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(54) Title: TOPICAL COMPOSITIONS FOR SKINCARE

(57) Abstract: The present invention relates to topical compositions comprising arbutin, corticosteroid, retinoid and optionally a sun protection factor (SPF). The present invention also relates to a process of preparation of said topical compositions.

TOPICAL COMPOSITIONS FOR SKINCARE

PRIORITY DETAILS

This patent application claims priority to Indian Patent Application No.1741/MUM/2007, filed on September 11, 2007, the contents of which are hereby incorporated as reference.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to topical compositions comprising arbutin, corticosteroid, retinoid and optionally a sun protection factor (SPF) for the treatment of skin diseases. The present invention also relates to a process of preparation of said topical compositions.

BACKGROUND OF THE INVENTION

A variety of topical preparations are currently available on the market. Some of these employ a single active ingredient while others employ a formulation of two or more additive or synergistic compounds. Unfortunately, the effect of a single ingredient is usually limited and each known formula has notable disadvantages and often introduces unintentional side effects concomitant with treatment of the primary condition of undesired pigmentation.

Arbutin, which is the β-D-glucopyranoside derivative of hydroquinone, is a naturally occurring plant-derived compound that has been used for postinflammatory hyperpigmentation. It is effective in the treatment of disorders of hyperpigmentation characterized by hyperactive melanocytes. In comparative in vitro studies of various compounds used to improve the appearance of disorders of hyperpigmentation, arbutin was found to be less toxic than hydroquinone. A dose-dependent reduction in tyrosinase activity and melanin content in melanocytes was also demonstrated.

Retinoids accelerate desquamation and remove preformed melanin. The role of retinoids is likely to be due to its promotion of keratinocyte proliferation

and acceleration of epidermal turnover. Retinoids are used in the treatment of many diverse diseases and are effective in the treatment of a number of dermatological conditions such as inflammatory skin disorders, skin cancers, psoriasis and photoaging. Tretinoin induces dispersion of pigment granules inside the keratinocyte, and accelerates the turn over of epidermal cells, facilitating the elimination of dispersed pigment.

Corticosteroids inhibit the tyrosinase activity, affect the secretary function of melanocytes and have anti metabolic effect on keratinocytes. Corticosteroids also inhibit the various mediators of inflammation and hence also inhibit the stimulatory impulses for melanocytes. Moreover, they also eliminate the irritation caused by other agents and so generally used in combination of other depigmenting agents.

US patent no. 3,856,934 assigned to kligman, discloses skin depigmenting composition comprising hydroquinone, retinoic acid and a corticosteroid selected from dexamethasone, hydrocortisone, hydrocortisone-17-valerate, and progesterone.

French patent no. 2383663B describes process for preparation of hydroquinone, retinoic acid and a corticosteroid combination cream.

US patent no. 5,998,395 assigned to Kligman, describes a composition comprising triamcinolone acetonide and tretinoin, said triamcinolone acetonide and tretinoin being present in synergistic effective amounts which are effective to suppress said inflammation and control and clear said dermatosis and pharmaceuticals composition comprising the same.

US patent publication no. 2004/0081668 assigned to Hill Dermaceuticals, disclose topical composition comprising fluocinolone acetonide, hydroquinone and tretinoin and process for making the same. The compositions are useful for the treatment of hyperpigmented skin conditions, such as melasma.

US Patent Application Publication no. 2006/0083697 assigned to Huynh, describes a topical skin lightening cream for the treatment of non-congenital dermal blemishes comprising hydroquinone, tretinoin, steroid and sun screening agent.

It has long been desirable that certain skin disorders or diseases of the skin be treated to reduce hyperpigmentation generally caused by the deposition of excess quantities of melanin. This hyperpigmentation is generally viewed as cosmetically undesirable and psychologically disabling. Examples of such hyperpigmentation include freckles, senile lentigo, lentigines (liver spots), melasma, contact allergy pigmentation, vitiligo, sunburn pigmentation, post-inflammatory hyperpigmentation due to abrasion, burns, wounds, dermatitis, phototosic reaction and other similar small, fixed pigmented lesions. It is also often desirable to decolorize normally pigmented skin to generally increase "fairness" of appearance or to blend hypo pigmented areas into surrounding normal skin, for example in the treatment of generally dark-skinned people suffering from vitiligo.

