Abstract:

Title: WATERBORNE TOPICAL COMPOSITIONS FOR THE DELIVERY OF AZELAIC ACID FOR TREATMENT OF SKIN CONDITIONS SUCH AS ACNE VULGARIS, ROSACEA SEBORRHEIC DERMATITIS

A waterborne topical composition is designed specifically to address the treatment of acne vulgaris, rosacea, seborrheic dermatitis and other skin conditions. One composition contains effective amounts of essential components azelaic acid, niacinamide, and glyc erin to create a rapidly penetrating and non-irritating compound. One composition contains effective amounts of essential components azelaic acid, niacinamide, and cyclodextran to create a rapidly penetrating and non-irritating compound.
WATERBORNE TOPICAL COMPOSITIONS FOR THE DELIVERY OF AZELAIC ACID FOR TREATMENT OF SKIN CONDITIONS SUCH AS ACNE VULGARIS, ROSACEA, SEBORRHEIC DERMATITIS

RELATED APPLICATIONS

[0001] This application further develops the invention set forth in U.S. Patent Application 12/486,625 filed on June 17, 2009 entitled "Waterborne Topical Compositions for the Delivery of Active Ingredients such as Azelaic Acid" and which issued as U.S. Patent 8,729,108, which patent is incorporated herein by reference.

BACKGROUND INFORMATION

[0002] 1. Field of the Invention

[0003] The present invention relates to waterborne topical compositions for humans, and more particularly to waterborne topical compositions delivering azelaic acid to the human skin. These formulations are suited for treatment of acne vulgaris, rosacea, seborrheic dermatitis, or other skin conditions. Specifically, the formulations of the present invention result in enhanced and rapid penetration of azelaic acid into human skin and substantiated reduced potential for irritant dermatitis. The reduction in irritant dermatitis potential also promotes patient compliance.

[0004] 2. Background Information

[0005] The term acne comes from a corruption of the Greek ἀκμή (acme in the sense of a skin eruption). The most common form of acne is known as "acne vulgaris", meaning "common acne". Many teenagers get this type of acne. Acne vulgaris is a skin disease; caused by changes in the pilosebaceous units, namely skin structures consisting of a hair follicle and its associated sebaceous gland. Severe acne is inflammatory, but acne can also manifest in non-inflammatory forms. Acne lesions are commonly referred to as pimples, spots, or zits.

[0006] Acne is most common during adolescence, affecting more than 85% of teenagers, and frequently continues into adulthood. For most people, acne diminishes over time and tends to disappear, or at least decrease, after one reaches their early twenties. There is, however, no way to predict how long it will take for it to disappear entirely, and some individuals will continue to suffer from acne decades later, into their thirties and forties and even beyond.
[0007] Acne develops as a result of blockages in follicles. Formation of a plug of keratin and sebum, a microcomedo, is the earliest change. Enlargement of sebaceous glands and an increase in sebum production occur with increased androgen (DHEA-S) production. The microcomedo may enlarge to form an open comedo, also commonly called a blackhead, or closed comedo, also commonly called a whitehead. In these conditions the naturally occurring, largely commensal bacteria, Propionibacterium acnes, can cause inflammation, leading to inflammatory lesions, such as papules, infected pustules, or nodules, in the dermis around the microcomedo or comedo, which results in redness and may result in scarring and/or hyper-pigmentation.

[0008] Rosacea is a common, but often misunderstood, condition that is estimated to affect over 45 million people worldwide. It typically affects white-skinned people of mostly north-western European descent, and has been nicknamed the "curse of the Celts" by some in the British Isles. It begins as erythema, flushing and redness, on the central face and across the cheeks, nose, or forehead but can also less commonly affect the neck and chest. As rosacea progresses, other symptoms can develop such as semi-permanent erythema, telangiectasia which is a dilation of superficial blood vessels on the face, red domed papules (small bumps) and pustules, red gritty eyes, burning and stinging sensations, and in some advanced cases, a red lobulated nose, known as rhinophyma. The disorder can be confused with and can co-exist with acne vulgaris.

