C&T

Potassium Azeloyl Diglycinate: A Multifunctional Skin Lightener

G. Maramaldi and M. A. Esposito
Sinerga Srl, Pero, Milan, Italy

Key words
Potassium azeloyl diglycinate, azelaic acid, skin lightener, sebum

Abstract
Skin lightening and sebum normalization are among the useful cosmetic functions of potassium azeloyl diglycinate, a soluble derivative of azelaic acid.

The dermatological use of azelaic acid is of interest because of its lightening, anti-seborrheic, anti-mycotic and anti-acne properties. However, its limits in cosmetic formulations are well known, even when it is used at lower concentrations than in pharmacological applications.

A new molecule, potassium azeloyl diglycinate, has been developed to overcome these limitations. This article describes the new ingredient, and reports preliminary results of its efficacy as a skin-lightening agent and as a sebum-normalizing agent.

Melanin and Skin Lighteners

Melanin is the substance responsible for the color of skin. Its main function is the protection of the deepest layers of epidermis, protecting them from damage by UV radiation. In fact, the exposure to UV rays, especially UVB, promotes the synthesis of new melanin that protects the genetic molecules inside keratinocytes from the damaging radiation.[2]

The synthesis of melanin takes place in specialized cells called melanocytes, where the amino acid tyrosine, in the presence of UVB radiation, is converted into dopa and dopaquinone due to the action of the enzyme tyrosinase. Tyrosinase also requires the presence of oxygen and copper.[3]

From the dermatological perspective, the treatment of hyperchromic spots involves several substances active at different stages:

- Use of sunscreens to reduce the stimulating effect of UV radiation on melanogenesis;
- Promotion of cellular turnover in order to replace corneocytes containing melanin granules;
- Inhibition of the synthesis of new melanin.

Compared to other skin lighteners, azelaic acid is not a photosensitizer, and skin shows moderate tolerance. Azelaic acid has been used for a long time, even at high levels (20%).[4]

Azelaic Acid

The use of azelaic acid (in its free-acid form) has long been known by dermatologists, who consider azelaic acid as a topical drug. This ingredient has found use as an important skin lightener and is also useful in treatment of seborrheic skin. Note that in Europe azelaic acid is not considered a drug and can be used as a cosmetic ingredient in skin care applications.[1]

Azelaic acid is produced by the microorganism *Pityrosporum ovale* (and other species). This organism is responsible for the cutaneous disease known as pitiryasis vescicolor, which causes leucodermic spots in which melanin is not present. Its mechanism of action has been shown to be a competitive inhibition of tyrosinase, the main enzyme involved in the formation of melanin. From this evidence, azelaic acid has been topically used in the dermatological treatment of hypermelanic spots (see sidebar).

Another important application of azelaic acid in dermatology is explained by its bacteriostatic activity. Azelaic acid has bacteriostatic properties against aerobic microorganisms such as *Staphylococcus epidermidis, Staphylococcus aureus, Proteus mirabilis, Escherichia coli, Pseudomonas aeruginosa and Candida albicans,* and against anaerobic ones such as *Propionibacterium acnes*. This activity is probably due to azelaic acid's ability to inhibit the cells' protein synthesis.

Additionally, azelaic acid may also cause a reduction of free fatty acids in cutaneous sebum due to a competitive

0361-4387/02/0003-0043$05.00/0

inhibition of the enzyme 5-α reductase, thus inhibiting the conversion of testosterone to 5-dehydrotestosterone.

These two properties also make azelaic acid especially effective in the treatment of acne, which involves sebum production and excretion, microbial colonization of the pilosebaceous unit and inflammatory reaction of the perifollicular area. Azelaic acid possesses activity against all these factors.[5]

Potassium Azeloyl Diglycinate

Azelaic acid, in spite of its valuable properties, presents some technical and formulating problems. First of all, it must be present in high concentrations to be effective; however, it is not soluble at high concentrations, and gives poor cosmetic properties to formulations, particularly thick systems difficult to spread.

Furthermore, it has a melting point around 105-106°C, which is quite high for a cosmetic ingredient, and makes azelaic acid difficult to handle under standard conditions.

Finally, the solubilization of azelaic acid through unusual chemical methods results in the loss of azelaic acid content over time because it undergoes decarboxylation.