Consequently, there is a need for a topical preparation that provides effective skin lightening capabilities and does not cause significant inflammation, irritation, or sun sensitivity of the skin following application.

Without being bound by any theory, the inventors of the present invention believe that the topical composition comprising arbutin, corticosteroid and retinoid of the present invention can be very effective in the treatment of skin diseases.

SUMMARY OF THE INVENTION

The present invention relates to a topical composition for the treatment of skin diseases comprising

a) arbutin in the range from about 0.5 % to 5 %w/w;

b) a corticosteroid in the range from about 0.01 % to 0.3 %w/w;

c) a retinoid in the range from about 0.01 % to 0.5 %w/w; and

d) a dermatologically acceptable vehicle;

wherein the range is based on 100% total weight of the composition.

Another embodiment of the present invention is a topical composition for the treatment of skin diseases comprising

a) arbutin in the range from about 2 % to 4 % w/w;

b) triamcinolone or desonide in the range from about 0.01 % to 0.1 % w/w;

c) tretinoin in the range from about 0.02 % to 0.1 % w/w; and

d) a dermatologically acceptable vehicle;

wherein the range is based on 100% total weight of the composition.

In another embodiment of the present invention, the fixed dose topical composition for the treatment of skin diseases comprises about 3 % w/w of arbutin, about 0.025 % w/w of triamcinolone and about 0.05 % w/w of tretinoin (based on 100% total weight of the composition) and a dermatologically acceptable vehicle.

In another embodiment of the present invention, the fixed dose topical composition for the treatment of skin diseases comprises about 3 % w/w of arbutin, about 0.05 % w/w of desonide and about 0.05 % w/w of tretinoin (based on 100% total weight of the composition) and a dermatologically acceptable vehicle.

In a further embodiment of the present invention, the topical composition for the treatment of skin diseases comprises about 3 % w/w of arbutin, about 0.025 % w/w of triamcinolone and about 0.05 % w/w of tretinoin (based on 100% total weight of the composition), a sun protection factor (SPF) and a dermatologically acceptable vehicle.

The present also relates to use of the topical composition comprising about 3 %w/w of arbutin, about 0.025 %w/w of triamcinolone and about 0.05 % w/w of tretinoin (based on 100% total weight of the composition) and a dermatologically acceptable vehicle for the treatment of skin diseases in human.

The present further relates to use of the topical composition comprising about 3 %w/w of arbutin, about 0.05 % w/w of desonide and about 0.05 % w/w of tretinoin (based on 100% total weight of the composition) and a dermatologically acceptable vehicle for the treatment of skin diseases in human.

In the context of present invention, the skin diseases include melasma, ephelides, post inflammatory hyperpigmentation, non–congenital hyperpigmentation, and solar lentigo, and the like.

In another embodiment of the present invention topical composition for the treatment of skin diseases can be in the form of cream, ointment, dispersion, suspension, solution, foam, lotion, plaster, gel, emulsion or the like, suitable for local use.

The present invention further relates to a process for preparation of a topical composition for the treatment of skin diseases comprising arbutin, triamcinolone or desonide, and tretinoin, wherein the process comprises the steps of:

(a) mixing the active ingredients, either separately or combinedly, with a dermatologically acceptable vehicle; and

(b) formulating the mixture of step (a) into a suitable form convenient for topical use.

The form includes cream, ointment, dispersion, suspension, solution, foam, lotion, plaster, gel, emulsion or the like.

Another embodiment of the present invention is a process for preparing topical compositions comprising arbutin, corticosteroid and retinoid, wherein the process comprises: (a) combining water and at least one hydrophilic compound to form an aqueous phase; (b) combining hydrophobic compounds to form a non-aqueous phase; (c) combining the aqueous phase and non-aqueous phase to form a biphasic mixture; (d) adding at least one active ingredient; and (e) homogenizing the mixture to form the emulsion.

Another embodiment of the present invention is a process for preparing topical compositions comprising arbutin, corticosteroid and retinoid, wherein the process comprises the steps of: (a) dispersing the active ingredients in solvent and co-solvents/ bulking agents under stirring; (b) adding the other excipients to the drug dispersion of step (a) under stirring; and (c) dispersing the thickening agent, if any in to the mixture of step (b).