[0009] Patients with rosacea suffer from redness, stinging, burning and chronic inflammation that results in sensitive skin and intolerance of many topical products. Drugs for treatment of rosacea must ideally be both clinically efficacious and coexist in a vehicle designed for sensitive skin. Most vehicles, such as propylene glycol and fatty acids damage the stratum corneum in order to allow a topical drug to penetrate adequately.

[0010] There are a variety of compositions available for treating inflammatory acne vulgaris and rosacea, including topical and systemic antibiotics and retinoids. For example Metronidazole, 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole, has long been known as an effective drug to treat a variety of disorders, and as a topical therapy, metronidazole has also been shown to be useful in treating various skin disorders, including acne rosacea, bacterial ulcers, and perioral dermatitis. See, U.S. Pat. No. 4,837,378 which is incorporated herein by reference. Metronidazole has been found to
have an anti-inflammatory activity when used topically to treat dermatologic disorders. See U.S. Pat. No. 5,849,776 which is incorporated herein by reference.

[0011] Compositions containing metronidazole for treatment of dermatologic disorders are available in cream, lotion and gel forms. One commercially available metronidazole cream product, sold under the NORITATE™ brand from Dermik Laboratories, Inc., Collegeville, Pa. 19426 USA, contains 1% metronidazole in which the insoluble drug is suspended in the opaque cream. A commercially available metronidazole gel product, METROGEL® brand from Galderma Laboratories, Inc. Fort Worth, Tex., 76133 USA, contains 0.75% metronidazole which is solubilized to produce a clear gel. U.S. Patents 7,348,3217 and 6,881,726 which patents are incorporated herein by reference, disclose a method for making an aqueous composition containing a dissolved concentration of metronidazole greater than 0.75% w/w comprising combining metronidazole, beta-cyclodextrin (BCD), and niacin or niacinamide in an aqueous fluid, wherein the BCD and the niacin or niacinamide are combined in the aqueous fluid in amounts that provide a synergistic effect on the solubility of metronidazole. U.S. Patent 7,981,916 which patent is incorporated herein by reference, discloses a method in which metronidazole is solubilized in an aqueous phase, by mixing same with niacinamide and at least two glycolic cosolvents; the resulting solutions and pharmaceutical compositions comprised thereof are described as useful for the treatment of dermatological conditions/afflictions, notably rosacea.

[0012] Azelaic acid, or nonanedioic acid, has been used to effectively treat acne. However, at higher concentrations, particularly at prescription strength, azelaic acid has been found to be irritating to skin. At lower concentrations, effectiveness of the azelaic acid is compromised. Carriers such as alcohols, added to enhance absorption of the azelaic acid at lower concentrations, have been found to cause drying of the skin and hence additional irritation. It would be desirable to provide an effective treatment composition for acne vulgaris and rosacea that is non-irritating and non-drying yet allow for effective release of azelaic acid from the vehicle and subsequent rapid penetration into the skin.

[0013] Ideal topical drugs for rosacea should not damage the skin barrier function and enhance hydration while allowing such difficult-to-dissolve drugs as azelaic acid to be solubilized and bioavailable. In an attempt to increase penetration of azelaic acid into skin, formulations containing hydrogels consisting of triglyceride, propylene glycol, at
least one polysorbate, polyacrylic acid and soy lecithin have been devised. These vehicles deliver more azelaic acid into the skin than the earlier formulation. Despite greater penetration into the skin, formulations with 15% azelaic acid, such as sold under the brand name FINACEA® utilizing this delivery vehicle have been found to be significantly more irritating when compared to other rosacea topical treatments, such as metronidazole 0.75%.

[0014] Patient compliance is very important to the success of medical treatment. In diseases such as rosacea, acne, and seborrheic dermatitis, there exists heightened skin sensitivity. In a study by the manufacturer of the FINACEA® brand (which had azelaic acid 15% gel) for rosacea; over 30% of treated patients complained of burning, stinging or tingling. This side effect would be expected to significantly and negatively impact patient compliance. Ideally, a delivery vehicle should not only effectively deliver azelaic acid to the skin but should do so rapidly in order to minimize irritation and hypersensitivity.

