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(54) Title: CORTICOSTEROID HAVING LOW SYSTEMIC ABSORPTION

(57) Abstract: The invention provides novel compositions of water-insoluble corticosteroid drug in optional combination with antimicrobial agents and surfactants and either ionic polymers or very low concentrations of non-ionic polymer for topical, otic, and ophthalmic treatment. The invention provides stable aqueous suspensions where the ingredients remain in such a state so as to allow for immediate re-suspension, when desired, even after extended periods of settling. The invention provides also a method for treating inflammation with low systemic absorption and side effects of the corticosteroid.

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## CORTICOSTEROID HAVING LOW SYSTEMIC ABSORPTION

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(Attorney Docket No.: DVM0074-PCT)

### BACKGROUND OF THE INVENTION

[0001] Typically topical, otic, or ophthalmic products containing water insoluble steroid(s) alone or in combination with antimicrobial agent(s) are very greasy because of mineral oil or petrolatum present in the suspension. Such products are very hard to instill and spread into the ear canal or skin folds, especially on haired areas. In the case of otic application, the "oily residue" stays in the ear canal after application for prolonged periods of time, which is not desirable.

[0002] There are some aqueous suspensions (for example, Lotemax Suspension, for ophthalmic use) or oil-in-water lotion products for topical use. However, many of these products still leave non-drug residues because of high concentrations of suspending agents (0.2%w/w for example), surfactants (2~5%w/w) and/or oily components (2~10%w/w) which may cause harmful effects. The ideal topical, otic, or ophthalmic formulation should be low in residues, isotonic, aqueous based, and physically and chemically stable.

[0003] In U.S. patent 5,540,930, the non-ionic polymer concentration in its steroid composition is about 0.2-2%w/w and the claimed molar concentration range for the steroid:non-ionic-polymer:surfactant is between about 1:20:1 and about 1:0.01:0.5. US5,540,930 indicates that the polymer used in the formulation has to be non-ionic.

[0004] A reduction in amount of polymer and surfactant used in a steroid composition should be beneficial to the biological membrane. Thus, there exists a need for aqueous suspensions of water insoluble corticosteroids, which are free of problems of prior art formulations which can be easily applied.

SUMMARY OF THE INVENTION

[0005] The present invention provides formulations having very low concentrations of non-ionic polymers and very low concentrations of surfactants. The present invention also provides formulations having ionic polymers and very low concentrations of surfactants. It is surprisingly found that at the low concentrations of non-ionic polymers (e.g., 0.005% to 0.2%w/w), the re-suspension of the drug substance is better than the formulation comprising conventional concentrations (i.e., 0.2-2%w/w) of non-ionic polymers. The following table shows molar ratios of steroid, polymers, and surfactant that can be used in this invention. These molar ratios of non-ionic polymer and surfactant range from about 1.7 to more than 1300 fold below the limits of US5,540,930,

	MW	%w/w	mM	Molar ratio	US5,540,930 Molar Ratio Lower limit
Etiprednol Dicloacetate	485.41	0.2	4.120228	1	1
Methocel® F4M	86,000	0.005- 0.2	0.005814- 0.0232558	0.000141- 0.0056443	0.01
Merquat® 550 (9% solid)	1,600,00 0	0.005-2	0.000313-0.0125	0.0000076- 0.003034	Doesn't have non-ionic polymers.
Tyloxapol	5,000	0.005- 0.3	0.01-0.2	0.0024271- 0.0485410	0.5

	MW	%w/w	mM	Molar ratio	US5,540,930 Molar Ratio Lower limit
Loteprednol etabonate	466.96	0.2	4.2830221	1	1
Methocel® F4M	86,000	0.005–0.2	0.005814-0.0232558	0.000141-0.0056443	0.01
Merquat® 550 (9% solid)	1,600,000	0.005–2	0.000313-0.0125	0.0000076-0.003034	Doesn't have non-ionic polymers.
Tyloxapol	5,000	0.005–0.3	0.01-0.2	0.0024271-0.0485410	0.5

[0006] In addition to the unexpected improvements in physical properties, the use of low concentrations of surfactant and non-ionic polymer also surprisingly improves the pharmacological profile when compared to the formulation of drug suspended in mineral oil or without polymer. This second unexpected result is the reduction in systemic absorption of steroid, which is highly desirable given the side effects of steroidal drugs. Furthermore, contrary to US5,540,930, which is limited to non-ionic polymer only, however, we have also discovered that ionic polymers (e.g., Merquat® 550 and/or Xanthan gum) also work well in the present steroidal formulations.

