

## CHAPTER 10

# Niacinamide: A Topical Vitamin with Wide-Ranging Skin Appearance Benefits

*Diane S. Berson<sup>1</sup>, Rosemarie Osborne<sup>2</sup>, John E. Oblong<sup>2</sup>, Tomohiro Hakozaki<sup>2</sup>, Mary B. Johnson<sup>2</sup>, and Donald L. Bissett<sup>2</sup>*

<sup>1</sup>Weill Medical College of Cornell University, New York-Presbyterian Hospital, New York, NY, USA

<sup>2</sup>The Procter & Gamble Company, Cincinnati, OH, USA

### Introduction

Niacinamide is vitamin B<sub>3</sub>, an essential nutrient. In the body, it is converted to the co-factors NADH and NADPH that are involved in many biochemical reactions. Dietary deficiency of this water-soluble member of the vitamin B family causes pellagra, a disease which includes dermatitis and red lesions. Pellagra caused thousands of deaths in the United States in the first half of the twentieth century, until simple dietary supplementation with this absorbable vitamin was found to cure the disorder.

NAD<sup>+</sup> and NADPH levels in skin cells decline with age. Thus, supplementing skin with the precursor to these vital co-factors has the potential to provide appearance benefits to aging skin. Since niacinamide penetrates the skin's surface readily, it is bioavailable from topical application for targeted delivery to specific skin sites. Clinical evaluations of topical formulations containing this vitamin have identified a wide range of skin care benefits. Among the many cosmetic effects for skin are reductions in the appearance of hyperpigmented spots, redness, yellowing (sallowness), surface sebum, pore size, surface texture, and fine lines and wrinkles. Additionally, there are improvements in moisturization, stratum corneum barrier integrity and elasticity. Further clinical evaluations have found that specific combinations of niacinamide with other cosmetic skin care ingredients can provide an even greater magnitude of appearance benefits.

Dermatological effects of topical niacinamide have also been observed in human testing, such as improvements in acne and bullous pemphigoid. A more recent evaluation demonstrated that topical niacinamide can provide appearance benefits in rosacea patients by improving skin barrier properties. The effect on the skin barrier also underlines the ability of

this vitamin, when applied topically prior to, or with, topical retinoids to increase the skin's tolerability to retinoid treatment and enhance the visible improvement of photodamaged skin.

This brief review chapter will focus on only a few of these skin appearance effects: surface sebum, pore size, surface texture, hyperpigmentation, and fine lines and wrinkles. In particular, new mechanistic insights underlying niacinamide's effects on skin's appearance and enhanced visible improvements when combined with other ingredients will be highlighted.

## Active ingredient

Vitamin B3 is present in many food sources (e.g., meat, nuts, wholegrains, legumes, yeast, to name a few). There are, of course, several commercial sources of the pure vitamin.

Three primary forms of vitamin B3 have been used in topical skin care products: niacinamide (aka nicotinamide), nicotinic acid, and nicotinate esters (e.g. benzyl nicotinate, myristoyl nicotinate). The bulk of the published in vitro and clinical studies revealing skin effects have been done with topical niacinamide (see below). Due to skin irritation concerns (see discussion on possible side effects below), clinical skin benefit studies with nicotinic acid and most nicotinate esters have not been done. There is some published clinical work with myristoyl nicotinate revealing effects on aging skin.

## Mechanisms of action

Since niacinamide is a precursor to the co-factors NAD(H) and NADP(H), which are involved in many biochemical reactions in the skin, it has the potential to impact a wide variety of metabolic pathways and thus impact skin functions that rely on those pathways. As a result of the complex interactions, several mechanisms for the actions of niacinamide in vitro have been described. For example, NADPH is a cofactor in the synthesis of fatty acids and more complex lipids such as ceramides. Also, NADH has been observed to inhibit some of the enzymes involved in the synthesis of glycosaminoglycans (GAGs) in vitro. Thus, niacinamide's precursor role appears to be important in connection with the observed increase in stratum corneum ceramides in vitro and subsequent improvement in skin barrier function, and with the observed reduction in excess dermal GAGs in vitro and the improved appearance of wrinkles. For other effects observed in vitro such as the increase in production of proteins (barrier layer proteins and collagen) and the inhibition of melanosome transfer,