Another embodiment of the present invention is a process for preparing topical compositions comprising arbutin, corticosteroid and retinoid, wherein the process comprises (a) heating all the ingredients with stirring at about 70°C and homogenized for 15 minutes, (b) stirring was continued and cooled to room temperature to form an ointment.

DETAILED DESCRIPTION OF THE INVENTION

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

The term "pharmaceutically acceptable" as used in connection with components includes those components approved by a governmental regulatory agency or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals, such as humans.

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

Active ingredient in the context of present invention includes triamcinolone, desonide, arbutin, and tretinoin.

In the context of present invention, the skin diseases include melasma, ephelides, post inflammatory hyperpigmentation, dermal blemishes, non–congenital hyperpigmentation, and solar lentigo, and the like.

The present invention provides topical compositions comprising of arbutin, corticosteroid, retinoid and optionally sun screening agent/ sun protection factor (SPF) for the treatment of skin diseases.

Arbutin according to the present invention ranges from about 0.5 % to 5 % w/w (based on 100% total weight of the composition). Preferably, from about 2 % to 4 % w/w

Corticosteroids according to the present invention include triamcinolone, desonide, hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone, betamethasone, fluocinolone, methylprednisolone, fluorometholone and their esters or pharmaceutically acceptable salts thereof. Corticosteroids according to the present invention range from about 0.01 to 0.3 %w/w (based on 100% total weight of the composition). Preferably, the corticosteroid is triamcinolone, or desonide.

The retinoids are a class of chemical compounds that are related chemically to vitamin A. Examples of retinoids include tretinoin, retinol, isotretinoin and alitretinoin, etretinate and its metabolite acitretin, tazarotene and bexarotene. Retinoids according to the present invention ranges from about 0.01 to 0.5 %w/w (based on 100% total weight of the composition). Tretinoin is the preferred retinoid.

The compositions of the present invention include sunscreens which has a SPF in the range of 5 to 50%. To provide a formula with a SPF value of not less than 5%, usually requires the use of more than a single UVB sunscreen. Suitable UVB sunscreens for use in the compositions of the present invention include avobenzone, octyl methoxycinnamate (also known as octinoxate), oxybenzone and octocrylene. Avobenzone additionally functions as the preferred UVA sunscreen. The amount of octyl methoxycinnamate, octocrylene, oxybenzone and/or avobenzone in a given formulation will vary depending on the sun protection factor desired. Preferably a higher sun protection factor such as SPF 50 % is desirable.

An embodiment of the present invention is a topical composition for the treatment of skin diseases comprising:

a) arbutin in the range from about 2 % to 4 % w/w;

b) triamcinolone or desonide in the range from about 0.01 % to 0.1 % w/w;

c) tretinoin in the range from about 0.02 % to 0.1 % w/w; and

d) a dermatologically acceptable vehicle;

wherein the range is based on 100% total weight of the composition.

In another embodiment of the present invention, the fixed dose topical composition for the treatment of skin diseases comprises about 3 % w/w of arbutin, about 0.025 % w/w of triamcinolone and about 0.05 % w/w of tretinoin (based on 100% total weight of the composition) and a dermatologically acceptable vehicle.

In another embodiment of the present invention, the fixed dose topical composition for the treatment of skin diseases comprises about 3 % w/w of arbutin, about 0.05 % w/w of desonide and about 0.05 % w/w of tretinoin (based on 100% total weight of the composition) and a dermatologically acceptable vehicle.

In a further embodiment of the present invention, the topical composition for the treatment of skin diseases comprises about 3 % w/w of arbutin, about 0.025 % w/w of triamcinolone and about 0.05 % w/w of tretinoin (based on 100% total weight of the composition), a sun protection factor (SPF) and a dermatologically acceptable vehicle.

The topical composition according to the present invention is in the form of cream, ointment, suspension, solution, foam, lotion, plaster, gel, and emulsion or the like.

