriene, piroxicam, diclofenac, indomethacin, imiquimod, rosiquimod, salicylic acid, alpha hydroxy acids, sulfur, rescorcinol, urea, benzoyl peroxide, allantoin, tretinoin, trichloroacetic acid, lactic acid, benzoic acid, progesterone, norethindrone, norethindroneacetate, desogestrel, drospirenone, ethynodiol diacetate, norelgestromin, norgestimate, levonorgestrel, dl-norgestrel, cyproterone acetate, dydrogesterone, medroxyprogesterone acetate, chlormadinone acetate, megestrol, promegestone, norethisterone, lynestrenol, gestodene, tibolene, testosterone, methyl testosterone, oxandrolone, androstenedione, dihydrotestosterone, estradiol, ethniyl estradiol, estiol, estrone, conjugated estrogens, esterified estrogens, estropipate, and combinations thereof.

28. A formulation as in claim 1, wherein the solidified layer is sufficiently flexible and adhesive to the skin such that when applied to the skin at a human joint, the solidified layer will remain substantially intact on the skin upon bending of the joint.

29. A formulation as in claim 1, wherein the solidified layer is sufficiently flexible and adhesive to the skin such that when applied to a curved skin surface or weight bearing surface on the body, the solidified layer will remain substantially intact on the skin upon bending or stretching of the skin surface or weight bearing surface.

30. A formulation as in claim 1, wherein the formulation is formulated to deliver the drug at a therapeutically effective rate for at least about 2 hours following the formation of the solidified layer.

31. A formulation as in claim 1, wherein the formulation is formulated to deliver the drug at a therapeutically effective rate for at least about 4 hours following the formation of the solidified layer.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

32. A formulation as in claim 1, wherein the formulation is formulated to deliver the drug at a therapeutically effective rate for at least about 8 hours following the formation of the solidified layer.

33. A formulation as in claim 1, wherein the formulation is formulated to deliver the drug at a therapeutically effective rate for at least about 12 hours following the formation of the solidified layer.

34. A formulation as in claim 1, wherein the weight ratio of the non-volatile solvent system to the solidifying agent is from about 0.1:1 to about 10:1.

35. A formulation as in claim 1, wherein the weight ratio of the non-volatile solvent system to the solidifying agent is from about 0.5:1 to about 2:1.

36. A formulation as in claim 1, wherein the volatile solvent system or the non-volatile solvent system is capable of causing human skin irritation and at least one of the at least two non-volatile solvents of the non-volatile solvent system reduces skin irritation.

37. A formulation as in claim 36, wherein the non-volatile solvent capable of reducing skin irritation includes a member selected from the group consisting of glycerin, propylene glycol, honey, and combinations thereof.

38. A formulation as in claim 1, wherein the solidified layer is formed within about 15 minutes of application to the skin surface under standard skin and ambient conditions.

39. A formulation as in claim 1, wherein the solidified layer is formed within about 5 minutes of the application to the skin surface under standard skin and ambient conditions.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

40. A formulation as in claim 1, wherein the formulation has an initial viscosity prior to skin application from about 100 cP to about 3,000,000 cP.

41. A formulation as in claim 1, wherein the formulation has an initial viscosity prior to skin application from about 1,000 cP to about 1,000,000 cP.

42. A formulation as in claim 1, wherein the volatile solvent system comprises a volatile solvent retaining substance.

43. A formulation as in claim 42, wherein the volatile solvent retaining substance is water.

44. A formulation as in claim 42, wherein the volatile solvent retaining substance is hygroscopic.

45. A formulation as in claim 42, wherein the volatile solvent retaining substance is honey, glycerol, or propylene glycol.

46. A formulation as in claim 1, wherein the weight percentage of the volatile solvent system is from about 10 wt% to about 85 wt%.

47. A formulation as in claim 1, wherein the weight percentage of the volatile solvent system is from about 20 wt% to about 50 wt%.

48. A formulation as in claim 1, wherein at least one of the at least two non-volatile solvents is included to improve compatibility with the solidifying agent.

49. A formulation as in claim 1, wherein the non-volatile solvent system is capable of generating higher flux than any single non-volatile solvent in the non-volatile solvent system alone.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

50. A formulation as in claim 1, wherein the non-volatile solvent system provides better plasticizing effect to the solidifying agent than any single non-volatile solvent in the non-volatile solvent system alone.

51. A formulation as in claim 1, wherein the solidified layer is coherent, flexible, and continuous.

52. A formulation as in claim 1, wherein the solidified layer, upon formation, is a soft, coherent solid that is peelable from a skin surface as a single piece or as only a few large pieces relative to the application size.

53. A formulation as in claim 1, wherein the non-volatile solvent system has better compatibility with the solidifying agent than any single non-volatile solvent in the non-volatile solvent system alone.

54. A formulation as in claim 1, wherein the solidified layer delivers the drug transdermally.

55. A formulation as in claim 1, wherein the solidifying agent includes polyvinyl alcohol, the volatile solvent system includes water and an alcohol solvent, and the water to polyvinyl alcohol weight ratio is from about 4:1 to about 1:1, and the water to alcohol solvent weight ratio is from about 0.33:1 to about 6:1.

56. A method of dermally delivering a drug, comprising:

a) applying an adhesive formulation as set forth in any of claims 1-53

b) solidifying the formulation to form a solidified layer on the skin surface by at least partial evaporation of the volatile solvent system; and

c) dermally delivering the drug from the solidified layer to the skin surface at a therapeutically effective rate over a sustained period of time.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

57. A method as in claim 56, wherein the step of applying includes applying the adhesive solidifying formulation at a thickness from about 0.01 mm to about 3 mm.

58. A method as in claim 56, wherein the step of applying includes applying the adhesive formulation at a thickness from about 0.05 mm to about 1 mm.

59. A method as in claim 56, wherein the solidified layer is kept on the skin for at least about 2 hours.

60. A method as in claim 56, wherein the solidified layer is kept on the skin for at least about 4 hours.

61. A method as in claim 56, wherein the solidified layer is kept on the skin for at least about 8 hours.

62. A method as in claim 56, wherein the solidified layer is kept on the skin for at least about 12 hours.

63. A method as in claim 56, further comprising the step of peeling the solidified layer from the skin after the sustained period of time to remove the solidified layer.

64. A method as in claim 56, further comprising the step of washing the solidified layer form the skin using a solvent after the sustained period of time to remove the solidified layer.

65. A solidified layer for delivering a drug, comprising:

a) a drug;

b) a non-volatile solvent system including at least one non-volatile solvent, wherein the non-volatile solvent system is capable of facilitating the

Padagis Ex. 1029
IPR Petition - USP 11,311,482

delivery of the drug at therapeutically effective rates over a sustained period of time; and

c) a solidifying agent,

wherein the solidified layer is stretchable by 5% in one direction without cracking, breaking, or separating from a skin surface to which the layer is applied,

with the proviso that the solidified layer include at least two non-volatile solvents or at least solidifying agents.

66. A solidified layer as in claim 65, wherein at least one non-volatile solvent in the non-volatile solvent system acts as a plasticizer for the solidifying agent.

67. A solidified layer as in claim 65, wherein solidified layer is sufficiently adhesive and flexible to remain substantially intact on a skin surface adjacent to a joint or muscle group where regular skin stretching occurs.

68. A solidified layer as in claim 65, wherein the weight ratio of the non-volatile solvent system to the solidifying agent is from about 0.1:1 to about 10:1.

69. A solidified layer as in claim 65, wherein the solidified layer is formed within 15 minutes of the application to the skin surface under standard skin and ambient conditions.

70. A solidified layer as in claim 65, wherein the solidified layer has a thickness from about 0.01 mm to about 3 mm.

71. A solidified layer as in claim 65, wherein the non-volatile solvent system includes at least two solvents selected from the group consisting of 1,2,6-hexanetriol, alkyltriols, alkyldiols, acetyl monoglycerides, tocopherol, alkyl dioxolanes, p-propenylanisole, anise oil, apricot oil, dimethyl isosorbide, alkyl glucosides, benzoic acid, benzyl alcohol, butyl alcohol, bees wax, benzyl

Padagis Ex. 1029
IPR Petition - USP 11,311,482

benzoate, butylene glycol, caprylic/capric triglyceride, caramel, cassia oil, castor oil, cinnamaldehyde, cinnamon oil, clove oil, coconut oil, cocoa butter, cocoglycerides, coriander oil, corn oil, coriander oil, corn syrup, cottonseed oil, cresol, cyclomethicone, diacetin, diacetylated monoglycerides, dibutyl subecate, diethanolamine, dietthylene glycol monoethyl ether, diglycerides, dipropylene glycol, ethylene glycol, eucalyptus oil, eugenol, fat, fatty acid (esters glycerides), fatty alcohols, liquid sugars, ginger extract, glycerin, high fructose corn syrup, hydrogenated castor oil, IPM, IP palmitate, isostearic acid, lemon oil, lime oil, limonene, milk, mineral oil, monoacetin, monoglycerides, nutmeg oil, oleic acid, octyldodecanol, oleyl alcohol, olive alcohol, orange oil, palm oil, polyethylene glycol (PEG), peanut oil, PEG vegetable oil, peppermint oil, petrolatum, phenol, pine needle oil, polypropylene glycol, propylene glycol, sesame oil, spearmint oil, soybean oil, trolamine, tromethemine, vegetable oil, vegetable shortening, vinyl acetate, vitamin E, wax, 2-(2-(octadecyloxy)ethoxy)ethanol, benzyl benzoate, butylated hydroxyanisole, candelilla wax, carnauba wax, ceteareth-20, cetyl alcohol, polyglyceryl, dipolyhydroxy stearate, PEG-7 hydrogenated castor oil, diethyl phthalate, diethyl sebacate, dimethicone, dimethyl phthalate, PEG fatty acid esters including PEG stearates, PEG oleates, PEG laurates, PEG fatty acid diesters including PEG dioleates, PEG distearates, PEG castor oils, glyceryl behenate, PEG glycerol fatty acid esters including PEG glyceryl laurate, PEG glyceryl stearate, PEG glyceryl oleate, hexylene glycerol, lanolin, lauric diethanolamide, lauryl lactate, lauryl sulfate, medronic acid, methacrylic acid multisterol extract, myristyl alcohol, neutral oil, PEG octyl phenyl ethers, PEG alkyl ethers including PEG cetyl ethers, PEG stearyl ethers, PEG sorbitan fatty acid esters including PEG sorbitan diisosterates, PEG sorbitan monostearates, propylene glycol fatty acid esters including propylene glycol stearate, propylene glycol caprylate/caprate, sodium pyrrolidone carboxylate, sorbitol, squalene, stear-o-wet, triacetin, triglycerides, alkyl aryl polyether alcohols, polyoxyethylene derivatives of sorbitan-ethers, saturated polyglycolyzed C8-C10 glycerides, N-methyl pyrrolidone, honey, polyoxyethylated glycerides, dimethyl sulfoxide, azone and related compounds, dimethylformamide, N-methyl formamaide, fatty alcohol ethers, alkyl-amides

Padagis Ex. 1029
IPR Petition - USP 11,311,482

(N,N-dimethylalkylamides), N-methyl pyrrolidone related compounds, sorbitan fatty acid surfactants including sorbitan monooleate, sorbitan trioleate, sorbitan monopalmitate, ethyl oleate, polyglycerized fatty acids, glycerol monooleate, glyceryl monomyristate, glycerol esters of fatty acids, and combinations thereof.

72. A solidified layer as in claim 65, wherein the solidifying agent includes at least one member selected from the group consisting of ammonia methacrylate, carrageenan, cellulose, cellulose derivatives including cellulose acetate phthalate aqueous, carboxymethylcellulose, methyl cellulose, hydroxyethylcellulose, ethylcellulose, hydroxypropylcellulose, cellulose acetate (microcrystalline), and cellulose polymers, carboxy polymethylene, xantham gum, divinyl benzene styrene, ethylene vinyl acetate, silicone, polyisobutylene, Shellac (FMC BioPolymer), guar gum, guar rosin, hypromellose phthalate, methyl acrylate, microcrystalline wax, polyvinyl alcohol, polyvinyl acetate, polyvinyl acetate phthalate, PVP ethyl cellulose, polyvinyl pyrrolidone (PVP), acrylate, polyethylene glycol/polyvinyl pyrrolidone copolymers, trimethyl siloxysilicate, maleic acid/anhydride copolymers, polacrilin, poloxamer, polyethylene oxide, poly glactic acid /poly-l-lactic acid, turpene resin, locust bean gum, prolamine (Zein), acrylic copolymers, polyurethane dispersions, gelatin, dextrin, starch, polyvinyl alcohol/polyethylene glycol copolymers, methyacrylic acid/ethyl acrylate copolymers, methacrylic acid and methacrylate based polymers including poly(methacrylic acid) copolymers and methylmethacrylate copolymers, esters of polyvinylmethylether/maleic anhydride copolymers, methyacrylic acid-ethyl acrylate copolymers, copolymers of methyl vinyl ether and maleic anhydride, aminoalkyl methacrylate copolymers, ammonioalkyl methacrylate copolymers, and combinations thereof.

73. A solidified layer as in claim 65, wherein the solidified layer is formulated to deliver the drug at a therapeutically effective rate for at least about 2 hours.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

74. A solidified layer as in claim 65, wherein the solidified layer is formulated to deliver the drug at a therapeutically effective rate for from 2 to 12 hours.

75. A solidified layer as in claim 65, wherein the formulation is formulated to deliver the drug at a therapeutically effective rate for at least about 12 hours.

76. A solidified layer as in claim 65, wherein the solidified layer is a soft, coherent solid that is peelable from a skin surface as a single piece or as only a few large pieces relative to the application size.

77. A solidified layer as in claim 65, wherein the solidified layer is at least substantially devoid of volatile solvents, including water and any solvent less volatile than water.

78. A solidified layer as in claim 65, wherein the solidified layer is substantially devoid of water and solvents more volatile than water when the solidified layer contains no more than 10 wt% of water and solvents more volatile than water.

79. A solidified layer as in claim 65, wherein the solidified layer is substantially devoid of water and solvents more volatile than water when the solidified layer contains no more than 5 wt% of water and solvents more volatile than water.

80. A solidified layer as in claim 65, wherein the solidified layer is adhesive to the skin surface on one surface, and is non-adhesive on an opposing surface.

81. A solidified layer as in claim 65, wherein the solidified layer is flux-enabling for the drug.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

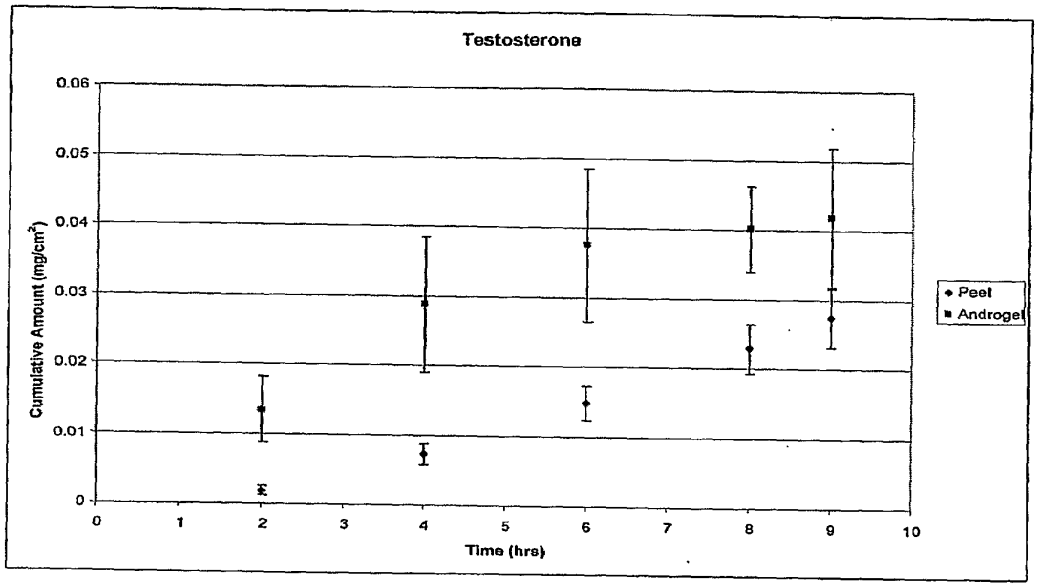


FIG. 1

Padagis Ex. 1029
IPR Petition - USP 11,311,482

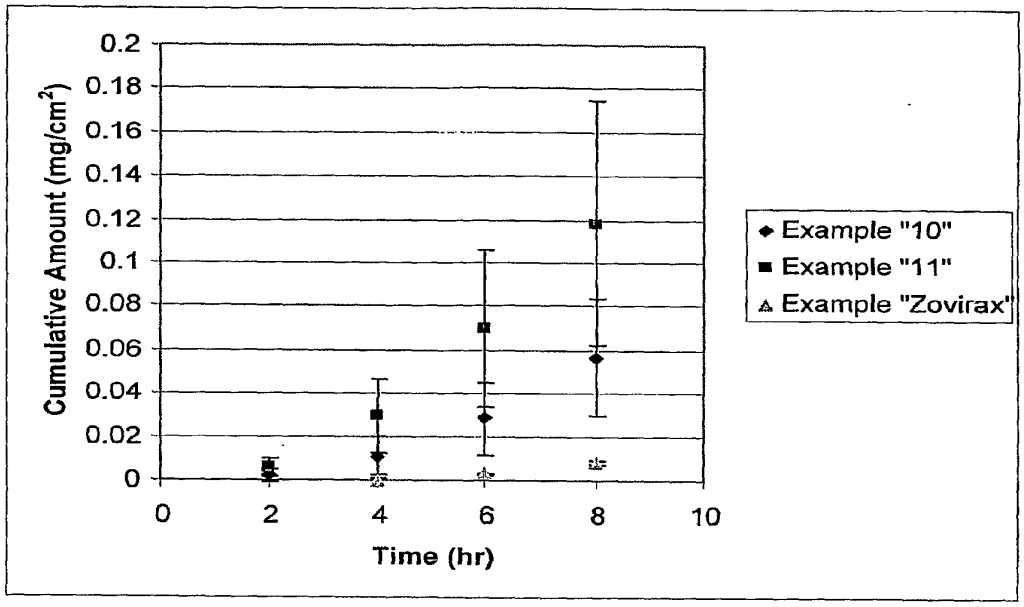


FIG. 2

Padagis Ex. 1029
IPR Petition - USP 11,311,482

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(54) **Title:** DJCARBOXYLIC ACID FOAMABLE VEHICLE AND PHARMACEUTICAL COMPOSITIONS THEREOF

(57) **Abstract:** The present invention teaches a foamable pharmaceutical carrier comprising a benefit agent, selected from the group consisting of a dicarboxylic acid and a dicarboxylic acid ester; a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; a solvent selected from the group consisting of water, a hydrophilic solvent, a hydrophobic solvent, a potent solvent, a polar solvent, a silicone, an emollient, and mixtures thereof, wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients. The invention further relates to a foamable composition further containing a liquefied hydrocarbon gas propellant.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

DICARBOXYLIC ACID FOAMABLE VEHICLE AND PHARMACEUTICAL COMPOSITIONS THEREOF

BACKGROUND OF THE INVENTION

[0001] This invention relates to foamable pharmaceutical and cosmetic compositions.

[0002] External topical administration is an important route for the administration of drugs in disease treatment. Many groups of drugs, including, for example, antibiotic, anti-fungal, anti-inflammatory, anesthetic, analgesic, anti-allergic, corticosteroid, retinoid and anti-proliferative medications are preferably administered in hydrophobic media, namely ointment. However, ointments often form an impermeable barrier, so that metabolic products and excreta from the wounds to which they are applied are not easily removed or drained away. Furthermore, it is difficult for the active drug dissolved in the carrier to pass through the white petrolatum barrier layer into the wound tissue, so the efficacy of the drug is reduced. In addition, ointments and creams often do not create an environment for promoting respiration of the wound tissue and it is not favorable to the normal respiration of the skin. An additional disadvantage of petroleum jelly-based products relates to the greasy feeling left following their topical application onto the skin, mucosal membranes and wounds.

[0003] Foams are considered a more convenient vehicle for topical delivery of active agents. There are several types of topical foams, including aqueous foams, such as commonly available shaving foams; hydroalcoholic foams, emulsion-based foams, comprising oil and water components, and oleaginous foams, which consist of high oil content. In skin therapy, oil containing foams are preferred, since oil contributes to skin protection and moisturization, which improve the therapeutic effect of the formulation.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

[0004] Dicarboxylic acids are known to possess therapeutic properties. Dicarboxylic acids, and their mercapto, ester and salt derivatives have been used in the treatment of a variety of skin disorders and/or conditions.

[0005] Azelaic acid (AZA) is a naturally occurring nine carbon straight chain molecule with two terminal carboxyl groups. AZA is an anti-keratinizing agent, displaying antiproliferative effects on keratinocytes and modulating the early and terminal phases of epidermal differentiation. AZA is a competitive inhibitor of the reduction of testosterone to dihydrotestosterone, and as such is supposed to reduce the production of sebum in the sebaceous gland. Furthermore, recent investigations have demonstrated that AZA and sebacic acid also have anti-bacterial and anti-fungal properties. Structure-activity relationship studies have revealed that these effects are retained when the dicarboxylic acid has a backbone of about 6 to about 14 carbons.

[0006] Dicarboxylic acid esters are also known to contribute to the skin penetration of an active agent. Enhancing effects on skin penetration of methyl nicotinate have been observed with dibutyl adipate and dioctyl adipate. Diisopropyl sebacate also markedly enhances the skin penetration of the erythromycin. The skin penetration enhancing properties of mono- or di-esters of dicarboxylic acid, including dibutyl adipate, diethyl sebacate, diisopropyl dimerate, diisopropyl adipate, diisopropyl sebacate and dioctyl succinate have been recognized.

[0007] There remains an unmet need for improved, easy to use, stable oil-containing foam formulations, containing oils, which effectively deliver and/or deposit various benefit agents into and onto the skin and/or other target sites and are relatively non-irritating and thus suitable for use by people having sensitive skin and eyes.

SUMMARY

[0008] The present invention relates to aqueous and non aqueous stable compositions comprising a dicarboxylic acid or ester derivative thereof in which

the dicarboxylic acid or ester derivative is a stabilizing emollient and or has a therapeutic effect.

[0009] There is provided a pharmaceutical or cosmetic composition comprising:

a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

   i. a dicarboxylic acid; and

   ii. a dicarboxylic acid ester;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

c. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

[0010] There is also provided a foamable composition as described above wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition, is substantially flowable and provides a foam upon release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

[0011] There is also provided a therapeutic composition comprising:

a. a therapeutically effective amount of an active agent;

b. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

   i. a dicarboxylic acid; and

   ii. a dicarboxylic acid ester;

c. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

d. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

[0012] There is also provided a method of treating a disorder of a mammalian subject, comprising:

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

e. a therapeutically effective amount of an active agent;

f. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

g. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

h. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

[0013] There is also provided a pharmaceutical or cosmetic non aqueous composition comprising:

a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

   i. a dicarboxylic acid; and

   ii. a dicarboxylic acid ester;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

c. a solvent selected from the group consisting of a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

[0014] There is also provided a therapeutic composition comprising:

a. a therapeutically effective amount of an active agent wherein the active agent is substantially insoluble in water;

b. a beneficially or therapeutically effective concentration of at least one benefit agent, comprising a dicarboxylic acid ester in which the active agent is substantially soluble;

c. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

d. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

[0015] There is also provided a foamable composition comprising:

a. a liquid dicarboxylic acid ester, said ester having emollient properties;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

c. an active agent, said active agent soluble in or having enhanced penetration due to the dicarboxylic acid;

wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

[0016] There is also provided a foamable composition comprising:

a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. an ester-based or ether-based surfactant;

c. a solvent selected from the group consisting of a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the composition is substantially free of polymeric material, and

wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

[0017] There is also provided a pharmaceutical or cosmetic composition comprising:

a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

c. a solvent selected from the group consisting of a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the composition is substantially free of water; and

wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

[0018] There is also provided a formulation of any of the compositions described above wherein the composition is in a non foam state.

[0019] There is also provided a formulation of any of the compositions described above for use in the manufacture of a medicament.

DETAILED DESCRIPTION

[0020] The present invention relates to a composition comprising a benefit agent, selected from the group consisting of (i) a dicarboxylic acid; and (ii) a dicarboxylic acid ester for use as vehicle composition.

[0021] According to one or more embodiments of the present invention, the composition includes:

a. a benefit agent, selected from the group consisting of

   i. a dicarboxylic acid; and

   ii. a dicarboxylic acid ester;

b. a surface-active agent;

c. about 0.01% to about 5% by weight of at least one polymeric agent selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent; and

d. water.

10

Padagis Ex. 1029
IPR Petition - USP 11,311,482

[0022] The present invention further relates to a foamable composition including:

a. a benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. a surface-active agent;

c. about 0.01% to about 5% by weight of at least one polymeric agent selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

d. water; and

e. liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition.

[0023] In one or more embodiments there is provided a pharmaceutical or cosmetic composition comprising:

a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

c. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

Padagis Ex. 1029
IPR Petition - USP 11,311,482

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients;

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

[0024] In one or more embodiments there is provided a foamable composition which produces a foam upon release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

[0025] In one or more embodiments there is provided a composition wherein the benefit agent, stabilizer and solvent are selected to generate an emulsion that is substantially resistant to phase reversal.

[0026] In one or more embodiments there is provided a composition wherein, the benefit agent, stabilizer and solvent are selected to generate a single phase.

[0027] In one or more embodiments there is provided a composition wherein, the benefit agent, stabilizer and solvent are selected to generate a substantially uniform suspension of benefit agent crystals.

[0028] In one or more embodiments there is provided a composition, wherein the breakable foam comprises micro or nano particles, crystals or bodies.

[0029] In one or more embodiments there is provided a composition, which is substantially resistant to one or more Freeze-Thaw cycles (FTC).

[0030] In one or more embodiments there is provided a composition wherein the surface-active agent is a solid, a liquid or a mixture thereof.

[0031] In one or more embodiments there is provided a composition wherein the surface active agent is selected from the group consisting of a polysorbate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, a polyoxyethylene fatty acid ester, Myrj 45, Myrj 49, Myrj 52 and Myrj 59; a polyoxyethylene alkylyl ether, polyoxyethylene cetyl ether, polyoxyethylene palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, brij 38, brij 52, brij 56 and brij W1, a sucrose ester, a partial ester of sorbitol, sorbitan monolaurate, sorbitan monolaurate a monoglyceride, a diglyceride, isoceteth-20, a sucrose ester, or selected from the group consisting of steareth 2, glyceryl monostearate/PEG 100 stearate, Glyceryl Stearate, Steareth-21, peg 40 stearate, polysorbate 60, polysorbate 80, sorbitan stearate, laureth 4, Sorbitan monooleate, ceteareth 20, steareth 20, ceteth 20, Macrogol Cetostearyl Ether, ceteth 2, PEG-30 Dipolyhydroxystearate, sucrose distearate, polyoxyethylene (100) stearate, PEG 100 stearate, laureth 4, cetomacrogol ether, Cetearyl alcohol, Cetearyl glucoside, Oleyl alcohol, Steareth-2, Diisopropyl adipate, Capric/caprilic triglicerides, Polysorbate 20; Montanov 68 (CETEARYL ALCOHOL (and) CETEARYL GLUCOSIDE.), Sharonmix 824(a liquid blend of methyl paraben, ethyl paraben and propyl paraben - in phenoxyethanol), Simusol 165 (Glyceryl stearate and PEG-100 stearate). Methyl glucose sequistearate, Peg 30 dipolyhydroxystearate, sucrose stearic acid esters, sorbitan laureth, sorbitan stearate and mixtures thereof.

[0032] In one or more embodiments there is provided a composition wherein the surface active agent comprises at least one ester based surfactant or at least one ether based surfactant.

[0033] In one or more embodiments there is provided a composition wherein the surface active agent is reduced about in proportion to the increase in dicarboxylic ester.

[0034] In one or more embodiments there is provided a composition wherein the stabilizer is not a polymeric agent.

[0035] In one or more embodiments there is provided a composition wherein the surface active agent comprises a non-ionic surfactant that does not contain a polyoxyethylene (POE) moiety.

[0036] In one or more embodiments there is provided a composition wherein the surface active agent is selected from the group consisting of a non-ethoxylated sorbitan ester, a glycerol fatty acid ester, a sucrose ester and an alkyl polyglycoside or is selected from the group consisting of sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate, sorbitan sesquioleate, glycerol monostearate, glycerol monooleate, sucrose stearate, sucrose distearate, sucrose palmitate sucrose laurate and lauryl diglucoside.

[0037] In one or more embodiments there is provided a composition wherein the polymeric agent is selected from the group consisting of carbopol 934, pemulen TR2, klucel EF, xanthan gum, methocel A4M, and carboxy methyl cellulose or 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 aluminum starch octenylsuccinate (ASOS), PEG 1000, PEG 4000, PEG 6000 and PEG 8000.

[0038] In one or more embodiments there is provided a composition wherein the polymeric agent is a derivatized polymer.

[0039] In one or more embodiments there is provided a composition wherein the derivatized polymer is a polymeric emulsifier.

[0040] In one or more embodiments there is provided a composition wherein the benefit agent is selected from the group consisting of diisopropyl adipate, dimethyl sebacate, dioctyl malate, diethyl sebacate, azelaic acid and TU-2100.

[0041] In one or more embodiments there is provided a composition wherein, further comprising an additional active agent.

[0042] In one or more embodiments there is provided a composition wherein the dicarboxylic acid has the molecular formula $HOOC-(CH_2)_n-COOH$; and wherein n is in the range between 0 and 32.

[0043] In one or more embodiments there is provided a composition wherein n is in the range between 4 and 10.

[0044] In one or more embodiments there is provided a composition 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 and dodecanedioic acid, maleic acid and fumaric acid.

[0045] In one or more embodiments there is provided a composition wherein the dicarboxylic acid is selected from the group consisting of adipic acid, azelaic acid and sebacic acid.

[0046] In one or more embodiments there is provided a composition wherein further containing a foam adjuvant selected from the group consisting of a fatty alcohol having 15 or more carbons in their carbon chain; a fatty acid having 16 or more carbons in their carbon chain; fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain; a fatty alcohol having at least one double bond; a fatty acid having at least one double bond; a branched fatty alcohol; a branched fatty acid and a fatty acid substituted with a hydroxyl group.

[0047] In one or more embodiments there is provided a composition wherein further containing at least one organic carrier selected from the group consisting of a hydrophobic organic carrier, an emollient and mixtures thereof, at a concentration of about 2% to about 50% by weight.

[0048] In one or more embodiments there is provided a composition wherein the dicarboxylic acid or dicarboxylic acid ester is in a concentration between about 0.1% and about 60%.

[0049] In one or more embodiments there is provided a composition wherein the dicarboxylic acid is azelaic acid, and wherein the concentration of azelaic acid is between 5% and 25%.

[0050] In one or more embodiments there is provided a composition wherein the pH of the composition is below the first pKa of the dicarboxylic acid.

[0051] In one or more embodiments there is provided a composition wherein the pH of the composition is between the first and second pKa of the dicarboxylic acid.

[0052] In one or more embodiments there is provided a composition wherein the pH of the composition is above the second pKa of the dicarboxylic acid.

[0053] In one or more embodiments there is provided a composition wherein the dicarboxylic acid is azelaic acid the pH of the composition is below 5.3.

[0054] In one or more embodiments there is provided a composition wherein the dicarboxylic acid is azelaic acid the pH of the composition is between about 4.5 and about 5.3.

[0055] In one or more embodiments there is provided a composition wherein the dicarboxylic acid ester is selected from the group consisting of a mono ester of said dicarboxylic acid, and a diester of the dicarboxylic acid.

[0056] In one or more embodiments there is provided a composition wherein the alcohol moiety of the dicarboxylic acid ester is selected from the group consisting of an alkyl alcohol, an aryl alcohol, methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, isobutyl alcohol, t-butyl alcohol, pentyl alcohol, hexyl alcohol, octyl alcohol, decyl alcohol, capryl alcohol, phenol and benzyl alcohol.

[0057] In one or more embodiments there is provided a composition wherein the alcohol moiety of the dicarboxylic acid ester is a biologically active alcohol.

[0058] In one or more embodiments there is provided a composition wherein the biologically active alcohol is selected from the group consisting of a hydroxyalkylbenzoate, salicylic acid, a dihydroxybenzene, hydroxytoluene, an alpha-hydroxy acid, retinol, a vitamin A derivative, a steroid, vitamin E, a vitamin E derivative, vitamin D and a vitamin D derivative.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

[0059] In one or more embodiments there is provided a composition wherein the dicarboxylic acid ester is selected from the group consisting of diisobutyl adipate, diisopropyl adipate, diisopropyl sebacate, diisosteary dimer dilinoleate, diisostearyl fumerate, diisopropyl dimerate, diethyl adipate, diethyl sebacate, diethylhexyl adipate, diethylhexyl malate, dioctyl malate, diethyl succinate, and dioctyl sebacate.

[0060] In one or more embodiments there is provided a composition wherein the dicarboxylic acid ester is diisopropyl adipate, in an amount from about 0.1% to about 60%

[0061] In one or more embodiments there is provided a composition wherein the organic carrier is selected from the group consisting of mineral oil, triglycerides, medium chain triglyceride (MCT) oil, capric/caprylic triglyceride, alkyl esters of fatty acids such as isopropyl palmitate, isopropyl myristate, isopropyl isostearate, poly propylene glycol 15-stearly ether, 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, maleated soybean oil, 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 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.

[0062] In one or more embodiments there is provided a composition wherein the organic carrier comprises a polypropylene glycol alkyl ether.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

[0063] In one or more embodiments there is provided a composition further containing at least one polar solvent.

[0064] In one or more embodiments there is provided a composition wherein the polar solvent is selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, other glycols, oleyl alcohol, alpha-hydroxy acids, such as lactic acid and glycolic acid, sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformanide, methyl dodecyl sulfoxide, dimethylacetamide, azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, alkanols, such as dialkylamino acetates, and admixtures thereof.

[0065] In one or more embodiments there is provided a composition wherein the organic carrier is capric/caprylic triglyceride and wherein the dicarboxylic acid is azelaic acid.

[0066] In one or more embodiments there is provided a composition wherein the polar solvent is selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid wherein the dicarboxylic acid is azelaic acid.

[0067] In one or more embodiments there is provided a composition wherein the organic carrier is capric/caprylic triglyceride.

[0068] In one or more embodiments there is provided a composition wherein the organic solvent comprises at least one organic carrier, selected from the group capric/caprylic triglyceride, a polypropylene glycol alkyl ether an ester of a fatty acid and mineral oil and wherein the dicarboxylic acid ester is diisopropyl adipate .

[0069] In one or more embodiments there is provided a composition further comprising a polar solvent, selected from the group consisting of dimethyl

isosorbide, glycerol, propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid.

[0070] In one or more embodiments there is provided a composition wherein the benefit agent, stabilizer and solvent are selected to generate an emulsion that can produce a substantially strong and closed packed barrier between the oil and the water phases whilst maintaining a fluid constitution

[0071] In one or more embodiments there is provided a composition further comprising an additional component selected from the group consisting of a modulating agent, a polar solvent, 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 pH-adjusting agent, a preservative, a skin penetration enhancer, a sunscreen, a sun blocking agent, a sunless tanning agent, and a vitamin.

[0072] In one or more embodiments there is provided a composition wherein the organic carrier is selected from the group consisting of PPG 15-stearyl ether, isopropyl myristate and medium chain triglyceride oil and capric/caprylic triglyceride and the benefit agent is a solid at ambient temperature.

[0073] In one or more embodiments there is provided a therapeutic composition comprising therapeutically effective amount of an active agent; and a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of:

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester

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, antibacterials, antibiotics, antiburn agents, anticancer agents, antidandruff agents, antidepressants, antidermatitis agents, antiedemics, antihistamines, antihelminths, antihyperkeratolyte agents, antiinflammatory agents, antiirritants, antilipemics, antimicrobials, antimycotics, antiproliferative agents, antioxidants, anti-wrinkle agents, antipruritics, antipsoriatic agents, antirosacea agents antiseborrheic agents, antiseptic, antiswelling agents, antiviral agents, antiyeast agents, 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, skin whitening agents, vasoconstrictors, vasodilators, vitamins, vitamin D derivatives, wound healing agents and wart removers.

[0074] In one or more embodiments there is provided a foamable therapeutic composition wherein the dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the active agent.

[0075] In one or more embodiments there is provided a foamable therapeutic composition wherein the active agent is a steroid.

[0076] In one or more embodiments there is provided a foamable therapeutic composition wherein the steroid is selected from the group consisting of bydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethsone dipropionate, clobetasol valemate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone,

Padagis Ex. 1029
IPR Petition - USP 11,311,482

halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortmate, mepreddisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone.

[0077] In one or more embodiments there is provided a foamable therapeutic composition wherein the active agent is an immunomodulator.

[0078] In one or more embodiments there is provided a foamable therapeutic composition, wherein the immunomodulator is selected from the group consisting of a cyclic peptides, cyclosporine, tacrolimus, tresperimus, pimecrolimus, sirolimus, verolimus, laflunimus, laquinimod and imiquimod.

[0079] In one or more embodiments there is provided a foamable therapeutic composition, wherein the dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the immunomodulator.

[0080] In one or more embodiments there is provided a foamable therapeutic composition, wherein the dicarboxylic acid ester is diisopropyl adipate.

[0081] In one or more embodiments there is provided a composition wherein the surface active agent comprises a non-ionic surfactant that does not contain a polyoxyethylene (POE) moiety.

[0082] In one or more embodiments there is provided a composition wherein the surface active agent is selected from the group consisting of a non-ethoxylated sorbitan ester, a glycerol fatty acid ester,a sucrose ester and an alkyl polyglycoside or is selected from the group consisting of sorbitan

Padagis Ex. 1029
IPR Petition - USP 11,311,482

monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate, sorbitan sesquioleate, glycerol monostearate, glycerol monooleate, sucrose stearate, sucrose distearate, sucrose palmitate sucrose laurate and lauryl diglucoside.

[0083] In one or more embodiments there is provided a composition wherein the dicarboxylic acid is azelaic acid.