**Table 10.1** Mechanistic effects of niacinamide and the postulated skin appearance benefits.

Niacinamide effect (ex vivo, in vitro)	Postulated skin appearance benefits
Inhibition of sebum production, specifically reducing the content of diglycerides, triglycerides, and fatty acids	Reduced acne Reduced pore size Improved texture
Stimulation of epidermal skin barrier lipids (ceramides) and proteins (keratin, involucrin, filaggrin)	Improved skin barrier and moisturization Reduced skin redness Rosacea appearance benefits
Anti-inflammatory (inhibition of inflammatory cytokines)	Anti-aging Reduced skin redness Rosacea appearance benefits
Increased production of collagen	Anti-wrinkle
Inhibition of production of excess dermal GAGs (glycosaminoglycans)	Anti-wrinkle
Inhibition of melanosome transfer from melanocytes to keratinocytes	Reduced hyperpigmentation
Inhibition of protein glycation via anti-oxidant effects (niacinamide, as precursor, increases levels of the redox co-factors NADH and NADPH)	Inhibit skin yellowing Sun protection

the specific mechanisms have not been elucidated to make connections to the skin benefits observed. However, it is possible that these effects also are a consequence of niacinamide's precursor role, the specifics of which have not been investigated in detail to define the processes involved. While all the mechanistic details have not been fully elucidated, Table 10.1 briefly presents an overview based on in vitro research and their potential connection to skin appearance benefits (discussed in more detail under Clinical Benefits).

More recent in vitro mechanistic studies have greatly expanded the number of potential skin targets affected by niacinamide in vitro. These new discoveries are summarized briefly in Table 10.2, and include a range of biomarkers related to skin structure, elasticity, wound healing and pigmentation. A relatively recent finding is the ability of niacinamide to impact UV-induced changes in skin. For example, in vitro testing showed that niacinamide can reduce production of PGE<sub>2</sub> from keratinocytes when stressed with non-lethal fluencies of UVB. Observations of cellular morphology also suggest an ability to protect overall integrity of the cellular structure from UV-induced changes in vitro. This supports published data showing the ability of both topical and oral niacinamide to prevent UV-induced immunosuppression. It has been hypothesized that, mechanistically, niacinamide protects cellular energy metabolism in vitro. The

**Table 10.2** Newly discovered mechanistic effects of niacinamide and the postulated skin appearance benefits.

Niacinamide effect (ex vivo, in vitro)	Postulated skin appearance benefits
Stimulation of keratinocyte proliferation via potentiation of KGF-mediated effects	Wound healing
Stimulate production of collagen and mRNA transcripts of several matrix components, associated enzymes, and cytokines: fibulin-1, fibronectin-1, elastin, lysyl oxidase (1 and 2), procollagen, collagen (I and III), TGF-beta (1, 2, and 3), actin, CTGF, tenascin XB)	Anti-wrinkle (anti-aging)
Down regulation of MITF, tyrosinase, TRP1, TRP2, and PMEL17	Reduce hyperpigmentation
Reducing UV-induced PGE <sub>2</sub> synthesis from keratinocytes	Inflammation
Preventing UV-induced immunosuppression	Actinic keratosis
Metabolic oscillator for circadian rhythm regulation	Skin barrier

concept of niacinamide impacting cellular metabolism is based on its rapid incorporation into both the NADH and NADPH cellular pools. However, newer research on regulation of circadian rhythms suggests that niacinamide plays an even more critical role in connecting cellular metabolism with regulator processes in vitro.

## Clinical benefits

In vehicle-controlled, randomized, double-blind, statistically powered human clinical testing (of duration up to six months), a wide range of skin care benefits have been observed with topical niacinamide.

### Reduction in surface sebum, pore size, and texture appearance

These effects are discussed as a group since reduction in facial surface sebum has been observed to be associated with reductions in pore size and count and in the appearance of skin surface texture. Niacinamide significantly reduces surface sebum in human skin biopsy specimens and in facial testing (after four weeks of topical treatment on Caucasian skin), with decreases specifically in the glyceride and fatty acid components of skin surface sebum. These surface sebum component changes are accompanied by significant reductions in the appearance of pore size and rough skin texture.

More recent testing has confirmed this effect on Caucasian facial skin, showing significant reductions in surface sebum, sebum spots, pore size, and pore count (based on Sebutape® and quantitative image analyses). This testing also extended the observation to Japanese facial skin, revealing significant reductions in surface sebum and pore size after two and four weeks of treatment.