The topical composition of the present invention contains dermatologically acceptable vehicle (synonymously, pharmaceutically acceptable excipient). Suitable dermatologically acceptable vehicles include, but are not limited to emulsifiers, emollients, antioxidants, stiffening agents, humectants, chelating agents, buffers, antimicrobial preservatives, vehicles and pharmaceutically acceptable mixtures thereof. Examples of these excipients are described in, for example, Howard C. Ansel et. al., Pharmaceutical Dosage Forms and Drug

Delivery Systems, (7th Ed. 1999); Alfonso R. Gennaro et al., Remington: The Science and Practice of Pharmacy, (20th Ed. 2000); and A. Kibbe, Handbook of Pharmaceutical Excipients, (3rd Ed. 2000), the contents of which are incorporated by reference herein.

Emulsifiers according to the present invention include , but are not limited to, polyoxyethylene glycol monocetyl ethers, polyoxyethylene alkyl ethers such as the material sold under the trade name cetomacrogol 1000, polyoxyl 20 cetostearyl ether (Atlas G-3713), poloxyl 2 cetyl ether (ceteth-2), poloxyl 10 cetyl ether (ceteth-10), poloxyl 20 cetyl ether and polyoxyethlene sorbitan monostearates, such as the material sold under the trade name Polysorbate 60, or polyoxyethylene sorbitan monoleates, as sold under the trade name Tween 80, sorbitol monostearate (Span 60), glyceryl monostearate and mixtures there of.

Emollients according to the present invention include, but are not limited to, caprylic/capric triglyerides, castor oil, ceteareth-20, ceteareth-30, cetearyl alcohol, ceteth 20, cetostearyl alcohol, cetyl alcohol, cetyl stearyl alcohol, cocoa butter, diisopropyl adipate, glycerin, glyceryl monooleate, glyceryl monostearate, glyceryl stearate, isopropyl myristate, isopropyl palmitate, lanolin, lanolin alcohol, hydrogenated lanolin, liquid paraffins, linoleic acid, mineral oil, oleic acid, white petrolatum, polyethylene glycol, polyoxyethylene glycol fatty alcohol ethers, polyoxypropylene 15-stearyl ether, propylene glycol stearate, squalane, steareth-2 or -100, stearic acid, stearyl alcohol and urea and the like or mixtures there of.

Examples of suitable antioxidants include ascorbic acid, ascorbyl tetraisopalmitate, butylated hydroxytoluene (BHT), vitamin E, sodium metabisulfite and propyl gallate and the like or mixtures there of.

Stiffening agents according to the present invention include, but are not limited to, fatty acids, fatty alcohols or esters such as stearic acid, stearyl alcohol, cetyl alcohol, myristyl alcohol, cetyl stearyl alcohol and glycerin monostearate and the like or mixtures there of.

Preservatives according to the present invention include, but are not limited to, hydoxy propyl butadex, methyl paraben, propyl paraben, butylated hydroxytoluene, sodium benzoate and the like or mixtures there of.

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

Spreading agents according to the present invention promotes ease of spreading when the product is being rubbed on the skin. By allowing easy spreading, it eliminates the feeling of frictional drag and tackiness while the product is being applied. Preferred non-limiting examples of spreading agents are polydimethylsiloxanes, alkyl modified polysiloxane copolymers, trimethyl phenyl silesquioxane and certain mono and di esters of benzoic acid, dimethicone and mixtures there of.

The pharmaceutical composition of the present invention may further comprise suitable chelating agents. Chelating agents according to the present invention include, but are not limited to, ethylenediaminetetraacetic acid (EDTA), disodium edetate and EDTA derivatives, or any combinations thereof.

The composition of this invention may also include conventional additives such as viscosity modifiers (such as xanthan gum), stabilizers and buffering agents to maintain a suitable pH and mixtures thereof. Aqueous phase consisting primarily of water.

The present invention also provides a process for preparing a topical composition comprising arbutin, triamcinolone and tretinoin, where in the process comprises the steps of: (a) combining water and at least one hydrophilic compound to form an aqueous phase; (b) combining hydrophobic compounds to form a non-aqueous phase; (c) combining the aqueous phase and non-aqueous phase to form a biphasic mixture; (d) adding at least one active ingredient; and (f) homogenizing the mixture to form an emulsion.