[0084] In one or more embodiments there is provided a composition wherein the dicarboxylic acid is azelaic acid and further comprising an organic solvent comprising capric/caprylic triglyceride.

[0085] In one or more embodiments there is provided a composition wherein the dicarboxylic acid is azelaic acid and further comprising an organic solvent comprising capric/caprylic triglyceride and further comprising at least one polar carrier, selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid.

[0086] In one or more embodiments there is provided a method of treating a disorder of a mammalian subject, comprising:

administering a foamable therapeutic composition to a target site, the composition comprising a therapeutically effective amount of an active agent; and a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

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.

[0087] In one or more embodiments there is provided a method of treating a disorder of a mammalian subject,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, granuloma 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; and wherein the active agent is suitable for treating said disorderm or is selected from the group consisting of chlamydia infection, gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranuloma venereum, mucopurulent cervicitis (MPC), molluscum contagiosum, nongonococcal urethritis (NGU), trichomoniasis, vulvar disorders, vulvodynia, vulvar pain, yeast infection, vulvar dystrophy, vulvar intraepithelial neoplasia (VIN), contact dermatitis,

Padagis Ex. 1029
IPR Petition - USP 11,311,482

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.

[0088] In one or more embodiments there is provided a method of treating a disorder of a mammalian subject,wherein the disorder is a dermatological disorder, which can be treated by a dicarboxylic acid or dicarboxylic acid ester.

[0089] In one or more embodiments there is provided a method of treating a disorder of a mammalian subject, wherein the disorder is a dermatological disorder, which can be treated by a topical steroid, an immunomodulator or an anti-infective agent.

[0090] In one or more embodiments there is provided a method of treating a disorder of a mammalian subject, wherein the disorder is selected from atopic dermatitis and psoriasis; and the active agent is selected from (i) steroid; and (ii) a combination of steroid and an additional non-steroidal active agent.

[0091] In one or more embodiments there is provided a method of treating a disorder of a mammalian subject, wherein the disorder is selected from psoriasis and atopic dermatitis and the active agent comprises an immunomodulator.

[0092] In one or more embodiments there is provided a therapeutic composition comprising: a therapeutically effective amount of an active agent wherein the active agent is substantially insoluble in water; and a beneficially or therapeutically effective concentration of at least one benefit agent, comprising a dicarboxylic acid ester in which the active agent is substantially soluble; wherein the benefit agent, stabilizer and solvent are selected to

Padagis Ex. 1029
IPR Petition - USP 11,311,482

generate an emulsion that can produce a substantially strong and closed packed barrier between the oil and the water phases whilst maintaining a fluid constitution.

[0093] In one or more embodiments there is provided a foamable composition comprising: a liquid dicarboxylic acid ester, said ester having emollient properties; a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof, an active agent, said active agent soluble in or having enhanced penetration due to the dicarboxylic acid; wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release

[0094] In one or more embodiments the stabilizer comprises a ether-based or ester-based surfactant.

[0095] In one or more embodiments the stabilizer comprises an alkyl-derivatized polymer having polymeric emulsifying properties.

[0096] In one or more embodiments the composition is an oil in water emulsion.

[0097] In one or more embodiments the dicarboxylic acid ester comprises about or more than 50 wt% of the composition.

[0098] In one or more embodiments the active agent is otherwise insoluble or unstable, but is solubilized or stabilized by DCA.

[0099] In one or more embodiments the composition is substantially free of water

In one or more embodiments the composition is in a non foam state.

[0100] In one or more embodiments there is provided a pharmaceutical or cosmetic composition comprising:

a. a benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. a surface-active agent;

c. about 0.01% to about 5% by weight of at least one polymeric agent selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent; and

d. water.

[0101] All % values are provided on a weight (w/w) basis.

Dicarboxylic acid and esters thereof

[0102] In an embodiment of the present invention, the organic carrier comprises an ester of a dicarboxylic acid. In the context of the present invention, a dicarboxylic acid is an organic material, having two carboxylic acid moieties on its carbon atom skeleton. They have the general molecular formula HOOC-$(CH_2)_n$-COOH.

[0103] Non limiting examples of some elementary dicarboxylic acids (DCA's) are succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid, phthalic acid, isophthalic acid, terephthalic acid.

[0104] In an embodiment of the present invention, the dicarboxylic acid is a short-chain dicarboxylic acid. The simplest Short-chain dicarboxylic acid are oxalic acid (n=0), malonic acid (n=1), succinic acid (n=2) and glutaric acid (n=3).

[0105] Additional members of dicarboxylic acid group are derived from natural products or from synthesis, having "n" value from 4 up to 21. In one or more

embodiments of the present invention, the dicarboxylic acid is selected from the group consisting of adipic acid (hexanedioic acid; n=4), pimelic acid (heptanedioic acid; n=5), suberic acid (octanedioic acid; n=6), azelaic acid (nonanedioic acid; n=7), sebacic acid (decanedioic acid; n=8) and dodecanedioic acid (n=10).

[0106] In an additional embodiment, the dicarboxylic acid contains 10 to 32 carbon atoms in their carbon atom skeleton, such as brassylic acid (n=11), thapsic acid (n=14), 14-methylnonacosanedioic acid (C29) and 14,15-dimethyltriacontanedioic acid (C30).

[0107] The carbon atom skeleton of the dicarboxylic acid can be saturated or unsaturated, such as in the case of maleic acid and fumaric acid.

[0108] In general terms non-esterified dicarboxylic acids are usually solid at ambient temperature. Non limiting examples of solid DCA's are oxalic, malonic glutaric, sebacic , phthalic and azaleic acid. Similarly, in general terms DCA's with short carbon chain skeleton are water soluble, such as oxalic, malonic, and succinic acid. Longer chain DCA's like adipic acid and having up to 10 carbon atoms in the carbon chain are slightly soluble in water. Also non "simple" DCA's are generally solid at ambient temperature , insoluble in water, and are usually more oil soluble than their parent DCA's

[0109] An ester of a dicarboxylic acid is a chemical compound produced by the reaction between a dicarboxylic acid and at least one alcohol, with the elimination of a molecule of water. The reaction of a dicarboxylic acid with one alcohol molecule results in a mono ester of a dicarboxylic acid. The reaction of a dicarboxylic acid with two alcohol molecules results in a diester of the dicarboxylic acid.

[0110] DCA esters are typically hydrophobic and generally insoluble in water. Most simple esters of DCA are liquid. By simple it is meant that the alcohol moiety linked to the DCA is a straight or branched alkyl chain. Examples of liquid simple diesters are dimethyl phthalate, diethyl phthalate, dibutyl phthalate, diethyl

Padagis Ex. 1029
IPR Petition - USP 11,311,482

sebacate, dibutyl sebacate, and diisopropyl adipate. Aromatic diesters of pthalic, isopthalic and therephalic acids are in the range of slightly soluble to insoluble.

[0111] The alcohol molecule, to be linked to the dicarboxylic acid, can be selected from the group of an alkyl an aryl alcohol. Exemplary alcohol, suitable according to the present invention include methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, isobutyl alcohol, t-butyl alcohol, pentyl alcohol, hexyl alcohol, octyl alcohol, decyl alcohol, capryl alcohol, phenol, benzyl alcohol and the like.

[0112] In one or more embodiments, the alcohol is a biologically active alcohol. In an embodiment, biologically active alcohol possesses keratolytic activities. Examples of keratolytically active alcohol suitable according to the present invention include ortho-, meta- and para-hydroxyalkylbenzoate, salicylic acid, ortho-, meta-, and para-dihydroxybenzene, ortho-, meta-, and para-hydroxytoluene, alpha-hydroxy acid, retinol, and derivatives thereof such as provided in U.S. Pat. 6,180,669, which is incorporated herein by reference. In another embodiment, the biologically active alcohol is selected from the group consisting of steroidal hormones, steroidal anti-inflammatory agents, vitamin E and vitamin D, such as provided in U.S. Pat. Appl. 20040191196, which is incorporated herein by reference.

[0113] In an embodiment of the present invention, the dicarboxylic acid is incorporated in the foamable composition in a safe and effective amount. The term "safe and effective" means an amount of an active agent that exerts a therapeutic effect on a specific disorder, without causing adverse effects that may prohibit the use of said active agent in the treatment of said disorder. The dicarboxylic acid can be incorporated in the foamable composition of the present invention in a concentration between about 0.1% and about 25%, more preferably between about 1% and about 20%.

[0114] In an embodiment of the present invention, the dicarboxylic acid is azelaic acid, and its concentration in the composition is between 5% and 25%, or between 10% and 20%.

[0115] In one or more embodiment, the dicarboxylic acid is present in the composition in an ionized state. The first and second pKa values for a dicarboxylic acid are different from one another. Depending on the pH of the composition and the specific first and second pKa of the dicarboxylic acid, said dicarboxylic acid can be non-ionized (both carboxy groups are in their acid state); semi-ionized (one carboxy group is in an acid state and the second is in an anionic state); or doubly-ionized, wherein both carboxy groups are anionic. For example, in maleic acid the first pKa is 1.9 and the second pKa is 4.4. Therefore, if the pH of the composition is between about 2 and about 4.3, the maleic acid is mostly semi-ionized and at pH above 4.5 the maleic acid is mostly doubly-ionized. Likewise, in the case of azelaic acid the first pKa is about 4.5 and the second pKa is about 5.3. Therefore, if the pH of the composition is below 4.5, the azelaic acid is non-ionized; between about 4.5 and about 5.3, it is mostly semi-ionized and at a pH above 5.3, the azelaic acid is mostly doubly-ionized.

[0116] The ionization state of the dicarboxylic acid has influence on its therapeutic potential. On one hand, if the dicarboxylic acid is doubly anionic, its penetration into the skin will be very low, due to the lipophilic nature of the skin. On the other hand, the non-ionic state is available at very low (acidic) pH values, which can cause skin irritation.

[0117] Hence, in one or more embodiments, the pH of the composition is adjusted to a value between the first and second pKa values of the dicarboxylic acid. For example, in the case of azelaic acid, the pH is adjusted in the range from about 2.0 to about 4.5, preferably in the range from about 3.0 to about 4.5. Thus, in an embodiment of the present invention, the dicarboxylic acid is azelaic acid, and the pH of the composition is adjusted in the range from about 4.0 to about 6.0, preferably in the range from about 4.5.0 to about 5.3.

30

Padagis Ex. 1029
IPR Petition - USP 11,311,482

[0118] Dicarboxylic acid esters are considered excellent emollients and their inclusion in a composition which is intended for topical application contributes to the overall improvement of skin condition. Emollient dicarboxylic esters typically include an alkyl alcohol moiety, wherein said alkyl alcohol has a carbon chain of at least one or two or more carbon atoms. In certain embodiments, the alkyl alcohol is a branched alkyl, such as isopropyl alcohol; and in other embodiments the alkyl alcohol has a long carbon backbone, e.g., a carbon chain length of 6-18.

[0119] Dicarboxylic acid esters can be complex substances. One example is TU 2100 (Nonanedioic acid, bis[(2-(ethoxycarbonyl)phenyl] ester). It is also known as Azelaoyl di(ethyl salicylate) and has a CAS Registry Number: [207972-39-2] and is a solid. TU-2100 is a "non-simple" diester; with a high molecular weight, and a melting point of 34-36, which is relatively low with reference to its molecular weight.

[0120] Non-limiting examples of emollient dicarboxylic acid esters include diisobutyl adipate, diisopropyl adipate, diisopropyl sebacate, diisosteary dimer dilinoleate, diisostearyl fumerate, diisopropyl dimerate, diethyl adipate, diethyl sebacate, diethylhexyl adipate, diethylhexyl malate, dioctyl malate, diethyl succinate, and dioctyl sebacate. Other diccarboxylic acid esters are dimethyl phthalate, diethyl phthalate, diethyl sebacate, diisopropyl dimerate, dibutyl sebacate, dibutyl phthalate and dioctyl phthalate. Additionally dicarboxylic acid esters are capable of solubilizing active components which are difficult to dissolve by other oils. Furthermore, certain dicarboxylic acid esters, such as diisopropyl adipate and dimethyl sebacate are known to enhance the skin penetration of active agents. Hence in an embodiment of the present invention, the dicarboxylic acid ester is incorporated in the foamable composition in an amount, suitable to exert its emollient effect, solubilizing effect or skin penetration enhancing effect. In one or more embodiments, the dicarboxylic acid ester is incorporated in the foamable composition of the present invention in a concentration between about 0.1% and about 30%, more preferably between about 1% and about 25%.

[0121] In one embodiment, the dicarboxylic acid ester is diisopropyl adipate (DISPA), in an amount between about 0.1% and about 30%, or about 1% and about 25%.

[0122] As can be appreciated by the discussion above, there is a varied range of dicarboxylic acids and esters; some are soild, some are liquid, some are water soluble, some are slightly soluble and others are insoluble in water. There is also a varied range of functions and physical properties. Some are active agents and others are solvents and some are penetration enhancers. The challenges of making a uniform solution of solid DCA's wihout crystal formation or precipitation or a uniform suspension of insoluble agent, or using a DCA to solubilise a substance which is otherwise insoluble or as an emollient or as a penetration enhancer or more than one of them are as varied as their different natures and properties as may be appreciated by a man of the art. In other words each agent has its own properties and challenges which are interrelated to the objectives and other ingredients of the formulation

[0123] The sensory properties of foams containing a dicarboxylic acid or a dicarboxylic acid ester are favorable, as revealed by consumer panel tests.

Foam adjuvant

[0124] Optionally, the foamable vehicle further includes a foam adjuvant selected from the group consisting of a fatty alcohol having 15 or more carbons in their carbon chain; a fatty acid having 16 or more carbons in their carbon chain; fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain; a fatty alcohol having at least one double bond; a fatty acid having at least one double bond; a branched fatty alcohol; a branched fatty acid and a fatty acid substituted with a hydroxyl group.

Additional organic carrier

[0125] Optionally, the foamable vehicle further includes at least one additional organic carrier selected from the group consisting of a hydrophobic organic carrier, an emollient and mixtures thereof, at a concentration of about 2% to about 50% by weight. The hydrophobic solvent and/or the emollient can be selected from the group consisting of mineral oil, triglycerides, capric/caprylic triglyceride, alkyl esters of fatty acids such as isopropyl palmitate, isopropyl isostearate, 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, maleated soybean oil, 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 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.

[0126] In an embodiment of the present invention, the organic carrier is a polypropylene glycol alkyl ether (PPG alkyl ether). PPG alkyl ethers are liquid, water-insoluble propoxylated fatty alcohols, having the molecular formula of $RO(CH_2CHOCH_3)_n$; wherein "R" is a straight-chained or branched C_4 to C_{22} alkyl group; and "n" is in the range between 4 and about 50. They are organic liquids that function as skin-conditioning agent in pharmaceutical and cosmetic formulations. Non-limiting exemplary PPG alkyl ethers include PPG stearyl ethers and PPG Butyl Ether. Preferred PPG alky ethers according to the present invention include PPG-15 Stearyl Ether, PPG-2 Butyl Ether, PPG-9-13 Butyl Ether and PPG-40 Butyl Ether.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

[0127] According to a preferred embodiment, the organic carrier does not contain petrolatum, which is also termed "white petrolatum" and "Vaseline". Petrolatum often forms an impermeable occlusive barrier, so that metabolic products and excreta from damaged tissue are not easily removed or drained away. Furthermore, it is difficult for the active drug dissolved in the carrier to pass through the white petrolatum barrier layer into the treated tissue, so the efficacy of the drug is reduced. An additional disadvantage of petroleum jelly-based products relates to the greasy feeling left following their topical application onto the skin, mucosal membranes and wounds causing inconvenience to the user, thereby decreasing treatment compliance.

Polymeric agent

[0128] The composition of the present invention contains a polymeric agent selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent. A polymeric agent enhances the creation of foam having fine bubble structure, which does not readily collapse upon release from the pressurized aerosol can. The polymeric agent serves to stabilize the foam composition and to control drug residence in the target organ.

[0129] Exemplary polymeric agents include, in a non-limiting manner, naturally-occurring polymeric materials, such as 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, amine-bearing polymers such as chitosan; acidic polymers obtainable from natural sources, such as alginic acid and hyaluronic acid; chemically modified starches and the like, carboxyvinyl polymers, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers, polyvinylidene chloride polymers and the like.

[0130] Additional exemplary polymeric agents include semi-synthetic polymeric materials such as cellulose ethers, such as methylcellulose,

hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxy propylmethyl cellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, hydroxyethylcarboxymethylcellulose, carboxymethyl cellulose, carboxymethylcellulose carboxymethylhydroxyethylcellulose, and cationic celluloses, carbomer (homopolymer of acrylic acid is crosslinked with an allyl ether pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene, such as Carbopol® 934, Carbopol® 940, Carbopo® 941, Carbopol® 980 and Carbopol® 981, pemulen and aluminum starch octenylsuccinate (ASOS). Polyethylene glycol, having molecular weight of 1000 or more (e.g., PEG 1,000, PEG 4,000, PEG 6,000 and PEG 10,000) also have gelling capacity and while they are considered herein as "secondary polar solvents", as detailed herein, they are also considered polymeric agents.

[0131] In one or more embodiments the polymeric agents have emulsifying properties. In certain preferred embodiments the polymeric agent is a derivatized hydrophilic polymer with hydrophobic alkyl moieties Other types that may also a similar stabilizing effect are silicone copolymers and derivatized starch ASOS.

[0132] Mixtures of the above polymeric agents are contemplated.

[0133] The concentration of the polymeric agent should be selected so that the composition, after filling into aerosol canisters, is flowable, and can be shaken in the canister. In one or more embodiments, the concentration of the polymeric agent is selected such that the viscosity of the composition, prior to filling of the composition into aerosol canisters, is less than 12,000 CPs, and more preferably, less than 10,000 CPs.

Surface Active Agent

[0134] The composition of the present invention further contains a surface-active agent. Surface-active agents (also termed "surfactants") include any agent linking oil and water in the composition, in the form of emulsion. A surfactant's hydrophilic/lipophilic balance (HLB) describes the emulsifier's affinity toward

water or oil. HLB is defined for non-ionic surfactants. The HLB scale ranges from 1 (totally lipophilic) to 20 (totally hydrophilic), with 10 representing an equal balance of both characteristics. Lipophilic emulsifiers form water-in-oil (w/o) emulsions; hydrophilic surfactants form oil-in-water (o/w) emulsions. The HLB of a blend of two emulsifiers equals the weight fraction of emulsifier A times its HLB value plus the weight fraction of emulsifier B times its HLB value (weighted average). In many cases a single surfactant may suffice. In other cases a combination of two or more surfactants is desired. Reference to a surfactant in the specification can also apply to a combination of surfactants or a surfactant system. As will be appreciated by a person skilled in the art which surfactant or surfactant system is more appropriate is related to the vehicle and intended purpose. In general terms a combination of surfactants is usually preferable where the vehicle is an emulsion. In an emulsion environment a combination of surfactants can be significant in producing breakable forms of good quality. It has been further discovered that the generally thought considerations for HLB values for selecting a surfactant or sufactant combination are not always binding for emulsions and that good quality foams can be produced with a surfactant or surfactant combination both where the HLB values are in or towards the lipophilic side of the scale and where the HLB values are in or towards the hydrophilic side of the scale. Surfactants also play a role in foam formation where the foamable formulation is a single phase composition.

[0135] According to one or more embodiments the composition contains a single surface active agent having an HLB value between about 2 and 9, or more than one surface active agent and the weighted average of their HLB values is between about 2 and about 9. Lower HLB values may in certain embodiments be more applicable to water in oil emulsions.

[0136] According to one or more embodiments the composition contains a single surface active agent having an HLB value between about 7 and 14, or more than one surface active agent and the weighted average of their HLB

Padagis Ex. 1029
IPR Petition - USP 11,311,482

values is between about 7 and about 14. Mid range HLB values may in certain embodiments be more suitable for oil in water emulsions.

[0137] According to one or more other embodiments the composition contains a single surface active agent having an HLB value between about 9 and about 19, or more than one surface active agent and the weighted average of their HLB values is between about 9 and about 19. In a waterless or substantially waterless environment a wide range of HLB values may be suitable.

[0138] Preferably, the composition of the present invention contains a non-ionic surfactant. Nonlimiting examples of possible non-ionic surfactants include a polysorbate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, a polyoxyethylene fatty acid ester, Myrj 45, Myrj 49, Myrj 52 and Myrj 59; a polyoxyethylene alkyl ether, polyoxyethylene cetyl ether, polyoxyethylene palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, steareths such as steareth 2, brij 21, brij 721, brij 38, brij 52, brij 56 and brij W1, a sucrose ester, a partial ester of sorbitol and its anhydrides, sorbitan monolaurate, sorbitan monolaurate, a monoglyceride, a diglyceride, isoceteth-20 and mono-, di- and tri-esters of sucrose with fatty acids. In certain embdiments, suitable sucrose esters include those having high monoester content, which have higher HLB values.

[0139] In certain embodimens with DCA esters as emollient, surfactants are selected which can provide a close packed sufacant layer separating the oil and water phases. To achieve such objectives combinations of at least two surfactants are selected. Preferrably, they should be complex emulgators and more preferably they should both be of a similar molecular type. For example, a pair of ethers like steareth 2 and steareth 21, or a pair of esters for example, PEG-40 stearate and polysorbate 80. In Certain circumstances POE esters cannot be used and a combination of sorbitan laurate and sorbitan stearate or a combination of sucrose stearic acid ester mixtures and sodium laurate may be used. All these combinations due to heir versatility and strength may also be used satisfactorily and effectively with solutions of DCA's and with

solid/crystalline suspensions, although the amounts and proportion may be varied according to the formulation and its objectives as will be appreciated by a man of the art.

[0140] It has been discovered also that by using a derivatized hydrophilic polymer with hydrophobic alkyl moieties as a polymeric emulsifier such as pemulen it is possible to stabilize the emulsion better about or at the region of phase reversal tension. Other types of derivatized polymers like silicone copolymers, derivatized starch [Aluminum Starch Octenylsuccinate (ASOS)] / [DRY-FLO AF Starch], and derivatized dexrin may also a similar stabilizing effect.

[0141] A series of dextrin derivative surfactants prepared by the reaction of the propylene glycol polyglucosides with a hydrophobic oxirane-containing material of the glycidyl ether are highly biodegradable. [Hong-Rong Wang and Keng-Ming Chen, Colloids and Surfaces A: Physicochemical and Engineering Aspects Volume 281, Issues 1-3, 15 June 2006, Pages 190-193] .

[0142] Non-limiting examples of non-ionic surfactants that have HLB of about 7 to about 12 include steareth 2 (HLB~4.9); glyceryl monostearate/PEG 100 stearate (Av HLB~11.2); stearate Laureth 4 (HLB~9.7) and cetomacrogol ether (e.g., polyethylene glycol 1000 monocetyl ether).

[0143] Non-limiting examples of preferred surfactants, which have a HLB of 4-19 are set out in the Table below:

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Surfactant	HLB
steareth 2	~4.9
glyceryl monostearate/PEG 100 stearate	Av ~11.2
Glyceryl Stearate	~4
Steareth-21	~15.5
peg 40 stearate	~16.9
polysorbate 80	~15
sorbitan stearate	~4.7
laureth 4	~9.7
Sorbitan monooleate (span 80)	~4.3
ceteareth 20	~15.7
steareth 20	~15.3
ceteth 20	~15.7
Macrogol Cetostearyl Ether	~15.7
ceteth 2 (Lipocol C-2)	~5.3
PEG-30 Dipolyhydroxystearate	~5.5
sucrose distearate (Sisterna SP30)	~6
polyoxyethylene (100) stearate	~18.8

[0144] More exemplary stabilizing surfactants which may be suitable for use in the present invention are found below.

PEG-Fatty Acid Monoester Surfactants

Chemical name	Product example name	HLB
PEG-30 stearate	Myrj 51	>10
PEG-40 laurate	Crodet L40 (Croda)	17.9
PEG-40 oleate	Crodet O40 (Croda)	17.4
PEG-45 stearate	Nikkol MYS-45 (Nikko)	18
PEG-50 stearate	Myrj 53	>10
PEG-100 stearate	Myrj 59, Arlacel 165 (ICI)	19

PEG-Fatty Acid Diester Surfactants:

Chemical name	Product example name	HLB
PEG-4 dilaurate	Mapeg .RTM. 200 DL (PPG), Kessco .RTM.PEG 200 DL (Stepan), LIPOPEG 2-DL (Lipo Chem.)	7
PEG-4	distearate Kessco .RTM. 200 DS (Stepan.sub)	5
PEG-32 dioleate	Kessco .RTM. PEG 1540 DO (Stepan)	15
PEG-400 dioleate	Cithrol 4DO series (Croda)	>10
PEG-400 disterate	Cithrol 4DS series (Croda)	>10
PEG-20 glyceryl oleate	Tagat .RTM. O (Goldschmidt)	>10

Transesterification Products of Oils and Alcohols

Chemical name	Product example name	HLB
PEG-30 castor oil	Emalex C-30 (Nihon Emulsion)	11
PEG-40 hydrogenated castor oil	Cremophor RH 40 (BASF), Croduret (Croda), Emulgin HRE 40 (Henkel)	13

Polyglycerized Fatty Acids, such as:

Chemical name	Product example name	LB
Polyglyceryl-6 dioleate	Caprol .RTM. 6G20 (ABITEC); PGO-62 (Calgene), PLUROL OLEIQUE CC 497 (Gattefosse)Hodag	8.5

PEG-Sorbitan Fatty Acid Esters

Chemical name	Product example name	HLB
PEG-20 sorbitan monolaurate	Tween-20 (Atlas/ICI), Crillet 1 (Croda), DACOL MLS 20 (Condea)	17
PEG-20 sorbitan Monopalmitate	Tween 40 (Atlas/ICI), Crillet 2 (Croda)	16
PEG-20 sorbitan monostearate	Tween-60 (Atlas/ICI), Crillet 3 (Croda)	15
PEG-20 sorbitan monooleate	Tween-80 (Atlas/ICI), Crillet 4 (Croda)	15

Polyethylene Glycol Alkyl Ethers

Chemical name	Product example name	HLB
PEG-2 oleyl ether	oleth-2 Brij 92/93 (Atlas/ICI)	4.9
PEG-3 oleyl ether	oleth-3 Volpo 3 (Croda)	<10
PEG-5 oleyl ether	oleth-5 Volpo 5 (Croda)	<10
PEG-10 oleyl ether	oleth-10 Volpo 10 (Croda), Brij 96/97 (Atlas/ICI)	12
PEG-20 oleyl ether	oleth-20 Volpo 20 (Croda), Brij 98/99 (Atlas/ICI)	15
PEG-4 lauryl ether	laureth-4Brij 30 (Atlas/ICI)	9.7
PEG-23 lauryl ether	laureth-23Brij 35 (Atlas/ICI)	17
PEG-10 stearyl ether	Brij 76 (ICI)	12
PEG-2 cetyl ether	Brij 52 (ICI)	5.3

Sugar Ester Surfactants

Chemical name	Product example name	HLB
Sucrose distearate	Sisterna SP50, Surfope 1811	11

Sorbitan Fatty Acid Ester Surfactants

Chemical name	Product example name	HLB
Sorbitan monolaurate	Span-20 (Atlas/ICI), Crill 1 (Croda), Arlacel 20 (ICI)	8.6
Sorbitan monopalmitate	Span-40 (Atlas/ICI), Crill 2 (Croda), Nikkol SP-10 (Nikko)	6.7
Sorbitan monooleate	Span-80 (Atlas/ICI), Crill 4 (Croda), Crill 50 (Croda)	4.3
Sorbitan monostearate	Span-60 (Atlas/ICI), Crill 3 (Croda), Nikkol SS-10 (Nikko)	4.7

[0145] In one or more embodiments the surface active agent is a complex emulgator in which the combination of two or more surface active agents can be more effective than a single surfactant and provides a more stable emulsion or improved foam quality than a single surfactant. For example and by way of non-limiting explanation it has been found that by choosing say two surfactants, one hydrophobic and the other hydrophilic the combination can produce a more stable emulsion than a single surfactant. Preferably, the complex emulgator comprises a combination of surfactants wherein there is a difference of about 4 or more units between the HLB values of the two surfactants or there is a significant difference in the chemical nature or structure of the two or more surfactants.

[0146] Specific non limiting examples of surfactant systems are, combinations of polyoxyethylene alkyl ethers, such as Brij 59 / Brij10; Brij 52 / Brij 10; Steareth 2 / Steareth 20; Steareth 2 / Steareth 21 (Brij 72 / Brij 721); combinations of polyoxyethylene stearates such as Myrj 52 / Myrj 59; combinations of sucrose esters, such as Surphope 1816 / Surphope 1807; combinations of sorbitan esters, such as Span 20 / Span 80; Span 20 / Span 60; combinations of sucrose esters and sorbitan esters, such as Surphope 1811 and Span 60; combinations of liquid polysorbate detergents and PEG compounds, such as Tween 80 / PEG-40 stearate; methyl glucaso sequistearate; polymeric emulsifiers, such as

Permulen (TRI or TR2); liquid crystal systems, such as Arlatone (2121), Stepan (Mild RM1), Nikomulese (41) and Montanov (68) and the like.

[0147] In certain embodiments the surfactant is preferably one or more of the following: a combination of steareth-2 and steareth-21 on their own or in combination with glyceryl monostearate (GMS); in certain other embodiments the surfactant is a combination of polysorbate 80 and PEG-40 stearate. In certain other embodiments the surfactant is a combination of glyceryl monostearate/PEG 100 stearate. In certain other embodiments the surfactant is a combination of two or more of stearate 21, PEG 40 stearate, and polysorbate 80. In certain orher embodiments the surfactant is a combination of two or more of laureth 4, span80, and polysorbate 80. In certain other embodiments the surfactant is a combination of two or more of GMS and ceteareth. In certain other embodiments the surfactant is a combination of two or more of steareth 21, ceteareth 20, ceteth 2 and laureth 4 In certain other embodiments the surfactant is a combination of ceteareth 20 and polysorbate 40 stearate. In certain orther embodiments the surfactant is a combination of span 60 and GMS.

[0148] In certain other embodiments the surfactant is one or more of sucrose stearic acid esters, sorbitan laureth, and sorbitan stearate.

[0149] In one or more embodiments the stability of the composition can be improved when a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed. The ratio between the at least one non-ionic surfactant having HLB of less than 9 and the at least one non-ionic surfactant having HLB of equal or more than 9, is between 1:8 and 8:1, or at a ratio of 4:1 to 1:4. The resultant HLB of such a blend of at least two emulsifiers is preferably between about 9 and about 14.

[0150] Thus, in an exemplary embodiment, a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed, at a ratio of between 1:8 and

8:1, or at a ratio of 4:1 to 1:4, wherein the HLB of the combination of emulsifiers is preferably between about 5 and about 18.

[0151] In certain cases, the surface active agent is selected from the group of cationic, zwitterionic, amphoteric and ampholytic surfactants, such as sodium methyl cocoyl taurate, sodium methyl oleoyl taurate, sodium lauryl sulfate, triethanolamine lauryl sulfate and betaines.

[0152] Many amphiphilic molecules can show lyotropic liquid-crystalline phase sequences depending on the volume balances between the hydrophilic part and hydrophobic part. These structures are formed through the micro-phase segregation of two Many amphiphilic molecules can show lyotropic liquid-crystalline phase sequences depending on the volume balances between the hydrophilic part and hydrophobic part. These structures are formed through the micro-phase segregation of two incompatible components on a nanometer scale. Soap is an everyday example of a lyotropic liquid crystal. Certain types of surfactants tend to form lyotropic liquid crystals in emulsions interface (oil-in-water) and exert a stabilizing effect

[0153] In one or more embodiments the surfactant is a surfactant or surfactant combination is capable of or which tends to form liquid crystals. Surfactants which tend to form liquid crystals may improve the quality of foams. Non limiting examples of surfactants with postulated tendency to form interfacial liquid crystals are: phospholipids, alkyl glucosides, sucrose esters, sorbitan esters.

[0154] In one or more embodiments the at least one surface active agent is liquid.

[0155] In one or more embodiments the at least one surface active agent is solid, semi solid or waxy.

[0156] It should be noted that HLB values may not be so applicable to non ionic surfactants, for example, with liquid crystals or with silicones. Also HLB

values may be of lesser significance in a waterless or substantially non-aqueous environment.

[0157] In one or more embodiments the surfactant can be, a surfactant system comprising of a surfactant and a co surfactant, a waxy emulsifier, a liquid crystal emulsifier, an emulsifier which is solid or semi solid at room temperature and pressure, or combinations of two or more agents in an appropriate proportion as will be appreciated a person skilled in the art. Where a solid or semi solid emulsifier combination is used it can also comprise a solid or semi solid emulsifier and a liquid emulsifier.

[0158] In one or more embodiments of the present invention, the surface-active agent includes at least one non-ionic surfactant. Ionic surfactants are known to be irritants. Therefore, non-ionic surfactants are preferred in applications including sensitive tissue such as found in most mucosal tissues, especially when they are infected or inflamed. Non-ionic surfactants alone can provide formulations and foams of good or excellent quality in the carriers and compositions of the present invention.

[0159] Thus, in a preferred embodiment, the surface active agent, the composition contains a non-ionic surfactant. In another preferred embodiment the composition includes a mixture of non-ionic surfactants as the sole surface active agent. Yet, in additional embodiments, the foamable composition includes a mixture of at least one non-ionic surfactant and at least one ionic surfactant in a ratio in the range of about 100:1 to 6:1. In one or more embodiments, the non-ionic to ionic surfactant ratio is greater than about 6:1, or greater than about 8:1; or greater than about 14:1, or greater than about 16:1, or greater than about 20:1. In further embodiments, surface active agent comprises a combination of a non-ionic surfactant and an ionic surfactant, at a ratio of between 1:1 and 20:1

[0160] In one or more embodiments of the present invention, a combination of a non-ionic surfactant and an ionic surfactant (such as sodium lauryl sulphate and cocamidopropylbetaine) is employed, at a ratio of between 1:1 and 20:1, or

at a ratio of 4:1 to 10:1; for example, about 1:1, about 4:1, about 8:1, about 12:1, about 16:1and about 20:1 or at a ratio of 4:1 to 10:1, for example, about 4:1, about 6:1, about 8:1 and about 10:1.

[0161] In selecting a suitable surfactant or combination thereof it should be borne in mind that the upper amount of surfactant that may be used may be limited by the shakability of the composition. If the surfactant is non liquid, it can make the formulation to viscous or solid. This can be particularly significant if the formulation has high molecular weight, e.g., a high molecular weight PEG or polymeric agents or petroleum or if the surfactants are large. Solvents and polymeric agents which have high molecular weight and are very viscous or solid or waxy (e.g., Peg 1500, 2000, etc. or petrolatum) can exacerbate the effect of a waxy or solid surfactant on shakability or flowability In general terms, as the amount of non-liquid surfactant is increased the shakability of the formulation reduces until a limitation point is reached where the formulation becomes non shakable and unsuitable. Thus in one embodiment, an effective amount of surfactant may be used provided the formulation remains shakable. In other certain exceptional embodiments the upper limit may be determined by flowability such as in circumstances where the composition is marginally or apparently non-shakable. The formulation is sufficiently flowable to be able to flow through an actuator valve and be released and still expand to form a good quality foam.

[0162] In certain embodiments of the present invention the amount of surfactant or combination of surfactants is between about 0.05% to about 20%; between about 0.05% to about 15%. or between about 0.05% to about 10%. In a preferred embodiment the concentration of surface active agent is between about 0.2% and about 8%. In a more preferred embodiment the concentration of surface active agent is between about 1% and about 6%.

[0163] In some embodiments, it is desirable that the surface active agent does not contain a polyoxyethylene (POE) moiety, such as polysorbate surfactants, POE fatty acid esters, and POE alkyl ethers, because the active agent is incompatible with such surface active agents. For example, the active agent

pimecrolimus is not stable the presence of POE moieties, yet benefits greatly from the use of dicarboxylic esters as penetration enhancers. In such cases, alternative surface active agents are employed. In an exemplary manner, POE – free surfactants include non-ethoxylated sorbitan esters, such as sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate and sorbitan sesquioleate; glycerol fatty acid esters, such as glycerol monostearate and glycerol monooleate; mono-, di- and tri-esters of sucrose with fatty acids (sucrose esters), sucrose stearate, sucrose distearate sucrose palmitate and sucrose laurate; and alkyl polyglycosides, such as lauryl diglucoside.

[0164] If the composition as formulated is a substantially non shakable composition it is nevertheless possible as an exception in the scope of the present invention for the formulation to be flowable to a sufficient degree to be able to flow through an actuator valve and be released and still expand to form a good quality foam. This surprising and unusual exception may be due one or more of a number of factors such as the high viscosity, the softness, the lack of crystals, the pseudoplastic or semi pseudo plastic nature of the composition and the dissolution of the propellant into the composition.

[0165] In one or more embodiments of the present invention, the surface-active agent includes mono-, di- and tri-esters of sucrose with fatty acids (sucrose esters), prepared from sucrose and esters of fatty acids or by extraction from sucro-glycerides. Suitable sucrose esters include those having high monoester content, which have higher

Phase inversion and tension

[0166] Phase inversion is a factor in the preparation and stabilization of emulsions and can be both an aid and a detriment. Phase inversion involves the change of emulsion type from o/w to w/o or vice versa. Prior to phase inversion occurring there is a tension in the emulsion which if destabilized or driven will lead to phase inversion and if controlled or ameliorated or dissipated will result in

Padagis Ex. 1029
IPR Petition - USP 11,311,482

a more stable emulsion. The occurrence of phase inversion during preparation can be a sign of instability. If controlled, it can result in a finer product but if due to other factors after the the emulsion was prepared it can cause problems. Inversion can occur by for example adding calcium chloride to an o/w emulsion stabilized with sodium stearate to form calcium stearate. Inversion can also occur as the product of changes to the phase- volume ratio. For example if a small amount of water is added to surfactant mixed with oil and agitated aw/o emulsion is formed As the amount of water added is gradually increased a point will be reached where the water and emulsifier envlop the oil as small droplets to form an o/w emulsion. The amount of each ingredient including the surfactants will have their part to play in the phenomenum.