By reacting the acid chloride of azelaic acid with two moles of glycine and one mole of potassium hydroxide (Figure 1), we obtain potassium azeloyl diglycinate,[a] a new molecule with better technical performance than its precursor, azelaic acid. Because this derivative of azelaic acid also contains the amino acid glycine, it exhibits very high water solubility, amphiphilicity, highly specific activities at low concentration and low toxicity, and excellent chemical stability and compatibilities.

Potassium azeloyl diglycinate is a soluble azelaic acid derivative that maintains all the cosmetic properties of the original molecule but improves upon its technical characteristics. Completely water soluble, potassium azeloyl diglycinate has increased bioavailability compared to azelaic acid, so its required use levels are much lower. Furthermore, skin tolerance is much enhanced.

The chemical modification of azelaic acid to potassium azeloyl diglycinate has therefore led to an equally active ingredient, but much improved from a technical point of view. Its physical and chemical properties are shown in Table 1.

Autoradiography techniques[6] have identified the mode of action of both azelaic acid and potassium azeloyl diglycinate to be the inhibition of tyrosinase. On melanocytes irradiated by radiotagged potassium azeloyl diglycinate (^{3}H dodecanoic acid), the localization of radioactivity in mitochondrions and cell nucleus was observed. Azelaic acid is similarly incorporated in the cell nucleus.

Efficacy Evaluations

In order to prove the effectiveness of the product, several efficacy evaluations were carried out on human volunteers.

Table 1. Physical and chemical properties of potassium azeloyl diglycinate

Property	Description
Appearance	clear liquid
Color	colorless to light yellow
Odor	odorless
pH	6.5-7.5
Active ingredient	28-32%
Specific Gravity (at 25°C)	1.160-1.170 g/mL
Molecular weight	341.42 g/mole
Water solubility	complete

[a]*Azeloglicina is a trade name of Sinerga Srl, Milan, Italy. The INCI name is Potassium Azeloyl Diglycinate.*

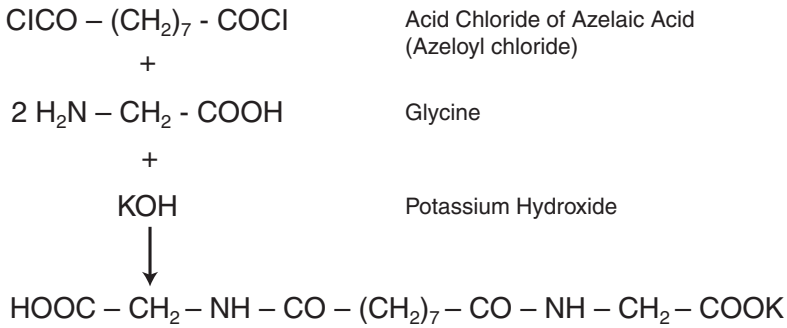

Figure 1. Synthesis of potassium azeloyl diglycinate

Whitening: The purpose of this test[7] was to evaluate the whitening efficacy of potassium azeloyl diglycinate on both hypermelanic and normal (unspotted) skin.

The product, in the form of a 3% aqueous solution, was applied to five volunteers having hypermelanic spots on the back of their hands. The spots were carefully selected and their location noted.

Each subject applied the product on the back of one hand (chosen randomly for each subject) twice a day for three weeks.

At the beginning and after three weeks of treatment, the skin color was measured using a colorimeter[b] on the following skin areas:

- A hypermelanic spot on the treated hand (treated spot);
- An area without hypermelanic spots on the treated hand (treated skin);
- A hypermelanic spot on the untreated hand (untreated spot);
- An area without hypermelanic spots on the untreated hand (untreated skin).

The parameters evaluated were "L*" (luminosity), "a*" (red-green axis), "b*" (yellow-blue axis); together they define skin color. As an internal reference, non-treated sites were measured as controls at the beginning and at the end of treatment.

The results of measuring the "L*" parameter (Figure 2) reveal a significant increase in skin brightness on both areas treated with the product. The whitening efficacy of the product was also confirmed by a decrease in skin color as measured by the "a*" parameter, which showed a decrease of 10.1% on treated spots and decrease of 12.2% on treated skin.