The present invention also provides a process for preparing a topical composition comprising arbutin, corticosteroid and retinoid. Generally, the process for preparing the topical composition as disclosed herein comprises the

steps of: (a) dispersing the active ingredients in solvent and co-solvents/ bulking agents under stirring; (b) adding the other excipients to the drug dispersion of step (a) under stirring; and (c) dispersing the thickening agent, if any in to the mixture of step (b).

The composition of the present invention may be applied by hand to areas of the skin which the user desires lightened by rubbing until the contact between the fingers and the application areas are no longer slippery.

The composition is used by applying, preferably on a regular treatment schedule to the area of skin to be treated until relatively complete and permanent depigmentation is achieved. The composition can be applied to the skin with or without any dressing but occlusive dressing has been found to facilitate depigmentation. In general, the depigmentation is reversible and cessation of treatment may lead to repigmentation unless a sustaining regimen to treatment is continued. Such a regimen may include less frequent application of the herein disclosed composition.

The invention is further exemplified with following examples and is not intended to limit the scope of the inventions. It is obvious to those skilled in the art to find out the composition for other dosage forms and substitute the equivalent excipients as described in this specification or with the one known to the industry.

EXAMPLES

Comparative example: A cream composition comprising hydroquinone, triamcinolone and tretinoin.

Steps	Ingredients	Concentration % w/w
I	Stearic Acid	3.000
	Cetyl Alcohol	2.000
	Stearyl Alcohol	2.000
	Glyceryl Monostearate(NSE)	2.000

	Polyoxy 20 Cetyl Ether (Brij 58)	2.000
	Liquid Paraffin	23.000
	Isopropyl Myristate	5.000
	Dimeticone 350	0.500
	Ascorbyl Tetraisopalmitate(NIKKOL VC-IP)	0.100
	Butylated Hydroxytolune (BHT)	0.100
	Tretinoin	0.050
	Triamcinolone Acetonide	0.025
II	Purified Water	34.605
	Disodium Edetate	0.100
	Hydroxypropyl β Cyclodextrin (HPβCD)	1.000
	Glycerin	4.000
	Xanthan Gum	0.100
	Citric Acid Monohydrate	0.120
III	Purified Water	14.000
	Hydroquinone	4.000
III	Purified Water	1.000
	Sodium Benzoate	0.200
IV	Purified Water	1.000
	Sodium Metabisulphite	0.100
	Total	100

Brief Manufacturing Process:

1. Oleaginous Phase: All the ingredients of step I were heated at about to 70°C.
2. Aqueous Phase: All the ingredients of step II were heated at about 70°C.
3. Emulsification (water in oil type): Contents of step (II) were added to contents of step (I) at about 65°C to 80°C and homogenized for 15 minutes and then cooled.
4. Hydroquinone solution (previously dissolved in purified water with maintain temperature 55°C to 58°C) was added at 55°C add under stirring

5. Sodium benzoate solution (previously dissolved in purified water) was added at 40°C.

6. Sodium metabisulfite is dissolved in water and added to bulk obtained (from the above steps) at 40°C under stirring, and stirring is continued and cooled to room temperature.

Observation: No cream was formed.

Example – 1: A cream composition comprising arbutin, triamcinolone and tretinoin.

STEPS	INGREDIENTS	CONCENTRATION (% w/w)
I	Stearic Acid	3.000
	Cetyl Alcohol	2.000
	Stearyl Alcohol	2.000
	Glyceryl Monostearate (NSE)	2.000
	Polyoxyl 20 Cetyl Ether (Brij 58)	2.000
	Liquid Paraffin (Mineral oil)	23.000
	Isopropyl Myristate	5.000
	Dimethicone 350	0.500
	Butylated Hydroxytoluene (BHT)	0.050
	Tretinoin	0.050
	Triamcinolone Acetonide	0.025
II	Purified Water	51.725
	Disodium Edetate	0.100
	Arbutin	3.000
	Glycerin	4.000
	Xanthan Gum	0.100
	Sodium Benzoate	0.200
	Citric Acid Monohydrate	0.050
	Ascorbic Acid	0.100

III	Purified Water	1.000
	Sodium Metabisulphite	0.100
	Total	100

Brief manufacturing process:

1. Oleaginous Phase:

   Stearic acid, cetyl alcohol, stearyl alcohol, glyceryl monostearate (NSE), polyoxyl 20 cetyl ether (Brij 58), liquid paraffin, isopropyl myristate, dimethicone 350 were added and heated up to 65°C to 80°C. After complete melting butylated hydroxytoluene (BHT), tretinoin and triamcinolone acetonide were dissolved by maintaining the temperature at 65°C to 80°C.