Substantially Alcohol-Free

[0167] According to one or more embodiments, the foamable composition is substantially alcohol-free, i.e., free of short chain alcohols. Short chain alcohols, having up to 5 carbon atoms in their carbon chain skeleton and one hydroxyl group, such as ethanol, propanol, isopropanol, butaneol, iso-butaneol, t-butaneol and pentanol, are considered less desirable solvents or polar solvents due to their skin-irritating effect. Thus, the composition is substantially alcohol-free and includes less than about 5% final concentration of lower alcohols, preferably less than about 2%, more preferably less than about 1%.

Substantially Non Aqueous

[0168] In certain cases, the active agent degrades in the presence of water, and therefore, in such cases the present of water in the composition is not desirable. Thus, in certain preferred embodiments, the composition is substantially non-aqueous. The term "substantially non-aqueous" or "substantially waterless" is intended to indicate that the composition has a water content below about 5%, preferably below about 2%, such as below about 1.5%. In certain other preferred embodiments the composition is non aqueous or waterless.

[0169] By non aqueous or waterless is meant that the composition contains no or substantially no, free or unassociated or absorbed water. It will be understood by a person of the art that the waterless solvents and substances miscible with them of the present invention can be hydrophilic and can contain water in an associated or unfree or absorbed form and may absorb water from the atmosphere and the ability to do so is its hygroscopic water capacity. It is intended that essentially non-aqueous formulations are included within its scope such that the formulations may have present a small amount of water. In some embodiments the composition ingredients are pretreated to reduce, remove or eliminate any residual or associated or absorbed water.

Shakability

[0170] 'Shakability' means that the composition contains some or sufficient flow to allow the composition to be mixed or remixed on shaking. That is, it has fluid or semi fluid properties. In some very limited cases possibly aided by the presence of silicone it may exceptionally be possible to have a foamable composition which is flowable but not apparently shakable.

Breakability

[0171] A breakable foam is one that is thermally stable, yet breaks under sheer force.

[0172] The breakable foam of the present invention is not "quick breaking", i.e., it does not readily collapse upon exposure to body temperature environment. Sheer-force breakability of the foam is clearly advantageous over thermally induced breakability, since it allows comfortable application and well directed administration to the target area.

Modulating Agent

[0173] The term modulating agent is used to describe an agent which can improve the stability of or stabilize a foamable carrier or composition and or an

Padagis Ex. 1029
IPR Petition - USP 11,311,482

active agent by modulating the effect of a substance or residue present in the carrier or composition.

[0174] In one or more embodiments the modulating agent is used in a water in oil or oil in water emulsion. In one or more other embodiments the modulating agent is used in a unique waterless emulsion.

[0175] In certain embodiments the substance or residue may for example be acidic or basic and potentially alter pH in an emulsion environment or it may be one or more metal ions which may act as a potential catalyst in an emulsion environment.

[0176] In certain other embodiments the substance or residue may for example be acidic or basic and potentially alter an artificial pH in a waterless or substantially non aqueous environment or it may be one or more metal ions which may act as a potential catalyst in a waterless or substantially non aqueous environment.

[0177] In one or more embodiments the modulating agent is used to describe an agent which can affect pH in an aqueous solution. The agent can be any of the known buffering systems used in pharmaceutical or cosmetic formulations as would be appreciated by a man of the art. It can also be an organic acid, a carboxylic acid, a fatty acid an amino acid, an aromatic acid, an alpha or beta hydroxyl acid an organic base or a nitrogen containing compound.

[0178] In one or more further embodiments the modulating agent is used to describe an agent, which is a chelating or sequestering or complexing agent that is sufficiently soluble or functional in the solvent to enable it to "mop up" or "lock" metal ions.

[0179] In an embodiment modulating agent is used to describe an agent which can effect pH in an aqueous solution the term modulating agent more particularly means an acid or base or buffer system or combinations thereof, which is introduced into or is present in and acts to modulate the ionic or polar

characteristics and any acidity or basesity balance of an emulsion carrier, composition, foamable carrier or foamable composition or resultant foam of the present invention.

[0180] In other embodiments modulating agent is used to describe an agent which can effect pH in an aqueous solution the term modulating agent more particularly means an acid or base or buffer system or combinations thereof, which is introduced into or is present in and acts to modulate the ionic or polar characteristics and any acidity or basesity balance of a waterless or substantially non aqueous carrier, composition, foamable carrier or foamable composition or resultant foam of the present invention.

[0181] The substance or residue can be introduced into the formulation from any one or more of the ingredients, some of which themselves may have acidic or basic properties. For example the polymer or solvent may contain basic residues in which case it may be desirable or beneficial to add an acid. Alternatively the surfactant may contain some acid residues in which case the addition of a base may be desirable and beneficial. In some cases more than one ingredient may contain residues which may ameliorate or compound their significance. For example if one ingredient provided weak acid residues and another stronger acid residues the pH in an emulsion environment (or artificial pH in a waterless environment) should be lower. In contrast if one residue was acid and the other basic the net effect in the formulation maybe significantly reduced. In some circumstances the active ingredient may favor an acidic pH or more significantly may need to be maintained at a certain acidic pH otherwise it may readily isomerize, chemically react or breakdown, in which case introducing acidic components such as an acidic polymer might be of help. In an embodiment of the present invention sufficient modulating agent is added to achieve a pH in which the active agent is preferably stable. In another embodiment of the present invention sufficient modulating agent is added to achieve an artificial pH in which the active agent is preferably stable.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

[0182] The terms pH, pKa, and pKb, buffers and the like are used in classical measurements of an aqueous solution. Such measurements are artificial in a waterless environment. Nevertheless, reference to and description below of such terms are made for convenience and clarity, since such terms are well defined and understood with reference to aqueous solutions and further due to the lack of an appropriate uniform way of describing and identifying the artificial or virtual pH, pK etc in a waterless environment in relation to the present invention. Although predictions of artificial pH can be made using dilution techniques of measurements of waterless formulations diluted in water they are formulation sensitive and specific and have to be carefully calibrated with complex formulas.

[0183] Waterless medium can be polar and protic yet it does not conform to classical ionic behavior.

[0184] A buffer, as defined by Van Slyke [Van Slyke, *J. Biol. Chem.* 52, 525 (1922)], is "a substance which by its presence in solution increases the amount of acid or alkali that must be added to cause unit change in pH."

[0185] A buffer solution is a solution of a definite pH made up in such a way that this pH alters only gradually with the addition of alkali or acid. Such a solution consists of a solution of a salt of the week acid in the presence of the three acid itself. The pH of the solution is determined by the dissociation equilibrium of the free acid.

[0186] An acid can be a strong acid or a weak acid. A strong acid is an acid, which is a virtually 100% ionized in solution. In contrast, a week acid is one which does not ionize fully. When it is dissolved in water. The lower the value for pKa, the stronger is the acid and likewise, the higher the value for pKa the weaker is the acid.

[0187] A base can be a strong base or a weak base. A strong base is something, which is fully ionic with 100% hydroxide ions. In contrast, a weak base is one which does not convert fully into hydroxide ions in solution. The

lower the value for pKb, the stronger is the base and likewise, the higher the value for pKb the weaker is the base.

[0188] In one or more embodiments of the present invention the modulating agent comprises an organic compound.

[0189] In one or more preferred embodiments of the present invention the chelating agent is selected from the group consisting of ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), hydroxyethylenediaminetriacetic acid (HEDTA), nitrilotriacetic acid (NTA), O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid (EGTA), trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid (CyDTA) or a pharmaceutically acceptable salt thereof (normally as a sodium salt), more preferably EDTA, HEDTA and their salts; most preferably EDTA and its salts.

[0190] In one or more embodiments of the present invention a preferred non limiting example of the chelating agent is EDTA. Typically, the chelating and sequestering agent is present in the composition at a level of up to about 5.0%, preferably 1.0 percent, by weight, of the composition.

[0191] In one or more embodiments of the present invention the modulating agent may also be a preservative or an antioxidant or an ionization agent. Any preservative, antioxidant or ionization agents suitable for pharmaceutical or cosmetic application may be used. Non limiting examples of antioxidants are tocopherol succinate, propyl galate, butylated hydroxy toluene and butyl hydroxy anisol. Ionization agents may be positive or may be negative depending on the environment and the active agent or composition that is to be protected. Ionization agents may for example act to protect or reduce sensitivity of active agents. Non limiting examples of positive ionization agents are benzyl conium chloride, and cetyl pyridium chloride. Non limiting examples of negative ionization agents are sodium lauryl sulphate, sodium lauryl lactylate and phospholipids.

Humectant

[0192] A humectant is a substance that helps retain moisture and also prevents rapid evaporation. Non limiting examples are propylene glycol, propylene glycol derivatives, glycerin, hydrogenated starch hydrosylate, hydrogenated lanolin, lanolin wax, D manitol, sorbitol, sodium 2-pyrrolidone-5-carboxylate, sodium lactate, sodium PCA, soluble collagen, dibutyl phthalate, and gelatin. Other examples may be found in the Handbook of Pharmaceutical Additives published by Gower.

Moisturizers

[0193] A moisturizer, is a substance that helps retain moisture or add back moisture to the skin. Examples are allantoin, petrolatum, urea, lactic acid, sodium PCV, glycerin, shea butter, caprylic/capric/stearic triglyceride, candelilla wax, propylene glycol, lanolin, hydrogenated oils, squalene, sodium hyaluronate and lysine PCA. Other examples may be found in the *Handbook of Pharmaceutical Additives* published by Gower.

[0194] Pharmaceutical compositions of the present invention may in one or more embodiments usefully comprise in addition a heumectant or a moisturizer or combinations thereof.

Polar solvent

[0195] Optionally, the foamable vehicle further includes at least one polar solvent.

[0196] A "polar solvent" is an organic solvent, typically soluble in both water and oil. Certain polar solvents, for example propylene glycol and glycerin, possess the beneficial property of a heumectant.

[0197] In one or more embodiments, the polar solvent is a heumectant.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

[0198] In one or more embodiments, the polar solvent is a polyol. Polyols are organic substances that contain at least two hydroxy groups in their molecular structure.

[0199] In one or more embodiments, the polar solvent contains an diol (a compound that contains two hydroxy groups in its molecular structure), such as propylene glycol (e.g., 1,2-propylene glycol and 1,3-propylene glycol), butaneediol (e.g., 1,4-butaneediol), butaneediol (e.g., 1,3-butaneediol and 1,4-butenediol), butynediol, pentanediol (e.g., 1,5-pentanediol), hexanediol (e.g., 1,6-hexanediol), octanediol (e.g., 1,8-octanediol), neopentyl glycol, 2-methyl-1,3-propanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, dipropylene glycol and dibutylene glycol.

[0200] In one or more embodiments, the polar solvent contains a triol (a compound that contains three hydroxy groups in its molecular structure), such as glycerin and 1,2,6-Hexanetriol.

[0201] Other non-limiting examples of polar solvents include pyrrolidones, (such as N-methyl-2-pyrrolidone and 1-methyl-2-pyrrolidinone), dimethyl isosorbide, 1,2,6-hexapetriol, dimethyl sulfoxide (DMSO), ethyl proxitol, dimethylacetamide (DMAc) and alpha hydroxy acids, such as lactic acid and glycolic acid.

[0202] According to still other embodiments, the polar solvent is a polyethylene glycol (PEG) or PEG derivative that is liquid at ambient temperature, including PEG200 (MW (molecular weight) about 190-210 kD), PEG300 (MW about 285-315 kD), PEG400 (MW about 380-420 kD), PEG600 (MW about 570-630 kD) and higher MW PEGs such as PEG 4000, PEG 6000 and PEG 10000 and mixtures thereof.

[0203] Polar solvents are known to enhance the penetration of active agent into the skin and through the skin, and therefore, their inclusion in the composition of the present invention can be desirable, despite their undesirable skin drying and irritation potential. There is at one level a commonality between

the different polar solvents and their penetration enhancement properties. Lower molecular weight alcohols can sometimes be more potent as a solvent, for example by extracting lipids from the skin layers more effectively, which characteristic can adversely affect the skin structure and cause dryness and irritation. Therefore the selection of lower molecular weight alcohols is ideally avoided.

[0204] Polar solvents, such as detailed below possess high solubilizing capacity and contribute to the skin penetration of an active agent. Non limiting examples include dimethyl isosorbide polyols, such as glycerol (glycerin), propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, other glycols, oleyl alcohol, alpha-hydroxy acids, such as lactic acid and glycolic acid, sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformanide, methyl dodecyl sulfoxide, dimethylacetamide, azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, alkanols, such as dialkylamino acetates, and admixtures thereof. In certain preferred embodiments, the polar solvent is selected from the group consisting of dimethyl isosorbide glycerol (glycerin), propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid.

Skin penetration enhancer

[0205] A "skin penetration enhancer", also termed herein "penetration enhancer," is an organic solvent, typically soluble in both water and oil. Examples of penetration enhancer include polyols, such as glycerol (glycerin), propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, terpen-ols, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, hexylene glycol, other glycols, sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformanide, methyl dodecyl sulfoxide, dimethylacetamide, dimethylisosorbide, monooleate of ethoxylated glycerides (with 8 to 10 ethylene oxide units), azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, esters, such as isopropyl myristate/palmitate, ethyl acetate,

Padagis Ex. 1029
IPR Petition - USP 11,311,482

butyl acetate, methyl proprionate, capric/caprylic triglycerides, octylmyristate, dodecyl-myristate; myristyl alcohol, lauryl alcohol, lauric acid, lauryl lactate ketones; amides, such as acetamide oleates such as triolein; various alkanoic acids such as caprylic acid; lactam compounds, such as azone; alkanols, such as dialkylamino acetates, and admixtures thereof.

[0206] According to one or more embodiments, the penetration enhancer is a polyethylene glycol (PEG) or PEG derivative that is liquid at ambient temperature

Potent Solvent

[0207] In one or more embodiments of the present invention, the foamable composition includes a potent solvent, in addition to or in place of one of the hydrophobic solvents, polar solvents or emollients of the composition. A potent solvent is a solvent other than mineral oil that solubilizes a specific active agent substantially better than a hydrocarbon solvent such as mineral oil or petrolatum. For example, a potent solvent solubilizes the active agent 5 fold better than a hydrocarbon solvent; or even solubilizes the active agent 10-fold better than a hydrocarbon solvent.

[0208] In one or more embodiments of the present invention, the composition includes at least one active agent in a therapeutically effective concentration; and at least one potent solvent in a sufficient amount to substantially solubilize the at least one active agent in the composition. The term "substantially soluble" means that at least 95% of the active agent has been solubilized, i.e., 5% or less of the active agent is present in a solid state. In one or more embodiments, the concentration of the at least one potent solvent is more than about 40% of the at least one solvent of the composition of the present invention; or even more than about 60%.

[0209] Non-limiting examples of pairs of active agent and potent solvent include: Betamethasone valerate: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol; Hydrocortisone butyrate: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol; Metronidazole:

Practically insoluble in mineral oil (<0.01%); soluble more than 1% in dimethyl isosrbide; Ketoconazole: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol, propylene glycol and dimethyl isosrbide; Mupirocin: Practically insoluble in mineral oil (<0.01%); soluble more than 1% in glycofurol, hexylene glycol, dimethyl isosorbide, propylene glycol and polyethylene glycol 400 (PEG 400); Meloxicam, a nonsteroidal anti-inflammatory agent: Practically insoluble in mineral oil (<0.001%); soluble in propylene glycol: 0.3 mg/mL; and in PEG 400: 3.7 mg/mL; and Progesterone: Practically insoluble in mineral oil (<0.001%); soluble in PEG 400: 15.3 mg/mL.

[0210] A non-limiting exemplary list of solvents that can be considered as potent solvents includes polyethylene glycol, propylene glycol, hexylene glycol, butaneediols and isomers thereof, glycerol, benzyl alcohol, DMSO, ethyl oleate, ethyl caprylate, diisopropyl adipate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, isosorbide derivatives, such as dimethyl isosorbide, glycofurol and ethoxydiglycol (transcutol) and laurocapram .

[0211] The use of a potent solvent in a foam composition provides an improved method of delivering poorly soluble therapeutic agents to a target area. It is known that low drug solubility results in poor bioavailability, leading to decreased effectiveness of treatment. Foam compositions of the present invention, for which the solvent includes a potent solvent, increase the levels of the active agent in solution and thus, provide high delivery and improved therapy.

[0212] Potent solvents, as defined herein, are usually liquid. Formulations comprising potent solvents and active agents are generally disadvantageous as therapeutics, since their usage involves unwanted dripping and inconvenient method of application; resulting in inadequate dosing. Surprisingly, the foams of the present invention, which are drip-free, provide a superior vehicle for such active agents, enabling convenient usage and accurate effective dosing.

[0213] In one or more embodiments of the present invention the present invention the foamable pharmaceutical composition may additionally include a

Padagis Ex. 1029
IPR Petition - USP 11,311,482

mixture of two or more of the solvents selected from the group of hydrophobic solvents, silicone oils, emollients, polar solvents and potent solvents in an appropriate proportion as would be appreciated to a person skilled in the art.

[0214] In one or more embodiments of the present invention, the PPG alkyl ether may act as a potent solvent

Additional components

[0215] In an embodiment of the present invention, a composition of the present invention includes one or more additional components. Such additional components include but are not limited to anti perspirants, anti-static agents, buffering agents, bulking agents, chelating agents, cleansers, colorants, conditioners, deodorants, diluents, dyes, emollients, fragrances, hair conditioners, humectants, pearlescent aids, perfuming agents, permeation enhancers, pH-adjusting agents, preservatives, protectants, skin penetration enhancers, softeners, solubilizers, sunscreens, sun blocking agents, sunless tanning agents, viscosity modifiers and vitamins. As is known to one skilled in the art, in some instances a specific additional component may have more than one activity, function or effect.

Propellants

[0216] Suitable propellants include volatile hydrocarbons such as butane, propane, isobutane and fluorocarbon gases, or mixtures thereof.

[0217] The propellant makes up about 5-25 wt% of the foamable composition. The propellants are used to generate and administer the foamable composition as a foam. The total composition including propellant, foamable compositions and optional ingredients is referred to as the foamable composition.

[0218] Alcohol and organic solvents render foams inflammable. It has been surprisingly discovered that fluorohydrocarbon propellants, other than chloro-fluoro carbons (CMCs), which are non-ozone-depleting propellants, are

particularly useful in the production of a non-flammable foamable composition. A test according to European Standard prEN 14851, titled "Aerosol containers - Aerosol foam flammability test" revealed that compositions containing an organic carrier that contains a hydrophobic organic carrier and/or a polar solvent, which are detected as inflammable when a hydrocarbon propellant is used, become non-flammable, while the propellant is an HFC propellant.

[0219] Such propellants include, but are not limited to, hydrofluorocarbon (HFC) propellants, which contain no chlorine atoms, and as such, fall completely outside concerns about stratospheric ozone destruction by chlorofluorocarbons or other chlorinated hydrocarbons. Exemplary non-flammable propellants according to this aspect of the invention include propellants made by DuPont under the registered trademark Dymel, such as 1,1,1,2 tetrafluorethane (Dymel 134), and 1,1,1,2,3,3,3 heptafluoropropane (Dymel 227). HFCs possess Ozone Depletion Potential of 0.00 and thus, they are allowed for use as propellant in aerosol products.

[0220] Notably, the stability of foamable emulsions including HFC as the propellant can be improved in comparison with the same composition made with a hydrocarbon propellant.

[0221] In one or more embodiments foamable compositions comprise a combination of a HFC and a hydrocarbon propellant such as n-butanee or mixtures of hydrocarbom propellants such as propane , ispbutane and butane.

MICROEMULSIONS AND NANOEMULSIONS

[0222] Microemulsions and nanoemulsion are monophasic, transparent (or slightly translucent) dispersions of oil and water. Unlike conventional emulsions, microemulsions and nanoemulsion are thermodynamically stable, making them a favorable vehicle for pharmaceutical compositions, which have to maintain stability for long periods of time. They and a method of manufacture are more particularly described in US2006/0233721 which is incorporated herein by way of

reference. As will be appreciated by a man of the art the methodology may be adapted according to the type of carrier composition.

AGING

[0223] In order to project the potential shelf life and stability of the compositions and their ingredients particularly active or benefit agents the compositions can subjected to a number of tests, including centrifugation to look for resistance to creaming, phase separation; one or more freeze thaw cycles, standing at room and higher temperatures as an indicator of resistance to aging.

Composition and Foam Physical Characteristics and Advantages

[0224] A pharmaceutical or cosmetic composition manufactured using the foamable carrier of the present invention is very easy to use. When applied onto the afflicted body surface of mammals, i.e., humans or animals, it is in a foam state, allowing free application without spillage. Upon further application of a mechanical force, e.g., by rubbing the composition onto the body surface, it freely spreads on the surface and is rapidly absorbed.

[0225] The foamable composition of the present invention is stable, having an acceptable shelf-life of at least one year, or preferably, at least two years at ambient temperature, as revealed in accelerated stability tests. The foamable compositions according to the present invention are stable. Following accelerated stability studies, they demonstrate desirable texture; they form fine bubble structures that do not break immediately upon contact with a surface, spread easily on the treated area and absorb quickly.

[0226] The composition should also be free flowing, to allow it to flow through the aperture of the container, e.g., and aerosol container, and create an acceptable foam.

[0227] Foam quality can be graded as follows:

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Grade E (excellent): very rich and creamy in appearance, does not show any bubble structure or shows a very fine (small) bubble structure; does not rapidly become dull; upon spreading on the skin, the foam retains the creaminess property and does not appear watery.

Grade G (good): rich and creamy in appearance, very small bubble size, "dulls" more rapidly than an excellent foam, retains creaminess upon spreading on the skin, and does not become watery.

Grade FG (fairly good): a moderate amount of creaminess noticeable, bubble structure is noticeable; upon spreading on the skin the product dulls rapidly and becomes somewhat lower in apparent viscosity.

Grade F (fair): very little creaminess noticeable, larger bubble structure than a "fairly good" foam, upon spreading on the skin it becomes thin in appearance and watery.

Grade P (poor): no creaminess noticeable, large bubble structure, and when spread on the skin it becomes very thin and watery in appearance.

Grade VP (very poor): dry foam, large very dull bubbles, difficult to spread on the skin.

[0228] Topically administrable foams are typically of quality grade E or G, when released from the aerosol container. Smaller bubbles are indicative of more stable foam, which does not collapse spontaneously immediately upon discharge from the container. The finer foam structure looks and feels smoother, thus increasing its usability and appeal.

[0229] As further aspect of the foam is breakability. The breakable foam is thermally stable, yet breaks under sheer force. Sheer-force breakability of the foam is clearly advantageous over thermally induced breakability. Thermally sensitive foams immediately collapse upon exposure to skin temperature and,

Padagis Ex. 1029
IPR Petition - USP 11,311,482

therefore, cannot be applied on the hand and afterwards delivered to the afflicted area.

[0230] Another property of the foam is specific gravity, as measured upon release from the aerosol can. Typically, foams have specific gravity of less than 0.12 g/mL; or less than 0.10 g/mL; or less than 0.08 g/mL, depending on their composition and on the propellant concentration.

Pharmaceutical composition

[0231] The foamable carrier of the present invention is an ideal vehicle for active pharmaceutical ingredients and active cosmetic ingredients. In the context of the present invention, active pharmaceutical ingredients and active cosmetic ingredients are collectively termed "active agent" or "active agents."

[0232] In one or more embodiments, the dicarboxylic acid or dicarboxylic ester is the active ingredient. It can be used in the formulation as a suspended solid or in solution, alone or in combination with other active agents. As is known to one skilled in the art, in some instances a specific active agent may have more than one activity, function or effect.

[0233] In one embodiment, the dicarboxylic acid or dicarboxylic acid ester is useful as an antibiotic, an antifungal agent, a keratolytic agent, an inhibitor of the reduction of testosterone to dihydrotestosterone, an inhibitor of the production of sebum in the sebaceous gland, an anti-acne agent, by way of example. Dicarboxylic acids, and azxelaic acid in particular, may be used for the treatment of diaper rash, hyperpigmentary drmatoses, acne, presbyderma of aging skin, hyperhydrosis, ischthyosis, and wrinkling of the skin, anti-tumor agents (for example, in conjunction with vitamins A, E and D), rosacea, a pigmentation disorder, a cell proliferation abnormality a skin infection and a skin inflammation and treatment of corns and callouses due to the anti-keratolytic effects.

[0234] In one or more embodiments, the dicarboxylic acid or dicarboxylic ester is used as a solvent for an active agent or as a penetration enhancer for an active agent.

[0235] Suitable active agents for use in conjunction with a dicarboxylic acid or a dicarboxylic ester include, but are not limited to, active herbal extracts, acaricides, age spot and keratose removing agents, allergen, analgesics, local anesthetics, antiacne agents, antiallergic agents, antiaging agents, antibacterials, antibiotics, antiburn agents, anticancer agents, antidandruff agents, antidepressants, antidermatitis agents, antiedemics, antihistamines, antihelminths, antihyperkeratolyte agents, antiinflammatory agents, antiirritants, antilipemics, antimicrobials, antimycotics, antiproliferative agents, antioxidants, anti-wrinkle agents, antipruritics, antipsoriatic agents, antirosacea agents antiseborrheic agents, antiseptic, antiswelling agents, antiviral agents, antiyeast agents, 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, skin whitening agents, vasoconstrictors, vasodilators, vitamins, vitamin D derivatives, wound healing agents and wart removers. As is known to one skilled in the art, in some instances a specific active agent may have more than one activity, function or effect.

[0236] In one or more embodiments, the formulation additionally includes a steroidal anti-inflammatory agent. The dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the steroid. Exemplary steroidal anti-inflammatory agents include, but are not limited to, corticosteroids such as bydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethsone dipropionate, clobetasol valemate,

desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortmate, mepreddisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, and mixtures thereof. In an embodiment of the present invention, the dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the steroid.

[0237] In one embodiment, the formulation additionally includes an immunomodulator. The dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the immunomodulator. Immunomodulators are chemically or biologically-derived agents that modify the immune response or the functioning of the immune system (as by the stimulation of antibody formation or the inhibition of white blood cell activity). Immunomodulators include, among other options, cyclic peptides, such as cyclosporine, tacrolimus, tresperimus, pimecrolimus, sirolimus (rapamycin), verolimus, laflunimus, laquinimod and imiquimod. Such compounds, delivered in the foam of the present invention, are especially advantageous in skin disorders such as psoriasis, eczema and atopic dermatitis, where the large skin areas are to be treated.

[0238] In an embodiment of the present invention, the active agent is selected from a dicarboxylic acid and a dicarboxylic acid ester.

[0239] Because of the multiple therapeutic properties of dicarboxylic acids and their respective esters, the combination of such dicarboxylic acids or their

respective esters with another active agents can result in a synergistic therapeutic benefit. For example, psoriasis is characterized by a heperkeratinization aspect and an inflammation, and therefore, its treatment can benefit from the combination of a dicarboxylic acid, which is keratolytic and a steroid.

Fields of Applications

[0240] The foamable carrier of the present invention is suitable for treating any inflicted surface. In one or more embodiments, foamable carrier is suitable for administration to the skin, a body surface, a body cavity or mucosal surface, e.g., the cavity and/or the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum (severally and interchangeably termed herein "target site").

[0241] In one embodiment, the disorder is a dermatological disorder, which can be treated by a dicarboxylic acid.

[0242] In another embodiment, the disorder is a dermatological disorder that benefits from the use of a dicarboxylic acid or dicarboxylic ester in conjunction with another active agent. The dicarboxylic acid or dicarboxylic ester may benefit by improving the solubility of the active agent or increasing the penetration of the active agent. The dicarboxylic acid or dicarboxylic ester may also provide a synergistic therapeutic effect in combination with the active agent.

[0243] By selecting a suitable active agent, or a combination of two or more active agents, the foamable composition of the present invention is useful in treating an animal or a human patient having any one of a variety of dermatological disorders, including 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,

Padagis Ex. 1029
IPR Petition - USP 11,311,482

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, granuloma 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.

[0244] Likewise, the foamable composition of the present invention is suitable for treating a disorder of a body cavity or mucosal surface, e.g., the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum. Non limiting examples of such conditions include chlamydia infection, gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma inguinale, lymphogranuloma venereum, mucopurulent cervicitis (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.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

[0245] In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by a dicarboxylic acid.

[0246] In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by a dicarboxylic acid ester.

[0247] In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by a topical steroid, and the dicarboxylic acid or dicarboxylic ester provides a beneficial effect by increasing the solubility or penetration of the topical steroid.

[0248] In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by an immunomodulator and the dicarboxylic acid or dicarboxylic ester provides a beneficial effect by increasing the solubility or penetration of the topical immunomodulator.

[0249] In an embodiment of the present invention, the disorder is a dermatological disorder, which can be treated by an anti-infective agent, such as an antibacterial agent, and antibiotic, an antifungal agent and an antiviral agent, and the dicarboxylic acid or dicarboxylic ester provides a beneficial effect as an anti-infective agent or by increasing the solubility or penetration of the anti-infective agent.

[0250] In an embodiment of the present invention, the disorder is a dermatological disorder, which is common in children. Foam is advantageous in the topical treatment of children, who are sensitive to treatment with a cream or ointment.

[0251] In an embodiment of the present invention, the disorder is atopic dermatitis and the active agent is a steroid, further including a dicarboxylic acid (DCA) or DCA ester to stabilize or solubilize the topical steroid.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

[0252] In an embodiment of the present invention, the disorder is psoriasis and the active agent is a steroid, further including a DCA or DCA ester to stabilize or solubilize the topical steroid.

[0253] In an embodiment of the present invention, the disorder is selected from psoriasis and atopic dermatitis and the active agent comprises a steroid and an additional non-steroidal active agent, such as a vitamin D derivative, further including a DCA or DCA ester to stabilize or solubilize the topical steroid and/or non-steroidal active agent.

[0254] In an embodiment of the present invention, the disorder is selected from psoriasis and atopic dermatitis and the active agent comprises an immunomodulator, further including a DCA or DCA ester to stabilize or solubilize the immunomodulator.

[0255] In an embodiment of the present invention, the composition is useful for the treatment of an infection. In one or more embodiments, the composition is suitable for the treatment of an infection, selected from the group of a bacterial infection, a fungal infection, a yeast infection, a viral infection and a parasitic infection.

[0256] In an embodiment of the present invention, the composition is useful for the treatment of wound, ulcer and burn.

[0257] The composition of the present invention is also suitable for administering a hormone to the skin or to a mucosal membrane or to a body cavity, in order to deliver the hormone into the tissue of the target organ, in any disorder that responds to treatment with a hormone.

[0258] Other foamable compositions are described in: U.S. Publication No. 05-0232869, published on October 20, 2005, entitled NONSTEROIDAL IMMUNOMODULATING KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 05-0205086, published on September 22, 2005, entitled RETINOID IMMUNOMODULATING KIT AND COMPOSITION AND USES

THEREOF; U.S. Publication No. 06-0018937, published on January 26, 2006, entitled STEROID KIT AND FOAMABLE COMPOSITION AND USES THEREOF; U.S. Publication No. 05-0271596, published on December 8, 2005, entitled VASOACTIVE KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0269485, published on November 30, 2006, entitled ANTIBIOTIC KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 07-0020304, published on January 25, 2007, entitled NON-FLAMMABLE INSECTICIDE COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0193789, published on August 31, 2006, entitled FILM FORMING FOAMABLE COMPOSITION; U.S. Patent Application No. 11/732547, filed on April 4, 2007, entitled ANTI-INFECTION AUGMENTATION OF FOAMABLE COMPOSITIONS AND KIT AND USES THEREOF; U.S. Provisional Patent Application No. 60/789186, filed on April 4, 2006, KERATOLYTIC ANTIFUNGAL FOAM; U.S. Provisional Patent Application No. 0/815948, filed on June 23, 2006, entitled FOAMABLE COMPOSITIONS COMPRISING A CALCIUM CHANNEL BLOCKER, A CHOLINERGIC AGENT AND A NITRIC OXIDE DONOR; U.S. Provisional Patent Application No. 60/818634, filed on July 5, 2006, entitled DICARBOXYLIC ACID FOAMABLE VEHICLE AND PHARMACEUTICAL COMPOSITIONS THEREOF; U.S. Provisional Patent Application No. 60/843140, filed on September 8, 2006, entitled FOAMABLE VEHICLE AND VITAMIN PHARMACEUTICAL COMPOSITIONS THEREOF, all of which are incorporated herein by reference in their entirety. More particularly any of the active ingredients; the solvents; the surfactants; foam adjuvants; penetration enhancers; humectants; moisturizers; and other excipients as well as the propellants listed therein can be applied herein and are incorporated by reference.

[0259] The following examples further exemplify the benefit agent foamable pharmaceutical carriers, pharmaceutical compositions thereof, methods for preparing the same, and therapeutic uses of the compositions. The examples are for the purposes of illustration only and are not intended to be limiting of the invention. Many variations may be carried out by one of ordinary skill in the art and are contemplated within the full scope of the present invention.

METHODOLOGY

[0260] A general procedure for preparing foamable compositions is set out in WO 2004/037225, which is incorporated herein by reference.

Emulsion Foam

1. Mix oily phase ingredients and heat to 75°C to melt all ingredients and obtain homogeneous mixture.
2. Mix polymers in water with heating or cooling as appropriate for specific polymer.
3. Add all other water soluble ingredients to water-polymer solution and heat to 75°C.
4. Add slowly internal phase to external phase at 75°C under vigorous mixing and homogenize to obtain fine emulsion. Alternatively the external phase is added slowly to the internal phase.
5. Cool to below 40°C and add sensitive ingredients with mild mixing.
6. Cool to room temperature.

Waterless Foam

1. Dissolve the polymers in the main solvent with heating or cooling as appropriate for specific polymer. Add the all other ingredients and heat to 75°C to melt and dissolve the various ingredients.
2. Cool to below 40°C and add sensitive ingredients with mild mixing.
3. Cool to room temperature.

Oily Waterless Foam

1. Mix all ingredients excluding polymers and heat to 75°C to melt and dissolve and obtain homogeneous mixture.
2. Mix well and cool to below 40°C and add the polymers and sensitive ingredients with moderate mixing.
3. Cool to room temperature.

Oily Foam with phospholipids and/or water

1. Swell the phospholipids in the main oily solvent under mixing for at least 20 minutes until uniform suspension is obtained.
2. Add all other ingredients excluding polymers and heat to 75°C to melt and dissolve and obtain homogeneous mixture.
3. Mix well and cool to below 40°C and add the polymers and sensitive ingredients with moderate mixing.
4. Cool to room temperature.
5. In case of polymers dissolved in water or organic solvent, dissolve the polymers in the solvent with heating or cooling as appropriate for specific polymer and add to the oily mixture under vigorous mixing at ~40°C.

Canisters Filling and Crimping

Each aerosol canister is filled with PFF and crimped with valve using vacuum crimping machine.

Pressurizing

Propellant Filling

Pressurizing is carried out using a hydrocarbon gas or gas mixture

Padagis Ex. 1029
IPR Petition - USP 11,311,482

Canisters are filled and then warmed for 30 sec in a warm bath at 50°C and well shaken immediately thereafter.

Closure Integrity Test.

Each pressurized canister is subjected to bubble and crimping integrity testing by immersing the canister in a 60°C water bath for 2 minutes. Canisters are observed for leakage as determined by the generation of bubbles. Canisters releasing bubbles are rejected.

TESTS

[0261] By way of non limiting example the objectives of hardness, collapse time and FTC stability tests are briefly set out below as would be appreciated by a person of the art.

[0262] Hardness

LFRA100 instrument is used to characterize hardness. A probe is inserted into the test material. The resistance of the material to compression is measured by a calibrated load cell and reported in units of grams on the texture analyzer instrument display. Preferably at least three repeat tests are made. The textural characteristics of a dispensed foam can effect the degree of dermal penetration, efficacy, spreadability and acceptability to the user. The results can also be looked at as an indicator of softness. Note: the foam sample is dispensed into an aluminum sample holder and filled to the top of the holder.

[0263] Collapse Time

Collapse time (CT) is examined by dispensing a given quantity of foam and photographing sequentially its appearance with time during incubation at 36°C. It is useful for evaluating foam products, which maintain structural stability at skin temperature for at least 1 min.

[0264] Viscosity

Viscosity is measured with Brookfield LVDV-II + PRO with spindle SC4-25 at ambient temperature and 10, 5 and 1 RPM. Viscosity is usually measured at 10RPM. However, at about the apparent upper limit for the spindle of ~>50,000CP, the viscosity at 1RPM may be measured, although the figures are of a higher magnitude.

[0265] FTC (Freeze Thaw Cycles)

To check the foam appearance under extreme conditions of repeated cycles of cooling, heating, (first cycle) cooling, heating (second cycle) etc., commencing with -100°C (24hours) followed by +400°C (24hours) measuring the appearance and again repeating the cycle for up to three times.

[0266] Creaming by centrifugation:

1. Principle of test

   The centrifugation used in this procedure serves as a stress condition simulating the aging of the liquid dispersion under investigation. Under these conditions, the centrifugal force applied facilitates the coalescence of dispersed globules or sedimentation of dispersed solids, resulting in loss of the desired properties of the formulated dispersion.

2. Procedure

   2.1. Following preparation of the experimental formulation/s, allow to stand at room temperature for ≥ 24 h.

   2.2. Handle pentane in the chemical hood. Add to each experimental formulation in a 20-mL glass vial a quantity of pentane equivalent to the specified quantity of propellant for that formulation, mix and allow formulation to stand for at least 1 h and not more than 24 h.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

2.3. Transfer each mixture to 1.5 mL microtubes. Tap each microtube on the table surface to remove entrapped air bubbles.

2.4. Place visually balanced microtubes in the centrifuge rotor and operate the centrifuge at 3,000 rpm for 10 min or at 1,000 rpm for 10 min.

[0267] Intra-canister uniformity

1. Representative product containers are collected, sample test solutions are prepared and the content of the analyte is determined according to standard methods in the art. Variability of content is characterized as percent difference or relative standard deviation, as appropriate, according to the number of samples evaluated.