[0015] U.S. Patent 6,534,070 is representative of the prior art and is incorporated herein by reference. U.S. Patent 6,534,070 teaches a pharmaceutical composition having the following constituents: azelaic acid, polyacrylic acid, triacylglyceride, propylene glycol, polysorbate, soya lecithin, water and salts. The composition is a hydrogel which is suited for the treatment of rosacea, presbyderma, melasma or skin irritations. This composition is essentially a description of the commercially available FINACEA® product. The composition appears to suggest the polyacrylic base enhances the relevant acid penetration.

[0016] U.S. Published Patent Application 2009-0182054, which is incorporated herein by reference teaches a topical composition containing solubilized azelaic acid formulated in an aqueous carrier. The publication asserts that in-vitro skin penetration and bioavailability study demonstrates higher bioavailability of the solubilized azelaic acid in the cutaneous organs. The topical composition is designated for the treatment of skin disorders associated with skin inflammation such as rosacea, seborrheic dermatitis, perioral dermatitis, and facial dermatitis.

[0017] U.S. Published Patent Application 2005-0169948, which is incorporated herein by reference, discloses topical composition for the treatment of acne vulgaris or acne rosacea comprises 1-12% nicotinamide by weight and less than 1% by weight of nicotinic
acid. The composition was described to be more effective in the treatment of acne than the same composition would be without the nicotinic acid.

[0018] U.S. 6,734,210 which is incorporated herein by reference discloses a composition useful for the treatment of acne and rosacea comprising an effective amount of a mixture of azelaic acid and chitosan whereby the mixture is prepared by mixing azelaic acid and chitosan in water to form a solution and drying the solution.

[0019] U.S. Patent Publication 2010-0004338 which is incorporated herein by reference discloses a gel composition comprising of about 15 wt % azelaic acid; about 0.1 wt % benzoic acid; about 0.1 wt % disodium ethylenediaminetetraacetic acid; about 0.85 wt % CARBOMER® 940 (or CARBOPOL® 980); about 1.5 wt % POLYSORBATE® 80; about 12 wt % propylene glycol; about 2.0 wt % isopropyl myristate; about 0.2 wt % sodium hydroxide and purified water. The composition is taught to be administered for the treatment of rosacea, presbyderma, melasma, acne and/or skin irritations.

[0020] The inventors work in U.S. Patent 8,729,108, which is incorporated herein by reference addresses many of the deficiencies of the prior art and is directed to waterborne topical compositions for humans, and more particularly to waterborne topical compositions delivering azelaic acid to the human skin. The formulations of the '108 patent are suited for treatment of acne vulgaris, rosacea, seborrheic dermatitis, or other skin conditions. Specifically, the formulations of the '108 patent application result in enhanced and rapid penetration of azelaic acid into human skin and substantiated reduced potential for irritant dermatitis relative to prior formulations. The reduction in irritant dermatitis in the formulations of the '108 patent also promotes patient compliance.

[0021] There is a need for delivery of effective concentrations of azelaic acid to the skin while minimizing irritation such as in the formulations of the '108 patent and to develop formulations that yield improved delivery, further reduced skin irritation and effective and stable compositions. The present invention allows for enhanced delivery of azelaic acid while minimizing irritation, thus encouraging optimal results and providing effective and stable compositions.

SUMMARY OF THE INVENTION

[0022] One embodiment of the present invention provides a waterborne topical composition for the enhanced penetration of azelaic acid into human skin in the treatment of acne vulgaris, rosacea and other skin conditions. The composition according to one
embodiment comprises effective amounts of azelaic acid, niacinamide, and hydroxypropyl beta and wherein the composition demonstrates a penetration rate of at least 5% active ingredient/hr, within 2.5 hours of application to human skin.

[0023] One embodiment of the invention provides a waterborne topical composition comprising: effective amounts of azelaic acid, wherein the azelaic acid is present in an amount of 4 percent to 20 percent by weight; effective amounts of niacinamide, wherein the niacinamide is present in an amount of 4 to 10 percent by weight; and effective amounts of cyclodextran, wherein the cyclodextran is present in an amount of 0.1 to 6 percent by weight.