[0007] Thus, surprisingly, we have found that by reducing the concentration of surfactant (e.g., Tyloxapol) from the prior art teaching of 0.3-2%w/w to 0.005-0.3%w/w and by either adding an ionic polymer or a low concentration, 0.005-0.2%w/w, of non-ionic polymer, the systemic absorption and as a consequence, the systemic (side) effect of anti-inflammatory corticosteroids, could be reduced by approximately 60%.

### DETAILED DESCRIPTION OF THE INVENTION

[0008] A soft steroid antimicrobial combination topical and/or otic formulation has broad application for inflammatory conditions complicated by secondary bacterial and/or fungal infections. In fact, most ear and skin infections in companion animals are precipitated by an inflammatory process.

[0009] Examples of cutaneous and otic inflammatory diseases include but are not limited to:

- Parasites such as *Otodectes cynotis*, *Demodex* spp., *Sarcoptes scabiei*, *Notoedres cati*, *Cheyletiella* spp., *Ctenocephalides felis*
- Foreign bodies such as plant awns
- Hypersensitivity and allergic diseases such as atopic dermatitis and otitis, food related dermatitis and otitis, contact allergic and irritant cutaneous and otic reactions, feline eosinophilic dermatitis
- Autoimmune diseases such as pemphigus foliaceus, pemphigus erythematosus, pemphigus vulgaris, pemphigus vegetans, discoid lupus erythematosus, cutaneous vasculitis, bullous pemphigoid, and mucous membrane pemphigoid

[00010] Bacterial and fungal infections may present secondary to the above inflammatory diseases or as primary infections. Common canine and feline cutaneous and/or otic pathogens include but are not limited to:

- *Staphylococcus intermedius*
- *Staphylococcus aureus*
- *Staphylococcus schleiferi*
- *Pseudomonas aeruginosa*
- *Streptococcus* spp.
- *Proteus mirabilis*
- *Escherichia coli*

- *Corynebacterium* spp.
- *Enterococcus* spp.
- *Malassezia pachydermatis*
- *Candida* spp.

[0011] Systemic side effects are a limiting factor in the long-term use of anti-inflammatory corticosteroids. These side effects are well documented and include

- suppression of the adreno-pituitary axis resulting in Cushing-syndrome,
- immunosuppression by a reduction in cell-mediated immunity and decreased antibody production, thus, increasing the risk of infections,
- retention of sodium and water and hence edema,
- urinary potassium increase, which leads to hypokalemia and metabolic alkalosis,
- hyperglycemia,
- delay in wound healing,
- altered calcium metabolism with prolonged treatment, resulting in osteoporosis and bone fractures,
- reduction in GI motility, thinning of the gastric mucosa, and reduced mucus production, thus resulting in gastrointestinal ulceration.

[0012] Therefore, a significant reduction in systemic absorption of steroid from formulation, which results in a safer long-term use of corticosteroids is highly desirable.

[0013] Some of the materials and their sources that can be used in the current inventions are listed below. The first table lists examples of water insoluble corticosteroids and anti-microbial agents that can be combined with the steroids. More than one steroid or more than one anti-microbial can be used in the present invention.

Drug substance	Manufacturer	Address
Hydrocortisone Acetate micronized	Shandong Xinhua	China
Hydrocortisone Acetate micronized	Roussel Uclaf	Paris, France
Betamethasone dipropionate micronized	Sicor	Via Terrazzano, Italy
Betamethasone dipropionate Micronized	Pfizer	Kalamazoo, MI
Betamethasone Valerate, Micronized	Pfizer	Kalamazoo, MI
Triamcinolone acetonide, Micronized	Pfizer	Kalamazoo, MI
Clotrimazole micronized	Erregierre, S. p. A.	Sovere, Italy
Polymyxin B sulfate	Alphrama APS	Copenhagen, Denmark