2. The results ascertain variability or uniformity within a given container in content of analytes (primarily active pharmaceutical ingredients, but also preservatives) taken from different parts of a pressurized canister drug products

3. Two full canisters were shaken according to product instructions. About 1-3g of Foam was dispensed from each canister and discarded. Foam sufficient for two replicate sample solution preparations was then dispensed into a glass beaker. This represents the initial sample. A middle portion is then dispensed from each canister being about half the canister contents. This middle dispensed portion may be discarded or collected for testing purposes, as necessary. Foam sufficient for two replicate sample solution preparations was then dispensed into a glass beaker. This represents the final sample. A small amount of formulation remains in the canister. The foam samples were stirred to remove gas / air bubbles. From both the initial and final foam portions from each canister 4 separate sample solutions are prepared and analyzed, 2 from the initial portion and 2 from the final portion. The percent difference is calculated as follows:

$$\frac{\text{Difference between content determined in initial \& final portions}}{\text{Mean of content of initial \& final portions}} \times 100$$

and the intra canister uniformity evaluated from the results.

STOCK COMPOSITIONS

[0268] Non-limiting examples of how stock solutions are made up with and without API. Other stock solutions may be made using the same methodology by simply varying adding or omitting ingredients as would be appreciated by one of the ordinary skills in the art.

Examples

[0269] The invention is described with reference to the following examples. This invention is not limited to these examples and experiments. Many variations will suggest themselves and are within the full intended scope of the appended claims.

SECTION A – AQUEOUS

A1 – EMOLLIENT FORMULATIONS

A1 - Example 1 – Vehicle composition containing diisopropyl adipate (DISPA)

The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

PHASE	Ingredient	GOG 08 %w/w	GOG 09 %w/w	GOG 10 %w/w	GOG 11 %w/w
Oil Phase (A)	Capric/caprylic triglyceride			10.00	10.00
	Diisopropyladipate (DISPA)	20.00	20.00	20.00	20.00
	Benzyl alcohol	2.00	2.00	2.00	2.00
	Oleyl alcohol	20.00	20.00	10.00	10.00
	PPG 15 stearyl ether	2.00	2.00	2.00	2.00
	Sorbitan laurate				1.50
	Sorbitan stearate	4.00	4.00	2.00	2.00
	Stearic acid	4.00	4.00	2.00	
	Stearyl alcohol				3.00
	Pemulen TR2	0.05		0.05	
Water Phase (B)	Hydroxypropyl methyl cellulose				0.15
	Xanthan gum				0.15
	Sucrose ester	2.00	2.00	1.00	2.00
	Propylene glycol	8.00	8.00	8.00	8.00
	Glycerin	5.00	5.00	5.00	8.00
	TEA	0.10	0.10	0.10	
	Water	37.85	32.90	37.85	31.20

Foam quality	E	E	G	E
Emulsion stability (10000 RPM)	Stable	Stable	Stable	Stable

[0270] Notes:

- Compositions GOG 08 and GOG 09 contain 20% DISPA and 20% oleyl alcohol to provide (1) high emolliency; (2) high solubilizing capacity of an oil-soluble active agent ; and (3) enhanced skin delivery of an active agent.
- Compositions GOG 10 and GOG 11 contain 20% DISPA, 20% oleyl alcohol and 10% capric/caprylic triglyceride to provide (1) enhanced emolliency; (2) high solubilizing capacity of an oil-soluble active agent ; and (3) enhanced skin delivery of an active agent.

- The compositions contain about 30% water. Therefore, they provide high skin barrier build-up effect.

- The compositions are oil in water emulsions, despite the fact that there is oil more than water in the formulation. Oil in water emulsion is maintained and stabiized by selecting a surfactant that favors oil in water emulsions over water in oil emulsions. Hence, the skin feeling of the composition is favorable.

- The surfactants, sorbitan laurate, sorbitan stearate and sucrose esters, are POE-free and hence this formulation may be used with active agents that are not compatible with POE.

- The compositions can be used as lotions for topical therapy of an inflammatory skin diorder.

- In order to create a foamable composition, the composition is filled into an aerosol canister and pressurized using a liquefied or gas propellant can be added at a concentration of about 3% to about 25%.

A1 - Example 2 –Vehicle composition containing diisopropyl adipate (DISPA)

The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

PHASE	Ingredient	GOG 13 %w/w	GOG 14 %w/w	GOG 15 %w/w
Oil Phase (A)	Capric/caprylic triglyceride	10.00	10.00	10.00
	Diisopropyladipate	20.00		
	Dimethyl sebacate		20.00	
	Dioctyl malate			20.00
	Benzyl alcohol	2.00	2.00	2.00
	Oleyl alcohol	10.00	10.00	10.00
	PPG 15 stearyl ether	2.00	2.00	2.00
	Sorbitan laurate		2.00	2.00
	Sorbitan stearate	2.00		
	Stearic acid			1.20
	Stearyl alcohol	3.00	1.00	
Water Phase (B)	Hydroxypropyl methyl cellulose	0.15	0.15	0.15
	Xanthan gum	0.15	0.15	0.15
	Sucrose ester HLB 16			
	Sucrose ester HLB 11	3.00	2.00	2.00
	Propylene glycol	17.70	17.70	17.70
	Glycerin			
	TEA			0.06
	Water	30.00	33.00	32.74

Foam quality	E	G	E
Emulsion stability (10000 RPM)	Stable	Stable	Stable

[0271] Notes:

- Composition GOG 13 contains 20% DISPA, 10% oleyl alcohol and 10% capric/caprylic triglyceride, to provide (1) enhanced emolliency; (2) high solubilizing capacity of an oil-soluble active agent ; and (3) enhanced skin delivery of an active agent.

- Composition GOG 14 contains 20% diethyl sebacate, 10% oleyl alcohol and 10% capric/caprylic triglyceride, to provide (1) enhanced emolliency; (2) high

solubilizing capacity of an oil-soluble active agent ; and (3) enhanced skin delivery of an active agent.

- Composition GOG 15 contains 20% dioctyl malate, 10% oleyl alcohol and 10% capric/caprylic triglyceride, to provide (1) enhanced emolliency; (2) high solubilizing capacity of an oil-soluble active agent ; and (3) enhanced skin delivery of an active agent.
- The compositions contain about 30% water. Therefore, they provide high skin barrier build-up effect
- The compositions are oil in water emulsions, despite the fact that there is oil more than water in the formulation. Hence, the skin feeling of the composition is favorable.
- The surfactants are POE-free: sorbitan laurate, sorbitan stearate and sucrose esters.
- The compositions can be used as lotions for topical therapy of an inflammatory skin diorder.
- In order to create a foamable composition, the composition is filled into an aerosol canister and pressurized using a liquefied or gas propellant can be added at a concentration of about 3% to about 25%.

A1 - Example 3 –Vehicle compositions containing 10% to 50% diisopropyl adipate (DISPA) as solvent

[0272] The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

	DCA001	DCA002	DCA003	DCA011
diisopropyl adipate (DISPA)	10.00	20.00	30.00	40.00
Steareth 2	3.06	3.67	4.89	4.89
Steareth 21	1.94	2.33	3.11	3.11
Carboxy methyl cellulose	0.50	0.50	0.50	0.50
Water purified	84.50	73.50	61.50	51.50
Total	**100.00**	**100.00**	**100.00**	**100.00**
Propellant propane, isobutene and butane mixture	8.00	8.00	8.00	8.00
Appearance:				
foam quality	E	E	E	E
color	White	White	White	White
odor	No odor	No odor	No odor	No odor
density	0.049	0.045	0.064	
collapse time		>300	>300	
Hardness		18.76	31.77	

[0273] Excellent foam formulations were prepared with DISPA, surfactant, and a nominal amount of polymeric agent.

[0274] In foamable compositions using less than 40 wt% DISPA, no solvent other than water is required to make foamable composition with resultant excellent foams. The use of a combination of ether-based or ester-based surfactants was found to be useful in forming excellent foams with a minimal number of ingredients. Without being bound by any particular theory or mode of operation, it is believed that the use of non-ionic surfactants with significant hydrophobic and hydrophilic components, increase the emulsifier or foam stabilization characteristics of the composition. Similarly, without being bound by any particular theory or mode of operation,using combinations of surfactants with high and low HLB's to provide a relatively close packed surfactant layer may strengthen the emulsion.

[0275] Visual test after addition of water indicated that DCA011 is an oil in water emulsion.

A1 - Example 4 – Minimal vehicle compositions, containing 40% diisopropyl adipate (DISPA) with and without polymer

[0276] The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

	DCA011	DCA011A
diisopropyl adipate (DISPA)	40.00	40.00
Steareth 2	4.89	4.89
Steareth 21	3.11	3.11
Carboxy methyl cellulose	0.50	
Water purified	51.50	52.00
Total	**100.00**	**100.00**
Propellant propane, isobutene and butane mixture	8.00	8.00

Appearance:		
foam quality	E	E
color	White	White
odor	No odor	No odor

[0277] Polymeric agents are introduced to improve foam. Surprisingly, it was possible to prepare excellent foam formulations without a polymeric agent from DISPA, surfactant, and water (and without a foam adjuvant or another solvent). This is especially surprising as the use of water in the composition is understood to benefit from the use of a polymeric agent that can thicken or increase the viscosity of the compositions and improve the resultant foam strength.

[0278] As in Example 3 and in Example 6, the combination of ether-based or ester-based surfactants was found to be useful in forming excellent foams with a minimal number of ingredients.

A1 - Example 5 –Vehicle compositions containing about 50% diisopropyl adipate (DISPA) with polymer

[0279] The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

	DCA012	**DCA013**
diisopropyl adipate (DISPA)	46.00	50.00
Steareth 2	4.58	
Steareth 21	2.92	
Isoceteth 20		3.00
Pemulen TR2		0.22
TEA		0.12
Carboxy methyl cellulose	0.50	
Water purified	46.00	46.66
Total	**100.00**	**100.00**
Propellant propane, isobutene and butane mixture	8.00	8.00
Appearance:		
foam quality	E	E
color	White	White
odor	No odor	No odor

- Increasing the amount of DISPA above 46% resulted in a poor foam and precipitation in formulations containing a polymer. Changing the surfactant to GMS eliminated the precipitation but the foam remained poor. Replacing the carboxy methyl cellulose polymeric agent with carbopol did not result in any improvement.

- Surprisingly, removal of the polymer at 50% DISPA, and steareth 21 and steareth 2 improved the foam quality but did not eliminate the precipitation.

- However, by changing the surfactants and polymeric agents it was possible to increase the level of the DISPA and achieve excellent foams without precipitation.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

- A combination of ether-based or ester-based surfactants was found to be useful in forming excellent foams with a minimal number of ingredients

- It has been discovered also that by using a derivatized hydrophilic polymer with hydrophobic alkyl moieties as a polymeric emulsifier it is possible to stabilize the emulsion better about or at the region of phase reversal tension. Other types of derivatized polymers like silicone copolymers, derivatized starch and derivatized dexrin may also a similar stabilizing effect.

A1 - Example 6–Vehicle compositions containing 60% diisopropyl adipate (DISPA) without polymer

[0280] The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

	DCA028	DCA029	DCA030	DCA031
diisopropyl adipate		60.00		60.00
diethyl sebacate	60.00		60.00	
Steareth 2			3.00	3.00
Steareth 21			2.00	2.00
PEG-40 Stearate	4.00	4.00		
Polysorbate 80	2.00	2.00		
Water purified	34.00	34.00	35.00	35.00
Total	**100.00**	**100.00**	**100.00**	**100.00**
Propellant (1681)	8.00	8.00	8.00	8.00
Appearance:				
foam quality	E	E	E	E
color	White	White	White	White
odor	No odor	No odor	No odor	No odor
1000 rpm for 10 mins	stable	stable	stable	stable
3000 rpm for 10 mins % creaming	80%	80%	stable	75%

DCA 028-80% Creaming, 029-80% Creaming, 030-Homogenous, 031-75% Creaming at 3K.

[0281] More surprisingly, by removal of the polymer and by reducing the levels of steareth 21 and steareth 2 (ethers) (by about 40 to 50%) it was possible to obtain excellent foams without precipitation at 60% DISPA and at 60% diethyl sebacate. .

[0282] Without being bound to any particular theory the physical change in the formulation may be due to DISPA reaching a concentration where phase reversal from o/w to w/o emulsion is possible. Also at this concentration range of DISPA removal of the polymeric agent, which itself can absorb water may –without being bound by any theory - have resulted in additional water being available and perhaps reducing internal emulsion tensions including any resulting from the presence of the polymeric agent and thereby unexpectedly resulting in improved foam quality even though polymeric agents are normally added to strengthen foam quality. Also as the concentration of DISPA increased and consequently the amount of water decreased it appears that the amount of surfactant required reduction as the external water phase is thinner.

[0283] It has also been discovered by using a different surfactant (ester based in place of an ether based) system it was possible to achieve compositions that can generate good quality foam and without precipitation with 60% DISPA or 60% diethyl sebacate in the absence of polymer. Addition of small amounts of xantham gum and methocel with 60% DISPA and the ester based surfactants resulted in poor foam.

[0284] It further appears to be the case that - without being limited by any theory - for any given emulsion system as the oil phase is increased with a corresponding decrease in the water phase the internal tension or pressure for phase reversal will increase and the point at which the phase reversal can occur can be retarded by selective use of non traditional derivatized polymeric agents with emulsifying properties, such as permulen that can stabilize the formulation and push back the point at which pressure for phase reversal might otherwise occur.

[0285] Surprisingly it was observed that more traditional polymeric agents like carboxy methyl cellulose or carbopol or combinations like xantham gum and methocel can interfere with foam formulation at higher levels of dicarboxylic esters.- all these formulations were examined by conductivity, by water addition test and by microscopic examination and were found to be oil in water emulsions despite the fact that the amount of oil phase was approximately double that of the aqueous phase.

A1 - Example 7 –Vehicle compositions containing 10% to 45% diethyl sebacate.

[0286] The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

	DCA004	**DCA005**	**DCA006**	**DCA024**	**DCA025**
diethyl sebacate	10.00	20.00	30.00	40.00	45.00
Steareth 2	4.00	5.00	5.33	6.00	6.00
Steareth 21	2.00	2.50	2.67	3.00	3.00
Carboxy methyl cellulose	0.50	0.50	0.50	0.50	0.50
Water purified	83.50	72.00	61.50	50.50	45.50
Total	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**
Propellant (1681)	8.00	8.00	8.00	8.00	8.00
Appearance:					
foam quality	E	E	E	E	E
color	White	White	White	White	White
odor	No odor	No odor	No odor	No odor	No odor
density	0.065	0.063	0.063		
collapse time	>300	>300	>300		
Hardness	17.23	24.67	27.39		

[0287] Excellent foam formulations were prepared with diethyl sebacate, surfactant, a nominal amount of polymeric agent and water (and without any foam adjuvant or another solvent).

A1 – Example 8 - DISPA Formulation to provide stable environment for Pimecrolimus

Part 1-Composition of Placebo or Stock Formulation PIMF-001P

Material	%w/w
Caprylic/capric triglyceride	10.00
Diisopropyl adipate (DISPA)	20.00
Oleyl alcohol	10.00
PPG-15 stearyl ether	2.00
Stearic acid	1.20
Sorbitan laurate	2.00
Benzyl alcohol	2.00
Methocel A4M (methylcellulose)	0.15
Xanthan gum	0.15
Sucrose stearic acid esters, mixture	2.00
Propylene glycol	17.70
Water purified	32.74
Trolamine (TEA)	0.06
Total	**100.00**
Propellant	8.00

[0288] Pimecrolimus is sensitive to polyethylene glycol polymers so it was necessary to develop formulations with emulsifying agents other than for example Twin, Myrj, or Brij surfactants, which are mainstream surfactants for pharmaceutical formulations. The combination of sorbitan laurate with sucrose stearic acid esters was found to be effective. Pimecrolimus is insoluble in water but is soluble in DISPA.

Part 2 - Pimecrolimus Content Determined by HPLC in PFF and Foam Formulation

Samples at Various Times and Storage Conditions

[0289] The formulations were comprised of 98.8%; 98.6% and 98.4% stock plus 1.2%, 1.4% and 1.6% pimecrolimus respectively.

Sample name		Zero time	14 days, 50°C, glass vials, PFF	30 days, 40°C, Foam	30 days, 50°C glass vials, PFF	30 days, 50°C canisters PFF
PIM 1.2%: batch PIMF001-060620	Result 1	1.12	1.14	1.22	1.05	1.13
	Result 2	1.12	1.13	1.22	1.05	1.13
	Average	1.12	1.14	1.22	1.05	1.13
PIM 1.4%: batch PIMF002-060620	Result 1	1.45	1.31	1.41	1.39	1.37
	Result 2	1.41	1.33	1.41	1.39	1.37
	Average	1.41	1.32	1.41	1.39	1.37
PIM 1.6%: batch PIMF003-060620	Result 1	1.58	1.5	1.59	1.56	1.55
	Result 2	1.58	1.5	1.59	1.56	1.56
	Average	1.58	1.5	1.59	1.56	1.56

[0290] As can be seen from the above there is no significant breakdown of the active agent after a month when solubilized in DISPA.

Part 3 - Physical Properties of PFF and Foam Preparations

	PFF		Foam Appearance		
Formula Name	**Centrifugation, 3000 rpm**	**Centrifugation, 10,000 rpm**	**Quality**	**Color**	**Odor**
PIMF001	stable	80% creaming	good	white	no odor
PIMF002	stable	stable	good	white	no odor
PIMF003	stable	95% creaming	excellent	white	no odor

[0291] The basic formulation is a liquid emulsion which is inherently not stable with a tendency to cream or separate. Two contradictory forces had to be overcome to produce a good to excellent stable foam. One is to have a liquid formulation that stabilizes the active agent and the other is to have a thick almost solid like constitution which resists or retards creaming and or separation. Nevertheless, by introducing into the formulation a mixture of non-poly ethylene glycol polymer surfactants, which can produce a strong and closed packed

barrier between the oil and the water that stabilizes the emulsion, together with polymeric agents that retard creaming and or separation whilst maintaining a fluid constitution, it was possible to stabilize the foam and active agent.

[0292] Microscopic examination disclosed that there were no crystals and that Pimecrolimus was solubilized.

A2 – SUSPENSIONS

A2 –Example 9 – Dicarboxylic acid composition

[0293] The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

Part A -Formulation

Ingredient	%w/w
Azelaic Acid	15.00
Water	51.90
Caprylic/Capric triglyceride	10.87
Propylene glycol	10.87
Dimethyl isosorbide	5.44
PEG-40 stearate	2.83
Cetostearyl alcohol	1.09
Polysorbate 80	0.98
Glyceryl stearate	0.54
Xanthan gum	0.27
Methylcellulose A4M	0.11
Benzoic acid	0.10
NaOH (18% Solution)	to pH=4.5
Total:	100

[0294] Notes

– The composition contains azelaic acid as a benefit agent, which is suitable for treating a skin disorder, selected from acne, rosacea, a pigmentation disorder, a cell proliferation abnormality a skin infection and a skin inflammation.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

- The composition contains about 10% capric/caprylic triglyceride to provide emolliency and about 10% propylene glycol and 10% dimethyl isosorbide, to provide (1) enhanced emolliency; (2) improved solubilizing capacity of the azelaic acid; and (3) enhanced skin delivery.

- The compositions contain about 50% water. Therefore, they provide high skin barrier build-up effect.

- The composition can be used as a cream/lotion for topical therapy of a skin diorder.

- In order to create a foamable composition, the composition is filled into an aerosol canister and pressurized using a liquefied or gas propellant can be added at a concentration of about 3% to about 25%.

Part B – 12 month stability test

Test parameter		T-0	T-12	
			upright	inverted
API* assay by HPLC (%)	% amount of label % w/w	99.3 14.90	100.5 15.07	101.7 15.26
Product content uniformity (Intra canister) of API (%)		1.79	0.10	0.88

*API = active pharmaceutical ingredient

[0295] The total amount of active agent at T-0 and at T-12 months as a percentage of 100% of ingredient that should be present according to the label and as a percentage in the formulation w/w, respectively was determined. As can be seen, no reduction in API content was observed within the limits of detection and that the content remained uniform. The differences between samples taken from the top of the canisters and from samples taken from the bottom of the canisters were not significant and were well within the acceptable range.

[0296] Furthermore, the formulation comprising active ingredient azaleic acid - despite being a suspension and subject to graviational effect - was able to withstand sedimentation and degredation such that it has remained stable and

Padagis Ex. 1029
IPR Petition - USP 11,311,482

uniformly distributed in the formulation as a suspension over a prolonged period of 12 months, whilst remaining flowable and shakable.

Example 10 – Additional dicarboxylic acid compositions

[0297] The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

Formulation :	AZL018	AZL034	AZL035	AZL036	AZL037	AZL038	AZL039
	%w/w	%w/w	%w/w	%w/w	%w/w	%w/w	%w/w
Azelaic Acid	15.00	15.00	15.00	15.00	15.00	15.00	15.00
Caprylic/capric triglyceride	5.00	10.00	5.00	5.00	5.00	5.00	10.00
Cetostearyl alcohol	0.90	1.00	1.00	1.00	1.00	1.00	1.00
Glyceryl stearate	0.45	0.50	0.50	0.50	0.50	0.50	0.50
Cholesterol	1.00	---	---	---	---	1.00	---
Benzoic acid		0.20	---	0.20	0.20	0.20	---
Benzyl alcohol	1.00	---	1.00	---	---	---	1.00
PEG-40 stearate		2.60	2.60	2.60	2.60	2.60	2.60
Methylcellulose		0.10	0.10	0.10	0.10	0.10	0.10
Hydroxypropyl methylcellulose	0.10	---	---	---	---	---	---
Xanthan gum	0.25	0.10	0.25	0.10	0.25	0.10	0.10
Polysorbate 80	0.90	0.90	0.90	0.90	0.90	0.90	0.90
EDTA disodium dehydrate	0.10	---	---	---	---	---	---
PEG-400	---	---	---	---	5.00	---	---
Dimethyl isosorbide	10.00	---	---	5.00	---	---	5.00
50% phosphotidylcholine in propylene glycol	---	2.80	2.80	---	2.80	---	2.80
propylene glycol	6.00	5.00	10.00	10.00	---	---	---
Sodium hydroxide	to pH=4.5	to pH=4.5	to pH=5.3	to pH=4.5	to pH=4.5	to pH=4.5	to pH=5.3
Propellant (butane+ isobutane + propane)	8.00	8.00	8.00	8.00	8.00	8.00	8.00
Purified water	to 100	to 100	to 100	to 100	to 100	to 100	to 100

Example 11 –Compositions with azalaic acid with and without different polymeric agents

[0298] The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

	DCA021	DCA023	DCA023A	DCA026	DCA026a
Isopropyl myristate				11.00	11.00
MCT oil		35.00	35.00		
Azelaic acid	20.00	15.00	15.00	15.00	15.00
Propylene glycol	30.00				
Steareth 2		8.00	8.00		
Steareth 21		2.00	2.00		
PEG-40 Stearate				4.00	6.00
Polysorbate 80	30.00			1.40	2.10
Xanthan gum	0.30			0.27	
Methocel A4M	0.30			0.11	
Carboxy methyl cellulose		0.50			
Water purified	19.40	39.50	40.00	68.22	65.90
Total	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**
Propellant (propane, isobutene and butane mixture	8.00	8.00	8.00	8.00	8.00
Appearance:					
foam quality	G-E	G-E	G-E	E	E
color	White	White	White	White	White
odor	No odor	No odor	No odor	No odor	No odor
Microscope	Crystals	Crystals	Crystals	Crystals	Crystals

[0299] Good to excellent foam formulations were prepared with azelaic acid, surfactant, polymeric agent, and either another oil or propylene glycol water (and without any foam adjuvant). Reducing the levels of azelaic acid to lower levels eliminated the appearance of crystals (See below).

[0300] Surprisingly, it was possible to prepare good to excellent foam after removal of the polymeric agent. Thus, the presence of a polymeric agent, is surprisingly not essential for foam quality. Nonetheless, polymeric agents may still contribute to and can be significant with respect to foam and active agent stability.

A3 – IN SOLUTION

Example 12 – Azalaic acid composition

[0301] The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

	DCA022
Azelaic acid	6.00
Propylene glycol	50.00
Polysorbate 80	20.00
Xanthan gum	0.30
Methocel A4M	0.30
Water purified	23.40
Total	**100.00**
Propellant) propane, isobutene and butane mixture	8.00
Appearance:	
foam quality	G-E
Color	White
Odor	No odor
Microscope	No crystals

Lower azaleic acid levels provide a soluble composition. No solids or precipitates are observed. No crystals were observed at the level of microscopic examination. By no crystals means the ingredients dissolve and it is not a suspension.

Example 13 –Compositions with diethyl salicylates azelate (TU-2100)

	DCA016	DCA017	DCA016A
PPG 15-Stearyl Ether (PPG)	40.00		40.00
Isopropyl myristate (IPM)		40.00	
TU-2100	10.00	10.00	10.00
Steareth 2	6.00	4.95	6.00
Steareth 21	1.50	3.00	1.50
Carboxy methyl cellulose	0.50	0.50	
Water purified	42.00	41.55	42.50
Total	**100.00**	**100.00**	**100.00**
Propellant propane, isobutene and butane mixture	8.00	8.00	8.00

Appearance:			
foam quality	G-E	G-	G-E
color	White	White	White
odor	No odor	No odor	No odor
Microscope	No crystals	No crystals	No crystals

[0302] When medium chain triglycerides were used as the emollient the formulation was poor. However, when they were substituted by PPG or IPM the foam quality increased substantially. Without being bound by any particular theory this may be because the formulations are close to phase reversal and or is due to internal tensions.

[0303] Good to excellent foam formulations were prepared with TU-2100, PPG or IPM, surfactant, polymeric agent, and water (and without any foam adjuvant). Surprisingly a good to excellent foam was produced even after removal of polymer.

SECTION B – NON AQUEOUS

B1 – Example 14 - PEG based non aqueous formulations with TU 2100

[0304] The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

	DCA014	DCA014A	DCA014B
TU-2100	10.00	10.00	10.00
PEG 400	87.50	85.00	88.00
Steareth 2	2.00	5.00	
Klucel EF	0.50		2.00
Total	**100.00**	**100.00**	**100.00**
Propellant propane, isobutene and butane mixture	8.00	8.00	8.00

Appearance:			
foam quality	G-E	G-E	G-E
Color	White	White	White
Odor	No odor	No odor	No odor
Microscope	No crystals	No crystals	No crystals

[0305] Surprisingly it was possible to make non aqueous PEG based minimal foam compositions of good to excellent quality with a) active ingredient , PEG, a single surfactant and optionally a polymeric agent and also with b) active ingredient , PEG, and a polymeric agent.

B2 – Example 15 - PG based non aqueous formulation with TU 2100 and with Azaleic acid

[0306] The following foamable vehicles were prepared and the quality of the resultant foam was ascertained.

	DCA015	DCA020
TU-2100	10.00	
Azelaic acid		9.00
PEG 400		
Propylene glycol	87.50	88.50
Steareth 2	2.00	2.00
Klucel EF	0.50	0.50
Total	**100.00**	**100.00**
Propellant propane, isobutene and butane mixture	8.00	8.00

Appearance:		
foam quality	G-E	G-E
color	White	White
odor	No odor	No odor
Microscope	crystals	No crystals

[0307] Surprisingly it was possible to make non aqueous PG based minimal foam compositions of good to excellent quality with active ingredient , PG, a single surfactant and a polymeric agent. Whilst TU 2100 was not soluble in the non aqueous PG based composition, azelaic acid was soluble.

Claims

What is claimed is:

1. A pharmaceutical or cosmetic composition comprising:

    e. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

    iii. a dicarboxylic acid; and

    iv. a dicarboxylic acid ester;

    f. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

    g. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients;

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

2. The composition of claim 1, wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition, is substantially flowable and provides a foam upon release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

3. The composition of claim 1, wherein the benefit agent comprises azelaic acid at a concentration of less than 6 wt%

4. The composition of claim 1, wherein the benefit agent, stabilizer and solvent are selected to generate an emulsion that is substantially resistant to phase reversal.

5. The composition of claim 1, the benefit agent, stabilizer and solvent are selected to generate a single phase.

6. The composition of claim 1, the benefit agent, stabilizer and solvent are selected to generate a substantially uniform suspension of benefit agent crystals.

7. The composition of claim 1, wherein the breakable foam comprises micro or nano particles, crystals or bodies.

8. The composition of claim 1, which is substantially resistant to one or more Freeze-Thaw cycles (FTC).

9. The composition of claim 1 wherein the surface-active agent is a solid, a liquid or a mixture thereof.

10. The composition of claim 1, wherein the surface active agent is selected from the group consisting of a polysorbate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, a

Padagis Ex. 1029
IPR Petition - USP 11,311,482

polyoxyethylene fatty acid ester, Myrj 45, Myrj 49, Myrj 52 and Myrj 59, a polyoxyethylene alkylyl ether, polyoxyethylene cetyl ether, polyoxyethylene palmityl ether, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, brij 38, brij 52, brij 56 and brij W1, a sucrose ester, a partial ester of sorbitol, sorbitan monolaurate, sorbitan monolaurate a monoglyceride, a diglyceride, isoceteth-20, a sucrose ester, or selected from the group consisting of steareth 2, glyceryl monostearate/PEG 100 stearate, Glyceryl Stearate, Steareth-21, peg 40 stearate, polysorbate 60, polysorbate 80, sorbitan stearate, laureth 4, Sorbitan monooleate, ceteareth 20, steareth 20, ceteth 20, Macrogol Cetostearyl Ether, ceteth 2, PEG-30 Dipolyhydroxystearate, sucrose distearate, polyoxyethylene (100) stearate, PEG 100 stearate, laureth 4, cetomacrogol ether, Cetearyl alcohol, Cetearyl glucoside, Oleyl alcohol, Steareth-2, Diisopropyl adipate, Capric/caprilic triglicerides, Polysorbate 20; Montanov 68.(CETEARYL ALCOHOL (and) CETEARYL GLUCOSIDE.), Sharonmix 824(a liquid blend of methyl paraben, ethyl paraben and propyl paraben - in phenoxyethanol), Simusol 165 (Glyceryl stearate and PEG-100 stearate). Methyl glucose sequistearate, Peg 30 dipolyhydroxystearate, sucrose stearic acid esters, sorbitan laureth, sorbitan stearate and mixtures thereof.

11. The composition of claim 1, wherein the surface active agent comprises at least one ester-based surfactant or at least one ether-based surfactant.

12. The composition of claim 1, wherein the surface active agent is reduced about in proportion to the increase in dicarboxylic ester.

13. The composition of claim 1 wherein the stabilizer is not a polymeric agent.

14. The composition of claim 1, wherein the surface active agent comprises a non-ionic surfactant that does not contain a polyoxyethylene (POE) moiety.

15. The composition of claim 13, wherein the surface active agent is selected from the group consisting of a non-ethoxylated sorbitan ester, a glycerol fatty acid ester, a sucrose ester and an alkyl polyglycoside or is selected from the group consisting of sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate, sorbitan sesquioleate, glycerol monostearate, glycerol monooleate, sucrose stearate, sucrose distearate, sucrose palmitate sucrose laurate and lauryl diglucoside.

16. The composition of claim 1 wherein the polymeric agent is selected from the group consisting of carbopol 934, pemulen TR2, klucel EF, xanthan gum, methocel A4M, and carboxy methyl cellulose or 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 aluminum starch octenylsuccinate (ASOS), PEG 1000, PEG 4000, PEG 6000 and PEG 8000.

17. The composition of claim 1 wherein the polymeric agent is a derivatized polymer.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

18. The composition of claim 1 wherein the derivatized polymer is a polymeric emulsifier.

19. The composition of claim 1 wherein the benefit agent is selected from the group consisting of diisopropyl adipate, dimethyl sebacate, dioctyl malate, diethyl sebacate, azelaic acid and TU-2100.

20. The composition of claim 1 further comprising an additional active agent.

21. The composition of claim 1, wherein the dicarboxylic acid has the molecular formula $HOOC-(CH_2)_n-COOH$; and wherein n is in the range between 0 and 32.

22. The composition of claim 21, wherein n is in the range between 4 and 10.

23. The composition of claim 1, 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 and dodecanedioic acid, maleic acid and fumaric acid.

24. The composition of claim 1, wherein the dicarboxylic acid is selected from the group consisting of adipic acid, azelaic acid and sebacic acid.

25. The composition of claim 2, further containing a foam adjuvant selected from the group consisting of a fatty alcohol having 15 or more carbons in their carbon chain; a fatty acid having 16 or more carbons in their carbon chain; fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain; a fatty alcohol having at least one double bond; a fatty acid having at least one double bond; a branched fatty alcohol; a branched fatty acid and a fatty acid substituted with a hydroxyl group.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

26. The composition of claim 1 further containing at least one organic carrier selected from the group consisting of a hydrophobic organic carrier, an emollient and mixtures thereof, at a concentration of about 2% to about 50% by weight.

27. The composition of claim 1, wherein the dicarboxylic acid or dicarboxylic acid ester is in a concentration between about 0.1% and about 60%.

28. The composition of claim 1, wherein the dicarboxylic acid is azelaic acid, and wherein the concentration of azelaic acid is between 5% and 25%.

29. The composition of claim 1, wherein the pH of the composition is below the first pKa of the dicarboxylic acid.

30. The composition of claim 1, wherein the pH of the composition is between the first and second pKa of the dicarboxylic acid.

31. The composition of claim 1, wherein the pH of the composition is above the second pKa of the dicarboxylic acid.

32. The composition of claim 1, wherein the dicarboxylic acid is azelaic acid the pH of the composition is below 5.3.

33. The composition of claim 1, wherein the dicarboxylic acid is azelaic acid the pH of the composition is between about 4.5 and about 5.3.

34. The composition of claim 1, wherein the dicarboxylic acid ester is selected from the group consisting of a mono ester of said dicarboxylic acid, and a diester of the dicarboxylic acid.

35. The composition of claim 33, wherein the alcohol moiety of the dicarboxylic acid ester is selected from the group consisting of an alkyl alcohol, an aryl alcohol, methyl alcohol, ethyl alcohol, propyl alcohol,

Padagis Ex. 1029
IPR Petition - USP 11,311,482

isopropyl alcohol, butyl alcohol, isobutyl alcohol, t-butyl alcohol, pentyl alcohol, hexyl alcohol, octyl alcohol, decyl alcohol, capryl alcohol, phenol and benzyl alcohol.

36. The composition of claim 33, wherein the alcohol moiety of the dicarboxylic acid ester is a biologically active alcohol.

37. The composition of claim 35, wherein the biologically active alcohol is selected from the group consisting of a hydroxyalkylbenzoate, salicylic acid, a dihydroxybenzene, hydroxytoluene, an alpha-hydroxy acid, retinol, a vitamin A derivative, a steroid, vitamin E, a vitamin E derivative, vitamin D and a vitamin D derivative.

38. The composition of claim 33, wherein the dicarboxylic acid ester is selected from the group consisting of diisobutyl adipate, diisopropyl adipate, diisopropyl sebacate, diisosteary dimer dilinoleate, diisostearyl fumerate, diisopropyl dimerate, diethyl adipate, diethyl sebacate, diethylhexyl adipate, diethylhexyl malate, dioctyl malate, diethyl succinate, and dioctyl sebacate.

39. The composition of claim 33, wherein the dicarboxylic acid ester is diisopropyl adipate, in an amount from about 0.1% to about 60%

40. The composition of claim 25, wherein the organic carrier is selected from the group consisting of mineral oil, triglycerides, medium chain triglyceride (MCT) oil, capric/caprylic triglyceride, alkyl esters of fatty acids such as isopropyl palmitate, isopropyl myristate, isopropyl isostearate, poly propylene glycol 15-stearly ether, 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, maleated soybean

Padagis Ex. 1029
IPR Petition - USP 11,311,482

oil, 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 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.

41. The composition of claim 25, wherein the organic carrier comprises a polypropylene glycol alkyl ether.

42. The composition of claim 1 further containing at least one polar solvent.

43. The composition of claim 41, wherein the polar solvent is selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, diethylene glycol, propylene glycol n-alkanols, terpenes, di-terpenes, tri-terpenes, limonene, terpene-ol, 1-menthol, dioxolane, ethylene glycol, other glycols, oleyl alcohol, alpha-hydroxy acids, such as lactic acid and glycolic acid, sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformanide, methyl dodecyl sulfoxide, dimethylacetamide, azone (1-dodecylazacycloheptan-2-one), 2-(n-nonyl)-1,3-dioxolane, alkanols, such as dialkylamino acetates, and admixtures thereof.

44. The composition of claim 39, wherein the organic carrier is capric/caprylic triglyceride and wherein the dicarboxylic acid is azelaic acid.

45. The composition of claim 41, wherein the polar solvent is selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid wherein the dicarboxylic acid is azelaic acid.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

46. The composition of claim 44, wherein the organic carrier is capric/caprylic triglyceride.

47. The composition of claim 39, wherein the organic solvent comprises at least one organic carrier, selected from the group capric/caprylic triglyceride, a polypropylene glycol alkyl ether an ester of a fatty acid and mineral oil and wherein the dicarboxylic acid ester is diisopropyl adipate .

48. The composition of claim 46, further comprising a polar solvent, selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid.

49. The composition of claim 1, wherein the benefit agent, stabilizer and solvent are selected to generate an emulsion that can produce a substantially strong and closed packed barrier between the oil and the water phases whilst maintaining a fluid constitution

50. The composition of claim 1, further comprising an additional component selected from the group consisting of a modulating agent, a polar solvent, 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 pH-adjusting agent, a preservative, a skin penetration enhancer, a sunscreen, a sun blocking agent, a sunless tanning agent, and a vitamin.

51. The composition of claim 39, wherein the organic carrier is selected from the group consisting of PPG 15-stearyl ether, isopropyl myristate and medium chain triglyceride oil and capric/caprylic triglyceride and the benefit agent is a solid at ambient temperature.

52. A therapeutic composition comprising:

Padagis Ex. 1029
IPR Petition - USP 11,311,482

a. a therapeutically effective amount of an active agent;

b. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

c. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

d. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

53. The therapeutic composition of claim 52, wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25%

by weight of the total composition, is substantially flowable and provides a foam upon release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

54. The therapeutic composition of claim 52, 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, antibacterials, antibiotics, antiburn agents, anticancer agents, antidandruff agents, antidepressants, antidermatitis agents, antiedemics, antihistamines, antihelminths, antihyperkeratolyte agents, antiinflammatory agents, antiirritants, antilipemics, antimicrobials, antimycotics, antiproliferative agents, antioxidants, anti-wrinkle agents, antipruritics, antipsoriatic agents, antirosacea agents antiseborrheic agents, antiseptic, antiswelling agents, antiviral agents, antiyeast agents, 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, skin whitening agents, vasoconstrictors, vasodilators, vitamins, vitamin D derivatives, wound healing agents and wart removers.