2. Aqueous Phase:

   2.1 Purified water was heated up to 65°C to 80°C and disodium edetate and arbutin are dissolved in it.

   2.2 Xanthan gum was dispersed in glycerin and the dispersion wais added to aqueous phase at 65°C to 80°C

   2.3 Sodium benzoate, citric acid monohydrate and ascorbic acid were added to aqueous phase and then dissolved temperature is maintained at 65°C to 80°C.

3. Emulsification (water in oil type):

   Contents of step (2) were added to contents of step (1) at 65°C to 80°C and homogenized for 15 minutes and then cooled.

4. Sodium metabisulphite phase

   Sodium metabisulfite is dissolved in water and added to bulk obtained (from the above steps) at 40°C under stirring, and stirring is continued to form cream.

Example – 2: A cream composition comprising arbutin, triamcinolone and tretinoin.

STEPS	INGREDIENTS	CONCENTRATION (% w/w)
I	Stearic Acid	3.000
	Cetyl Alcohol	2.000
	Stearyl Alcohol	2.000
	Glyceryl Monostearate(NSE)	2.000
	Polyoxy 20 Cetyl Ether (Brij 58)	2.000
	Liquid Paraffin	23.000
	Isopropyl Myristate	5.000
	Dimeticone 350	0.500
	Ascorbyl Tetraisopalmitate(NIKKOL VC-IP)	0.100
	Butylated Hydroxytolune (BHT)	0.100
	Tretinoin	0.050
	Triamcinolone Acetonide	0.025
II	Purified Water	35.605
	Disodium Edetate	0.100
	Hydroxypropyl β Cyclodextrin (HPβCD)	1.000
	Glycerin	4.000
	Xanthan Gum	0.100
	Citric Acid Monohydrate	0.120
III	Purified Water	14.000
	Arbutin	3.000
III	Purified Water	1.000
	Sodium Benzoate	0.200
IV	Purified Water	1.000
	Sodium Metabisulphite	0.100
	Total	100

Brief Manufacturing Process:

1. Oil phase: Ingredients of step I were heated at 70°C to 72°C.
2. Aqueous Phase: Ingredients of step II were heated at 70°C to 72°C.
3. Emulsification: step 1 ingredients were added to step 2 at 70°C to 72°C and homogenized for 15 minutes.
4. Arbutin solution (previously dissolved in purified water and maintained at temperature of 55°C to 58°C) was added under stirring at 55°C.
5. Sodium benzoate solution (previously dissolved in purified water) was added at 40°C
6. Sodium metabisulphite solution (previously dissolved in purified water) was added at 40°C
7. Stirring was continued and cooled to room temperature to form cream.

Example – 3: A cream composition comprising arbutin, desonide and tretinoin.

STEPS	**INGREDIENTS**	**CONCENTRATION (% w/w)**
I	Stearic Acid	3.000
	Cetyl Alcohol	2.000
	Stearyl Alcohol	2.000
	Glyceryl Monostearate (NSE)	2.000
	Polyoxy 20 Cetyl Ether (Brij 58)	2.000
	Liquid Paraffin	23.000
	Isopropyl Myristate	5.000
	Dimeticone 350	0.500
	Ascorbyl Tetraisopalmitate (NIKKOL VC-IP)	0.100
	Butylated Hydroxytolune (BHT)	0.100
	Tretinoin	0.050
	Desonide	0.05
II	Purified Water	35.530
	Disodium Edetate	0.100

	Hydroxypropyl β Cyclodextrin (HPβCD)	1.000
	Glycerin	4.000
	Xanthan Gum	0.100
	Citric Acid Monohydrate	0.120
III	Purified Water	14.000
	Arbutin	3.000
III	Purified Water	1.000
	Sodium Benzoate	0.200
IV	Purified Water	1.000
	Sodium Metabisulphite	0.100
	Total	100

Brief manufacturing process

1. Oil phase: Ingredients of step I were heated at 70°C to 72°C.
2. Aqueous Phase: Ingredients of step II were heated at 70°C to 72°C.
3. Emulsification: Ingredients of step I were added to step 2 at 70°C to 72°C and homogenized for 15 minutes.
4. Arbutin solution (previously dissolved in purified water and maintained at a temperature of 55°C to 58°C) was added under stirring at 55°C.
5. Sodium benzoate solution (previously dissolved in purified water) was added At 40°C
6. Sodium metabisulphite solution (previously dissolved in purified water) was added at 40°C
7. Stirring was continued and cooled to room temperature to form cream.