## Polymers and Surfactants

Generic name	Trade Name	Manufacturer	Address
Hydroxypropylcellulose	Klucel GF Pharm	Hercules	Wilmington DE
HydroxyETHYLcellulose	Natrosol 250HHX	Hercules	Wilmington DE
HydroxyETHYLcellulose	Natrosol 250H	Hercules	Wilmington DE
Hydroxypropylmethylcellulose	Methocel® F4M Prem	Dow Chem	Midland Michigan
Hydroxypropylmethylcellulose	Methocel® K4M Prem	Dow Chem	Midland Michigan
Polyvinyl alcohol	Celvol V540	Celanese	Dallas, Tx
Polyethylene glycol	Polyox WSR N60K NF	Dow Chem	Midland Michigan
Xanthan gum	Kaltrol CGF	Kelco Biopolymers	Chicago, IL
Polyquaternium 7 series	Merquat® 550 (9% solid)	Nalco	Naperville, IL
Tyloxapol	Tyloxapol, USP	Ruger Chemical Co.	Irvington, NJ

**[0014]** Additional surfactants include, but are not limited to, polysorbate 80, TWEEN 80 (ICI America Inc., Wilmington, Del.), PLURONIC F-68 (from BASF, Ludwigshafen, Germany) and poloxamer surfactants. Additional non-ionic polymers include, but are not limited to dextrans and other hydroxypropylmethylcelluloses, hydroxyethylcelluloses, hydroxypropylcelluloses, polyvinyl alcohols, and polyethylene

glycols not listed above. Additional ionic polymers include, but are not limited to other xanthan gums and other highly charged cationic homo- or co-polymers (e.g., other copolymers of diallyl dimethyl ammonium chloride and acrylamide) not listed above.

**[0015]** The amount of surfactant present can range from 0.005, 0.006, 0.007, 0.008, 0.009, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.20, to 0.3%w/w, with other ranges and examples including (a) 0.005, 0.006, 0.007, 0.008, 0.009, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.20, to <0.3%w/w, (b) 0.005, 0.006, 0.007, 0.008, 0.009, 0.01, 0.02, 0.03, 0.04, to 0.05%w/w, and (c) 0.01%w/w. When no ionic polymer is present in the formulation, then the amount of surfactant present is preferably <0.3%w/w. The amount of non-ionic polymer present can range from 0.005, 0.006, 0.007, 0.008, 0.009, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, to 0.20%w/w with other ranges and examples including (a) 0.005, 0.006, 0.007, 0.008, 0.009, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, to <0.20%w/w, (b) 0.005, 0.006, 0.007, 0.008, 0.009, 0.01, 0.02, 0.03, 0.04, to 0.05%w/w, and (c) 0.01%w/w. When no ionic polymer is present in the formulation, then the amount of non-ionic polymer present is preferably <0.2%w/w. The amount of ionic polymer is not specifically limited, but can range from 0.005, 0.006, 0.007, 0.008, 0.009, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70, 0.80, 0.90, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70, 0.80, 0.90, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, to 2.0%w/w with other ranges and examples including (a) 0.005, 0.006, 0.007, 0.008, 0.009, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70, 0.80, 0.90, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70, 0.80, 0.90, to 1.0%w/w, (b) 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.20, 0.30, 0.40, to 0.50, %w/w, (c) 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, to 0.12%w/w, (d) 0.12%w/w and (e) 0.01%w/w. Both a non-ionic and ionic polymer can be present in the present invention.

**[0016]** The molar ratio of water insoluble corticosteroid, polymer (e.g., non-ionic polymer), and surfactant can be between about 1:0.000001:0.001 to about 1:0.01:0.49. Another example of this molar ratio is between about 1:0.0014:0.002 to about 1:0.006:0.15. These ratios are typically used when a non-ionic polymer is present, but can also apply when an ionic polymer is present.

[0017] Pharmaceutically acceptable excipients, as used herein, include anything that one of ordinary skill in the art would add to a composition in order to aid in its manufacture, stability, marketing, etc. Examples of excipients include, but are not limited to, preservatives (e.g., EDTA salts), glycerin, mineral oil, additional surfactants (e.g., Brij® 72 and Brij® 721), base (e.g., sodium hydroxide), acid (e.g., hydrochloric acid), methyl paraben, and water.