55. The foamable therapeutic composition of claim 52, wherein the dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the active agent.

56. The foamable therapeutic composition of claim 52, wherein the active agent is a steroid.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

57. The foamable therapeutic composition of claim 55, wherein the steroid is selected from the group consisting of bydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethsone dipropionate, clobetasol valemate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinolone, dichlorisone, difluprednate, flucloronide, flunisolide, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortmate, mepreddisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone.

58. The foamable therapeutic composition of claim 52, wherein the active agent is an immunomodulator.

59. The foamable therapeutic composition of claim 58, wherein the immunomodulator is selected from the group consisting of a cyclic peptides, cyclosporine, tacrolimus, tresperimus, pimecrolimus, sirolimus, verolimus, laflunimus, laquinimod and imiquimod.

60. The foamable therapeutic composition of claim 58, wherein the dicarboxylic acid ester is present in the composition in an amount sufficient to solubilize the immunomodulator.

61. The foamable therapeutic composition of claim 60, wherein the dicarboxylic acid ester is diisopropyl adipate.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

62. The composition of claim 52, wherein the surface active agent comprises a non-ionic surfactant that does not contain a polyoxyethylene (POE) moiety.

63. The composition of claim 62, wherein the surface active agent is selected from the group consisting of a non-ethoxylated sorbitan ester, a glycerol fatty acid ester,a sucrose ester and an alkyl polyglycoside or is selected from the group consisting of sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate, sorbitan sesquioleate, glycerol monostearate, glycerol monooleate, sucrose stearate, sucrose distearate, sucrose palmitate sucrose laurate and lauryl diglucoside.

64. The composition of claim 52, wherein the dicarboxylic acid is azelaic acid.

65. The composition of claim 64, further comprising an organic solvent comprising capric/caprylic triglyceride.

66. The composition of claim 65, further comprising at least one polar carrier, selected from the group consisting of dimethyl isosorbide, glycerol, propylene glycol, hexylene glycol, terpene-ol, oleyl alcohol, lactic acid and glycolic acid.

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

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

a. a therapeutically effective amount of an active agent;

b. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

Padagis Ex. 1029
IPR Petition - USP 11,311,482

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

c. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

d. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

68. The method of claim 67, wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition, is substantially flowable and provides a foam upon release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

69. The method of claim 67, 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.

70. The method of claim 67, 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, granuloma 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; and wherein the active agent is suitable for treating said disorderm or is selected from the group consisting of chlamydia infection, gonorrhea infection, hepatitis B,

herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranuloma venereum, mucopurulent cervicitis (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.

71. The method of claim 67, wherein the disorder is a dermatological disorder, which can be treated by a dicarboxylic acid or dicarboxylic acid ester.

72. The method of claim 67, wherein the disorder is a dermatological disorder, which can be treated by a topical steroid, an immunomodulator or an anti-infective agent.

73. The method of claim 67, wherein the disorder is selected from atopic dermatitis and psoriasis; and the active agent is selected from (i) steroid; and (ii) a combination of steroid and an additional non-steroidal active agent.

74. The method of claim 67, wherein the disorder is selected from psoriasis and atopic dermatitis and the active agent comprises an immunomodulator.

75. A pharmaceutical or cosmetic non aqueous composition comprising:

Padagis Ex. 1029
IPR Petition - USP 11,311,482

a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

c. a solvent selected from the group consisting of a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

76. The composition of claim 75, wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition, is substantially flowable and provides a foam upon

Padagis Ex. 1029
IPR Petition - USP 11,311,482

release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

77. A therapeutic composition comprising:

a. a therapeutically effective amount of an active agent wherein the active agent is substantially insoluble in water;

b. a beneficially or therapeutically effective concentration of at least one benefit agent, comprising a dicarboxylic acid ester in which the active agent is substantially soluble;

c. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

d. a solvent selected from the group consisting of water; a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the benefit agent is an emollient solvent and or a pharmaceutical or cosmetic agent;

wherein the polymeric agent is about 0.01% to about 5% by weight and is selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent;

wherein the benefit agent, stabilizer and solvent are selected to provide a composition that is substantially resistant to aging and to phase separation and or can substantially stabilize other active ingredients; and

wherein if the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

78. The therapeutic composition of claim 77, wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition, is substantially flowable and provides a foam upon release and wherein the benefit agent, stabilizer and solvent are selected to generate a breakable foam of good to excellent quality.

79. The composition of claim 78, wherein the benefit agent, stabilizer and solvent are selected to generate an emulsion that can produce a substantially strong and closed packed barrier between the oil and the water phases whilst maintaining a fluid constitution.

80. A foamable composition comprising:

a. a liquid dicarboxylic acid ester, said ester having emollient properties;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof; and

c. an active agent, said active agent soluble in or having enhanced penetration due to the dicarboxylic acid;

wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

81. The composition of claim 80, wherein the stabilizer comprises a ether-based or ester-based surfactant.

82. The composition of claim 80 wherein the stabilizer comprises an alkyl-derivatized polymer having polymeric emulsifying properties.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

83. The composition of claim 80, further comprising water, wherein the composition is an oil in water emulsion.

84. The composition of claim 83, wherein the dicarboxylic acid ester comprises about or more than 50 wt% of the composition.

85. A foamable composition comprising:

i. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

j. an ester-based or ether-based surfactant;

k. a solvent selected from the group consisting of a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the composition is substantially free of polymeric material, and

wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release.

86. The composition of claim 85, further comprising an active agent.

87. The composition of claim 86, wherein active agent is otherwise insoluble or unstable, but is solubilized or stabilized by DCA.

88. A pharmaceutical or cosmetic composition comprising:

Padagis Ex. 1029
IPR Petition - USP 11,311,482

a. a beneficially or therapeutically effective concentration of at least one benefit agent, selected from the group consisting of

i. a dicarboxylic acid; and

ii. a dicarboxylic acid ester;

b. a stabilizer selected from the group consisting of at least one surface-active agent; at least one polymeric agent and mixtures thereof.

c. a solvent selected from the group consisting of a hydrophilic solvent; a hydrophobic solvent; a potent solvent; a polar solvent, a silicone, an emollient, and mixtures thereof;

wherein the composition is substantially free of water

wherein the composition is contained in a pressurized container and further comprises a liquefied hydrocarbon gas propellant at a concentration of about 3% to about 25% by weight of the total composition it is substantially flowable and provides a foam upon release

89. The composition of claim 88, further comprising an additional component selected from the group consisting of a modulating agent, a polar solvent, 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, a moisturizer, an occlusive agent, a penetration enhancer, a perfuming agent, a permeation enhancer, a pH-adjusting agent, a preservative, a skin penetration enhancer, a sunscreen, a sun blocking agent, a sunless tanning agent,

90. The composition of claim 1 in a non foam state.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

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(54) Title: COMPOSITIONS WITH MODULATING AGENTS

(57) Abstract: The present invention relates to a waterless composition and foam as a vehicle in which an active pharmaceutical or cosmetic agent, when added is stable or stabilized by or its destabilization is impeded by the presence of a modulating agent. The pharmaceutical or cosmetic composition and foam, includes: a waterless solvent, a modulating agent and one or more active pharmaceutical or cosmetic agents. The present invention also relates to a method of treatment administering the waterless compostition and foam.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

COMPOSITIONS WITH MODULATING AGENTS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. §119(e) of U.S. Provisional Application Serial No. 60/861620, filed on November 29, 2007, which is hereby incorporated by reference.

[0002] This application is a continuation-in-part application of co-pending United States Patent Application Serial No. 10/835505, filed on April 28, 2004, which claims the benefit of priority under 35 U.S.C. §119(e) to United States Patent Application Serial No. 60/530015, filed on December 16, 2003, and United States Patent Application Serial No. 60/492385, filed on August 4, 2003, all hereby incorporated in their entirety by reference.

[0003] This application is a continuation in part of U.S. Patent Application No. 11/430599, filed on May 9, 2006, which claims the benefit under 35 U.S.C. §119(e) of U.S. Provisional Patent Application No. 60/784793, filed on March 21, 2006, and of U.S. Provisional Patent Application No. 60/679020, filed on May 9, 2005, which are herein incorporated by reference in its entirety.

BACKGROUND

[0004] This invention relates to pharmaceutical and cosmetic compositions, particularly waterless compositions.

[0005] External topical administration is an important route for the administration of drugs in disease treatment. Many groups of drugs, including, for example, antibiotic, anti-fungal, anti-inflammatory, anesthetic, analgesic, anti-allergic, corticosteroid, anti-psoriasis, retinoid, vitamins and anti-proliferative medications are preferably administered in hydrophobic media, namely ointment. However, ointments often form an impermeable barrier, so that metabolic products and excreta from the wounds to which they are applied are not easily removed or drained away. Furthermore, it is difficult for the active drug dissolved in the carrier to pass through the white petrolatum barrier layer into the wound

tissue, so the efficacy of the drug is reduced. In addition, ointments and creams often do not create an environment for promoting respiration of the wound tissue and it is not favorable to the normal respiration of the skin. An additional disadvantage of petroleum jelly-based products relates to the greasy feeling left following their topical application onto the skin, mucosal membranes and wounds. A further problem of non aqueous compositions is achieving formulations in which the active agent is stable.

[0006] Some active agents are known to be generally unstable or susceptible to isomerisation or to breakdown, resulting in loss of activity and the use of stabilizers, anti oxidants antimicrobials and buffers and the like in aqueous compositions to protect active or cosmetic agents is known. The problems of protecting active pharmaceutical and cosmetic agents in waterless environments, such as polar compositions are multifold and can vary according to the type of waterless environment and the nature of the agent being used. It has been surprisingly found that factors like small levels of acid residues in the raw materials can be significant in influencing agent stability. Similarly, the presence of low levels of metal ions can act to catalyze reactions or breakdown. Likewise, the presence of agents in a waterless environment that results in ionization or leads to oxidation can act to cause reactions or breakdown. There is therefore a need for simple and elegant solutions to stabilize active ingredients in a waterless or substantially environment.

[0007] It would be particularly advantageous and there is an unmet need to have a waterless vehicle addative that is suitable for use not merely one type of API but is adaptable for use with one or more API's from a wide range of different types of API's with relatively minimal or minor adjustment.

[0008] Foams and, in particular, foam emulsions are complicated systems which do not form under all circumstances. Changes in foam emulsion composition, such as by the addition of active ingredients may destabilize the foam. There is, therefore, a need for a foam composition, which provides

desirable properties to the skin and can remain stable whilst accommodating a variety of active ingredients.

[0009] Formulations based on oil or ointment, emollients have a number of useful attributes making them suitable candidates for topical pharmaceutical and cosmetic compositions including foamable compositions. They are inherently stable and inert which are clearly desirable characteristics. They are able to moisturize and soften the skin and in appropriate amounts can act as a protective or barrier layer and can form a barrier to water. By appropriate formulation they can act to improve drug delivery to the skin and yet remain resistant to being washed off. On the other hand they are by their nature greasy materials and can be difficult to formulate particlarly into a topical foamable composition that can deliver substantially uniform and stable composition or foam that ameliorates or overcomes the look and feel of a greasy material, especially where that composition is waterless or substantially so. It is further a problem to incorporate into such a vehicle pharmaceutically effective amounts of one or more active pharmaceutical ingredients such that they are uniformly present throughout the formulation and are effectively delivered without the use of an alcohol in the formulation.

[0010] On one level it is far from simple or obvious to produce waterless foamable compositions that when released produce foams of quality suitable for pharmaceutical or cosmetic application. On a further level having realized a carrier that will produce a waterless foam of quality there is an additional difficulty to be overcome, namely how to adapt the formula and achieve a formulation, which can accept a range of various active pharmaceutical and cosmetic agents such that the composition and active agent are stable and the foam produced remains of quality. Specifically, one of the challenges in preparing such waterless or substantially waterless foamable compositions is ensuring that the active pharmaceutical or therapeutic agent does not react, isomerizes or otherwise break down to any significant extent during is storage and use. Particularly, there remains an unmet need for improved, easy to use, stable and non-irritating foam

formulations, with unique therapeutic or beneficial properties containing a stable or stabilized active pharmaceutical or cosmetic agent.

[0011] There remains an unmet need for improved, easy to use, stable and non-irritating topical foam formulations containing a stable or stabilized active pharmaceutical or cosmetic agent having a therapeutic or beneficial effect, intended for treatment of dermal and mucosal tissues.

SUMMARY

[0012] The present invention relates to a waterless composition as a vehicle in which an active pharmaceutical or cosmetic agent, when added is stable or stabilized.

[0013] The present invention also relates to a foamable waterless composition as a vehicle in which an active pharmaceutical or cosmetic agent, when added is stable or stabilized by the presence of a modulating agent.

[0014] The present invention more particularly relates to modulating agents that are able to be effective in relatively low concentrations and which have little or no significant effect on the compositions and on the foam compositions of the present invention. **[0015]** According to one or more embodiments there is provided a waterless composition as a vehicle in which a modulating agent is incorporated and which is capable of stabilizing an active pharmaceutical or cosmetic agent, when added.

[0016] According to one or more embodiments there is provided a waterless vehicle, an active agent that is susceptible, to one or more of reaction, breakdown, ionization or oxidation and a modulating agent. In an embodiment the waterless vehicle comprises a hydrophobic solvent. In another embodiment it comprises a hydrophilic solvent.

[0017] According to one or more embodiments, the carrier, includes: a waterless solvent, a stabilizing surfactant, and or a polymeric agent, and in which is incorporated a modulating agent.

[0018] According to one or more embodiments, the carrier is a foamable carrier, and includes: a waterless solvent, a stabilizing surfactant, and or a polymeric agent, and a propellant and in which is incorporated a modulating agent.

[0019] In an embodiment the carrier and modulating agent formulation is capable of stabilizing an active pharmaceutical or cosmetic agent in a substantially waterless environment.

[0020] According to one or more embodiments there is provided 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.

[0021] According to one or more embodiments of the present invention, pharmaceutical or cosmetic composition is foamable and, includes: a waterless solvent, a stabilizing surfactant, and or a polymeric agent, a modulating agent, a propellant and one or more active pharmaceutical or cosmetic agents.

[0022] According to one or more embodiments of the present invention, the active agent itself can have characteristics of a modifying agent.

[0023] According to one or more embodiments of the present invention, the carrier, includes:

a. a waterless solvent comprising 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;

b. a modulating agent;

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

wherein the carrier is shakable and wherein if the composition is stored in an aerosol container and comprises a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition it will upon release expand to form a breakable foam.

[0024] According to one or more embodiments the active agent is susceptible to reaction, breakdown, ionization, or oxidization.

[0025] According to one or more embodiments of the present invention, the foamable pharmaceutical composition, includes:

1. a waterless solvent comprising 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;
2. a modulating agent;
3. a stabilizing agent selected from the group consisting of a surface-active agent and about 0.01% to about 5% by weight of at least one polymeric agent;
4. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition; and
5. an effective amount of an active pharmaceutical or cosmetic agent;

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

[0026] According to one or more embodiments there is provided 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.

[0027] The present invention further relates to said composition comprising one or more additional active agents.

[0028] The present invention further relates to said composition comprising one or more additional or secondary polar solvents.

[0029] In some embodiments, the foamable cosmetic or pharmaceutical composition is non-flammable, wherein said gas propellant contains hydrofluorocarbon.

[0030] According to one or more embodiments there is provided 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.

[0031] According to one or more embodiments there is also provided 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.

[0032] According to one or more embodiments there is also provided 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.

[0033] According to one or more embodiments there is also provided a carrier where the modulating agent acts by impeding ionization and or by impeding oxidation.

[0034] According to one or more embodiments there is also provided 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.

[0035] The present invention further provides a method of treating, alleviating or preventing a disorder of mammalian subject, comprising administering a therapeutically effective amount of the above-mentioned compositions to an afflicted target site.

[0036] The present invention further provides use of a therapeutically effective amount of the above-mentioned compositions as a medicament or in the manufacture of a medicament.

[0037] The present invention further provides a therapeutically effective amount of the above-mentioned compositions for use as a medicament or in the manufacture of a medicament.

[0038] All % values are provided on a weight (w/w) basis.

DETAILED DESCRIPTION

[0039] In one or more embodiments there is provided a waterless composition for use as a vehicle in which an active pharmaceutical or cosmetic agent, when added is stable or stabilized. Active pharmaceutical and cosmetic agents are more generally referred to as a therapeutic agent.

[0040] In one or more embodiments there is provided a waterless composition as a vehicle in which a modulating agent is incorporated and which is capable of stabilizing an active pharmaceutical or cosmetic agent, when added.

[0041] In an embodiment the carrier and modulating agent formulation is capable of stabilizing an active pharmaceutical or cosmetic agent in a substantially waterless or mon aqueous environment.

[0042] In an embodiment the carrier and modulating agent formulation is capable of stabilizing an active pharmaceutical or cosmetic agent in a substantially waterless environment, where the active agent has low or minimal susceptibility to water and can withstand up to about 10% water and more preferably upto about 5% water.

[0043] In one or more embodiments there is provided a waterless composition for use as a vehicle in which an active pharmaceutical or cosmetic agent, when added is stable or stabilized by the presence of a modulating agent.

[0044] In one or more embodiments there is provided a foamable waterless composition for use as a vehicle in which an active pharmaceutical or cosmetic agent, when added is stable or stabilized by the presence of a modulating agent.

[0045] According to one or more embodiments, it is possible to make excellent lotions, creams, ointments and foams from waterless compositions. Such

compositions containing a modulating agent as described herein are ideal carriers for active pharmaceutical ingredients that are soluble in polar solvents and which may be potentially unstable in an aqueous environment, for example, following a change in pH, or the introduction a metal catalyst or in the presence of an ionization or oxidation agent.

[0046] It has been found that differences in the level and type of residues in cosmetic and pharmaceutical grade materials and agents can significantly and seriously influence the stability of an active pharmaceutical or cosmetic agent. Whilst it might be expected that active agents would be more stable in pure raw materials with practically no residues it was surprisingly observed that small levels of residues in raw materials were actually helpful in improving the stability of and stabilizing active ingredients in certain waterless compositions. On the other hand active ingredients were unstable in certain other waterless compositions.

[0047] In the waterless polar environments the concepts of pH, pK, and the like are artificial and may only give approximate guidance. It has been surprisingly found that in a non-classical waterless polar environment of foamable carriers, compositions and foam's that active ingredients can be susceptible to break down, isomerization, oxidisation or reaction in the presence of acid or basic residues, which in small quantities are able in a non classical way to take the active agent outside its preferred environmental window and facilitate instability. Likewise such breakdown etc. could be catalyzed by the presence of metal ions in the waterless polar environment. Following investigation it has been discovered that the introduction of an acid or base or buffer in a non classical non-aqueous polar environment of foamable carriers, compositions and foam's can act to prevent or impede such breakdown etc,. Similarly, the introduction of a chelating agent can also act to prevent or impede catalyzation of such breakdown etc. Likewise, introduction of an anti ionization or antioxidation agent may also act to prevent or impede such reaction etc.

[0048] It has been surprisingly discovered that one can modulate the environment of a non-aqueous foamable, carrier, composition or foam to provide a stable environmental window for the active agent in the non-aqueous environment. The modifying or modulating affect of the modulating agent on the waterless environment prevents or minimizes a so-called 'change in the artificial pH range' and/or locks up available metal ions which could otherwise act as a catalyst in the waterless environment and/or impedes ionization or oxidation of the active agent .

[0049] Following investigation, modulating agents are identified, which by their presence are able to stabilize active pharmaceutical or cosmetic agents in a waterless or substantially waterless environment. More particularly, they can be effective at relatively low concentrations that have little or no significant effect on the foam compositions of the present invention.

[0050] According to one or more embodiments there is provided a waterless composition as a vehicle in which a modulating agent is incorporated and which is capable of stabilizing an active pharmaceutical or cosmetic agent, when added.

[0051] According to one or more embodiments there is provided a waterless vehicle, an active agent that is susceptible, to one or more of reaction, breakdown, ionization or oxidation and a modulating agent. In an embodiment the waterless vehicle comprises a hydrophobic solvent. In another embodiment it comprises a hydrophilic solvent.

[0052] According to one or more embodiments, the carrier, includes: a waterless solvent, a stabilizing surfactant, and or a polymeric agent, and in which is incorporated a modulating agent.

[0053] According to one or more embodiments, the carrier is a foamable carrier, and includes: a waterless solvent, a stabilizing surfactant, and or a polymeric agent, and a propellant and in which is incorporated a modulating agent.

[0054] According to one or more prefered embodiments, the carrier comprises a stabilizing agent comprising a surfactant and a polymeric agent. This is particularly helpful for foamable compositions where the combination can be synergistic or complimentary in providing a robust stable foam of quality with a reasonable collase time.

[0055] In an embodiment the carrier and modulating agent formulation is capable of stabilizing an active pharmaceutical or cosmetic agent in a substantially waterless environment.

[0056] According to one or more embodiments, pharmaceutical or cosmetic composition is foamable and, includes: a waterless solvent, a stabilizing surfactant, and or a polymeric agent, a modulating agent, a propellant and one or more active pharmaceutical or cosmetic agents.

[0057] According to one or more embodiments, the active agent itself can have characteristics of a modifying agent.

[0058] According to one or more embodiments, the carrier, includes:

(a) a waterless solvent comprising 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;

(b) a modulating agent;

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

wherein the carrier is shakable or flowable and wherein if the composition is stored in an aerosol container and further comprises a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition it will upon release expand to form a breakable foam.

[0059] According to one or more embodiments the active agent is susceptible to reaction, breakdown, ionization, or oxidization.

[0060] According to one or more embodiments, the active agent itself can have characteristics of a modifying agent.

[0061] According to one or more embodiments, the foamable carrier, includes:

1. a waterless solvent comprising 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;
2. a modulating agent;
3. a stabilizing agentselectedfrom from the group consisting of a surface-active agent;and about 0.01% to about 5% by weight of at least one polymeric agent and mixtures thereof; and
4. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition;

wherein the composition is shakable or flowable; and

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

[0062] According to one or more embodiments, the foamable pharmaceutical composition, includes:

1. a waterless solvent comprising 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;
2. a modulating agent;
3. a surface-active agent;
4. about 0.01% to about 5% by weight of at least one polymeric agent;

5. a liquefied or compressed gas propellant at a concentration of about 3% to about 25% by weight of the total composition; and
6. an effective amount of an active pharmaceutical or cosmetic 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.

[0063] The problem of producing a pharmaceutical composition that can provide a stable or stabilized environment or or he more formidable problem a foamable composition which can produce a breakable foam of quality and a stabilized envirinment so that the active pharmaceutical agent does not substantially break down over a reasonable time period sufficient for normal pharmaceutical or cosmetic use is surprisingly resolved by having both a polymeric agent and modulating agent present in the foamable composition.

[0064] In one or more embodiments the polymeric agent is selected from a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent and can be from about 0.01% to about 5% by weight, preferably 0,2 to 3%.

[0065] In one or more embodiments the ratio of polymeric agent to surfactant is about 1:10 to about 10:1; about 1:5 to about 5:1; about 3:7 to about 7:3; and about 2:1 to about 1:2.

[0066] The provision and selection of polymeric agent is however not straightforward. The polymers should be miscible or swell in the waterless solvent. It has been found that in the case of modified cellulose that lower molecular weight cellulose polymer derivatives are preferable.

[0067] In one or more preferred embodiments the polymeric agent is hydroxypropyl cellulose.

[0068] In another preferred embodiments the polymeric agent is or Carbomer such as Carbopol 934®.

[0069] According to one or more embodiments, the pre-foamable carrier; the pre-foamable pharmaceutical or cosmetic composition; the foamable carrier, or the foamable pharmaceutical or cosmetic composition further includes 0.1% to about 75% of a secondary polar solvent.

[0070] In one or more embodiments there is provided a vehicle additive, preferably a foamable vehicle additive that is suitable for use with not merely one type of active pharmaceutical ingredient ("API") but is adaptable for use with one or more API's from a wide range of different types of API's with appropriate and usually relatively minimal or minor adjustment. For example, by altering the amount of a component or by the addition or replacement of a buffer, stabilizer, anti ionization agent or an antioxidant as would be appreciated by a person skilled in the art with the benefit of the teachings herein. In one or more other embodiments there is provided one or more pharmaceutical or cosmetic base compositions that are suitable for use with modulating agents.

[0071] In one or more embodiments there is provided a vehicle additive, preferably a foamable one that is suitable for use as a vehicle base for delivery for API's, which are by their nature unstable or reactive or isomerizes or oxidize..

[0072] In a further embodiment the modulating agent is preferably between about 0.05% to about 5% by weight of the composition.

[0073] In a further embodiment the surfactant and polymeric agent and their amounts are selected so that the composition is sufficiently shakable or in certain limited cases so that it is flowable albeit not shakable so that extrusion and substantially uniform composition formation, particularly foam extrusion and formation is not hampered. To this extent, the maximum effective amount of surfactant and polymeric agent that may be used may be limited by the need for shakability and as a minimum by the need for flowability.

[0074] In a further embodiment of the present invention the propellant is preferably between about 5% to about 12% by weight of the composition.

[0075] In one or more embodiments of the pharmaceutical or cosmetic foamable product is non-flammable.

[0076] By waterless is meant that the composition contains no or substantially no, free or unassociated or absorbed water. It will be understood by a person of the art that the waterless solvents and substances miscible with them of the present invention can be hydrophilic and can contain water in an associated or unfree or absorbed form and may absorb water from the atmosphere and the ability to do so is its hygroscopic water capacity.

[0077] In one or more embodiments the carrier comprises an active pharmaceutical or cosmetic agent, which degrades in the presence of water, and in such cases the present of water in the composition is clearly not desirable. Thus, in certain preferred embodiments, the composition is waterless. In other embodiments the active agent may tolerate the presence of a small amount of water and the waterless composition is substantially non-aqueous. The term "substantially non-aqueous" is intended to indicate that the waterless composition has water content below about 5%, preferably below about 2%, such as below about 1.5%.

[0078] In one or more embodiments the active agent has low or minimal sensitivity and can tolerate water to about 10% or less.

[0079] Upon release from an aerosol container, the foamable carrier forms an expanded foam suitable for the treatment of an infected surface and for topical administration to the skin, a body surface, a body cavity or a mucosal surface.

Waterless solvent

[0080] In one or more embodiments of the present invention the waterless solvent comprises about 25% to about 98% of at least a polar solvent selected from the group consisting of (1) a polyol; and (2) a polyethylene glycol or combinations thereof.

[0081] In one or more embodiments of the present invention the waterless solvent comprises about 0.1% to about 75% of a secondary polar solvent.

Polar solvent

[0082] The identification of a "polar solvent", as used herein, is not intended to characterize the solubilization capabilities of the solvent for any specific active agent or any other component of the foamable composition. Rather, such information is provided to aid in the identification of materials suitable for use as a part in the foamable compositions described herein.

Polyol

[0083] In an embodiment of the present invention, the polar solvent is a polyol. A polyol is an organic substance that contains at least two hydroxy groups in its molecular structure.

[0084] In one or more embodiments, the foamable carrier contains at least one diol (a compound that contains two hydroxy groups in its molecular structure). Examples of diols include propylene glycol (e.g., 1,2-propylene glycol and 1,3-propylene glycol), butanediol (e.g., 1,2-butanediol, 1,3-butanediol, 2,3-butanediol and 1,4-butanediol), butanediol (e.g., 1,3-butanediol and 1,4-butenediol), butynediol, pentanediol (e.g., pentane-1,2-diol, pentane-1,3-diol, pentane-1,4-diol, pentane-1,5-diol, pentane-2,3-diol and pentane-2,4-diol), hexanediol (e.g., hexane-1,6-diol hexane-2,3-diol and hexane-2,56-diol), octanediol (e.g., 1,8-octanediol), neopentyl glycol, 2-methyl-1,3-propanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, dipropylene glycol and dibutylene glycol.

[0085] In one or more embodiments, the foamable carrier contains at least one triol (a compound that contains three hydroxy groups in its molecular structure), such as glycerin, butane-1,2,3-triol, butane-1,2,4-triol and hexane-1,2,6-triol.

[0086] In one or more embodiments, the polyol is a mixture of polyols. In one or more embodiments, the mixture of polyols contains at least one diol and at least one triol. According to certain embodiments the ratio between the diol and triol is between 9:1 and 1:1.

[0087] In one or more embodiments, part of mixture of polyols is a saccharide. Exemplary saccharides include, but are not limited to monosaccharide, disaccharides, oligosaccharides and sugar alcohols.

[0088] A monosaccharide is a simple sugar that cannot be hydrolyzed to smaller units. Empirical formula is (CH2O)n and range in size from trioses (n=3) to heptoses (n=7). Exemplary monosaccharide compounds are ribose, glucose, fructose and galactose.

[0089] Disaccharides are made up of two monosaccharides joined together, such as sucrose, maltose and lactose.

[0090] A sugar alcohol (also known as a polyol, polyhydric alcohol, or polyalcohol) is a hydrogenated form of saccharide, whose carbonyl group (aldehyde or ketone, reducing sugar) has been reduced to a primary or secondary hydroxyl group. They are commonly used for replacing sucrose in foodstuffs, often in combination with high intensity artificial sweeteners to counter the low sweetness. Some exemplary sugar alcohols, which are suitable for use according to the present invention are mannitol, sorbitol, xylitol, maltitol, lactitol. (Maltitol and lactitol are not completely hydrogenated compounds - they are a monosaccharide combined with a polyhydric alcohol). Mixtures of polyols, including (1) at least one polyol selected from a diol and a triol; and (2) a saccharide are contemplated within the scope of the present invention.

Polyethylene glycol

[0091] In an embodiment of the present invention, the polar solvent consists of a polymerized ethylene glycol, namely polyethylene glycol, which is also termed "PEG". Exemplary PEGs are provided in the following table.

Composition	Av. Molecular weight	Appearance	Melting point (°C)
PEG 200	190 ~ 210	Oily liquid	
PEG 300	285 ~ 315	Oily liquid	
PEG 400	380 ~ 420	Oily liquid	
PEG 600	570 ~ 630	Oily liquid	17 ~ 22
PEG 1000	950 ~ 1050	Solid	35 ~ 40
PEG 4000	3800 ~ 4400	Solid	53 ~ 58
PEG 6000	5600 ~ 6400	Solid	55 ~ 60
PEG 8000	7500 ~ 8500	Solid	58 ~ 65

[0092] Thus, in an embodiment of the present invention, 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. The foamable carrier according to the present invention can contain a single PEG or a mixture of two or more PEGs. PEGs having molecular weight of more that about 1000 possess gelling properties; i.e., they increase the viscosity of a composition. Therefore, by combining PEGs with different molecular weights/melting points, one can attain varying levels of flowability as desirable for the treatment of a given target site. The concentration of the PEG should be in a level that results in viscosity, prior to filling of the composition into aerosol canisters, of less than 12,000 CPs, and more preferably, less than 10,000 CPs.

Secondary polar solvent

[0093] Optionally, a secondary polar solvent is added to the foamable composition of the present invention. The secondary polar solvent is selected from a variety of organic solvents that are typically miscible on both water and oil. Examples of polar solvent that can be contained in the foamable carrier of the present invention include dimethyl isosorbide, tetrahydrofurfuryl alcohol polyethyleneglycol ether (glycofurol), DMSO, pyrrolidones, (such as N-Methyl-2-pyrrolidone and 1-Methyl-2-pyrrolidinone), ethyl proxitol, dimethylacetamide (DMAc), PEG-type surfactants and alpha hydroxy acids, such as lactic acid and glycolic acid.

[0094] Appropriate use of a secondary solvent in a waterless foam composition can help improve delivery of active agents to a target area. Foam compositions of the present invention, for which the solvent includes a secondary solvent, can increase the levels of the active agent in the waterless composition and thus, provide high delivery and improved therapy.

Solubilization and penetration enhancement

[0095] In many cases, polyols, PEGs and polar solvents possess a high solubilizing power and thus, they can enable increased concentrations of a pharmaceutical active agent. Polyols, PEGs and polar solvents are also known for their skin penetration enhancement properties. These properties enable high drug bioavailability in the target area of treatment, resulting in an enhanced therapeutic effect. Occasionally, combinations of a polyol, PEGs and a secondary polar solvent, exhibit an increased permeability across the skin, as suggested, for example, in Eur J Pharm Biopharm. 1998 Nov; 46(3):265-71.

[0096] Thus, in one or more embodiments, the foamable carrier contains (1) at least one polar solvent, selected from a polyol (selected from a diol and a triol) and PEG; and (2) at least one secondary polar solvent.

[0097] In one or more embodiments, the foamable carrier contains (1) a mixture of at least two polyols; and (2) at least one secondary polar solvent. In additional embodiments, the foamable carrier contains a mixture of at least one polyol and at least one PEG; yet in other embodiments the foamable carrier contains (1) a mixture of at least one polyol and at least one PEG and (2) at least one secondary polar solvent.

[0098] According to certain embodiments the ratio between the polyol and/or PEG and the secondary polar solvent is between 9:1 and 1:1.

[0099] In certain embodiments, the polyol is selected from the group consisting of propylene glycol, hexylene glycol and glycerin (and mixtures thereof); and the secondary polar solvent is selected from the group consisting of

Padagis Ex. 1029
IPR Petition - USP 11,311,482

dimethyl isosorbide, diethylene glycol monoethyl ether, a liquid polyethylene glycol and glycofurol.

[0100] In certain embodiments, the foamable carrier contains (1) at least one polyol; and (2) dimethyl isosorbide.

[0101] Short chain alcohols, such as ethanol and propanol are known as polar solvents, however, according to one or more embodiments, the composition of the present invention is substantially alcohol-free, i.e., free of short chain alcohols. Short chain alcohols, having up to 5 carbon atoms in their carbon chain skeleton and one hydroxyl group, such as ethanol, propanol, isopropanol, butanol, iso-butanol, t-butanol and pentanol, are considered less desirable polar solvents due to their skin-irritating effect.

[0102] Thus, in certain embodiments, the composition is substantially alcohol-free and includes less than about 5% final concentration of lower alcohols, preferably less than about 2%, more preferably less than about 1%. However, in other embodiments, a short chain alcohol can be included in the composition, as long as the ratio between the short chain alcohol and the polyol is less than 1:4 by weight.

Modulating Agent

[0103] The term modulating agent is used to describe an agent which can improve the stability of or stabilize a carrier or a foamable composition and or an active agent by modulating the effect of a substance or residue present in the carrier or composition. The substance or residue may for example be acidic or basic and potentially alter an artificial pH in a waterless or substantially non aqueous environment or it may be one or more metal ions which may act as a potential catalyst in a waterless or substantially non aqueous environment or it may be an ionisation agent or it may be an oxidizing agent.

[0104] In one or more other embodiments the modulating agent is used in a waterless composition. In one or more embodiments the modulating agent is used in a substantially non aqueous composition

[0105] In one or more embodiments the modulating agent is used to describe an agent which can affect pH in an aqueous solution.

[0106] The agent can be any of the known buffering systems used in pharmaceutical or cosmetic formulations as would be appreciated by a man of the art. It can also be an organic acid, a carboxylic acid, a fatty acid an amino acid, an aromatic acid, an alpha or beta hydroxyl acid an organic base or a nitrogen containing compound.

[0107] In one or more further embodiments the modulating agent is used to describe an agent, which is a chelating or sequestering or complexing agent that is sufficiently soluble or functional in the waterless solvent to enable it to "mop up" or "lock" metal ions.

[0108] In the embodiment modulating agent is used to describe an agent which can effect pH in an aqueous solution the term modulating agent more particularly means an acid or base or buffer system or combinations thereof, which is introduced into or is present in and acts to modulate the ionic or polar characteristics and any acidity or basesity balance of a waterless or substantially non aqueous carrier, composition, foamable carrier or foamable composition or resultant foam of the present invention.

[0109] The substance or residue can be introduced into the formulation from any one or more of the ingredients, some of which themselves may have acidic or basic properties. For example the polymer or solvent may contain basic residues in which case it may be desirable or beneficial to add an acid. Alternatively the surfactant may contain some acid residues in which case the addition of a base may be desirable and beneficial. In some cases more than one ingredient may contain residues which may ameliorate or compound their significance. For example if one ingredient provided weak acid residues and another stronger acid residues the artificial pH in a waterless environment should be lower. In contrast, if one residue was acid and the other basic the net effect in the formulation maybe significantly reduced. In some circumstances the active

ingredient may favor an acidic pH or more significantly may need to be maintained at a certain acidic pH otherwise it may readily isomerize, chemically react or breakdown, in which case introducing acidic components might be of help. Likewise in some circumstances the active ingredient may favor a basic pH or more significantly may need to be maintained at a certain basic pH otherwise it may readily hydrolyse, undergo rearrangement, isomerize, chemically react or breakdown, in which case introducing basic components might be of help. In an embodiment of the present invention sufficient modulating agent is added to achieve an artificial pH in which the active agent is preferably stable. Such artificial pH may be acidic, maybe basic or may be neutral.

[0110] The terms pH, pKa, and pKb, buffers and the like are used in classical measurements of an aqueous solution. Such measurements are artificial in a waterless environment. Nevertheless, reference to and description below of such terms are made for convenience and clarity, since such terms are well defined and understood with reference to aqueous solutions and further due to the lack of an appropriate uniform way of describing and identifying the artificial or virtual pH, pK etc in a waterless environment in relation to the present invention. Although predictions of artificial pH can be made using dilution techniques of measurements of waterless formulations diluted in water they are formulation sensitive and specific and have to be carefully calibrated with complex formulas.

[0111] Waterless medium can be polar and protic yet it does not conform to classical ionic behavior.

[0112] A buffer, as defined by Van Slyke [Van Slyke, J. Biol. Chem. 52, 525 (1922)], is "a substance which by its presence in solution increases the amount of acid or alkali that must be added to cause unit change in pH".

[0113] A buffer solution is a solution of a definite pH made up in such a way that this pH alters only gradually with the addition of alkali or acid. Such a solution consists of a solution of a salt of the week acid in the presence of the

three acid itself. The pH of the solution is determined by the dissociation equilibrium of the free acid.