[0024] One embodiment of the invention provides a waterborne topical composition for topical application of at least one active ingredient comprising effective amounts of azelaic acid, niacinamide, and hydroxypropyl beta.

[0025] These and other advantages of the present invention will be clarified in the brief description of the preferred embodiment taken together with the drawings in which like reference numerals represent like elements throughout.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0026] Other than in any operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0027] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contain certain errors necessarily resulting from the standard deviation found in their respective testing measurements.
[0028] Also, it should be understood that any numerical range recited herein is intended to include all sub-ranges subsumed therein. For example, a range of "1 to 10" is intended to include all sub-ranges between (and including) the recited minimum value of 1 and the recited maximum value of 10, that is, having a minimum value equal to or greater than 1 and a maximum value of equal to or less than 10.

[0029] As used in this specification and the appended claims, the articles "a," "an," and "the" include plural referents unless expressly and unequivocally limited to one referent.

[0030] The various embodiments and examples of the present invention as presented herein are each understood to be non-limiting with respect to the scope of the invention.

[0031] The compositions of the present invention are waterborne. They may be prepared in the form of a liquid, cream, gel, fluid, lotion, emulsion or microemulsion as desired. Viscosity of the composition may be altered using any of various formulating methods, such as by changing the amount of carrier medium.

[0032] As discussed above, the inventors work in U.S. Patent 8,729,108, which is incorporated herein by reference addresses many of the deficiencies of the prior art and is directed to waterborne topical compositions for humans, and more particularly to waterborne topical compositions delivering azelaic acid to the human skin. The formulations of the '108 patent are suited for treatment of acne vulgaris, rosacea, seborrheic dermatitis, or other skin conditions. Specifically, the formulations of the '108 patent application result in enhanced and rapid penetration of azelaic acid into human skin and substantiated reduced potential for irritant dermatitis relative to prior formulations. The reduction in irritant dermatitis in the formulations of the '108 patent also promotes patient compliance. The present invention builds upon the teachings of the '108 patent and improves the effective amounts, the stability of the composition and the irritation caused by the compositions.

[0033] The composition of one embodiment of the present invention contains effective amounts of components azelaic acid, niacinamide, and cyclodextran.

[0034] Azelaic acid (nonanedioic acid) is a saturated dicarboxylic acid found naturally in wheat, rye, and barley. It is a natural substance that is produced by Malassezia furfur (also known as Pityrosporum ovale), a yeast that lives on healthy skin. Azelaic acid is typically present in the composition of the present invention in amounts of about 3 to 30 percent by weight, preferably 4 to 20 percent by weight, with 5 to 20 percent by weight being most common, although 10 to 20 percent by weight and 15 to 20 percent by weight
have proven to yield effective formulations. In prescription strength formulations of the composition, azelaic acid is present in an amount typically of at least 4 percent by weight. In countries other than the United States, azelaic acid may be allowed in over-the-counter (OTC) formulations and typically contain azelaic acid at less than 4 percent by weight.

[0035] Azelaic acid is only slightly soluble in water, cosmetic oils and alcohols; thus each of these solvents has conventionally had limitations as a carrier for topical formulations containing azelaic acid. For example, an aqueous solution of azelaic acid would contain a maximum of about 0.24% by weight (w/w) azelaic acid, which is not enough to be effective. Azelaic acid has little or no solubility in cosmetic oils. Alcohols are unsatisfactory in high concentrations as they have the undesirable side effect of drying and irritating the skin.

[0036] Niacinamide, also known as nicotinamide and nicotinic acid amide, is the amide of nicotinic acid (vitamin B₃). Nicotinamide is a water-soluble vitamin and is part of the vitamin B group. Typically the niacinamide is present in an amount of up to 10 percent by weight in the composition, typically 1 to 10 percent by weight in the composite on, and commonly 4 to 10 percent by weight in the composition of the present invention. Though not intending to be bound by theory, it is believed that the combination of azelaic acid and niacinamide in the composition of the present invention surprisingly offers greater therapeutic benefits than either component used alone. Azelaic acid is believed to enhance the penetration and effect of niacinamide. In turn, the effect of azelaic acid on follicular inflammatory conditions such as acne rosacea is enhanced by the niacinamide. It is believed that this effect is due in part to increased aqueous solubility of dicarboxylic acids such as azelaic acid in the presence of niacinamide.