[0018] As an example, the present invention includes oil/lotion based suspensions. This type of suspension includes an oil (e.g., mineral oil) and a second surfactant capable of emulsifying the oil. The second surfactant can be two (or more) surfactants. Surfactants capable of emulsifying oil in pharmaceutical compositions are well known. Examples of surfactant pairs include, but are not limited to Brij® 72/Brij® 721, Brij® 78/Arlacel™ 60, Brij® 72/Brij® 78, and Brij® 52/Brij® 58 (Brij® surfactants are etherified polyethylene glycols, which are available from Uniqema)(Arlacel™ 60 is a sorbitan stearate surfactant available from Uniqema). The amount of second surfactant present can be from about 0.1 to 2%w/w. This amount includes the total amount of second surfactant, if the second surfactant is a pair (or more). The molar ratio of second surfactant to corticosteroid can be about 1:1.2 to 1:10 and 1:7 to 1:9. This ratio includes the total amount of second surfactant, if the second surfactant is a pair (or more).

### EXAMPLES

[0019] Formulations in this invention include the following.

ED-Poly-B-Clo Otic suspension	1578-57A	1578-64	1578-89T	1578-90B	1578-90D	1578-90E	1578-90F
Ingredients	%w/w	%w/w	%w/w	%w/w	%w/w	%w/w	%w/w
Etiprednol dicloacetate	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Polymyxin B sulfate 10,000U/g	0.125	0.125	0.125	0.125	0.125	0.125	0.125
Clotrimazole Micronized	1	1	1	1	1	1	1
Tyloxapol	0.300	0.300	0.01	0.01	0.01	0.01	0.01
Methocel® K4M	0.2	--	--	0.01	--	--	0.01
Methocel® F4M	--	--	--	--	0.01	--	--
Merquat® 550	--	2	0.556	--	--	0.278	0.01
Methylparaben	--	0.18	0.18	0.18	0.18	0.18	0.18
EDTA disodium salts	0.100	0.1	0.1	0.1	0.1	0.1	0.1
Glycerin	2.50	2.50	2.50	2.50	2.50	2.50	2.50
NaOH pH 5.0-5.5	QS	QS	QS	QS	QS	QS	QS
Purified water	95.775	93.595	95.33	95.775	95.775	95.61	95.775
Total	100	100	100	100	100	100	100

[0020] The following procedures can be used to manufacture the formulations of the present invention. The non-ionic polymer, Methocel® F4M, is used as a non-limiting example.

1. Heat the purified water to 57-85°C, dissolve disodium edentate and tyloxapol first, then dissolve methylparaben. Disperse the Methocel® F4M and then cool to about 30°C. (Methocel® does not dissolve in hot water, so first disperse it in hot water and upon cooling, the Methocel® solution will become clear.)
2. Add glycerin to the vehicle in Step 1 and mix to dissolve.
3. For active drug substances, dissolve the water soluble drug substance (Polymyxin B sulfate in this example) in the vehicle first.
4. Add and disperse the water insoluble clotrimazole and etiprednol dicloacetate. High shear mixer would facilitate the dispersion for better uniformity.
5. Adjust the pH and QS to the final proper weight.

[0021] Formulation 1578-90D (Methocel® F4M 0.01%, tyloxapol 0.01%) can be re-suspended easily when compared to formulation 1578-57A, which comprises higher concentration of non-ionic polymer (0.2%) and surfactant (0.3%). It takes about 25~30 vigorous shakes to suspend the drug substances in formulation 1578-57A. It takes only about 4 shakes for formulation 1578-90D. As non-ionic polymer concentration increases, it becomes harder to re-suspend the water insoluble corticosteroid.

[0022] The following additional formulations demonstrated the applicability of this type of formulation to other steroids (hydrocortisone acetate, betamethasone dipropionate, betamethasone valerate, triamcinolone acetonide) as well as polymer (Klucel, Natrosol, Methocel®, polyethylene glycol, polyvinyl alcohol, xanthan gum) combinations,