Example – 4: An ointment composition comprising arbutin, desonide and tretinoin.

STEPS	**INGREDIENTS**	**CONCENTRATION (% w/w)**
I	White Soft Paraffin	81.150
	Liquid Paraffin	10.000

	White Beeswax	3.000
	Sorbitan Monostearate	2.000
	Dimeticone 350	0.500
	Ascorbyl Tetraisopalmitate(NIKKOL VC-IP)	0.100
	Butylated Hydroxytolune (BHT)	0.100
	Tretinoin	0.050
	Desonide	0.05
	Arbutin	3.000
	Total	100

Brief manufacturing process:

1. All the ingredients of step I were heated at about 70°C and homogenized for 15 minutes.
2. Stirring was continued and cooled to room temperature to form an ointment.

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention.

We claim:

1. A topical composition for the treatment of skin diseases comprising
   a) arbutin in the range from about 1 % to 5 %w/w;
   b) a corticosteroid in the range from about 0.01 % to 0.3 %w/w;
   c) a retinoid in the range from about 0.01 % to 0.5 %w/w; and
   d) a dermatologically acceptable vehicle;
   wherein the range is based on 100 % total weight of the composition.

2. A topical composition for the treatment of skin diseases comprising
   a) arbutin in the range from about 2 % to 4 % w/w;
   b) triamcinolone or desonide in the range from about 0.01 % to 0.1 % w/w;
   c) tretinoin in the range from about 0.02 % to 0.1 % w/w; and
   d) a dermatologically acceptable vehicle;
   wherein the range is based on 100 % total weight of the composition.

3. A fixed dose topical composition for the treatment of skin diseases comprising a) about 3 %w/w of arbutin, b) about 0.025 % w/w of triamcinolone and c) about 0.05 %w/w of tretinoin (based on 100% total weight of the composition) and a dermatologically acceptable vehicle.

4. A fixed dose topical composition for the treatment of skin diseases comprising about 3 %w/w of arbutin, about 0.05 % w/w of desonide and about 0.05 %w/w of tretinoin (based on 100% total weight of the composition) and a dermatologically acceptable vehicle.

5. The topical composition for the treatment of skin diseases according to any of the claims 1-4, wherein the composition comprises a sun protection factor.

6. Use of the topical composition comprising about 3 %w/w of arbutin, about 0.025 %w/w of triamcinolone and about 0.05 %w/w of tretinoin (based on 100% total weight of the composition) and a dermatologically acceptable vehicle for the treatment of skin diseases in human.

7. Use of the topical composition comprising about 3 %w/w of arbutin, about 0.05 % w/w of desonide and about 0.05 % w/w of tretinoin (based on 100% total weight of the composition) and a dermatologically acceptable vehicle for the treatment of skin diseases in human.

8. The use of the topical composition according to claim 6 or 7, wherein the skin disease includes melasma, ephelides, post inflammatory hyperpigmentation, dermal blemishes, non–congenital hyperpigmentation, and solar lentigo.

9. The topical composition according to any of the claims 1-5, wherein the composition is in the form of cream, ointment, dispersion, suspension, solution, foam, lotion, plaster, gel, and emulsion.

10. A process for preparation of a topical composition for the treatment of skin diseases comprising arbutin, triamcinolone or desonide, and tretinoin, wherein the process comprises the steps of:

a) mixing the active ingredients, either separately or combinedly, with a dermatologically acceptable vehicle; and
b) formulating the mixture of step (a) into a suitable form convenient for topical use.

11. The process for preparation of a topical composition according to claim 10, wherein the suitable form convenient for topical use includes cream, ointment, dispersion, suspension, solution, foam, lotion, plaster, gel, and emulsion.