[0037] One embodiment of the present invention uses discussed further below effective amounts of a cyclodextran, niacinamide and azelaic acid. The Niacinamide in combination with cyclodextrin is believed to act as a solubility enhancer of azelaic acid.

[0038] In certain embodiments of the present invention, the niacinamide is present in an amount at least sufficient to enhance penetration of the azelaic acid into skin. Niacinamide may be used in combination with nicotinic acid in the composition of the present invention; usually, however, the composition is essentially free of nicotinic acid. By "essentially free" it is meant that if the material is present in the composition, it is present incidentally in an amount less than 0.1 percent by weight, preferably less than trace amounts.
Glycerin is a chemical compound also commonly called glycerol or glycerine. It is a colorless, odorless, viscous liquid. Glycerin is a sugar alcohol, and has three hydrophilic alcoholic hydroxyl groups that are responsible for its solubility in water and its hygroscopic nature. Typically, the glycerin is present in the composition of the present invention in an amount of up to 10 percent by weight, generally 1 to 10 percent by weight.

Glycerol has been found to enhance penetration of monoazelaate esters into the skin. It is proposed in U.S. Pat. No. 7,300,957, incorporated herein by reference, that glycerin esterified with azelaic acid enhances the percutaneous penetration of azelaic acid into the skin, after which the glycerin disassociates. Unexpectedly, it has been found that this process does not necessarily require the prior esterification of azelaic acid with glycerol to form glycerol monoazelaate. Compositions of the present invention are essentially free of azelaic acid esters, including reaction products of azelaic acid and glycerin.

Aquaporins are fairly newly-discovered "channels" in biological tissues such as skin that allow for the passage of certain molecules into cells to enhance cellular hydration. Aquaporins are integral membrane proteins from a larger family of major intrinsic proteins (MIP) that form pores in the membranes of biological cells. They compose six trans-membrane alpha helical structures arranged in a right-handed bundle and form tetramers in the cell membrane. The main aquaporin in the epidermis is-known as aquaporin-3 also known as aquaglyceroporin. Aquaporin-3 controls water transport in addition to movement of glycerol, CO₂, ammonia and urea. Aquaporin-3 expression is increased in human skin diseases with elevated transepidermal water loss such as rosacea. Not intending to be bound by theory, it is believed that glycerin in the composition of the present invention allows for enhanced absorption of the active ingredients into the skin through aquaporins as well as function as hydrators of the skin to minimize the potential for skin irritation from azelaic acid.

The topical composition of the present invention may optionally contain additional components as active ingredients or as inert additives. For example, the composition of the present invention may further comprise hyaluronic acid and/or a derivative thereof. Other suitable components include alcohols such as cetyl alcohol, stearyl alcohol, and benzyl alcohol, surfactants such as sodium lauryl sulfate, isopropyl palmitate, sorbitol, and lactic acid. Mixtures of these components are often used.
Sunscreens may be used in combination with other ingredients in the composition of the present invention; usually, however, the composition is essentially free of sunscreens.

[0043] It is recognized that the commercially available azelaic acid topicals prior to the commercialization of the formulations of the '108 patent were sold under the brands AZELEX® and FINACEA® and commonly cause skin irritation. This is due in part to irritant dermatitis induced by azelaic acid as delivered by present vehicle technology.

[0044] Although topical products in aqueous bases have been used to emulsify azelaic acid, see U.S. Pat. No. 6,734,210; these products either penetrate poorly into the skin or demonstrate significant irritation. The proposed formulation of the present invention demonstrates superior, rapid skin penetration using an in vitro human skin model when compared to the prior art before the '108 patent formulations, while the formulations of the present invention further yield increased stability and thus further allows for larger amounts of pharmaceutical active ingredient to penetrate living skin layers. The rate of penetration (% dose/hr) is nearly 3X that of azelaic acid-cream according to prior art commercially available prior to the compositions of the '108 patent. The formulations of the present invention maintain and improve upon these results.