Sebum normalization: The purpose of this study[8] was to evaluate the sebum-normalizing efficacy of potassium azeloyl diglycinate. The product was applied as a 3% aqueous solution on the face of five volunteers with oily and acne-affected skin twice a day for three weeks.

Measurements of the resultant levels of cutaneous lipids were obtained through the use of a sebometer[c] on the forehead, nose and chin.

---

[b] *Minolta Chroma Meter CR 300, Minolta, Osaka, Japan*
[c] *Sebometer SM 810, Courage & Khazaka, Cologne, Germany*

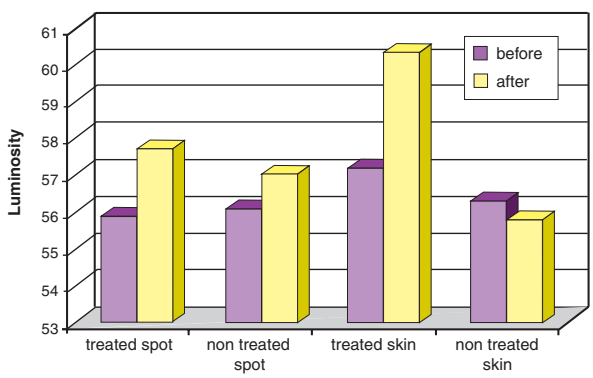

Figure 2. Whitening efficacy of potassium azeloyl diglycinate in 3% aqueous solution on human hands (N = 5)

At the end of the treatment, the measured levels of cutaneous lipids were lower than initial levels by 29.4%, 27.0% and 31.5% for forehead, nose and chin, respectively. We conclude that potassium azeloyl diglycinate is effective in the treatment of oily and acne-affected skin, effectively reducing the excess of cutaneous lipids.

Formula 1. Protective and Lightening Day Cream

Arachidyl alcohol (and) behenyl alcohol (and) arachidyl glucoside	5.0%wt
Triticum vulgare (wheat germ) oil	5.0
Olea europaea (olive) oil unsaponifiables	5.0
Persea gratissima (avocado) oil	3.0
Oryzanol (Gamma Oryzanol)	0.5
Dimethicone	0.48
Tocopheryl acetate	0.5
Zinc oxide	1.0
Tocopherol (and) lecithin (and) ascorbyl palmitate (and) citric acid	0.02
Phenoxyethanol (and) methylparaben (and) ethylparaben (and) propylparaben (and) butylparaben	0.5
Fragrance *(parfum)*	0.2
Water *(aqua)*	qs
Glycerin	2.0
Potassium azeloyl diglycinate (Azeloglicina, Sinerga)	5.0

Properties

Appearance: homogeneous viscous emulsion
Color: ivory
pH: 6.35
Viscosity: 10000 mPa.s (Viscotester Haak, spindle 1.25 rpm)
Stability: centrifuge (30' at 4000 rpm)

Formula 2. Low Viscosity Lightening Cream

Glyceryl stearate (and) ceteareth-20 (and) ceteareth-12 (and) cetearyl alcohol (and) cetyl palmitate	4.5%wt
Ceteareth-20	1.2
Squalane	5.0
Coco caprylate/caprate	5.0
Phenoxyethanol (and) methylparaben (and) ethylparaben (and) propylparaben (and) butylparaben	0.5
Water *(aqua)*	qs
Potassium azeloyl diglycinate (Azeloglicina, Sinerga)	5.0
Fragrance *(parfum)*	0.5

Properties

Appearance: low viscosity emulsion
Color: white, (Tyndall effect)
pH: 6.55
Viscosity: <100 mPa.s (Viscotester Haak, spindle 3.25 rpm)
Stability: centrifuge (30' at 4000 rpm) - stable

Hydration and elasticity: The purpose of this test[9] was to evaluate the efficacy of the product in improving skin elasticity, moisture, and smoothness after long-term use. Five volunteers applied a 3% aqueous solution to specific facial areas twice a day for three weeks.

At the beginning and at the end of the treatments, instrumental measurements of moisture[d] and elasticity[e] were taken.

Measurements showed that the basal value of skin moisture increased by 12.7% and 8.2% for forehead and cheek, respectively. Skin viscoelasticity on the forehead increased by 2.5%.