Steroid-antimicrobial suspensions	2170-90	2170-93-3	2170-96 – TRM10	2170-96 – TRM17
Ingredients	%w/w	%w/w	%w/w	%w/w
Hydrocortisone Acetate, Micronized	1.12	--	--	--
Etiprednol dicloacetate Micronized	--	0.1	--	--
Triamcinolone acetonide Micronized	--	--	0.1	0.1
Clotrimazole Micronized	1.00	1.00	1.00	1.00
Tyloxapol	0.010	0.01	0.01	0.01
Hydroxypropyl methylcellulose (Methocel® F4M)	0.010	--	0.01	--
Hydroxypropyl cellulose, Klucel GF	--	0.01	--	--
Polyethylene glycol, Polyox WSR N60K	--	--	--	0.01
Methylparaben	0.18	0.18	0.18	0.18
EDTA disodium Salts	0.100	0.1	0.1	0.1
Glycerin	2.50	2.50	2.50	2.50
NaOH pH 5.0-5.5	QS	QS	QS	QS
Purified Water	95.775	95.775	95.775	95.775
Total	100	100	100	100

Steroid-antimicrobial suspensions	2170-96- BD5	2170-96- BD-15	2170-96 -BV4	2170-96 -BV15	2170-96 -BV20
Ingredients	%w/w	%w/w	%w/w	%w/w	%w/w
Betamethasone dipropionate, Micronized	0.10	0.10	--	--	--
Btamethasone valerate, Micronize	--		0.10	0.10	0.10
Clotrimazole Micronized	1.00	1.00	1.00	1.00	1.00
Tyloxapol	0.01	0.01	0.01	0.01	0.01
Hydroxyethylcellulose, Natrosol 250H	0.01	--	--	--	--
Hydroxyethylcellulose, Natrosol 250HHX	--	--	0.01	--	--
Polyvinal alcohol (Celvol V540)	--	0.01	--	0.01--	--
Xanthan gum (Kaltrol)	--	--	--	--	0.01
Methylparaben	0.18	0.18	0.18	0.18	0.18
EDTA disodium Salts	0.10	0.1	0.1	0.1	0.1
Glycerin	2.50	2.50	2.50	2.50	2.50
Purified Water	95.775	95.775	95.775	95.775	95.775
Total	100	100	100	100	100

[0023] The formulation with low concentration of surfactant (for example Tyloxapol at 0.01%) and non-ionic polymer (for example Methocel® F4M at 0.01% w/w) also

reduced the systemic absorption of anti-inflammatory corticosteroids when applied topically. This was demonstrated in a validated mouse model as follows.

[0024] In the following experiment, the irritant, croton oil, was applied to one earlobe of the mice in the untreated control group and to both earlobes of the mice in the treatment groups to induce inflammation. The control group was left untreated after induction of inflammation. In the treatment group, the anti-inflammatory treatment was applied to one ear, one hour after croton oil application; the opposite ear was left untreated. Assessment of the reduction in ear-weight and ear-thickness on the non-treated earlobe was performed 3 hours after treatment application. Since the measurement is performed on the untreated ear, the reduction of ear weight or thickness is due to the drug that reached the untreated ear from systemic circulation after absorption of drug at the area of treatment. Results showed statistical significance ( $p < 0.05$ ) when the aqueous formulation with low concentration of surfactant and non-ionic polymer (Formulation 2170-79 & 2170-64) was compared to pure mineral oil formulation or aqueous formulation with no polymer (Formulation 2170-20).

[0025] Systemic effect of aqueous suspension and oil suspension on the opposite non-treated ear,

Ear weight (mg) mean +/- sd		
N = 20	N = 20	N = 20
Untreated control group	Betamethasone 0.1% in aqueous formulation 2170-64* group	Betamethasone 0.1% in pure mineral oil* group
47.53 +/- 5.66	40.18 +/- 4.29 <sup>a</sup>	34.93 +/- 3.09 <sup>a,b</sup>
Reduction in systemic effect =	$(40.18 - 47.53) / (34.93 - 47.53) \times 100 = 58\%$	

Ear thickness (x10 <sup>-2</sup> mm) mean +/- sd		
N = 20	N = 20	N = 20
Untreated control group	Betamethasone 0.1% in aqueous formulation 2170-64* group	Betamethasone 0.1% in pure mineral oil* group
36.4 +/- 4.85	28.95 +/- 3.97 <sup>a</sup>	24.92 +/- 2.20 <sup>a,b</sup>
Reduction in systemic effect =	$(28.95-36.4)/(24.92-36.4) \times 100 = 65\%$	