[0045] The compositions of the present invention are also non-irritating and as such promote patient compliance.

[0046] The present formulations are the continuation of result of years of dermatologic research spelled out in the '108 patent to improve the effects of both azelaic acid and niacinamide while creating a product that was hydrating. The formulations of the present invention not only supports the skin's hydration and barrier function, it remains non-comedogenic. Previous prior art formulations containing azelaic acid have typically used either sd alcohol or propylene glycol to solubilize and dissolve azelaic acid into a cream or gel base, thus increasing the potential for skin irritation. The present formulations effectively shrink the size of azelaic acid and niacinamide particles into micron sized droplets and then envelop these micronized particles with the hydrating effects of non-animal derived glycerin which improves and creates synergy between the well documented and favorable skin effects of both azelaic acid and niacinamide while preserving the skin's epidermal barrier function.

[0047] A further embodiment of the present invention provides that by combining azelaic acid, niacinamide/niacin and a cyclodextrin, then greater than 10%, even 15%, azelaic acid can be easily stabilized without the use of previously necessary and irritating
glycols such as propylene glycol. Essentially the same compositions discussed in the '108 patent and further including with 0.1 to 6% by weight cyclodextrin. Cyclodextrins (sometimes called cycloamyloses) are a family of compounds made up of sugar molecules bound together in a ring (cyclic oligosaccharides). Cyclodextrins are produced from starch by means of enzymatic conversion. Cyclodextrins are composed of 5 or more a-D-glucopyranoside units linked 1-4, as in amylase (a fragment of starch). Typical cyclodextrins contain a number of glucose monomers ranging from six to eight units in a ring, creating a cone shape: a (alpha)-cyclodextrin: 6-membered sugar ring molecule; β (beta)-cyclodextrin: 7-membered sugar ring molecule; γ (gamma)-cyclodextrin: 8-membered sugar ring molecule. The formulation uses the niacinamide as a penetration and solubilization enhancer thus the relative concentration of cyclodextrin may be low. Essentially this embodiment of the present invention is increasing the solubility of azelaic acid in an aqueous vehicle by combination with a cyclodextrin, preferably betacyclodextrin, and niacinamide.

[0048] This embodiment of the present invention may be a water based gel solubilizing azelaic acid with niacinamide and betacyclodextrin. When betacyclodextrin and niacinamide are both utilized in the solution, the two compounds act synergistically to increase the solubility of azelaic acid in an aqueous vehicle. Thus the betacyclodextrin may be added in amounts of 0.1 to 6 percent by weight, generally 1 to less than 5% by weight and 2-3% by weight cyclodextrin are contemplated. Preliminary formulations suggest that maximum solubility of azelaic acid in a formulation can be increased with either niacinamide, or betacyclodextran but with both the results exhibit a synergistic effect with regard to the solubility of azelaic acid in an aqueous vehicle.

[0049] The presents invention use hydroypropyl beta cyclodextran as the preferred cyclodextran agent and the formulation preferably utilizes less than 5%, generally 2-3% by weight, of this relatively expensive agent.

[0050] The present invention provides effective formulations of azelaic acid and other agents that are water-based in order to minimize irritation and drying to the skin. An advantage of the formulations is they avoid harsh surfactants and organic solvents and contains only incidental concentrations of non-polar alcohols. Further they provide a vehicle that contains humectants that allow for moisturization of the skin and avoid the side effects of irritating substances such as azelaic acid. The formulations allow for rapid penetration to the applied skin. The formulations avoid fat and oil content so as to
minimize comedogenicity to the skin. The formulation demonstrates good physical and chemical stability over time. Additionally the formulations disclosed are designed as a green cosmeceutical products, as azelaic acid is derived from whole grain, and niacinamide is a form of naturally occurring B vitamin.