[0114] An acid can be a strong acid or a weak acid. A strong acid is an acid, which is a virtually 100% ionized in solution. In contrast, a week acid is one which does not ionize fully when it is dissolved in water. The lower the value for pKa, the stronger is the acid and likewise, the higher the value for pKa the weaker is the acid.

[0115] A base can be a strong base or a weak base. A strong base is something, which is fully ionic with 100% hydroxide ions. In contrast, a weak base is one which does not convert fully into hydroxide ions in solution. The lower the value for pKb, the stronger is the base and likewise, the higher the value for pKb the weaker is the base.

[0116] In general terms, three factors, which influence the strength of a base, are firstly the ease with which the lone pair takes up a hydrogen ion; secondly, the stability of ions being formed and thirdly, the way they interact with water such that if they pick up hydrogen ion's more readily it is a stronger base.

[0117] An acid in an amount to affect the composition's pH selected from the group consisting of:

(a) An alpha hydroxyl acid of formula I:

I: $(R_a)(R_b)C(OH)COOH$;

or a pharmaceutically acceptable salt, lactone, or solvate thereof, wherein R_a and R_b are independently selected from the group consisting of H, F, Cl, Br, and saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic C_1-C_{25} alkyl, aralkyl, or aryl groups, wherein each of R_a and R_b may be optionally substituted with an OH, SH, CHO, COOH group;

(b) An aliphatic beta hydroxyacid of formula II:

II: $(R_a)(R_b)C(OH)C(R_c)(R_d)COOH$;

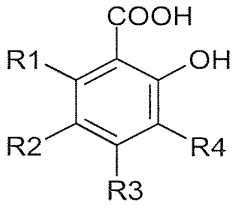
or a pharmaceutically acceptable salt, lactone, or solvate thereof, wherein R_a, R_b, R_c and R_d are independently selected from the group consisting of H, F, Cl, Br, and saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic C_1-C_{25} alkyl, aralkyl, or aryl groups, wherein each of R_a and R_b may be optionally substituted with an OH, SH, CHO, COOH group.

[0118] Exemplary alpha hydroxyl acids and beta hydroxyl acids include, but are not limited to 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.

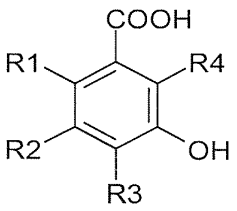
(c) An aromatic acid.

[0119] Exemplary aromatic acids include, but are not limited to benzoic acid, toluic acid, dimethyl benzoic acid, phthalic acid and nicotinic acid (heterocyclic).

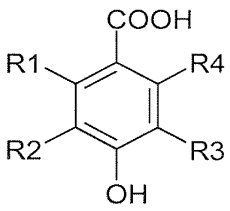
(d) an aromatic hydroxyl acid of formula IIIa, IIIb and IIIc:



IIIa



IIIb



IIIc

Padagis Ex. 1029
IPR Petition - USP 11,311,482

[0120] The aromatic ring can contain solely carbon atoms or a combination of carbon atoms and other atoms (heterocyclic), wherein R_1, R_2, R_3 and R_4 are independently selected from the group consisting of H, F, Cl, Br, and saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic C_1-C_{25} alkyl, aralkyl, or aryl groups.

[0121] Formula IIIa, wherein R is H, is identified as salicylic acid, yet another example of an aromatic hydroxyl acid is acetylsalicylic acid.

(e) an alpha ketoacid of formula IV:

IV: $(R_a)COCOO(R_b)$;

or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein R_a and R_b are independently selected from the group consisting of H and saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic C_1-C_{25} alkyl, aralkyl, or aryl groups, wherein R_a may be optionally substituted with an F, Cl, Br, I, OH, CHO, COOH, or alkoxy group having 1 to 9 carbon atoms;

(f) An aliphatic carboxylic acid.

[0122] Short chain carboxylic acids include formic acid, acetic acid and propionic acid.

[0123] A fatty acid is a carboxylic acid often with a long unbranched aliphatic tail (chain), which is either saturated or unsaturated. Carboxylic acids as short as butyric acid (4 carbon atoms) are considered to be fatty acids, while fatty acids derived from natural fats and oils may be assumed to have at least 8 carbon atoms, as exemplified in the following list:.

- Butyric (butanoic acid): $CH_3(CH_2)_2COOH$
- Caproic (hexanoic acid): $CH_3(CH_2)_4COOH$
- Caprylic (octanoic acid): $CH_3(CH_2)_6COOH$
- Nonanoic acid: $CH_3(CH_2)_7COOH$
- Capric (decanoic acid): $CH_3(CH_2)_8COOH$

- Lauric (dodecanoic acid): $CH_3(CH_2)_{10}COOH$
- Myristic (tetradecanoic acid): $CH_3(CH_2)_{12}COOH$
- Palmitic (hexadecanoic acid): $CH_3(CH_2)_{14}COOH$
- Stearic (octadecanoic acid): $CH_3(CH_2)_{16}COOH$
- Arachidic (eicosanoic acid): $CH_3(CH_2)_{18}COOH$
- Behenic (docosanoic acid): $CH_3(CH_2)_{20}COOH$
- Octacosanoic: $CH_3(CH_2)_{26}COOH$

[0124] Optionally, the carbon atom chain of the fatty acid may have at least one double bond, as exemplifies in the following list:

- Oleic acid: $CH_3(CH_2)7CH=CH(CH_2)_7COOH$
- Linoleic acid: $CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7COOH$
- Alpha-linolenic acid: $CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7COOH$
- Arachidonic acid
  $CH_3(CH_2)_4CH=CHCH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_3COOH$
- Eicosapentaenoic acid
- Docosahexaenoic acid
- Erucic acid: $CH_3(CH_2)7CH=CH(CH2)11COOH$

[0125] Alpha-linolenic, docosahexaenoic, and eicosapentaenoic acids are examples of omega-3 fatty acids. Linoleic acid and arachidonic acid are omega-6 fatty acids. Oleic and erucic acid are omega-9 fatty acids.

[0126] A further class of carboxylic acids according to the present invention comprises a carboxylic acid, wherein the carbon atom chain is branched, such as valproic acid. The carbon chain of the fatty acid or fatty alcohol can be substituted with a hydroxyl group, such as 12-hydroxy stearic acid.

[0127] Short chain carboxylic acids such as formic acid and acetic acid are reasonably strong acids (pKa 3.77 and 4.76, respectively). Longer chain fatty acids have higher pKa values. Nonanoic acid, for example, has a pKa of 4.96.

(g) a dicarboxylic acid

[0128] In the context of the present invention, a dicarboxylic acid is an organic compound, having two carboxylic acid moieties on its carbon atom skeleton. They have the general molecular formula HOOC-$(CH_2)_n$-COOH.

[0129] In an embodiment of the present invention, the dicarboxylic acid is a short-chain dicarboxylic acid. The simplest short-chain dicarboxylic acid are oxalic acid (n=0), malonic acid (n=1), succinic acid (n=2) and glutaric acid (n=3).

[0130] Additional members of dicarboxylic acid group are derived from natural products or from synthesis, having "n" value from 4 up to 21. In one or more embodiments of the present invention, the dicarboxylic acid is selected from the group consisting of adipic acid (hexanedioic acid; n=4), pimelic acid (heptanedioic acid; n=5), suberic acid (octanedioic acid; n=6), azelaic acid (nonanedioic acid; n=7), sebacic acid (decanedioic acid; n=8) and dodecanedioic acid (n=10).

[0131] In an additional embodiment, the dicarboxylic acid contains 10 to 32 carbon atoms in their carbon atom skeleton, such as brassylic acid (n=11), thapsic acid (n=14), 14-methylnonacosanedioic acid (C29) and 14,15-dimethyltriacontanedioic acid (C30).

[0132] The carbon atom skeleton of the dicarboxylic acid can be saturated or unsaturated, such as in the case of undecylenic acid, maleic acid and fumaric acid.

[0133] In an additional embodiment, the dicarboxylic acid is branched, i.e., the carbon atom skeleton of the dicarboxylic acid can be substituted with at least one group selected from the group consisting of R, F, Cl, Br, OH, OR, SH, CHO, COOH, and NR_aR_b, wherein R, R_a and R_b are independently selected from the group consisting of H, saturated or unsaturated, isomeric or non-isomeric, straight, branched, or cyclic C_1-C_{25} alkyl, aralkyl, or aryl groups. Exemplary

branched dicarboxylic acids include 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, tartronic acid,

(h) Miscellaneous organic acids

[0134] In an embodiment of the present invention, the organic acid is selected from the group consisting of 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, carnitine, nicotinic acid and retinoids, such as retinoic acid and isotretinoin.

(i) Amino acid

[0135] The a-COOH and a-NH_2 groups in amino acids are capable of ionizing (as are the acidic and basic R-groups of the amino acids). As a result of their ionizability the following ionic equilibrium reactions may be written:

R-COOH <--------> R-COO- + H+

R-NH3+ <---------> R-NH2 + H+

[0136] The equilibrium reactions, as written, demonstrate that amino acids contain at least two weakly acidic groups. However, typically the carboxyl group is a far stronger acid than the amino group. At physiological pH (around 7.4) the carboxyl group will be unprotonated and the amino group will be protonated. An amino acid with no ionizable R-group would be electrically neutral at this pH. This species is termed a zwitterion.

[0137] Like typical organic acids, the acidic strength of the carboxyl, amino and ionizable R-groups in amino acids can be defined by the association constant, Ka or more commonly the negative logarithm of Ka, the pKa. The net charge (the algebraic sum of all the charged groups present) of any amino acid,

peptide or protein, will depend upon the pH of the surrounding aqueous environment. As the pH of a solution of an amino acid or protein changes so too does the net charge. This phenomenon can be observed during the titration of any amino acid or protein. When the net charge of an amino acid or protein is zero the pH will be equivalent to the isoelectric point: pI.

[0138] The following table lists amino acids and their pKa's:

Acid	pK_1 (COOH)	pK_2 (NH_2)	pK R Group
Glycine	2.4	9.8	
Alanine	2.4	9.9	
Valine	2.2	9.7	
Leucine	2.3	9.7	
Isoleucine	2.3	9.8	
Serine	2.2	9.2	~13
Threonine	2.1	9.1	~13
Cysteine	1.9	10.8	8.3
Methionine	2.1	9.3	
Aspartic Acid	2.0	9.9	3.9
Asparagine	2.1	8.8	
Glutamic Acid	2.1	9.5	4.1
Glutamine	2.2	9.1	
Arginine	1.8	9.0	12.5
Lysine	2.2	9.2	10.8
Histidine	1.8	9.2	6.0
Phenylalanine	2.2	9.2	
Tyrosine	2.2	9.1	10.1
Tryptophan	2.4	9.4	
Proline	2.0	10.6	

[0139] In addition, nonprotein amino acids are also suitable in accordance to the present invention, including but not limited to: 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-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.

[0140] In an embodiment of the present invention the organic modulating agent is a dimer or oligomer of amino acids.

[0141] In an embodiment of the present invention the organic modulating agent is an organic base.

[0142] In an embodiment the organic base is a nitrogen-containing organic compound.

[0143] In an embodiment the nitrogen-containing organic modulating compound is selected from, primary, secondary, tertiary and quaternary amines. The organic primary amine may include alkylamines such as methylamine and ethylamine; ethanolamine such as monoethanolamine and monoisopropanolamines; diamines such as ethylenediamine and 1,2-diaminopropane. The organic secondary amines include dialkylamines such as dimethylamine and diethylamine, diethanolamine and diisopropanolamine; N-methylethanolamine and N-ethylethanolamine. The organic tertiary amines include trialkylamines such as triethylamine and triethylamine; triethanolamine; N-methyldiethanolamine and tri-isopropanolamine. The quaternary compounds preferably include basic choline.

[0144] In an embodiment the nitrogen-containing organic modulating compound is an amide. Amides are derivatives of oxoacids in which an acidic hydroxy group has been replaced by an amino or substituted amino group. Compounds having one, two, or threeacyl groups on a given nitrogen are generically included and may be designated as primary, secondary and tertiary amides, respectively.

[0145] In an embodiment the nitrogen-containing organic modulating compound is an amine oxide. amine oxide are compounds derived from tertiary amines by the attachment of one oxygen atom to the nitrogen atom: R_3N^+-O^-.

[0146] In an embodiment the nitrogen-containing organic modulating compound is a lactam. Lactams are **c**yclic amides amino carboxylic acids, having a 1-azacycloalkan-2-one structure, or analogues having unsaturation or heteroatoms replacing one or more carbon atoms of the ring, as exemplified in the following structures:



[0147] Urea is another example of a nitrogen-containing modulating compound.

[0148] The modulating agent to the foamable composition of the present invention is useful for stabilizing pharmaceutical and cosmetic active agents which are unstable in certain pH conditions. It is known, for example, that active agents, which contain ester bond in their structure tend to undergo hydrolysis of the ester bond at basic pH levels. Therefore, the addition of an agent which avoids the formation of basic pH condition and thus, prevents degradation of such active agents. Many steroid compounds are known to undergo rearrangement at high pH, and again, adding an acidic modulating agent helps prevent such degradation. This is clearly exemplified by the stark difference in stability results for BMV in the absence and presence of a modulating agent as demonstrated in Examples 1 and 2 below. Another example of a pH-sensitive active agent is vitamin D, which degrades at low pH levels. In such a case, the addition of a basic modulating agent, such as triethanol amine is useful to maintain acceptable stability of this active agents as can be seen an exemplified in Example 5 below.

[0149] In certain cases, the stability of an active agent may be influenced by small quantities of, for example, metal ions in the waterless compositions. Such

metal ions may act as a catalyst in facilitating the reaction or breakdown of the agent. Thus the modulating agent can be a chelating or sequestering or complexing agent on its own. In one or more embodiments of the present invention there is provided an effective amount of chelating agent which is sufficiently soluble or functional in the waterless solvent to enable it to "mop up" or "lock" metal ions.

[0150] For instance it is known that Polyphenols through the chelation of transition-metal ions, particularly those of iron and copper inhibit free radical formation and the propagation of free radical reactions (Brown et al. in Biochem. J 330, 1173 1178 (1998)). Citric acid, amino acids, and thylenediaminetetraacetic acid also form chelates with metallic ions such as copper and iron, thus avoiding their catalytic action on the oxidation of lipids. Most of these chelating agents exhibit little or no antioxidant activity when used alone, and therefore they are considered as synergistic agents of other antioxidants. Thus, they increase, to a great extent, the action of primary antioxidants.

[0151] In one or more embodiments of the present invention the chelating agent is selected from the group consisting of 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.]

[0152] Other authorized chelating agents are listed pursuant to annex 1, paragraph E.3.1 of regulation (EC) No 2003 (See Directive 67/548/EEC OJ 196, 16.8 1967, p1) and are also incorporated herein by reference.

[0153] In one or more preferred embodiments of the present invention the chelating agent is selected from the group consisting of ethylenediaminetetraacetic acid ("EDTA") and salts thereof such as disodium EDTA, tetrasodium EDTA and calsium disodium EDTA; diethylenetriaminepentaacetic acid ("DTPA") and salts thereof; hydroxyethlethylenediaminetriacetic acid ("HEDTA") and salts thereof and nitrilotriacetic acid ("NTA"); more preferably EDTA, HEDTA and their salts; most preferably EDTA and its salts.

[0154] In one or more embodiments of the present invention a preferred non limiting example of the chelating agent is EDTA. Typically, the chelating and sequestering agent is present in the composition at a level of up to about 5.0%, preferably 1.0 percent, by weight, of the composition.

[0155] Combinations of Modulating Agents may be a useful aspect of the present invention. For example, as will be appreciated by a man of the art combinations of a strong acid and a weak base; a weak acid and a strong base: a weak acid and a strong acid; a weak base and a strong base; a weak base and a second weak base ; and a weak acid and a second weak acid; may prove more effective in protecting or stabilizing an active agent in the waterless solvents of the present invention than a base or acid on its own. It will be understood that each of the active agents may have an artificial pH at which it can be more stable in a waterless composition. For example, ascorbic acid in aqueous solution is known to be more stable at an acidic pH of about 5.4. It is therefore desirable to

add a combination of modulating agents in a waterless composition that will generate an artificial pH approximately of the order of or equivalent to that at which ascorbic acid is more stable in a waterless medium. In order to do so it will be appreciated a man of the art that that some adjustment will have to be made as ascorbic acid is itself a strong acid and displays the characteristics of a modulating agent. Similarly chelating agents may be usefully used in combination with another modulating agent such as an acid, a base or a buffer system or with various combinations of modulating agents.

[0156] The modulating agent to the foamable composition of the present invention is further useful for adjusting the pH of the target area of application. Skin is the first line of defense against all elements, such as microorganisms, wind, and pollutants, and it's the acid mantle, a fine film with a slightly acidic pH on the surface of the skin that provides protection for the skin. It plays a very important role as an integral part of the barrier function of the stratum corneum. Recent studies have demonstrated that increased enzyme activity of phospholipase A2 is related to the formation of the acid mantle in the stratum corneum. This combination makes the skin less permeable to water and other polar compounds. Normal skin surface pH is between 4 and 6.5 in healthy people, though it varies among the different areas of the skin. Newborn infants do have a higher skin surface pH compared to adults, but this normalizes within three days. Therefore, it is important to maintain skin surface pH in order to prevent susceptibility to bacterial skin infections or skin damage and disease. Thus, adding a modulating agent, which contributes to the stabilization of skin pH at the desirable level, is advantageous.

[0157] In the same fashion, adding an acidic modulating agent to a foamable composition, which is intended for vaginal application is advantageous, since the best protection against vaginal infection is attained in pH lower than 4.

[0158] While the organic modulating agent can serve to stabilize an active agent in the foam composition, it often provides additional therapeutic properties to the composition. The following table exemplifies, in a non-limiting fashion, the

therapeutic benefits expected from an organic modulating agent. It is to be understood that this table provides a non-exhaustive list of modulating agents that possess therapeutic effects, however, many other compounds listed in the present specification also possess therapeutic benefits.

Class	Examples	Exemplary therapeutic properties
Alpha hydroxy acids	Lactic acid Glycolic acid	Humectant Keratnocyte growth modifier Anti-psoriasis Anti acne
Beta hydroxyl acid	Salicylic acid	Keratolytic Antiinflammatory
Short chain carboxylic acid	Propionic acid Butyric acid	Antiinfective
Fatty acids	Nonanoic acid Behenic acid	Hair growth stimulant Antiinflammatory Antiinfective Humectant Skin protection
Unsaturated fatty acids	Omega-3 fatty acids Omega-6 fatty acids	Radical scavenger Anti-oxidant
Aromatic acids	Benzoic acid Phthalic acid Nicotinic acid	Antiinflammatory Anti-acne Anti-pigmentation Antiinfective Insect repellant
Dicarboxylic acids	Malonic acid, succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid, sebacic acid	Antiinflammatory Keratolytic Anti-acne Anti-rosacea Anti-pigmentation
Amino acids		Keratnocyte growth modifier Hair growth stimulant Sebum control
Retinoids	Retinoic acid Isotretinoin	Antiinflammatory Keratolytic Anti-acne Anti-rosacea Anti-pigmentation
Nitrogen containing	Urea	Humectant Keratolytic Anti-psiriasis

Padagis Ex. 1029
IPR Petition - USP 11,311,482

[0159] In one or more embodiments, the modulating agent may also be a preservative or an antioxidant or an ionization agent. Any preservative, antioxidant or ionization agents suitable for pharmaceutical or cosmetic application may be used. Non limiting examples of antioxidants are tocopherol succinate, propyl galate, butylated hydroxy toluene and butyl hydroxy anisol. Ionization agents may be positive or may be negative depending on the environment and the active agent or composition that is to be protected. Ionization agents may for example act to protect or reduce sensitivity of active agents. Non limiting examples of positive ionization agents are benzyl conium chloride, and cetyl pyridium chloride. Non limiting examples of negative ionization agents are sodium lauryl sulphate, sodium lauryl lactylate and phospholipids.

[0160] In one or more embodiments the modulating agent is a flavonoid.

[0161] Flavonoids (or bioflavonoids) are a large group of polyphenolic antioxidant compounds, which often occur as glycosides and are ubiquitously present in foods of plant origin. Some flavonoids (e.g. quercetin, rutin) are available as dietary supplements. Flavonoids can be further subdivided into:

- flavonols (e.g. kaempferol, quercetin and myricetin)
- flavones (e.g. apigenin and luteolin)
- flavonones (e.g. hesperetin, naringenin, eriodictyol)
- flavan-3-ols (e.g. (+)-catechin, (+)-gallocatechin, (–)-epicatechin, (–)-epigallocatechin)
- anthocyanins (e.g. cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin)
- proanthocyanidins.

[0162] More than 4000 flavonoids have been identified, and many have been studied. Most are colorless but some are responsible for the bright colors of many fruit and vegetables. Flavonoids are distinguished from the carotenoids.

[0163] Flavonoids appear to

- act as scavengers of free radicals, including superoxide anions, singlet oxygen, and lipid peroxyl radicals (they have antioxidant properties);
- sequester metal ions;
- inhibit *in vitro* oxidation of LDL cholesterol;
- inhibit cyclo-oxygenase, leading to lower platelet aggregation, decreased thrombotic tendency and reduced anti-inflammatory activity;
- inhibit histamine release;
- improve capillary function by reducing fragility of capillary walls and thus preventing abnormal leakage; and
- inhibit various stages of tumor development (animal studies only).

[0164] The activities of flavonoids are dependent on their chemical structure.Estimates of dietary flavonoid intake vary from 10 to 100 mg daily, but may be several hundreds of milligrams a day. Dietary supplements of quercetin and rutin provide around 500 mg in a single dose.

[0165] Flavonoids may have a potential role in the prevention of CVD, cancer and cataracts and possibly other diseases, for anti-viral activity., and they may be useful in treating ulcers. include hemorrhoids, allergy, asthma, menopausal symptoms and the prevention of habitual abortion.

Quercetin

[0166] As a dietary supplement, quercetin is promoted for prevention and treatment of atherosclerosis and hyperlipidaemia, diabetes, cataracts, hay fever, peptic ulcer, inflammation, prevention of cancer and for treating prostatitis. A preliminary, double-blind, placebo-controlled trial in chronic non-bacterial

prostatitis showed that quercetin reduced pain and improved quality of life, but had no effect on voiding dysfunction.

Rutin

[0167] As a dietary supplement, rutin is used to reduce capillary permeability and treat symptoms of varicose veins. In combination with bromelain and trypsin, rutin is used to treat osteoarthritis.

[0168] A non limiting list of flavonoid compounds is: benzquercin, diosmin, ethoxazorutoside, flavodate, sodium hesperidin, leucocianido, monoxerutin, oxerutin, quercetin, rutoside, rosmarinic acid. The above information was noted from Dietary Supplements, Electronic Version, Pharmaceutical Press 2007.

[0169] In an embodiment a single flavonoid is provided and in a further embodiment a combination of two or more flavonoid are provided. In certain embodiments the flavonoids act synergistically. In an embodiment water soluble flavonoids are combined with water insoluble flavonoids. It is known for example that whole polyphenolic extracts have greater antioxidant effect than their known individual components. In an embodiment flavonoids are used in combination with other phenolics. In an embodiment one or more flavonoids are provided in combination with one or more vitamins. In an embodiment flavonoids are provided that are more reactive than the vitamins. In an embodiment the flavonoids act as a conservational agent.

Microsponges

[0170] The Microsponges are rigid, porous and spongelike round microscopic particles of cross-linked polymer beads (e.g., polystyrene or copolymers thereof), each defining a substantially noncollapsible pore network. The Microsponges can be loaded with an active ingredient and can provide a controlled time release of the active ingredient to skin or to a mucosal membrane upon application of the formulation. The slow release is intended to reduce irritation by the active.

Microsponge® delivery technology was developed by Advanced Polymer Systems. In one or more embodiments the composition comprisises one or more active agents loaded into Microponges with a waterless carrier comprising a modulating agent.

Polymeric agent

[0171] The composition of the present invention contains a polymeric agent. It has been documented that the presence of a polymeric agent is necessary for the creation of foam, having fine bubble structure, which does not readily collapse upon release from the pressurized aerosol can. The polymeric agent serves to stabilize the foam composition and to control drug residence in the target organ. Preferably, the polymeric agent is soluble or readily dispersible in the polyol; or in the mixture of a polyol and an additional polar solvent.

[0172] Non-limiting examples of polymeric agents that are soluble or readily dispersible in propylene glycol are Hydroxypropylcellulose and carbomer (homopolymer of acrylic acid is crosslinked with an allyl ether pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene, such as Carbopol® 934, Carbopol® 940, Carbopo® 941, Carbopol® 980 and Carbopol® 981.

[0173] Other polymeric agents are suitable for use according to the present invention provided that they are soluble or readily dispersible in the polyol; or in the mixture of a polyol and an additional polar solvent, on a case by case basis.

[0174] Exemplary polymeric agents include, in a non-limiting manner, naturally-occurring polymeric materials, such as 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, amine-bearing polymers such as chitosan; acidic polymers obtainable from natural sources, such as alginic acid and hyaluronic acid; chemically modified starches and the like, carboxyvinyl polymers, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid polymers,

polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers, polyvinylidene chloride polymers and the like.

[0175] Additional exemplary polymeric agents include semi-synthetic polymeric materials such as cellulose ethers, such as, hydroxypropyl cellulose, Polyethylene glycol, having molecular weight of 1000 or more (e.g., PEG 1,000, PEG 4,000, PEG 6,000 and PEG 10,000) also have gelling capacity and while they are considered herein as "secondary polar solvents", as detailed herein, they are also considered polymeric agents.

[0176] Mixtures of the above polymeric agents are contemplated.

[0177] The concentration of the polymeric agent should be selected so that the composition, after filling into aerosol canisters, is flowable, and can be shaken in the canister. In one or more embodiments, the concentration of the polymeric agent is selected such that the viscosity of the composition, prior to filling of the composition into aerosol canisters, is less than 12,000 CPs, and more preferably, less than 10,000 CPs.

Surface-active agent

[0178] The composition further contains a surface-active agent. Surface-active agents (also termed “surfactants”) include any agent linking oil and water in the composition, in the form of emulsion. A surfactant’s hydrophilic/lipophilic balance (HLB) describes the emulsifier’s affinity toward water or oil. HLB is defined for non-ionic surfactants. The HLB scale ranges from 1 (totally lipophilic) to 20 (totally hydrophilic), with 10 representing an equal balance of both characteristics. Lipophilic emulsifiers form water-in-oil (w/o) emulsions; hydrophilic surfactants form oil-in-water (o/w) emulsions. The HLB of a blend of two emulsifiers equals the weight fraction of emulsifier A times its HLB value plus the weight fraction of emulsifier B times its HLB value (weighted average). In many cases a single surfactant may suffice. In other cases a combination of two or more surfactants is desired. Reference to a surfactant in the specification can also apply to a combination of surfactants or a surfactant system. As will be

appreciated by a person skilled in the art which surfactant or surfactant system is more appropriate is related to the vehicle and intended purpose. In general terms a combination of surfactants can be significant in producing breakable forms of good quality. It has been further discovered that the generally thought considerations for HLB values for selecting a surfactant or surfactant combination are not always binding for emulsions and moreover for waterless and substantially non aqueous carriers the usual guidelines are less applicable . Surfactants also play a significant role in foam formation where the foamable formulation is a single phase composition.

[0179] According to one or more embodiments the composition contains a single surface active agent having an HLB value between about 2 and 9, or more than one surface active agent and the weighted average of their HLB values is between about 2 and about 9.

[0180] According to one or more embodiments the composition contains a single surface active agent having an HLB value between about 7 and 14, or more than one surface active agent and the weighted average of their HLB values is between about 7 and about 14.

[0181] According to one or more other embodiments the composition contains a single surface active agent having an HLB value between about 9 and about 19, or more than one surface active agent and the weighted average of their HLB values is between about 9 and about 19.

[0182] In a waterless or substantially waterless environment a wide range of HLB values may be suitable.

[0183] Preferably, the composition contains a non-ionic surfactant. Nonlimiting examples of possible non-ionic surfactants include a polysorbate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, a polyoxyethylene fatty acid ester, Myrj 45, Myrj 49, Myrj 52 and Myrj 59; a polyoxyethylene alkyl ether, polyoxyethylene cetyl ether, polyoxyethylene palmityl ether, polyethylene oxide hexadecyl ether, polyethylene

glycol cetyl ether, steareths such as steareth 2, brij 21, brij 721, brij 38, brij 52, brij 56 and brij W1, a sucrose ester, a partial ester of sorbitol and its anhydrides, sorbitan monolaurate, sorbitan monolaurate, a monoglyceride, a diglyceride, isoceteth-20 and mono-, di- and tri-esters of sucrose with fatty acids. In certain embdiments, suitable sucrose esters include those having high monoester content, which have higher HLB values.

[0184] In an embodiment the surfactant is an ether for example polyoxyethylene (26) glycerol ether.

[0185] In certain embodiments, surfactants are selected which can provide a close packed surfactant layer. To achieve such objectives combinations of at least two surfactants are selected. Preferably, they should be complex emulgators and more preferably they should both be of a similar molecular type;for example, a pair of ethers, like steareth 2 and steareth 21, or a pair of esters, for example, PEG-40 stearate and polysorbate 80. Ideally, the surfactants can be ethers. In certain circumstances POE esters cannot be used and a combination of sorbitan laurate and sorbitan stearate or a combination of sucrose stearic acid ester mixtures and sodium laurate may be used. All these combinations due to their versatility and strength may also be used satisfactorily and effectively with ether frormulations, although the amounts and proportion may be varied according to the formulation and its objectives as will be appreciated by a man of the art.

[0186] It has been discovered also that by using a derivatized hydrophilic polymer with hydrophobic alkyl moieties as a polymeric emulsifier such as pemulen it is possible to stabilize the emulsion better about or at the region of phase reversal tension. Other types of derivatized polymers like silicone copolymers, derivatized starch [Aluminum Starch Octenylsuccinate (ASOS)] / [DRY-FLO AF Starch], and derivatized dexrin may also a similar stabilizing effect.

[0187] A series of dextrin derivative surfactants prepared by the reaction of the propylene glycol polyglucosides with a hydrophobic oxirane-containing

Padagis Ex. 1029
IPR Petition - USP 11,311,482

material of the glycidyl ether are highly biodegradable. [Hong-Rong Wang and Keng-Ming Chen, Colloids and Surfaces A: Physicochemical and Engineering Aspects Volume 281, Issues 1-3, 15 June 2006, Pages 190-193] .

[0188] Non-limiting examples of non-ionic surfactants that have HLB of about 7 to about 12 include steareth 2 (HLB~4.9); glyceryl monostearate/PEG 100 stearate (Av HLB~11.2); stearate Laureth 4 (HLB~9.7) and cetomacrogol ether (e.g., polyethylene glycol 1000 monocetyl ether).

[0189] Non-limiting examples of preferred surfactants, which have a HLB of 4-19 are set out in the Table below:

Surfactant	HLB
steareth 2	~4.9
glyceryl monostearate/PEG 100 stearate	Av ~11.2
Glyceryl Stearate	~4
Steareth-21	~15.5
peg 40 stearate	~16.9
polysorbate 80	~15
sorbitan stearate	~4.7
laureth 4	~9.7
Sorbitan monooleate (span 80)	~4.3
ceteareth 20	~15.7
steareth 20	~15.3
ceteth 20	~15.7
Macrogol Cetostearyl Ether	~15.7
ceteth 2 (Lipocol C-2)	~5.3
PEG-30 Dipolyhydroxystearate	~5.5
sucrose distearate (Sisterna SP30)	~6
polyoxyethylene (100) stearate	~18.8

[0190] More exemplary stabilizing surfactants which may be suitable for use in the present invention are found below.

PEG-Fatty Acid Monoester Surfactants

Chemical name	Product example name	HLB
PEG-30 stearate	Myrj 51	>10
PEG-40 laurate	Crodet L40 (Croda)	17.9
PEG-40 oleate	Crodet O40 (Croda)	17.4
PEG-45 stearate	Nikkol MYS-45 (Nikko)	18
PEG-50 stearate	Myrj 53	>10
PEG-100 stearate	Myrj 59, Arlacel 165 (ICI)	19

PEG-Fatty Acid Diester Surfactants:

Chemical name	Product example name	HLB
PEG-4 dilaurate	Mapeg .RTM. 200 DL (PPG), Kessco .RTM.PEG 200 DL (Stepan), LIPOPEG 2-DL (Lipo Chem.)	7
PEG-4	distearate Kessco .RTM. 200 DS (Stepan.sub)	5
PEG-32 dioleate	Kessco .RTM. PEG 1540 DO (Stepan)	15
PEG-400 dioleate	Cithrol 4DO series (Croda)	>10
PEG-400 disterate	Cithrol 4DS series (Croda)	>10
PEG-20 glyceryl oleate	Tagat .RTM. O (Goldschmidt)	>10

Transesterification Products of Oils and Alcohols

Chemical name	Product example name	HLB
PEG-30 castor oil	Emalex C-30 (Nihon Emulsion)	11
PEG-40 hydrogenated castor oil	Cremophor RH 40 (BASF), Croduret (Croda), Emulgin HRE 40 (Henkel)	13

Polyglycerized Fatty Acids, such as:

Chemical name	Product example name	LB
Polyglyceryl-6 dioleate	Caprol .RTM. 6G20 (ABITEC); PGO-62 (Calgene), PLUROL OLEIQUE CC 497 (Gattefosse)Hodag	8.5

PEG-Sorbitan Fatty Acid Esters

Chemical name	Product example name	HLB
PEG-20 sorbitan monolaurate	Tween-20 (Atlas/ICI), Crillet 1 (Croda), DACOL MLS 20 (Condea)	17
PEG-20 sorbitan Monopalmitate	Tween 40 (Atlas/ICI), Crillet 2 (Croda)	16
PEG-20 sorbitan monostearate	Tween-60 (Atlas/ICI), Crillet 3 (Croda)	15
PEG-20 sorbitan monooleate	Tween-80 (Atlas/ICI), Crillet 4 (Croda)	15

Polyethylene Glycol Alkyl Ethers

Chemical name	Product example name	HLB
PEG-2 oleyl ether	oleth-2 Brij 92/93 (Atlas/ICI)	4.9
PEG-3 oleyl ether	oleth-3 Volpo 3 (Croda)	<10
PEG-5 oleyl ether	oleth-5 Volpo 5 (Croda)	<10
PEG-10 oleyl ether	oleth-10 Volpo 10 (Croda), Brij 96/97 (Atlas/ICI)	12
PEG-20 oleyl ether	oleth-20 Volpo 20 (Croda), Brij 98/99 (Atlas/ICI)	15
PEG-4 lauryl ether	laureth-4Brij 30 (Atlas/ICI)	9.7
PEG-23 lauryl ether	laureth-23Brij 35 (Atlas/ICI)	17
PEG-10 stearyl ether	Brij 76 (ICI)	12
PEG-2 cetyl ether	Brij 52 (ICI)	5.3

Sugar Ester Surfactants

Chemical name	Product example name	HLB
Sucrose distearate	Sisterna SP50, Surfope 1811	11

Sorbitan Fatty Acid Ester Surfactants

Chemical name	Product example name	HLB
Sorbitan monolaurate	Span-20 (Atlas/ICI), Crill 1 (Croda), Arlacel 20 (ICI)	8.6
Sorbitan monopalmitate	Span-40 (Atlas/ICI), Crill 2 (Croda), Nikkol SP-10 (Nikko)	6.7
Sorbitan monooleate	Span-80 (Atlas/ICI), Crill 4 (Croda), Crill 50 (Croda)	4.3
Sorbitan monostearate	Span-60 (Atlas/ICI), Crill 3 (Croda), Nikkol SS-10 (Nikko)	4.7

[0191] In one or more embodiments the surface active agent is a complex emulgator in which the combination of two or more surface active agents can be more effective than a single surfactant and provides a more stable formulation or improved foam quality than a single surfactant. For example and by way of non-limiting explanation it has been found that by choosing say two surfactants, one hydrophobic and the other hydrophilic the combination can produce a more stable emulsion than a single surfactant. Preferably, the complex emulgator comprises a combination of surfactants wherein there is a difference of about 4 or more units between the HLB values of the two surfactants or there is a significant difference in the chemical nature or structure of the two or more surfactants.

[0192] Specific non limiting examples of surfactant systems are, combinations of polyoxyethylene alkyl ethers, such as Brij 59 / Brij10; Brij 52 / Brij 10; Steareth 2 / Steareth 20; Steareth 2 / Steareth 21 (Brij 72 / Brij 721); combinations of polyoxyethylene stearates such as Myrj 52 / Myrj 59; combinations of sucrose esters, such as Surphope 1816 / Surphope 1807; combinations of sorbitan esters, such as Span 20 / Span 80; Span 20 / Span 60; combinations of sucrose

esters and sorbitan esters, such as Surphope 1811 and Span 60; combinations of liquid polysorbate detergents and PEG compounds, such as Tween 80 / PEG-40 stearate; methyl glucaso sequistearate; polymeric emulsifiers, such as Permulen (TRI or TR2); liquid crystal systems, such as Arlatone (2121), Stepan (Mild RM1), Nikomulese (41) and Montanov (68) and the like.

[0193] In certain embodiments the surfactant is preferably one or more of the following: a combination of steareth-2 and steareth-21 on their own or in combination with glyceryl monostearate (GMS); in certain other embodiments the surfactant is a combination of polysorbate 80 and PEG-40 stearate. In certain other embodiments the surfactant is a combination of glyceryl monostearate/PEG 100 stearate. In certain other embodiments the surfactant is a combination of two or more of stearate 21, PEG 40 stearate, and polysorbate 80. In certain orher embodiments the surfactant is a combination of two or more of laureth 4, span80, and polysorbate 80. In certain other embodiments the surfactant is a combination of two or more of GMS and ceteareth. In certain other embodiments the surfactant is a combination of two or more of steareth 21, ceteareth 20, ceteth 2 and laureth 4 In certain other embodiments the surfactant is a combination of ceteareth 20 and polysorbate 40 stearate. In certain orther embodiments the surfactant is a combination of span 60 and GMS. In certain other embodiments the surfactant is a combination of two or all of PEG 40 stearate, sorbitan stearate and polysorbate 60

[0194] In certain other embodiments the surfactant is one or more of sucrose stearic acid esters, sorbitan laureth, and sorbitan stearate.