**[0026]** Systemic effect of two aqueous suspensions on the opposite non-treated ear,

Ear weight (mg) mean +/- sd		
N = 40	N = 20	N = 20
Untreated control group	Etiprednol dicloacetate 0.2% in aqueous suspension 2170-79*with 0.01% polymer	Etiprednol dicloacetate 0.2% in aqueous suspension 2170-20* with. no polymer
46.51 +/- 4.77	39.34 +/- 6.27 <sup>a</sup>	35.75 +/- 3.27 <sup>a,b</sup>
Reduction in systemic effect	$(39.34-46.51)/(35.75-46.51) \times 100 = 67\%$	

Ear thickness (x10 <sup>-2</sup> mm) ) mean +/- sd		
N = 40	N = 20	N = 20
Untreated control group	Etiprednol dicloacetate 0.2% in aqueous suspension 2170-79*with 0.01% polymer	Etiprednol dicloacetate 0.2% in aqueous suspension 2170-20* with. no polymer
34.58 +/- 4.58	28.60 +/- 3.95 <sup>a</sup>	25.40 +/- 3.23 <sup>a,b</sup>
Reduction in systemic effect	$(28.60-34.58)/(25.40-34.58) \times 100 = 65\%$	

\* See below for formulation.

ANOVA (p < 0.05; Two-sides)

<sup>a</sup> Statistically significant when compared to the untreated control group

<sup>b</sup> Statistically significant when compared to the formulation 2170-64 or 2170-79

ED-Otic suspension	2170-20 series	2170-79 series	2170-64 with betamethasone	Betamethasone in mineral oil
Ingredients	%w/w	%w/w	%w/w	%w/w
Etiprednol dicloacetate	0.2-0.8	0.05-0.2	--	--
Betamethasone	--	--	0.1	0.1
Tyloxapol	0.300	0.01	0.01	--
Methocel® F4M	--	0.01	0.01	--
Methylparaben	0.18	0.18	0.18	--
EDTA disodium Salts	0.050	0.1	0.1	--
Glycerin	2.500	2.50	2.50	--
Mineral oil	--	--	--	QS
NaOH pH 5.0-5.5	QS	QS	QS	--
Purified Water	95.775	95.775	95.775	--
Total	100	100	100	100

[0027] When comparing re-suspensions of (1) an aqueous based suspension and (2) an oil/lotion based suspension, it was found that the better choice was the oil/lotion based suspension. Surprisingly, the suspension in oil/lotion improved upon aging as it stayed suspended for a longer period than the non-lotion suspension (i.e., no mineral oil or Brij® surfactants). Oil/lotion based suspension have an oil (e.g., mineral) that is suspended

by the presence of a surfactant (e.g., Brij® 72 and 721). The surfactant of the oil/lotion based suspension is in addition to the first surfactant discussed previously. An example of an oil/lotion formulation is shown below.

Oil/lotion based suspension

Ingredient	% w/w
Etidprednol dicloacetate, micronized	0.2
Clotrimazole, micronized	1
Polymyxin B sulfate USP	0.1375
Tyloxapol USP	0.01
disodium Edetate, USP	0.1
Glycerine USP	2.5
Hypromellose USP 2906 (Methocel® F4M)	0.01
Merquat® 550 9%	0.12
Light mineral oil	2
Brij® 72 (Polyethylene Glycol 2 Sterayl ether)*	0.45
Brij® 721 (Polyethylene Glycol 21 Sterayl ether)*	0.55
Sodium hydroxide NF	0.001
Sodium hydroxide NF adjust pH to 5.0~5.5	QS
Hydrochloric acid, adjust pH to 5.0~5.5	QS
Purified water USP, QS	QS

\*Brij® 72 and Brij® 721 are surfactants the act in combination as the second surfactants of the present invention.