[0051] Others have identified the percutaneous absorption and penetration of radiolabeled azelaic acid from 15% gel (FINACIA®) and 20% cream (AZELEX®) preparations in vitro has been assessed after 24 hours of topical application of a dose of 8-16mg/2 cm² to hairless mouse skin using a modified Franz flow diffusion cell study. See Draelos ZC, Grupe K. entitled "A new topical formulation for the treatment of moderate papulopustular rosacea: azelaic acid 15% gel". American journal of Clinical Dermatology: 2004 - Volume 5 - Issue 1 - pp 57-64. When Finacea® was compared to it's vehicle as well as AZELEX® 20% azelaic acid cream for irritation in 20 humans using scarification to impair the epidermal barrier, the FINACIA® was found to be much more irritating than either it's vehicle or 20% azelaic acid cream (AZELEX®). Percutaneous absorption was lower for the gel (Finacea®) than for the cream (5.8% vs 16.3%), while most importantly, the dose fraction delivered into the viable skin layers was higher (25.3% vs 3.4%). With both formulations, the majority as the applied azelaic acid dose remained on the skin surface 56.7% for the gel vs 68.4% for the cream. Dermal penetration is critical for an effect and even small percentage differences can result in a significantly improved pharmacologic effect.

[0052] A study of the formulations of the present invention compared with FINACIA® combined with equal parts of OLAY TOTAL EFFECTS® cream done to investigate if simply adding this known commercial niacinamide containing product might reproduce the enhanced penetration and dermal partitioning characteristics of the proposed formulations of the present invention.

[0053] For reference OLAY TOTAL EFFECTS® Daily Moisturizer ingredients are: water, glycerin, niacinamide, isohexadecane, dimethicone, isopropyl istearate, polyacrylamide, sodium ascorbyl phosphate, panthenol, tocopherol acetate, camellia senensis leaf extract, zinc oxide, titanium dioxide, sucrose polycottonseedate, sorbitan stearate, cetyl alcohol, c13-14 isoparaffin, stearyl alcohol, dimethiconol, laureth-7, peg-100 stearate, stearic acid, citric acid, propylparaben, disodium edta, bht, benzyl alcohol, ethyl paraben, ammonium polyacrylate, triethoxycaprylylsilane, fragrance, yellow 5, red 40, vitamin b3, vitamin C, provitamin b5, vitamin E
The proposed formulations of the present invention again demonstrated an unexpectedly enhanced penetration of azelaic acid into the dermis and also a desirable reduced flow completely through the skin into the receptor fluid. The dermal percentage of azelaic acid was 4.3%, compared to the Olay/Finacea combination of 2.8%, a 71% increase. Flow through the skin into the receptor fluid was 3.9% for the proposed formulation vs 9.5% for the Finacea® Olay Total Effects® combination. Epidermal percentages were 18% for the proposed formulation, vs 38% for the Finacea ® Olay Total Effects® combination.

In summary, the optimized formula gave the lowest penetration into receptor fluid (which is desirable because the site of action is the skin) and the highest penetration into the dermis (which is good because that is where the hair follicles and sebaceous glands are located - e.g. site of action). The FINACEA® plus OLAY TOTAL EFFECTS® combination significantly increased the amount of azelaic acid left in the epidermis 38% vs 18% for the proposed formulation. The past experience is that most of what is in the epidermis is in the upper layers of the stratum corneum, so this does not get to the desired, dermal site of action. The optimized formulation with excellent dermal penetration and concentration cannot be reproduced by simply adding a niacinamide and glycerin containing product such as OLAY TOTAL EFFECTS® to an optimized aqueous azelaic acid formulation such as FINACEA®.

Although the present invention has been described with particularity herein, the scope of the present invention is not limited to the specific embodiment disclosed. It will be apparent to those of ordinary skill in the art that various modifications may be made to the present invention without departing from the spirit and scope thereof.
What is claimed is:

1. A waterborne topical composition for the treatment of acne vulgaris, rosacea, seborrheic dermatitis or other skin conditions comprising effective amounts of azelaic acid, niacinamide, and cyclodextran, and wherein the composition demonstrates a penetration rate of at least 5% active ingredient/hr, within 2.5 hours of application to human skin.