[0195] Without being bound by any particular theory or mode of operation, it is believed that the use of non-ionic surfactants with significant hydrophobic and hydrophilic components, increase the emulsifier or foam stabilization characteristics of the composition. Similarly, without being bound by any particular theory or mode of operation, using combinations of surfactants with high and low HLB's to

provide a relatively close packed surfactant layer may strengthen the formulation.

[0196] In one or more embodiments the stability of the composition can be improved when a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed. The ratio between the at least one non-ionic surfactant having HLB of less than 9 and the at least one non-ionic surfactant having HLB of equal or more than 9, is between 1:8 and 8:1, or at a ratio of 4:1 to 1:4. The resultant HLB of such a blend of at least two emulsifiers is preferably between about 9 and about 14.

[0197] Thus, in an exemplary embodiment, a combination of at least one non-ionic surfactant having HLB of less than 9 and at least one non-ionic surfactant having HLB of equal or more than 9 is employed, at a ratio of between 1:8 and 8:1, or at a ratio of 4:1 to 1:4, wherein the HLB of the combination of emulsifiers is preferably between about 5 and about 18.

[0198] In certain cases, the surface active agent is selected from the group of cationic, zwitterionic, amphoteric and ampholytic surfactants, such as sodium methyl cocoyl taurate, sodium methyl oleoyl taurate, sodium lauryl sulfate, triethanolamine lauryl sulfate and betaines.

[0199] Many amphiphilic molecules can show lyotropic liquid-crystalline phase sequences depending on the volume balances between the hydrophilic part and hydrophobic part. These structures are formed through the micro-phase segregation of two Many amphiphilic molecules can show lyotropic liquid-crystalline phase sequences depending on the volume balances between the hydrophilic part and hydrophobic part. These structures are formed through the micro-phase segregation of two incompatible components on a nanometer scale. Soap is an everyday example of a lyotropic liquid crystal. Certain types of surfactants tend to form lyotropic liquid crystals in emulsions interface (oil-in-water) and exert a stabilizing effect

[0200] In one or more embodiments the surfactant is a surfactant or surfactant combination is capable of or which tends to form liquid crystals. Surfactants which tend to form liquid crystals may improve the quality of foams. Non limiting examples of surfactants with postulated tendency to form interfacial liquid crystals are: phospholipids, alkyl glucosides, sucrose esters, sorbitan esters.

[0201] In one or more embodiments the at least one surface active agent is liquid. Moreover for the purposes of formulating with liquid ethers a liqiid surfactant is preferred

[0202] In one or more embodiments the liquid surfactant is a polysorbate, preferably polysorbate 80 or 60.

[0203] In one or more embodiments the at least one surface active agent is solid, semi solid or waxy. In a further embodiment they are soluble in oil and in another embodiment have a HLB of less than about 12.

[0204] It should be noted that HLB values may not be so applicable to non ionic surfactants, for example, with liquid crystals or with silicones. Also HLB values may be of lesser significance in a waterless or substantially non-aqueous environment.

[0205] In one or more embodiments the surfactant can be, a surfactant system comprising of a surfactant and a co surfactant, a waxy emulsifier, a liquid crystal emulsifier, an emulsifier which is solid or semi solid at room temperature and pressure, or combinations of two or more agents in an appropriate proportion as will be appreciated a person skilled in the art. Where a solid or semi solid emulsifier combination is used it can also comprise a solid or semi solid emulsifier and a liquid emulsifier. In apreferred embodiment at least one surfactant is a liquid.

[0206] In one or more embodiments, the surface-active agent includes at least one non-ionic surfactant. Ionic surfactants are known to be irritants. Therefore, non-ionic surfactants are preferred in applications including sensitive tissue such as found in most mucosal tissues, especially when they are infected or inflamed.

Non-ionic surfactants alone can provide formulations and foams of good or excellent quality in the carriers and compositions of the present invention.

[0207] Thus, in a preferred embodiment, the surface active agent, the composition contains a non-ionic surfactant. In another preferred embodiment the composition includes a mixture of non-ionic surfactants as the sole surface active agent. Yet, in additional embodiments, the foamable composition includes a mixture of at least one non-ionic surfactant and at least one ionic surfactant in a ratio in the range of about 100:1 to 6:1. In one or more embodiments, the non-ionic to ionic surfactant ratio is greater than about 6:1, or greater than about 8:1; or greater than about 14:1, or greater than about 16:1, or greater than about 20:1. In further embodiments, surface active agent comprises a combination of a non-ionic surfactant and an ionic surfactant, at a ratio of between 1:1 and 20:1

[0208] In one or more embodiments , a combination of a non-ionic surfactant and an ionic surfactant (such as sodium lauryl sulphate and cocamidopropylbetaine) is employed, at a ratio of between 1:1 and 20:1, or at a ratio of 4:1 to 10:1; for example, about 1:1, about 4:1, about 8:1, about 12:1, about 16:1and about 20:1 or at a ratio of 4:1 to 10:1, for example, about 4:1, about 6:1, about 8:1 and about 10:1.

[0209] For foams in selecting a suitable surfactant or combination thereof it should be borne in mind that the upper amount of surfactant that may be used may be limited by the shakability of the composition. If the surfactant is non liquid, it can make the formulation to viscous or solid. Subject to its miscibily solid surfactants may be added first, and may require gentle warming and then cooling before being combined with the other ingredients. In general terms, as the amount of non-liquid surfactant is increased the shakability of the formulation reduces until a limitation point is reached where the formulation can become non shakable and unsuitable. Thus in one embodiment, any effective amount of surfactant may be used provided the formulation remains shakable. In other certain limited embodiments the upper limit for foamable formulations may be determined by flowability such that any effective amount can be used provided

the formulation is sufficiently flowable to be able to flow through an actuator valve and be released and still expand to form a good quality foam. This may be due without being bound by any theory to one or more of a number of factors such as the viscosity, the softness, the lack of crystals, the pseudoplastic or semi pseudo plastic nature of the composition and the dissolution of the propellant into the composition.

[0210] In certain embodiments the amount of surfactant or combination of surfactants is between about 0.05% to about 20%; between about 0.05% to about 15%. or between about 0.05% to about 10%. In a preferred embodiment the concentration of surface active agent is between about 0.2% and about 8%. In a more preferred embodiments the concentration of surface active agent is between about 1% and about 6% or between about 1% and about 4%.

[0211] In some embodiments, it is desirable that the surface active agent does not contain a polyoxyethylene (POE) moiety, such as polysorbate surfactants, POE fatty acid esters, and POE alkyl ethers, because the active agent is incompatible with such surface active agents. For example, the active agent pimecrolimus is not stable the presence of POE moieties, yet benefits greatly from the use of dicarboxylic esters as penetration enhancers. In such cases, alternative surface active agents are employed. In an exemplary manner, POE – free surfactants include non-ethoxylated sorbitan esters, such as sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan trioleate, sorbitan monolaurate and sorbitan sesquioleate; glycerol fatty acid esters, such as glycerol monostearate and glycerol monooleate; mono-, di- and tri-esters of sucrose with fatty acids (sucrose esters), sucrose stearate, sucrose distearate sucrose palmitate and sucrose laurate; and alkyl polyglycosides, such as lauryl diglucoside.

[0212] In one or more embodiments , the surface-active agent includes mono- , di- and tri-esters of sucrose with fatty acids (sucrose esters), prepared from sucrose and esters of fatty acids or by extraction from sucro-glycerides. Suitable

sucrose esters include those having high monoester content, which have higher HLB values.

[0213] In one or more preferred embodiments of the present invention the surfactant includes at least one surfactant selected from a polyoxyethylene fatty ether, a polyoxyethylene fatty ester,a carbohydrate ester and a sucrose ester.

[0214] In one or more embodiments non limiting examples of non-ionic surfactants include steareth-2, steareth-20, steareth-21, ceteareth 2, PEG-100 stearyl ether, cetearyl glucoside, methyl glucose sesquistearate, sorbitan monostearate, GMS NE and span 20.

[0215] In one or more embodiments non limiting other examples of surfactant combinations are glyceryl stearate and PEG 100 stearate and laureth4; steareth 2, PEG 100 searate and laureth4; and cetearyl glucoside and cetearyl alcohol.

[0216] In an embodiment the surfactant containing formulations are further boosted by a foam adjuvant for example stearyl alcohol.

[0217] A non limiting example of a combination of surfactants having a weighted average of their HLB values of 11 is Glyceryl Stearate and PEG-100 Stearate (for example trade name "simulsol 165" from Sepic).

Hydrophobic solvent

[0218] Optionally, the foamable carrier further contains at least one hydrophobic solvent. The identification of a "hydrophobic solvent", as used herein, is not intended to characterize the solubilization capabilities of the solvent for any specific active agent or any other component of the foamable composition. Rather, such information is provided to aid in the identification of materials suitable for use as a part in the foamable compositions described herein.

[0219] A “hydrophobic solvent” as used herein refers to a material having solubility in distilled water at ambient temperature of less than about 1 gm per

100 mL, more preferable less than about 0.5 gm per 100 mL, and most preferably less than about 0.1 gm per 100 mL.

[0220] In one or more embodiments, the hydrophobic organic carrier is an oil, such as 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, propylene glycol 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 oil, evening primrose oils; essential oils; and silicone oils, such as dimethicone, cyclomethicone, polyalkyl siloxanes, polyaryl siloxanes, polyalkylaryl siloxanes and polyether siloxane copolymers, polydimethylsiloxanes (dimethicones) and poly(dimethylsiloxane)-(diphenyl-siloxane) copolymers. In one or more further embodiments the hydrophobic organic carrier is petrolatum.

Humectant

[0221] A humectant, is a substance that helps retain moisture and also prevents rapid evaporation. Non limiting examples of suitable heumectants are propylene glycol, propylene glycol derivatives, and glycerin. Other examples of humectants and moisturizers may be found in the Handbook of Pharmaceutical Additives published by Gower. Suitable ones for use with and soluble in the waterless compositions of the present invention may be selected as will be appreciated by a person skilled in the art.

Moisturizers

[0222] A moisturizer, is a substance that helps retain moisture or add back moisture to the skin. Examples are allantoin, petrolatum, urea, lactic acid, sodium PCV, glycerin,

shea butter, caprylic/capric/stearic triglyceride, candelilla wax, propylene glycol, lanolin, hydrogenated oils, squalene, sodium hyaluronate and lysine PCA. Glycerine and sodium pCA work in combination. Other examples may be found in the *Handbook of Pharmaceutical Additives* published by Gower.

[0223] Pharmaceutical compositions of the present invention may in one or more embodiments usefully comprise in addition a humectant or a moisturizer or combinations thereof.

Foam adjuvant

[0224] Optionally, a foam adjuvant is included in the foamable carriers of the present invention to increase the foaming capacity of surfactants and/or to stabilize the foam. In one or more embodiments of the present invention, the foam adjuvant agent includes fatty alcohols having 15 or more carbons in their carbon chain, such as cetyl alcohol and stearyl alcohol (or mixtures thereof). Other examples of fatty alcohols are arachidyl alcohol (C20), behenyl alcohol (C22), 1-triacontanol (C30), as well as alcohols with longer carbon chains (up to C50). Fatty alcohols, derived from beeswax and including a mixture of alcohols, a majority of which has at least 20 carbon atoms in their carbon chain, are especially well suited as foam adjuvant agents. The amount of the fatty alcohol required to support the foam system is inversely related to the length of its carbon chains. Foam adjuvants, as defined herein are also useful in facilitating improved spreadability and absorption of the composition.

[0225] In one or more embodiments of the present invention, the foam adjuvant agent includes fatty acids having 16 or more carbons in their carbon chain, such as hexadecanoic acid (C16) stearic acid (C18), arachidic acid (C20), behenic acid (C22), octacosanoic acid (C28), as well as fatty acids with longer carbon chains (up to C50), or mixtures thereof. As for fatty alcohols, the amount of fatty acids required to support the foam system is inversely related to the length of its carbon chain.

[0226] Optionally, the carbon atom chain of the fatty alcohol or the fatty acid may have at least one double bond. A further class of foam adjuvant agent

includes a branched fatty alcohol or fatty acid. The carbon chain of the fatty acid or fatty alcohol also can be substituted with a hydroxyl group, such as 12-hydroxy stearic acid.

Additional components

[0227] In an embodiment of the present invention, a composition of the present invention includes one or more additional components. Such additional components include but are not limited to anti perspirants, anti-static agents, buffering agents, bulking agents, chelating agents, cleansers, colorants, conditioners, deodorants, diluents, dyes, emollients, fragrances, hair conditioners, humectants, pearlescent aids, perfuming agents, permeation enhancers, pH-adjusting agents, preservatives, protectants, skin penetration enhancers, softeners, solubilizers, sunscreens, sun blocking agents, sunless tanning agents, viscosity modifiers and vitamins and flavonoids. As is known to one skilled in the art, in some instances a specific additional component may have more than one activity, function or effect.

[0228] In an embodiment of the present invention, the additional component is a pH adjusting agent or a buffering agent. Suitable buffering agents include but are not limited to acetic acid, adipic acid, calcium hydroxide, citric acid, glycine, hydrochloric acid, lactic acid, magnesium aluminometasilicates, phosphoric acid, sodium carbonate, sodium citrate, sodium hydroxide, sorbic acid, succinic acid, tartaric acid, and derivatives, salts and mixtures thereof.

[0229] In an embodiment of the present invention, the additional component is an emollient. Suitable emollients include but are not limited to mineral oil, lanolin oil, coconut oil, cocoa butter, olive oil, aloe vera extract, jojoba oil, castor oil, fatty acids, fatty alcohols, diisopropyl adipate, hydroxybenzoate esters, benzoic acid esters of C9 to C15 alcohols, isononyl iso-nonanoate, silicone oils, polyethers, C12 to C15 alkyl benzoates, oleic acid, stearic fatty acid, cetyl alcohols, hexadecyl alcohol, dimethyl polysiloxane, polyoxypropylene cetyl ether, polyoxypropylene butyl ether, and derivatives, esters, salts and mixtures thereof.

[0230] In an embodiment of the present invention, the additional component is a humectant. Suitable humectants include but are not limited to guanidine, urea, glycolic acid, glycolate salts, ammonium glycolate, quaternary alkyl ammonium glycolate, lactic acid, lactate salts, ammonium lactate, quaternary alkyl ammonium lactate, aloe vera, aloe vera gel, allantoin, urazole, alkoxylated glucose, hyaluronic acid, lactamide monoethanolamine, acetamide monoethanolamine and derivatives, esters, salts and mixtures thereof.

[0231] In an embodiment of the present invention, the additional component is a preservative. Suitable preservatives include but are not limited to C12 to C15 alkyl benzoates, alkyl p-hydroxybenzoates, aloe vera extract, ascorbic acid, benzalkonium chloride, benzoic acid, benzoic acid esters of C9 to C15 alcohols, butylated hydroxytoluene, castor oil, cetyl alcohols, chlorocresol, citric acid, cocoa butter, coconut oil, diazolidinyl urea, diisopropyl adipate, dimethyl polysiloxane, DMDM hydantoin, ethanol, fatty acids, fatty alcohols, hexadecyl alcohol, hydroxybenzoate esters, iodopropynyl butylcarbamate, isononyl iso-nonanoate, jojoba oil, lanolin oil, methylparaben, mineral oil, oleic acid, olive oil, polyethers, polyoxypropylene butyl ether, polyoxypropylene cetyl ether, potassium sorbate, silicone oils, sodium propionate, sodium benzoate, sodium bisulfite, sorbic acid, stearic fatty acid, vitamin E, vitamin E acetate and derivatives, esters, salts and mixtures thereof.

[0232] In an embodiment of the present invention, the additional component is a skin penetration enhancer. Suitable skin penetration enhancers include but are not limited to acetone, acyl lactylates, acyl peptides, acylsarcosinates, alkanolamine salts of fatty acids, alkyl benzene sulphonates, alkyl ether sulphates, alkyl sulphates, anionic surface-active agents, benzyl benzoate, benzyl salicylate, butan-1,4-diol, butyl benzoate, butyl laurate, butyl myristate, butyl stearate, cationic surface-active agents, citric acid, cocoamidopropylbetaine, decyl methyl sulfoxide, decyl oleate, dibutyl azelate, dibutyl phthalate, dibenzyl sebacate, dibutyl sebacate, dibutyl suberate, dibutyl succinate, dicapryl adipate, didecyl phthalate, diethylene glycol, diethyl sebacate,

diethyl-m-toluamide, di(2-hydroxypropyl) ether, diisopropyl adipate, diisopropyl sebacate, N,N-dimethyl acetamide, dimethyl azelate, N,N-dimethyl formamide, 1,5-dimethyl-2-pyrrolidone, dimethyl sebacate, dimethyl sulphoxide, dioctyl adipate, dioctyl azelate, dioctyl sebacate, 1,4 dioxane, 1-dodecylazacyloheptan-2-one, dodecyl dimethyl amine oxides, ethyl caprate, ethyl caproate, ethyl caprylate, 2-ethyl-hexyl pelargonate, ethyl-2-hydroxypropanoate, ethyl laurate, ethyl myristate, 1-ethyl-2-pyrrolidone, ethyl salicylate, hexyl laurate, 2-hydroxyoctanoic acid, 2-hydroxypropanoic acid, 2-hydroxypropionic acid, isethionates, isopropyl isostearate, isopropyl palmitate, guar hydroxypropyltrimonium chloride, hexan-2,5-diol, khellin, lamepons, lauryl alcohol, maypons, metal salts of fatty acids, methyl nicotinate, 2-methyl propan-2-ol, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, methyl taurides, miranol, nonionic surface-active agents, octyl alcohol, octylphenoxy polyethoxyethanol, oleic ethanolamide, pleyl alcohol, pentan-2,4-diol, phenoxyethanol, phosphatidyl choline, phosphine oxides, polyalkoxylated ether glycollates, poly(diallylpiperidinium chloride), poly(dipropyldiallylammonium chloride), polyglycerol esters, polyoxyethylene lauryl ether, polyoxy:polyoxyethylene stearate, polyoxypropylene 15 stearyl ether, poly(vinyl pyridinium chloride), propan-1-ol, propan-2-ol, propylene glycol dipelargonate, pyroglutamic acids, 2-pyrrolidone, pyruvic acids, Quaternium 5, Quaternium 18, Quaternium 19, Quaternium 23, Quaternium 31, Quaternium 40, Quaternium 57, quartenary amine salts, quaternised poly (dimethylaminoethylmethacryl- ate), quaternised poly (vinyl alcohol), sapamin hydrochloride, sodium cocaminopropionate, sodium dioctyl sulphonsuccinate, sodium laurate, sodium lauryl ether sulphate, sodium lauryl sulphate, sugar esters, sulphosuccinate, tetrahydrofuran, tetrahydrofurfural alcohol, transcutol, triethanolamine dodecyl benzene sulphonate, triethanolamine oleate, urea, water and derivatives, esters, salts and mixtures thereof.

[0233] In an embodiment the composition with modulating agent may be used as is without addition of a propellant. In other embodiments propellant is added to form a foamable compostion that produces a foam when the formulation is

expelled from a pressurized canister. The foam may be of various qualities as indicated herein. In a preferred embodiment the foam is of about good quality. In a more preferred embodiment it is of about excellent quality.

Propellants

[0234] Examples of suitable propellants include volatile hydrocarbons such as butane, propane, isobutane and fluorocarbon gases, or mixtures thereof.

[0235] In an embodiment the propellant is AP 70 which is a mixture of propane, isobutene and butane.

[0236] The propellant makes up about 5-25 wt% of the foamable composition. In some circumstances the propellant may be upto 35%. The propellants are used to generate and administer the foamable composition as a foam. The total composition including propellant, foamable compositions and optional ingredients is referred to as the foamable composition.

[0237] Alcohol and organic solvents render foams inflammable. It has been surprisingly discovered that fluorohydrocarbon propellants, other than chloro-fluoro carbons (CMCs), which are non-ozone-depleting propellants, are particularly useful in the production of a non-flammable foamable composition. A test according to European Standard prEN 14851, titled "Aerosol containers - Aerosol foam flammability test" revealed that compositions containing an organic carrier that contains a hydrophobic organic carrier and/or a polar solvent, which are detected as inflammable when a hydrocarbon propellant is used, become non-flammable, while the propellant is an HFC propellant.

[0238] Such propellants include, but are not limited to, hydrofluorocarbon (HFC) propellants, which contain no chlorine atoms, and as such, fall completely outside concerns about stratospheric ozone destruction by chlorofluorocarbons or other chlorinated hydrocarbons. Exemplary non-flammable propellants according to this aspect of the invention include propellants made by DuPont under the registered trademark Dymel, such as 1,1,1,2 tetrafluorethane (Dymel 134), and 1,1,1,2,3,3,3 heptafluoropropane (Dymel 227) 1,1, difluoro ethane (Dymel 152)

and 1,1,1,3,3,3 hexafluoropropane HFCs possess Ozone Depletion Potential of 0.00 and thus, they are allowed for use as propellant in aerosol products.

[0239] Notably, the stability of foamable emulsions including HFC as the propellant can be improved in comparison with the same composition made with a hydrocarbon propellant.

[0240] In one or more embodiments foamable compositions comprise a combination of a HFC and a hydrocarbon propellant such as n-butane or mixtures of hydrocarbom propellants such as propane, isobutane and butane.

Composition and Foam Physical Characteristics and Advantages

[0241] A pharmaceutical or cosmetic composition manufactured using the foamable carrier of the present invention is very easy to use. When applied onto the afflicted body surface of mammals, i.e., humans or animals, it is in a foam state, allowing free application without spillage. Upon further application of a mechanical force, e.g., by rubbing the composition onto the body surface, it freely spreads on the surface and is rapidly absorbed.

[0242] The foamable composition of the present invention is stable, having an acceptable shelf-life of months or preferably at least one year, or more preferably, at least two years at ambient temperature, as revealed in accelerated stability tests. Organic carriers and propellants tend to impair the stability of emulsions and to interfere with the formation of stable foam upon release from a pressurized container. It has been observed, however, that the foamable compositions according to the present invention are surprisingly stable. Following accelerated stability studies, they demonstrate desirable texture; they form fine bubble structures that do not break immediately upon contact with a surface, spread easily on the treated area and absorb quickly.

[0243] The composition should also be free flowing, to allow it to flow through the aperture of the container, e.g., and aerosol container, and create an acceptable foam.

[0244] Foam quality can be graded as follows:

Grade E (excellent): very rich and creamy in appearance, does not show any bubble structure or shows a very fine (small) bubble structure; does not rapidly become dull; upon spreading on the skin, the foam retains the creaminess property and does not appear watery.

Grade G (good): rich and creamy in appearance, very small bubble size, "dulls" more rapidly than an excellent foam, retains creaminess upon spreading on the skin, and does not become watery.

Grade FG (fairly good): a moderate amount of creaminess noticeable, bubble structure is noticeable; upon spreading on the skin the product dulls rapidly and becomes somewhat lower in apparent viscosity.

Grade F (fair): very little creaminess noticeable, larger bubble structure than a "fairly good" foam, upon spreading on the skin it becomes thin in appearance and watery.

Grade P (poor): no creaminess noticeable, large bubble structure, and when spread on the skin it becomes very thin and watery in appearance.

Grade VP (very poor): dry foam, large very dull bubbles, difficult to spread on the skin.

[0245] Topically administrable foams are typically of quality grade E or G, when released from the aerosol container. Smaller bubbles are indicative of more stable foam, which does not collapse spontaneously immediately upon discharge from the container. The finer foam structure looks and feels smoother, thus increasing its usability and appeal.

[0246] A further aspect of the foam is breakability. Thermally sensitive foams immediately collapse upon exposure to skin temperature and, therefore, cannot be applied on the hand and afterwards delivered to the afflicted area.

[0247] The foam of the present invention has several advantages, when compared with hydroalcoholic foam compositions, such as

(1) Breakability. The foam of the present invention is thermally stable and breakable under sheer force but is not "quick breaking which allows comfortable application and well directed administration to the target area;

(2) Skin drying and skin barrier function. Short chain alcohols are known to dry the skin and impair the integrity of the skin barrier. By contrast, including a film forming agent in the composition of the present invention foes not cause unwanted skin barrier damage; and

(3) Irritability. Due to the lack of alcohol and improvement in skin barrier function, skin irritability is eliminated or reduced.

[0248] Another property of the foam is specific gravity, as measured upon release from the aerosol can. Typically, foams have specific gravity of less than 0.12 g/mL; or less than 0.10 g/mL; or less than 0.08 g/mL, depending on their composition and on the propellant concentration.

Pharmaceutical composition

[0249] The compositions, the foamable compositions and the foams of the present invention are ideal vehicles for active pharmaceutical ingredients and active cosmetic ingredients. In the context of the present invention, active pharmaceutical ingredients and active cosmetic ingredients are collectively termed "active agent" or "active agents". A foamable composition, comprising an active agent has the following advantages:

1. The foamable composition provides a preferred solvent for active agents, particularly water-insoluble agents.
2. The inclusion of a polyol and/or a PEG and a secondary polar solvent in the foamable composition facilitates a co-solvent effect, resulting increased concentrations of soluble active agent in the dosage form, thus facilitating enhanced skin penetration of the active agent. In many cases, increased penetration is positively correlated with improved clinical outcome. In certain case, attaining an increased drug penetration into the target site of action enables

a decrease of treatment frequency, for example, from twice or three times daily to once daily.

3. Polyols and PEGs; and combinations of a polyol and/or PEG with a secondary polar solvent are known as skin penetration enhancers, thus, increasing drug residence in the target area and increasing clinical efficacy, as detailed above.
4. The fact that the compositions contains no water, or merely up to 5% and water minimizes the probability of degradation of water-sensitive active agents. Furthermore, as exemplified herein, a foam containing a polyol and/or PEG with no water at all can be formed in accordance with the composition and process of the present invention. Such compositions ensure high stability of water sensitive active agents.
5. Combining the anti-infective effect of a water-free, thus hygroscopic composition, which acts through a dehydration mechanism, with an additional anti-infective agent, selected from the group of an antibiotic agent, an antibacterial agent, an antifungal agent, an agent that controls yeast, an antiviral agent and an antiparasitic agent, that acts through alternate mechanisms results in a synergistic effect and consequently higher success rate of the treatment.
6. The foamable polyol composition in contained in an impermeable pressurized packaging presentation is impermeable and thus, the active agent is not exposed to environmental degradation factors, such as light and oxidating agent during storage.

[0250] Thus, in a preferred embodiment of the present invention, the composition includes at least one active agent.

a. a therapeutically effective concentration of an active agent;
b. a modulating agent;

c. about 50% to about 98% of a polar solvent, selected from the group consisting of a polyol and a polyethylene glycol;

d. 0% to about 48% of a secondary polar solvent;

e. about 0.2% to about 5% by weight of a surface-active agent;

f. about 0.01% to about 5% by weight of at least one polymeric agent; and for a foamable composition additionally

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

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

Active agents

[0251] Suitable active agents include but are not limited to active herbal extracts, acaricides, age spot and keratose removing agents, allergen, analgesics, local anesthetics, antiacne agents, antiallergic agents, antiaging agents, antibacterials, antibiotics, antiburn agents, anticancer agents, antidandruff agents, antidepressants, antidermatitis agents, antiedemics, antihistamines, antihelminths, antihyperkeratolyte agents, antiinflammatory agents, antiirritants, antilipemics, antimicrobials, antimycotics, antiproliferative agents,,antioxidants, anti-wrinkle agents, antipruritics, antipsoriatic agents, antirosacea agents antiseborrheic agents, antiseptic, antiswelling agents, antiviral agents, antiyeast agents, 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, skin whitening agents, asoconstrictors, vasodilators, vitamins, vitamin D derivatives, flavonoids, wound healing agents and wart removers. As is known to one skilled

in the art, in some instances a specific active active agent may have more than one activity, function or effect.

[0252] In an embodiment of the present invention, the active agent is an active herbal extract. Suitable active herbal extracts include but are not limited to angelica, anise oil, astragali radix, azalea, benzyl acetate, birch tar oil, bomyl acetate, cacumen biotae, camphor, cantharidin, capsicum, cineole, cinnamon bark, cinnamon leaf, citronella, citroneliol, citronellyl acetate, citronellyl formate, eucalyptus, eugenyl acetate, flos carthami, fructus mori, garlic, geraniol, geranium, geranyl acetate, habanera, isobutyl angelicate, lavender, ledum latifolium, ledum palustre, lemongrass, limonene, linalool, linalyl acetate, methyl anthranilate, methyl cinnamate, mezereum, neem, nerol, neryl acetate, nettle root extract, oleum ricini, oregano, pinenes, .alpha.-pinene, .beta.-pinene, radix angelicae sinesis, radix paenoiae rubra, radix polygoni multiflori, radix rehmanniae, rhizoma pinelliae, rhizoma zingiberis recens, sabadilla, sage, sandalwood oil, saw palmetto extract, semen sesami nigrum, staphysagria, tea tree oil, terpene alcohols, terpene hydrocarbons, terpene esters, terpinene, terpineol, terpinyl acetate and derivatives, esters, salts and mixtures thereof. In an embodiment of the present invention, the active agent is an acaricide. Suitable acaricides include but are not limited to amitraz, flumethrin, fluvalinate and derivatives, esters, salts and mixtures thereof.

[0253] In an embodiment of the present invention, the active agent is an age spot and keratoses removing agent. Suitable age spot and keratoses removing agent include but are not limited to hydroxy acids, azelaic acid and other related dicarboxylic acids, retinoids, kojic acid, arbutin, nicotinic, ascorbic acid, hydroquinone and derivatives, esters, salts and mixtures thereof. Certain nonsteroidal anti-inflammatory agents, such as diclofenac are also useful for the treatment of keratoses.

[0254] In an embodiment of the present invention, the active agent is an analgesic. Suitable analgesics include but are not limited to benzocaine,

butamben picrate, dibucaine, dimethisoquin, dyclonine, lidocaine, pramoxine, tetracaine, salicylates and derivatives, esters, salts and mixtures thereof.

[0255] In an embodiment of the present invention, the active agent is a local anesthetic. Suitable local anesthetics include but are not limited to benzocaine, benzyl alcohol, bupivacaine, butamben picrate, chlorprocaine, cocaine, dibucaine, dimethisoquin, dyclonine, etidocaine, hexylcaine, ketamine, lidocaine, mepivacaine, phenol, pramoxine, procaine, tetracaine, salicylates and derivatives, esters, salts and mixtures thereof.

[0256] In an embodiment of the present invention, the active agent is an antiacne agent. Suitable antiacne agents include but are not limited to N-acetylcysteine, adapalene, azelaic acid, benzoyl peroxide, cholate, clindamycin, deoxycholate, erythromycin, flavinoids, glycolic acid, meclocycline, metronidazol, mupirocin, octopirox, phenoxy ethanol, phenoxy proponol, pyruvic acid, resorcinol, retinoic acid, salicylic acid, scymnol sulfate, sulfacetamide-sulfur, sulfur, tazarotene, tetracycline, tretinoin triclosan and derivatives, esters, salts and mixtures thereof.

[0257] In an embodiment of the present invention, the active agent is an antiaging agent. Suitable antiaging agents include but are not limited to sulfur-containing D and L amino acids, alpha-hydroxy acids s, beta-hydroxy acids (e.g. salicylic acid), urea, hyaluronic acid, phytic acid, lipoic acid; lysophosphatidic acid, skin peel agents (e.g., phenol, resorcinol and the like), vitamin B3 compounds (e.g., niacinamide, nicotinic acid and nicotinic acid salts and esters, including non-vasodilating esters of nicotinic acid (such as tocopheryl nicotinate), nicotinyl amino acids, nicotinyl alcohol esters of carboxylic acids, nicotinic acid N-oxide and niacinamide N-oxide), vitamin B5 and retinoids (e.g., retinol, retinal, retinoic acid, retinyl acetate, retinyl palmitate, retinyl ascorbate) skin barrier forming agents, melatonin and derivatives, esters, salts and mixtures thereof.

[0258] In an embodiment of the present invention, the active agent is an antibiotic. The terms “antibiotic” as used herein shall include, but is not limited to,

any substance being destructive to or inhibiting the growth of bacteria or any substance having the capacity to inhibit the growth of or to destroy bacteria. In one or more embodiments, the antibiotic agent is selected from the group consisting of a beta-lactam antibiotic, an aminoglycoside, an ansa-type antibiotic, an anthraquinone, an azole, an antibiotic glycopeptide, a macrolide, an antibiotic nucleoside, an antibiotic peptide, an antibiotic polyene, an antibiotic polyether, an antibiotic quinolone, an antibiotic steroid, a sulfonamide, an antibiotic metal, an oxidizing agent, 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, a triguanide, a bisbiguanide, a polymeric biguanide, and analogs, derivatives, salts, ions and complexes thereof.

[0259] Suitable antibiotics include but are not limited to amanfadine hydrochloride, amanfadine sulfate, amikacin, arnikacin sulfate, aminoglycosides, amoxicillin, ampicillin, ansamycins, bacitracin, beta-lactams, candicidin, capreomycin, carbenicillin, cephalexin, cephaloridine, cephalothin, cefazolin, cephapirin, cephradine, cephaloglycin, chloramphenicols, chlorhexidine, chlorhexidine gluconate, chlorhexidine hydrochloride, chloroxine, chlorquinaldol, chlortetracycline, chlortetracycline hydrochloride, ciprofloxacin, circulin, clindamycin, clindamycin hydrochloride, clotrimazole, cloxacillin, demeclocycline, diclosxacillin, diiodohydroxyquin, doxycycline, ethambutol, ethambutol hydrochloride, erythromycin, erythromycin estolate, erythromycin stearate, farnesol, floxacillin, gentamicin, gentamicin sulfate, gramicidin, griseofulvin, haloprogin, haloquinol, hexachlorophene, iminocyldline, iodate, iodine, iodochlorhydroxyquin, kanamycin, kanamycin sulfate, lincomycin, lineomycin, lineomycin hydrochloride, macrolides, meclocycline, methacycline, methacycline hydrochloride, methenamine, methenamine hippurate, methenamine mandelate, methicillin, metronidazole, miconazole, miconazole hydrochloride, microcrystalline and nanocrystalline particles of silver, copper, zinc, mercury, tin, lead, bismuth, cadmium and chromium, minocycline, minocycline hydrochloride, mupirocin, nafcillin, neomycin, neomycin sulfate, netilmicin, netilmicin sulfate,

Padagis Ex. 1029
IPR Petition - USP 11,311,482

nitrofurazone, norfloxacin, nystatin, octopirox, oleandomycin, orcephalosporins, oxacillin, oxytetracycline, oxytetracycline hydrochloride, parachlorometa xylenol, paromomycin, paromomycin sulfate, penicillins, penicillin G, penicillin V, pentamidine, pentamidine hydrochloride, phenethicillin, polymyxins, quinolones, streptomycin sulfate, tetracycline, tobramycin, tolnaftate, triclosan, trifampin, rifamycin, rolitetracycline, spectinomycin, spiramycin, streptomycin, sulfonamide, tetracyclines, tetracycline, tobramycin, tobramycin sulfate, triclocarbon, triclosan, trimethoprim-sulfamethoxazole, tylosin, vancomycin, yrothricin and derivatives, esters, salts and mixtures thereof.

[0260] In an embodiment of the present invention, the active agent is an antidandruff agent. Suitable antidandruff agents include but are not limited to aminexil, benzalkonium chloride, benzethonium chloride, 3-bromo-1-chloro-5,5-dimethyl-hydantoin, chloramine B, chloramine T, chlorhexidine, N-chlorosuccinimide,climbazole- , 1,3-dibromo-5,5-dimethylhydantoin, 1,3-dichloro-5,5-dimethyl-hydantoin, betulinic acid, betulonic acid, celastrol, crataegolic acid, cromakalin, cyproterone acetate, dutasteride, finesteride, ibuprofen, ketoconozole, oleanolic acid, phenytoin, picrotone olamine, salicylic acid, selenium sulphides, triclosan, triiodothyronine, ursolic acid, zinc gluconate, zinc omadine, zinc pyrithione and derivatives, esters, salts and mixtures thereof.

[0261] In an embodiment of the present invention, the active agent is an antihistamine. Suitable antihistamines include but are not limited to chlorcyclizine, diphenhydramine, mepyramine, methapyrilene, tripelennamine and derivatives, esters, salts and mixtures thereof.

[0262] In an embodiment of the present invention, the active agent is an antimycotic Also termed antifungal agent. The terms "antimycotic" and “antifungal” as used herein include, but is not limited to, any substance being destructive to or inhibiting the growth of fungi and yeast or any substance having the capacity to inhibit the growth of or to destroy fungi and/or yeast.

[0263] In one or more embodiments, the antifungal agent is an agent that is useful in the treatment of a superficial fungal infection of the skin, dermatophytosis, microsporum, trichophyton and epidermophyton infections, candidiasis, oral candidiasis (thrush), candidiasis of the skin and genital mucous membrane, candida paronychia, which inflicts the nail and nail bed and genital and vaginal candida, which inflict genitalia and the vagina.

[0264] Suitable antimycotics include but are not limited to allylamines, amorolfine, amphotericin B, azole compounds, bifonazole, butoconazole, chloroxine, clotrimazole, ciclopirox olamine, clotrimazole, econazole, elubiol, fenticonazole, fluconazole, flucytosine (5FC), griseofulvin, itraconazole, ketoconazole, mafenide acetate, miconazole, naftifine, natamycin, tolnaftate, nystatin, polyenes, oxiconazole, sulbentine, sulconazole, terbinafine, terconazole, tioconazole, undecylenic acid and derivatives, esters, salts and mixtures thereof.

[0265] In an embodiment of the present invention, the active agent is an antipruritic. Suitable antipruritics include but are not limited to menthol, methdilazine, trimeprazine, urea and derivatives, esters, salts and mixtures thereof.

[0266] In an embodiment of the present invention, the active agent is an additional antipsoriatic agent. Suitable additional antipsoriatic agents include but are not limited to 6-aminonicotinamide, 6-aminonicotinic acid, 2-aminopyrazinamide, anthralin, 6-carbamoylnicotinamide, 6-chloronicotinamide, 2-carbamoylpyrazinamide, corticosteroids, 6-dimethylaminonicotinamide, dithranol, 6-formylaminonicotinamide, 6-hydroxy nicotinic acid, 6-substituted nicotinamides, 6-substituted nicotinic acid, 2-substituted pyrazinamide, tazarotene, thionicotinamide, trichothecene mycotoxins and derivatives, esters, salts and mixtures thereof.