What is claim is:

1. An aqueous topical composition for the treatment of inflammation, comprising:
  - a. a water insoluble corticosteroid,
  - b. an ionic polymer, and
  - c. from 0.005 to 0.3%w/w of a surfactant.
2. The composition of claim 1 wherein the corticosteroid is a soft steroid having anti-inflammatory activity.
3. The composition of Claim 2 wherein the soft steroid is loteprednol etabonate or etiprednol dichloacetate or a mixture thereof.
4. The composition of Claim 1, further comprising: a first antimicrobial agent.
5. The composition of Claim 4, further comprising: a second antimicrobial agent.
6. The composition of Claim 1, wherein the surfactant is tyloxapol.
7. The composition of Claim 6, wherein 0.01%w/w of tyloxapol is present.
8. The composition of Claim 1, wherein 0.005 to 2%w/w of the ionic polymer is present.
9. The composition of Claim 8, wherein from 0.01 to 1%w/w of the ionic polymer is present and the ionic polymer is Merquat® 550 (9% solid).
10. The composition of Claim 1, further comprising: from 0.005 to 0.2%w/w of a non-ionic polymer.
11. The composition of Claim 10, wherein 0.01%w/w of the non-ionic polymer is present.
12. The composition of Claim 11, wherein the non-ionic polymer is Methocel® F4M.
13. The composition of Claim 1, further comprising: pharmaceutically acceptable excipients.
14. The composition of Claim 1, wherein the composition is an oil/lotion based suspension.

15. The composition of Claim 14, wherein the oil/lotion based suspension, further comprises a second surfactant in a molar ratio of steroid to second surfactant of from 1:1.2 to 1:10.
16. The composition of Claim 15, wherein oil/lotion based suspension, further comprises: mineral oil, and wherein the second surfactant is a pair of surfactants that are capable of emulsifying mineral oil
17. The composition of Claim 16, wherein the second surfactant is a pair of surfactants, Brij® 72 and Brij® 721.
18. The composition of Claim 1, wherein the steroid is etidprednol dicloacetate and 0.2%w/w is present, the ionic polymer is of Merquat® 550 (9% solids) and 0.12%w/w is present, and the surfactant is tyloxapol and 0.01%w/w is present.
19. The composition of Claim 18, further comprising: 1%w/w clotrimazole, 0.01%w/w of Methocel® F4M, 2%w/w mineral oil, 0.45%w/w Brij® 72, and 0.55%w/w Brij® 721.
20. An aqueous composition for topical application, comprising:
  - a. a water insoluble corticosteroid,
  - b. a non-ionic polymer,
  - c. and from 0.005 to <0.3%w/w surfactant,wherein the molar ratio of steroid to polymer to surfactant of about 1:0.000001:0.001 to about 1:0.01:0.49.
21. The composition in Claim 20, wherein the molar ratio of corticosteroid, polymer, and surfactant is between about 1:0.0014:0.002 to about 1:0.006:0.15.
22. The composition of Claim 20, wherein the corticosteroid is soft steroid having anti-inflammatory activity.
23. The composition of Claim 22, wherein the soft steroid is loteprednol etabonate or etiprednol dichloacetate or a mixture thereof.
24. The composition of Claim 20, further comprising: a first antimicrobial agent.
25. The composition of Claim 24, further comprising: a second antimicrobial agent.

26. The composition of Claim 20, wherein the surfactant is tyloxapol.
27. The composition of Claim 26, wherein 0.01%w/w of tyloxapol is present.
28. The composition of Claim 20, wherein 0.005 to <0.2%w/w of the non-ionic polymer is present.
29. The composition of Claim 28, wherein 0.01%w/w of the non-ionic polymer is present and the non-ionic polymer is Methocel® F4M.
30. The composition of Claim 20, further comprising: from 0.005 to 0.2%w/w of an ionic polymer.
31. The composition of Claim 30, wherein from 0.01 to 0.2%w/w of the ionic polymer is present.
32. The composition of Claim 31, wherein the ionic polymer is Merquat® 550 (9% solid).
33. The composition of Claim 20, further comprising: pharmaceutically acceptable excipients.
34. The composition of Claim 20, wherein the composition is an oil/lotion based suspension.
35. The composition of Claim 34, wherein the oil/lotion based suspension, further comprises a second surfactant in a molar ratio of steroid to second surfactant of from 1:1.2 to 1:10.
36. The composition of Claim 35, wherein oil/lotion based suspension, further comprises: mineral oil, and wherein the second surfactant is a pair of surfactants that are capable of emulsifying mineral oil
37. The composition of Claim 36, wherein the second surfactant is a pair of surfactants, Brij® 72 and Brij® 721.
38. A method for reducing inflammation, comprising: contacting the inflamed area with a composition of Claim 1.
39. A method for reducing inflammation, comprising: contacting the inflamed area with a composition of Claim 20.