2. The waterborne topical composition of claim 1 wherein the azelaic acid is present in an amount of up to 20 percent by weight.

3. The waterborne topical composition of claim 2 wherein the azelaic acid is present in an amount of at least 10 percent by weight and the cyclodextran is less than 6 percent by weight.

4. The waterborne topical composition of claim 1 wherein the waterborne composition is in the form of one of a liquid, emulsion and microemulsion.

5. The waterborne topical composition of claim 1 wherein the niacinamide is present in an amount of up to 10 percent by weight and wherein the cyclodextran is in an amount less than 6 percent by weight.

6. The waterborne topical composition of claim 1 further including glycerin which is present in an amount of up to 10 percent by weight.

7. The waterborne topical composition of claim 1 further comprising hyaluronic acid and/or a derivative thereof and further including hydroxypropyl beta.

8. The waterborne topical composition of claim 1 wherein the composition includes effective amounts of glycerin and wherein the waterborne composition is in the form of one of a liquid, emulsion and microemulsion and further including hydroxypropyl beta.
free of azelaic acid esters and further including hydroxypropyl beta.

10. The waterborne topical composition of claim 1 and further comprising one or more alcohols, a surfactant, isopropyl palmitate, sorbitol, and lactic acid; and further including hydroxypropyl beta.

11. The waterborne topical composition of claim 10 wherein the alcohol comprises cetyl alcohol, stearyl alcohol, and/or benzyl alcohol.

12. The waterborne topical composition of claim 10 wherein the surfactant comprises sodium lauryl sulfate.

13. The waterborne topical composition of claim 10 further including effective amounts of glycerin and wherein the waterborne composition is in the form of one of a liquid, emulsion and microemulsion.

14. The waterborne topical composition of claim 10 wherein the composition is essentially free of azelaic acid esters.

15. A waterborne topical composition comprising:
   effective amounts of azelaic acid, wherein the azelaic acid is present in an amount of 4 percent to 20 percent by weight;
   effective amounts of niacinamide, wherein the niacinamide is present in an amount of 4 to 10 percent by weight; and
   effective amounts of cyclodextran, wherein the cyclodextran is present in an amount of 0.1 to 6 percent by weight.

16. The waterborne topical composition of claim 15 wherein the waterborne composition is in the form of one of a liquid, emulsion and microemulsion.

17. The waterborne topical composition of claim 15 wherein the composition demonstrates a penetration rate of at least 5% active ingredient/hour, within 2.5 hours of application to human skin and the composition is a gel.
18. A waterborne topical composition for topical application of at least one active ingredient comprising effective amounts of azelaic acid, niacinamide, and hydroxypropyl beta.

19. The waterborne topical composition of claim 18 wherein the azelaic acid is present in an amount of 4 to 20 percent by weight, and the niacinamide is present in an amount of up to 10 percent by weight, and the hydroxypropyl beta is present in an amount of up to 6 percent by weight.

20. The waterborne topical composition of claim 19 wherein the composition demonstrates a penetration rate of at least 5% active ingredient/hour, within 2.5 hours of application to human skin.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

<table>
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<th>Classification</th>
<th>Number</th>
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<td>(2006.01)</td>
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<td>A61P 17/10</td>
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 31/19, 31/724, 31/16, A61P 17/10

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

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

Espacenet, USPTO, PubMed, Eapatis, PAJ, PatSearch (RUPTO internal)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
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<th>Relevant to claim No.</th>
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<td>Y</td>
<td>US 2010/004296 A1 (DANNAKER CHRISTOPHER J) 07.01.2010, abstract, paragraph [0021], claims 1-14</td>
<td>1-20</td>
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</table>

* Special categories of cited documents:

'A' document defining the general state of the art which is not considered to be of particular relevance

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'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

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

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

'k' document member of the same patent family

Date of the actual completion of the international search: 12 August 2015 (12.08.2015)

Date of mailing of the international search report: 08 October 2015 (08.10.2015)

Authorized officer: N. Litvinenko

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