We conclude that potassium azeloyl diglycinate maintains all of the valuable properties of azelaic acid, but shows additional characteristics as a multifunctional ingredient.

Toxicological Evaluations

Innocuousness and skin tolerance of cosmetic products and cosmetic raw materials are important concerns for suppliers, formulators, and consumers. Here we report our evaluations of the major toxicological properties of potassium azeloyl diglycinate.

Skin irritation: This test[10] aimed to evaluate the skin irritation potential of potassium azeloyl diglycinate. The product, as received (30% active), was applied in an occlusive patch on the backs or forearms of 20 selected subjects for 48 hours. The irritating activity was clinically evaluated at 30 minutes after application (immediate irritating effect) and again 48 hours later.

None of the subjects showed any signs related either to immediate irritation or to long-term irritation. Therefore, potassium azeloyl diglycinate can be considered as a non-irritant.

Hypoallergenicity: The aim of this test[11] was to determine if potassium azeloyl diglycinate contains either a single ingredient or mixtures that behave as common allergens. The product, as received, was applied as an occlusive application on the backs or forearms of 20 subjects for 48 hours. After removing the occlusive patch, the cutaneous reactions induced by the product were evaluated at 24 and 48 hours.

No allergic reactions were observed, allowing us to conclude that potassium azeloyl diglycinate is hypoallergenic.

Eye irritation: Irritation potential on mucous membrane was evaluated by observing the adverse changes occurring to egg chorioallantoic membrane after exposure to the product being tested.[12] Results enabled us to conclude that potassium azeloyl diglycinate can be viewed as a non-irritant to mucous membranes.

Formulations

Formulas 1 and 2 are examples of lightening products. Note that because it is not sensitive to temperature, potassium azeloyl diglycinate is very easily added to emulsions at any step during processing.

[d] *Corneometer CM 820PC, Courage & Khazaka, Cologne, Germany*
[e] *Cutometer SEM 474, Courage & Khazaka, Cologne, Germany*

Conclusion

Potassium azeloyl diglycinate is a new derivative of azelaic acid. In preliminary results from efficacy tests on humans, this new material proved very effective as a skin-lightening agent and as a sebum-normalizing agent. In addition, skin moisturization and viscoelasticity parameters showed remark–able improvements.

Potassium azeloyl diglycinate is a multifunctional ingredient that also provides other beneficial characteristics, yet presents no toxicity in cosmetic application. Potassium azeloyl diglycinate enriches, through innovation, the panorama of lightening ingredients on the market today.

References

Address correspondence to G. Maramaldi, c/o Editor, *Cosmetics & Toiletries* magazine, 362 South Schmale Road, Carol Stream, IL 60188-2787 USA.

1. M Cucchiara, G Proserpio and H Sedghi, Dall' acido azelaico insolubile all' acido azelaico solubile, a technical paper from Sinerga R&D (Mar 1998)
2. R Caputo and M Monti, *Manuale di Dermocosmetologia Medica*, Milano: Raffaello Cortina (1995) pp 319-378
3. G Prota, Melanine e melanogenesi, *Cosmet Toil*, Italian ed, 18(2) 9-22 (1997)
4. G Penazzi and H Sedghi, Pigmentazione cutanea e depigmentanti, *Cosm Tech* 3(1) 30-33 (2000)
5. S Passi, M Picardo, C de Luca and M Nazzaro Porro, Mechanism of azelaic acid action in acne, *Ital Dermatol Venereol* 124(10) 455-463 (1989)
6. A Fitton and KL Goa, Azelaic acid – a review of its pharmacological properties and therapeutic efficacy in acne and hyperpigmentary skin disorders, *Drugs* 41(5) 780-798 (1991)
7. Institute of Skin and Product Evaluation (ISPE) Study 104/97/00 (Oct 8, 1997)
8. ISPE Study 102/97/00 (Oct 8, 1997)
9. ISPE Study 103/97/00 (Oct 8, 1997)
10. ISPE Study 31/98/00 (Feb 23, 1998)
11. ISPE Study 52/01/01 (Mar 21, 2001)
12. ISPE Study 26/98/00 (Mar 6, 1998)

C&T