[0267] In an embodiment of the present invention, the active agent is an antirosacea agent. Suitable antirosacea agents include but are not limited to azelaic acid, metronidazole, sulfacetamide and derivatives, esters, salts and

mixtures thereof. Certain nonsteroidal anti-inflammatory agents, such as salicylic acid, salycilates, piroxicam and diclofenac are also useful for the treatment of Rosacea.

[0268] In an embodiment of the present invention, the active agent is an antiseborrheic agent. Suitable antiseborrheic agents include but are not limited to glycolic acid, salicylic acid, selenium sulfide, zinc pyrithione, a dicarboxylic acid, such as azelaic acid and derivatives, esters, salts and mixtures thereof.

[0269] In an embodiment of the present invention, the active agent is an antiviral agent. Suitable antiviral agents include but are not limited to acyclovir, gancyclovir, ribavirin, amantadine, rimantadine nucleoside-analog reverse transcriptase inhibitors, such as zidovudine, didanosine, zalcitabine, tavudine, lamivudine and vidarabine, non-nucleoside reverse transcriptase inhibitors, such as nevirapine and delavirdine, protease inhibitors, such as saquinavir, ritonavir, indinavir and nelfinavir, and interferons and derivatives, esters, salts and mixtures thereof.

[0270] In an embodiment of the present invention, the active agent is a chemotherapeutic agent. Suitable chemotherapeutic agents include but are not limited to daunorubicin, doxorubicin, idarubicin, amrubicin, pirarubicin, epirubicin, mitoxantrone, etoposide, teniposide, vinblastine, vincristine, mitomycin C, 5-FU, paclitaxel, docetaxel, actinomycin D, colchicine, topotecan, irinotecan, gemcitabine cyclosporin, verapamil, valspodor, probenecid, MK571, GF120918, LY335979, biricodar, terfenadine, quinidine, pervilleine A, XR9576 and derivatives, esters, salts and mixtures thereof.

[0271] In an embodiment of the present invention, the active agent is a corticosteroid. Suitable corticosteroids include but are not limited to 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, salts and mixtures thereof.

[0272] In an embodiment of the present invention, the active agent is a hair growth regulator. Suitable hair growth regulators include but are not limited to N-acetylgalactosamine, N-acetylglucosamine, N-acetylmannosamine, acitretin, aminexil, ascomycin, asiatic acid, azelaic acid, benzalkonium chloride, benzethonium chloride, benzydamine, benzyl nicotinate, benzoyl peroxide, benzyl peroxide, betulinic acid, betulonic acid, calcium pantothenate, celastrol, cepharanthine, chlorpheniramine maleate, clinacycin hydrochloride, crataegolic acid, cromakalin, cyproterone acetate, diazoxide, diphenhydramine hydrochloride, dutasteride, estradiol, ethyl-2-hydroxypropanoate, finasteride, D-fucono-1,5-lactone,furoate, L-galactono-1,4-lactone, D-galactosamine, D-glucaro-1,4-lactone, D-glucosamine-3-sulphate, hinokitiol, hydrocortisone, 2-hydroxypropionic acid, isotretinoin, itraconazole, ketoconazole, latanoprost, 2-methyl propan-2-ol, minocyclin, minoxidil, mipirocin, mometasone, oleanolic acid,

panthenol, 1,10-phenanthroline, phenytoin, prednisolone, progesterone, propan-2-ol, pseudoterins, resorcinol, selenium sulfide, tazarotene, triclocarbon, triclosan, triiodothyronine, ursolic acid, zinc pyrithione and derivatives, esters, salts and mixtures thereof.

[0273] In an embodiment of the present invention, the active agent is a hormone. Suitable hormones include but are not limited to methyltestosterone, androsterone, androsterone acetate, androsterone propionate, androsterone benzoate, androsteronediol, androsteronediol-3-acetate, androsteronediol-17-acetate, androsteronediol 3-17-diacetate, androsteronediol-17-benzoate, androsteronedione, androstenedione, androstenediol, dehydroepiandrosterone, sodium dehydroepiandrosterone sulfate, dromostanolone, dromostanolone propionate, ethylestrenol, fluoxymesterone, nandrolone phenpropionate, nandrolone decanoate, nandrolone furylpropionate, nandrolone cyclohexane-propionate, nandrolone benzoate, nandrolone cyclohexanecarboxylate, androsteronediol-3-acetate-1-7-benzoate, oxandrolone, oxymetholone, stanozolol, testosterone, testosterone decanoate, 4-dihydrotestosterone, 5a-dihydrotestosterone, testolactone, 17a-methyl-19-nortestosterone, desogestrel, dydrogesterone, ethynodiol diacetate, medroxyprogesterone, levonorgestrel, medroxyprogesterone acetate, hydroxyprogesterone caproate, norethindrone, norethindrone acetate, norethynodrel, allylestrenol, 19-nortestosterone, lynoestrenol, quingestanol acetate, medrogestone, norgestrienone, dimethisterone, ethisterone, cyproterone acetate, chlormadinone acetate, megestrol acetate, norgestimate, norgestrel, desogrestrel, trimegestone, gestodene, nomegestrol acetate, progesterone, 5a-pregnan-3b,20a-diol sulfate, 5a-pregnan-3b,20b-diol sulfate, 5a-pregnan-3b-ol-20-one, 16,5a-pregnen-3b-ol-20-one, 4-pregnen-20b-ol-3-one-20-sulfate, acetoxypregnenolone, anagestone acetate, cyproterone, dihydrogesterone, flurogestone acetate, gestadene, hydroxyprogesterone acetate, hydroxymethylprogesterone, hydroxymethyl progesterone acetate, 3-ketodesogestrel, megestrol, melengestrol acetate, norethisterone, progestins and derivatives, esters, salts and mixtures thereof.

[0274] In an embodiment of the present invention, the active agent is a hydroxyacid. Suitable hydroxy acids include but are not limited to agaricic acid, aleuritic acid, allaric acid, altraric acid, arabiraric acid, ascorbic acid, atrolactic acid, benzilic acid, citramalic acid, citric acid, dihydroxytartaric acid, erythraric acid, galactaric acid, galacturonic acid, glucaric acid, glucuronic acid, glyceric acid, glycolic acid, gularic acid, gulonic acid, hydroxypyruvic acid, idaric acid, isocitric acid, lactic acid, lyxaric acid, malic acid, mandelic acid, mannaric acid, methyllactic acid, mucic acid, phenyllactic acid, pyruvic acid, quinic acid, ribaric acid, ribonic acid, saccharic acid, talaric acid, tartaric acid, tartronic acid, threaric acid, tropic acid, uronic acids, xylaric acid and derivatives, esters, salts and mixtures thereof.

[0275] In an embodiment of the present invention, the active agent is a keratolytic agent. The term "keratolytic agent" is used herein to mean a compound which loosens and removes the stratum corneum of the skin, or alters the structure of the keratin layers of skin. Keratolytic agents are used in the treatment of many dermatological disorders, which involve dry skin, hyperkeratiinization (such as prsoriasis), skin itching (such as xerosis), acne and rosacea. Suitable keratolytic agents include but are not limited to N-acetylcysteine, azelaic acid, cresols, dihydroxy benzene compounds, such as resorcinol and hydroquinone, alpha-hydroxy acids, such as lactic acid and glycolic acid, phenol, pyruvic acid, resorcinol, sulfur, salicylic acid, retinoic acid, isoretinoic acid, retinol, retinal, urea and derivatives, esters, salts and mixtures thereof.

[0276] In an embodiment of the present invention, the active agent is a lactam. Suitable lactams include but are not limited to L-galactono-1,4-lactam, L-arabino-1,5-lactam, D-fucono-1,5-lactam, D-glucaro-1,4-lactam, D-glucurono-6,3-lactam, 2,5-tri-O-acetyl-D-glucurono-6,3-lactam, 2-acetamido-2-deoxyglucono-1,5-l- actam, 2-acetamido-2-deoxygalactono-1,5-lactam, D-glucaro-1,4:6,3-dilactam- , L-idaro-1,5-lactam, 2,3,5,tri-O-acetyl-D-glucaro-1,4-lactam, 2,5-di-O-acetyl-D-glucaro-1,4:6,3-dilactam, D-glucaro-1,5-lactam methyl ester, 2-

propionoamide-2-deoxyglucaro-1,5-lactam and derivatives, esters, salts and mixtures thereof.

[0277] In an embodiment of the present invention, the active agent is a non-steroidal anti-inflammatory agent. Suitable non-steroidal anti-inflammatory agent include but are not limited to azelaic acid, oxicams, piroxicam, isoxicam, tenoxicam, sudoxicam, CP-14,304, salicylates, aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, fendosal, acetic acid derivatives, diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, ketorolac, fenamates, mefenamic, meclofenamic, flufenamic, niflumic, tolfenamic acids, propionic acid derivatives, ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indopropfen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofen, pyrazoles, phenylbutazone, oxyphenbutazone, feprazone, azapropazone, trimethazone and derivatives, esters, salts and mixtures thereof.

[0278] In an embodiment of the present invention, the active agent is insecticide. The term "insecticide, is used herein to mean a compound which kills, inhibits the growth of, impeded the proliferation of or repels insects. Insecticides include, for example, agents that can kill lice, flees, ticks, mites, scabies and mousquitos, as well as agents that repel such insects. Suitable insecticides include but are not limited to DDT, lindane, malathion, permethrin, allethrin, biopermethrin, transpermethrin, phenothrin, diethyl-m-toluamide, dimethyl phthalate, piperonyl butoxide, pyrethroids and derivatives, esters, salts and mixtures thereof.

[0279] In an embodiment of the present invention, the active agent is a vasodilator. Suitable vasodilators include but are not limited to agents that modulate the activity of the enzyme nitric oxide synthase, nicotinic acid, ethyl nicotinate, amyl nitrite, amyl nitrate, ethyl nitrite, butyl nitrite, isobutyl nitrite, glyceryl trinitrate, octyl nitrite, sodium nitrite, sodium nitroprusside, clonitrate, erythrityl tetranitrate, isosorbide mononitrate, isosorbide dinitrate, mannitol

hexanitrate, pentaerythritol tetranitrate, penetrinitol, triethanolamine trinitrate, trolnitrate phosphate (triethanolamine trinitrate diphosphate), propatylnitrate, nitrite esters of sugars, nitrite esters of polyols, nitrate esters of sugars, nitrate esters of polyols, nicorandil, apresoline, diazoxide, hydralazine, hydrochlorothiazide, minoxidil, pentaerythritol, tolazoline, scoparone, a beta-adrenergic blocker, an alpha-adrenoceptor blocker, a prostaglandin, sildenafil, dipyridamole, catecholamine, isoproternol, furosemide, prostaglandin, prostacyclin, enalaprilat, morphine, acepromazine, prazosin (α-blocker), enalapril, Captopril, amlodipine, minoxidil, tadalafil, vardenafil, phenylephrin, etilefein, caffeine, capsaicin, an extract capsicum, achillea millefolium (Yarrow), allium sativum (garlic), amoracia rusticana (horseradish), berberis vulgaris (barberry), cimicifuga racemosa (black cohosh), coleus forskholii (coleus), coptis (goldenthread), crataegus (hawthorn), eleutherococcus senticosus (siberian ginseng), ginkgo biloba(ginkgo), melissa offiicnalis (lemon balm), olea europaea (olive leaf), panax ginseng (Chinese ginseng), petroselinum crispum (parsley), scutellaria baicalensis (baical skullcap), tilia europaea (linden flower), trigonella foenum-graecum (fenugreek), urtica dioica (nettles), valeriana officinalis (valerian), viburnum (cramp, bark, black haw), veratrum viride (American hellebore), verbena officinalis (vervain), xanthoxylum americanum (prickly ash), zingiber officinale (ginger), rauwolfia serpentina (Indian snakeroot), viscum album, wild yam, sasparilla, licorice, damiana, yucca, saw palmetto, gotu kola (centella asiatica), yohimbine and salts, hazel nut, brazil nut and walnut, and derivatives, esters, salts and mixtures thereof.

[0280] In an embodiment of the present invention, the active agent is a vasoconstrictor. Suitable vasodilators include but are not limited to ephedrine, epinephrine, phenylephrine, angiotensin, vasopressin; an extract ephedra sinica (ma huang), polygonum bistorta (bistort root), hamamelis virginiana (witch hazel), hydrastis canadensis (goldenseal), lycopus virginicus (bugleweed), aspidosperma quebracho (quebracho blanco), cytisus scoparius (scotch broom) and cypressand and derivatives, esters, salts and mixtures thereof.

Padagis Ex. 1029
IPR Petition - USP 11,311,482

[0281] In an embodiment of the present invention, the active agent is a retinoid. Suitable retinoids include but are not limited to retinol, retinal, retinoic acid, all-trans retinoic acid, isotretinoin, tazarotene, adapalene, 13-*cis*-retinoic acid, acitretin all-trans beta carotene, alpha carotene, lycopene, 9-cis-beta-carotene, lutein and zeaxanthin.

[0282] In an embodiment of the present invention, the active agent is a vitamin D analog. Suitable retinoids include but are not limited to calcipotriene, cholecalciferol, 25-hydroxycholecalciferol, 1α,25-dihydroxycholecalciferol, ergocalciferol, 1α,25-dihydroxyergocalciferol, 22,23-dihydroergocalciferol, 1,24,25-trihydroxycholecalciferol, previtamin D_3, tachysterol$_3$ (also termed tacalciol), isovitamin D_3, dihydrotachysterol$_3$, (1*S*)-hydroxycalciol, (24*R*)-hydroxycalcidiol, 25-fluorocalciol, ercalcidiol, ertacalciol, (5*E*)-isocalciol, 22,23-dihydroercalciol, (24*S*)-methylcalciol, (5*E*)-(10*S*)-10,19-dihydroercalciol, (24*S*)-ethylcalciol and (22*E*)-(24*R*)-ethyl-22,23-didehydrocalciol. In a preferred embodiment, the vitamin D analog is calcipotriene, which is useful in the treatment of psoriasis.

[0283] In an embodiment of the present invention, the active agent is selected from the group consisting of an immunosuppressants and immunoregulating agents. Suitable immunosuppressants and immunoregulating agents include but are not limited to cyclic peptides, such as cyclosporine, tacrolimus, tresperimus, pimecrolimus, sirolimus (rapamycin), verolimus, laflunimus, laquinimod, imiquimod derivatives, esters, salts and mixtures thereof. In one or more embodiments, the immunomodulator is a calcineurin Inhibitor.

[0284] In an embodiment of the present invention, the active agent is a wart remover. Suitable wart removers include but are not limited to imiquimod, podophyllotoxin and derivatives, esters, salts and mixtures thereof.

[0285] In an embodiment of the present invention, the active agent is a photodynamic therapy (PDT) agent. Suitable PDT agents include but are not limited to modified porphyrins, chlorins, bacteriochlorins, phthalocyanines,

naphthalocyanines, pheophorbides, purpurins, m-THPC, mono-L-aspartyl chlorin e6, bacteriochlorins, phthalocyanines, benzoporphyrin derivatives, as well as photosensitiser precursors, such as aminolevulinic acid and derivatives, esters, salts and mixtures thereof.

[0286] In an embodiment of the present invention, the active agent is an antioxidant or a radical scavenger. Suitable antioxidants and radical scavengers agents include but are not limited to ascorbic acid, ascorbyl esters of fatty acids, magnesium ascorbyl phosphate, sodium ascorbyl phosphate, ascorbyl sorbate, tocopherol, tocopheryl sorbate, tocopheryl acetate, butylated hydroxy benzoic acid, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, gallic acid, propyl gallate, uric acid, sorbic acid, lipoic acid, diethylhydroxylamine, amino-guanidine, glutathione, dihydroxy fumaric acid, lycine pidolate, arginine pilolate, nordihydroguaiaretic acid, bioflavonoids, curcumin, lysine, methionine, proline, superoxide dismutase, silymarin, tea extracts, grape skin/seed extracts, melanin, and polyunsaturated oils, containing omega-3 and omega-6 fatty acids (e.g., linoleic and linolenic acid, gamma-linoleic acid, eicosapentaenoic acid and docosahexaenoic acid and derivatives, esters, salts and mixtures thereof.

[0287] In an embodiment of the present invention, the active agent is a self-tanning agent, such as dihydroxyacetone.

[0288] In an embodiment of the present invention, the active agent is an agent, capable of treating hyperhidrosis. Suitable hyperhidrosis agents include but are not limited to anticholinergic drugs, boric acid, tannic acid, resorcinol, potassium permanganate, formaldehyde, glutaraldehyde, methenamine, a Lewis acid, aluminum chloride, aluminum chlorohydrates, zirconium chlorohydrates, aluminum-zirconium-Glycine (AZG) complex, aluminum hydroxybromide, a glycopyrrolate compound, a 5-alpha-reductase inhibitor, finasteride, epristeride, flutamide, spironolactone, saw palmetto extract, cholestan-3-one, a mono- and dicarboxylic acid having 4 to 18 carbon atoms, botulinum toxin, a 5-HT2C receptor antagonist, a 5-HT2C receptor antagonist, ketanserin, ritanserin,

mianserin, mesulergine, cyproheptadine, fluoxetine, mirtazapine, olanzapine and ziprasidone.

[0289] In an embodiment of the present invention, the active agent is a sunscreen agent. Suitable sunscreen agents include but are not limited to titanium dioxide, zinc oxide, zirconium oxide, iron oxide, p-aminobenzoic acid and its derivatives (ethyl, isobutyl, glyceryl esters; p-dimethylaminobenzoic acid); anthranilic acid derivatives (i.e., o-amino-benzoates, methyl, menthyl, phenyl, benzyl, phenylethyl, linalyl, terpinyl, and cyclohexenyl esters); salicylates (amyl, phenyl, octyl, benzyl, menthyl, glyceryl, and di-pro-pyleneglycol esters); cinnamic acid derivatives (menthyl and benzyl esters, a-phenyl cinnamonitrile; butyl cinnamoyl pyruvate); dihydroxycinnamic acid derivatives (umbelliferone, methylumbelliferone, methylaceto-umbelliferone); trihydroxy-cinnamic acid derivatives (esculetin, methylesculetin, daphnetin, and the glucosides, esculin and daphnin); hydrocarbons (diphenylbutadiene, stilbene); dibenzalacetone and benzalacetophenone; naphtholsulfonates (sodium salts of 2-naphthol-3,6-disulfonic and of 2-naphthol-6,8-disulfonic acids); di-hydroxynaphthoic acid, o- and p-hydroxybiphenyldisulfonates, coumarin derivatives (7-hydroxy, 7-methyl, 3-phenyl), diazoles (2-acetyl-3-bromoindazole, phenyl benzoxazole, methyl naphthoxazole, quinine salts (bisulfate, sulfate, chloride, oleate, and tannate); quinoline derivatives (8-hydroxyquinoline salts, 2-phenylquinoline); hydroxy- or methoxy-substituted benzophenones; uric and violuric acids; tannic acid and its derivatives (e.g., hexaethylether); (butyl carbotol) (6-propyl piperonyl) ether; hydroquinone; benzophenones (oxybenzene, sulisobenzone, dioxybenzone, benzoresorcinol, 2,2',4,4'-tetrahydroxybenzophenone, 2,2'-dihydroxy-4,4'-dimethoxybenzophenone, octabenzone; 4-isopropyldibenzoylmethane; butylmethoxydibenzoylmethane; etocrylene; octocrylene; [3-(4'-methylbenzylidene bornan-2-one), terephthalylidene dicamphor sulfonic acid and 4-isopropyl-di-benzoylmethane.

[0290] In an embodiment of the present invention, the active agent is a figure-forming agent and an agent, capable of treating cellulite. Suitable such agents

include but are not limited to baldderwack extract, butcher's, broom, cayenne, dandelion, red clover, ginkgo biloba, horse chestnut, witch hazel and borage oil, caffeic acid, nicotinic acid, theophiline and pentoxyphilline and salts and derivatives thereof.

[0291] Several disorders of the skin, body cavity or mucosal surface (e.g., the mucosa or the cavity of the nose, mouth, eye, ear, vagina or rectum) involve a combination of etiological factors. For example, fungal and bacterial infections and that are inflamed and have symptoms of redness and/or itching warrant therapy that combines an anti-infective agent and an anti-inflammatory agent. Thus, in several cases, combining at least two active agents that treat different etiological factors results in a synergistic effect and consequently higher success rate of the treatment.

[0292] In certain cases, the composition contains two active agents, where each of the active agents require a different pH environment in order to remain stable. For example, corticosteroids are typically stable at acidic pH values (they have a maximum stability at a pH of about 4-6) and of vitamin D analogues are typically stable at basic pH values (they have a maximum stability at pH values above about 8). In order to circumvent the problem of instability it is preferred that the composition is substantially non-aqueous or preferably waterless. The term "substantially non-aqueous" is intended to indicate that the composition has a water content below about 5%, preferably below about 2%, such as below about 1.5%. The formulation can then be modulated by a modulating agent addative that provides, for example, an artificial pH closer to the more sensitive of the two sensitive actives or alternatively closer to the more pH sensitive of the two actives. On a pragmatic level formulating the composition with an artificial pH close to that of skin may be an advantage.

[0293] In one or more embodiments the actve pharmaceutical or cosmetic agent is an agent which is sensitive to pH such that it is more stable at a certain pH or pH range and tends to react or break down or isomerise at a different pH or pH range. In a preferred embodiment the active agent includes the following non

limiting examples: steroids (most are stable at acidic ph of about 4.5); antibiotics, such as tetracycline's which are stable at acidic ph (e.g. oxytetracycline, clindamycin,); penicillinic and cephalosporinic antibiotics, (such as, ampicillin, benzylpenicillin, carbenicillin, cephadroxil, cefotaxime, cephalotin, and cephradine); triamcinolone; nystatin (stable at about ph 7.0); sulfacetamide; and amphotericin; vitamins are generally ph sensitive and examples are ascorbic acid which is stable in slightly acidic conditions and vitamin D analogues that are stable at basic pH, and nicotine amide; NSAID's such as aspirin and indomethacin; atropine; piloarpine; procaine amide; aztrenam; barbiturates; captopril nucletide derivatives such as cytarabineepinephrine; parabens such as ethylparaben methlparaben; anticancer agents such as fluorouracil and iodoxuridine; morphine analgesic; prostaglandins and thiamine HCl.

Fields of Applications

[0294] The foamable carrier of the present invention is suitable for treating any infected surface. In one or more embodiments, foamable carrier is suitable for administration to the skin, a body surface, a body cavity or mucosal surface, e.g., the cavity and/or the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum (severally and interchangeably termed herein "target site").

[0295] By selecting a suitable active agent, or a combination of at least two active agents, the foamable composition of the present invention is useful in treating an animal or a human patient having any one of a variety of dermatological disorders, including 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.

[0296] Likewise, the foamable composition of the present invention is suitable for treating a disorder of a body cavity or mucosal surface, e.g., the mucosa of the nose, mouth, eye, ear, respiratory system, vagina or rectum. Non limiting examples of such conditions include chlamydia infection, gonorrhea infection, hepatitis B, herpes, HIV/AIDS, human papillomavirus (HPV), genital warts, bacterial vaginosis, candidiasis, chancroid, granuloma Inguinale, lymphogranloma venereum, mucopurulent cervicitis (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.

[0297] In an embodiment of the present invention, the composition is useful for the treatment of an infection. In one or more embodiments, the composition is

suitable for the treatment of an infectiion, selected from the group of a bacterial infection, a fungal infection, a yeast infection, a viral infection and a parasitic infection.

[0298] In an embodiment of the present invention, the composition is useful for the treatment of wound, ulcer and burn. This use is particularly important since the composition of the present invention creates a thin, semi-occlusive layer, which coats the damaged tissue, while allowing exudates to be released from the tissue.

[0299] The composition of the present invention is also suitable for administering a hormone to the skin or to a mucosal membrane or to a body cavity, in order to deliver the hormone into the tissue of the target organ, in any disorder that responds to treatment with a hormone.

[0300] In light of the hygroscopic nature of the water-free composition, it is further suitable for the treatment and prevention of post-surgical adhesions. Adhesions are scars that form abnormal connections between tissue surfaces. Post-surgical adhesion formation is a natural consequence of surgery, resulting when tissue repairs itself following incision, cauterization, suturing, or other means of trauma. When comprising appropriate protective agents, the foam is suitable for the treatment or prevention of post surgical adhesions. The use of foam is particularly advantageous because foam can expand in the body cavity and penetrate into hidden areas that cannot be reached by any other alternative means of administration.

Substantially Alcohol-Free

[0301] According to one or more embodiments, the foamable composition is substantially alcohol-free, i.e., free of short chain alcohols. Short chain alcohols, having up to 5 carbon atoms in their carbon chain skeleton and one hydroxyl group, such as ethanol, propanol, isopropanol, butaneol, iso-butaneol, t-butaneol and pentanol, are considered less desirable solvents or polar solvents due to their skin-irritating effect. Thus, the composition is substantially alcohol-free and

includes less than about 5% final concentration of lower alcohols, preferably less than about 2%, more preferably less than about 1%.

Shakability

[0302] 'Shakability' means that the composition contains some or sufficient flow to allow the composition to be mixed or remixed on shaking. That is, it has fluid or semi fluid properties. In some very limited cases it may still be possible to have a foamable composition which is flowable but not apparently shakable.

Breakability

[0303] A breakable foam is thermally stable or substantially so, yet breaks under sheer force. The breakable foam of the present invention is not "quick breaking", i.e., it does not readily collapse upon exposure to body temperature environment. Sheer-force breakability of the foam is clearly advantageous over thermally induced breakability, (due to, for example, the presence of alcohol) since it allows comfortable application and well directed administration to the target area.

Chemical Instability and Stability

[0304] By chemical instability of one or more active agents is meant that at least one of the one or more active agents is susceptible to one or more of inter alia reaction, breakdown, ionization or oxidation or the rate thereof is increased when incorporated into a pharmaceutical or cosmetic carrier that is non aqueous or substantially non aqueous and not comprising a modulating agent .

[0305] Conversely by chemical stability of one or more active agents is meant that at least one of the one or more active agents is less susceptible to one or more of inter alia reaction, breakdown, ionization or oxidation or the rate thereof is impeded when incorporated into a pharmaceutical or cosmetic carrier that is non aqueous or substantially non aqueous and comprising a modulating agent.

[0306] Other foamable compositions are described in: U.S. Publication No. 05-0232869, published on October 20, 2005, entitled NONSTEROIDAL IMMUNOMODULATING KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 05-0205086, published on September 22, 2005, entitled RETINOID IMMUNOMODULATING KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0018937, published on January 26, 2006, entitled STEROID KIT AND FOAMABLE COMPOSITION AND USES THEREOF; U.S. Publication No. 05-0271596, published on December 8, 2005, entitled VASOACTIVE KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0269485, published on November 30, 2006, entitled ANTIBIOTIC KIT AND COMPOSITION AND USES THEREOF; U.S. Publication No. 07-0020304, published on January 25, 2007, entitled NON-FLAMMABLE INSECTICIDE COMPOSITION AND USES THEREOF; U.S. Publication No. 06-0193789, published on August 31, 2006, entitled FILM FORMING FOAMABLE COMPOSITION; U.S. Patent Application No. 11/732547, filed on April 4, 2007, entitled ANTI-INFECTION AUGMENTATION OF FOAMABLE COMPOSITIONS AND KIT AND USES THEREOF; U.S. Provisional Patent Application No. 60/789186, filed on April 4, 2006, KERATOLYTIC ANTIFUNGAL FOAM; U.S. Provisional Patent Application No. 0/815948, filed on June 23, 2006, entitled FOAMABLE COMPOSITIONS COMPRISING A CALCIUM CHANNEL BLOCKER, A CHOLINERGIC AGENT AND A NITRIC OXIDE DONOR; U.S. Provisional Patent Application No. 60/818634, filed on July 5, 2006, entitled DICARBOXYLIC ACID FOAMABLE VEHICLE AND PHARMACEUTICAL COMPOSITIONS THEREOF; U.S. Provisional Patent Application No. 60/843140, filed on September 8, 2006, entitled FOAMABLE VEHICLE AND VITAMIN PHARMACEUTICAL COMPOSITIONS THEREOF, all of which are incorporated herein by reference in their entirety. More particularly any of the active ingredients; the solvents; the surfactants; foam adjuvants; polymeric agents, penetration enhancers; preservatives, humectants; moisturizers; and other excipients as well as the propellants listed therein can be applied herein and are incorporated by reference.

[0307] The invention is described with reference to the following examples. This invention is not limited to these examples and experiments. Many variations will suggest themselves and are within the full intended scope of the appended claims.

Methodology

[0308] The formulas of the present invention may be made in the following general way with appropriate adjustments for each formulation as will be appreciated by someone skilled in the art. Polymers, if any, are mixed, swelled and solubilized in the waterless medium, when necessary, with appropriate heat until it forms a clear solution. Stabilizing surfactants added usually with heat, until a homogeneous mixture is obtained, the mixture is then allowed to cool. The remainder of the ingredients, are then added with mixing until they have dissolved in the medium. The active agent is usually added at the end once the modulating agent has been incorporated. For foam the canisters are then filled with the above waterless formula, sealed and crimped with a valve and pressurized with the propellant.

[0309] A general procedure for preparing foamable compositions is set out in WO 2004/037225, which is incorporated herein by reference.

Waterless Foam

1. Dissolve the polymers, if any, in the main solvent with heating or cooling as appropriate for specific polymer. Add the all other ingredients and heat to 75°C to melt and dissolve the various ingredients.
2. Cool to below 40°C and add sensitive ingredients with mild mixing.
3. Cool to room temperature.

Note that for substantially waterless foam a small amount of water is added before step 2.

Oily Waterless Foam

1. Mix all ingredients excluding polymers and heat to 75°C to melt and dissolve and obtain homogeneous mixture.
2. Mix well and cool to below 40°C and add the polymers, if any, and sensitive ingredients with moderate mixing.
3. Cool to room temperature.

Note that for substantially waterless foam a small amount of water is added before step 2.

Oily Foam with phospholipids

1. Swell the phospholipids in the main oily solvent under mixing for at least 20 minutes until uniform suspension is obtained.
2. Add all other ingredients excluding polymers and heat to 75°C to melt and dissolve and obtain homogeneous mixture.
3. Mix well and cool to below 40°C and add the polymers, if any, and sensitive ingredients with moderate mixing.
4. Cool to room temperature.
5. In case of polymers dissolved or organic solvent, dissolve the polymers in the solvent with heating or cooling as appropriate for specific polymer and add to the oily mixture under vigorous mixing at ~40°C.

Note that for substantially waterless foam a small amount of water is added step 5.

Production under vacuum

[0310] Optionally, the foamable formulation may be prorduced under nitrogen and under vacuum. Whilst the whole process can be carried out under an oxygen free environment, it can be sufficient to apply a vacuum after heating and mixing all the ingredients to obtain an emulsion or homogenous liquid. Preferrably the production chamber is equipped to apply a vacuum but if not the formulation can

be for example placed in a dessicator to remove oxygen prior to filing and crimping.

Canisters Filling and Crimping

[0311] Each aerosol canister is filled with PFF and crimped with valve using vacuum crimping machine. The process of applying a vacuum will cause most of the oxygen present to be eliminated. Addition of hydrocarbon propellant may without being bound by any theory further help to reduce the likelihood of any remaining oxygen reacting with the active ingredient. It may do so, without being bound by any theory, by one or more of dissolving in the oil or hydrophobic phase of the formulation, by dissolving to a very limited extent in the aqueous phase, by competing with some oxygen from the formulation, by diluting out any oxygen, by a tendency of oxygen to occupy the dead space, and by oxygen ocuupying part of the space created by the vacuum being the unfilled volume of the canister or that remaining oxygen is rendered substantially ineffective in the formulation.

Pressurizing

Propellant Filling

[0312] Pressurizing is carried out using a hydrocarbon gas or gas mixture. Canisters are filled and then warmed for 30 sec in a warm bath at 50°C and well shaken immediately thereafter.

Closure Integrity Test.

[0313] Each pressurized canister is subjected to bubble and crimping integrity testing by immersing the canister in a 60°C water bath for 2 minutes. Canisters are observed for leakage as determined by the generation of bubbles. Canisters releasing bubbles are rejected.

TESTS

[0314] By way of non limiting example the objectives of hardness, collapse time and FTC stability tests are briefly set out below as would be appreciated by a person of the art.

Hardness

[0315] LFRA100 instrument is used to characterize hardness. A probe is inserted into the test material. The resistance of the material to compression is measured by a calibrated load cell and reported in units of grams on the texture analyzer instrument display. Preferably at least three repeat tests are made. The textural characteristics of a dispensed foam can affect the degree of dermal penetration, efficacy, spreadability and acceptability to the user. The results can also be looked at as an indicator of softness. Note: the foam sample is dispensed into an aluminum sample holder and filled to the top of the holder.

Collapse Time

[0316] Collapse time (CT) is examined by dispensing a given quantity of foam and photographing sequentially its appearance with time during incubation at 36°C. It is useful for evaluating foam products, which maintain structural stability at skin temperature for at least 1 min.

Viscosity

[0317] Viscosity is measured with Brookfield LVDV-II + PRO with spindle SC4-25 at ambient temperature and 10, 5 and 1 RPM. Viscosity is usually measured at 10RPM. However, at about the apparent upper limit for the spindle of ~>50,000CP, the viscosity at 1RPM may be measured, although the figures are of a higher magnitude.

Conductance

[0318] The conductance meter is calibrated. The electrode is inserted into a suficient volume of composition and the conductance reading is recorded. Mesurements with foamable compositions are made prior to addition of propellant.

FTC (Freeze Thaw Cycles)

[0319] To check the foam appearance under extreme conditions of repeated cycles of cooling, heating, (first cycle) cooling, heating (second cycle) etc.,

commencing with -100°C (24hours) followed by +400°C (24hours) measuring the appearance and again repeating the cycle for up to three times.

Focus Group

[0320] Five healthy volunteers selected at random were give a sample of foam formulation and applied it to the skin on their forearm and were asked to complete a questionnaire.

Chemical Stability

[0321] The amount of active agent present is analysed in foam expelled from various presurized canisters containing foam formulations using HPLC. Analysis is carried out at zero time and at appropriate time intervals thereafter. The canisters are stored in controlled temperature incubators at 5C, at 25C, at, 40C and at 50C. At appropriate time intervals canisters are removed and the amount of active agent in the foam sample is measured.

Analysis

[0322] About 1 g of foam or pre-foam formulation is dissolved in 0.1% acetic acid in methanol (diluent), to which internal standard (IS) solution is added. BMV, BMV-21 and IS are extracted by heating, cooling and centrifugation of the sample solution. The clear layer is analyzed by UPLC using a C-18 column; elution is performed with a mobile phase containing acetonitrile:water 55:45. The content of BMV and BMV-21 is calculated using the respective peak area ratio against average peak area ratio of BMV standard (0.2 mg/mL) to the IS present in the standard solution at the same concentration as in samples. The details of the method conditions are as follows: the column type is Acquity BEH C-18, 1.7 µm, 50 x 2.1mm in 40°C, the flow is 0.5 mL/min, the detector: UV, at 254 nm injection volume is 4 µL.; the diluents is 0.1% acetic acid in water : acetonitrile, 45:55 (v/v) and the mobile phase content is water : acetonitrile, 45:55 (v/v). The run time is 4 min. The method can be carried out by HPLC using a different but appropriate column of the same type.

Bubble Size

[0323] Foams are made of gas bubbles entrapped in liquid. The bubble size and distribution reflects in the visual texture and smoothness of the foam. Foam bubbles size is determined by dispensing a foam sample on a glass slide, taking a picture of the foam surface with a digital camera equipped with a macro lens. The diameter of about 30 bubbles is measured manually relatively to calibration standard template. Statistical parameters such as mean bubble diameter, standard deviation and quartiles are then determined. Measuring diameter may also be undertaken with image analysis software. The camera used was a Nikon D40X Camera (resolution 10MP) equipped with Sigma Macro Lens (ref: APO MACRO 150mm F2.8 EX DG HSM). Pictures obtained are cropped to keep a squared region of 400 pixels x 400 pixels.

STOCK COMPOSITIONS

[0324] Non-limiting examples of how stock solutions are made up with and without API are illustrated. Other stock solutions may be made using the same methodology by simply varying adding or omitting ingredients as would be appreciated by one of the ordinary skills in the art.

Examples

[0325] The invention is described with reference to the following examples. For the purpose of the Examples below it was sufficient to apply a vacuum only at the crimping stage although for long term stability preferably any vacuum should be applied during manufacture as well at a sufficient pressure so that any oxygen remaining in the formulation is virtually negligible. This invention is not limited to these examples and experiments. Many variations will suggest themselves and are within the full intended scope of the appended claims.

Example 1: – A Waterless Steroid Foamable Composition with out a Modulating Agent

[0326] The components of this waterless foamable composition and the results of the measurements of the stability of the active agent are set our below:

Material chemical name		% W/W
Propylene glycol		31.60
Glycerin anhydrous		37.40
Stearyl alcohol		1.00
Hydroxypropyl cellulose		1.50
Laureth-4		2.00
Glyceryl Monostearate /PEG 100 Stearate		1.50
Stock solution	Betamethasone 17-Valerate	0.12
	Propylene glycol	24.88
Total		**100.00**

ACCELORATED CHEMICAL STABILITY TESTS FOR **FOAM**		
Time point	**% of BMV-17 (w/w)**	**%BMV-21 of BMV 0.12% (w/w)**
ZT	0.120	0.32
2 weeks, 40°C	0.079	33.98
1month, 40°C	0.066	40.07

ACCELORATED CHEMICAL STABILITY TESTS FOR **PRE-FOAM FORMULATION**		
Time point	**% of BMV-17 (w/w)**	**%BMV-21 of BMV 0.12% (w/w)**
ZT	0.120	0.63
2 weeks, 50°C	0.059	51.33
1month, 50°C	0.036	41.77

[0327] Comment: Significant amounts of BMV-17 break down into its unwanted isomer BMV-21 within a relatively short period of time in the absence of a Modulating agent. For foam, a propellant, which is a mixture of propane, butane and isobutane was added at 8% by weight of the total composition.