In the search for additional ingredients, screening in an *in vitro* sebocyte assay confirmed the effectiveness of niacinamide and identified another potent surface sebum-reducing ingredient, dehydroacetic acid or its salt sodium dehydroacetate (SDA), which has previously been used in the cosmetic industry as a preservative. In facial skin testing, the topical combination of niacinamide and SDA was significantly more effective than topical niacinamide alone, the combination more than doubling the reductions in skin surface sebum and bumpy facial texture appearance.

In other testing, a regimen of products containing niacinamide (N) and salicylic acid (SA) versus an OTC benzoyl peroxide (BP) product regimen were evaluated in women with Skin Types I–V. The N-SA regimen provided a significantly better skin hydration effect than the BP regimen and comparable acne lesion benefits. The former was also significantly more effective in improving visible skin surface texture, pore size, and pore count (Figure 10.1). Additionally, significant correlations among these skin parameters were found, indicating a connection between pore parameters and texture appearance, establishing that reduction of surface sebum, and thus visible pore size, is a valid target for improving skin texture appearance. The surface sebum and pore effects are also relevant to acne treatment.



**Figure 10.1** Topical regimen of niacinamide and salicylic acid significantly reduces the appearance of facial skin texture and pore size (baseline vs. week 12).

### Reduction in fine lines and wrinkle appearance

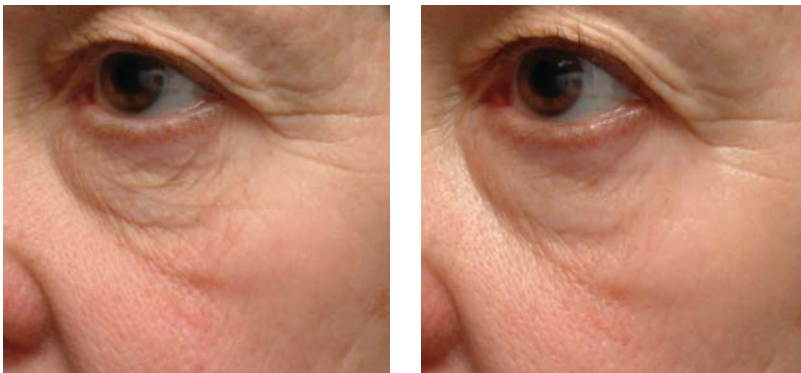
Previous studies have shown a decrease in the appearance of facial fine lines and wrinkles following topical application of a niacinamide-containing moisturizer. Results from the clinical study showed significant reductions in these parameters after 8 and 12 weeks of treatment.

In recent clinical facial testing, a cosmetic moisturizing product regimen containing the combination of niacinamide (N), peptide (pal-KTTKS, which affects the dermal matrix *in vitro*), and retinyl propionate (RP) was evaluated versus a regimen that included a prescription 0.02% tretinoin product. While both regimens improved the appearance of facial fine lines and wrinkles significantly and to the same extent by the end of the study (24 weeks), the N/peptide/RP regimen was significantly more effective early in the study (after 8 weeks) and better tolerated by the test subjects, based on measures of skin barrier, erythema, and skin dryness (Figure 10.2).

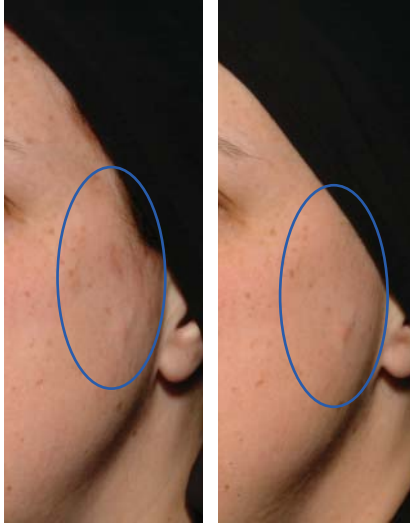
### Reduction in hyperpigmentation appearance

Topical niacinamide has been shown in several clinical studies to significantly reduce facial hyperpigmentation appearance, in particular, hyperpigmented spots. The effect is significant after four weeks of treatment.

More recent clinical testing has revealed the greater effectiveness of niacinamide in reducing the appearance of facial hyperpigmentation when combined with ingredients that inhibit different points in the pigmentation pathway *in vitro*. For example, N-acetyl glucosamine (which inhibits activation of tyrosinase *in vitro*) and N-undecyl-10-enoyl-L-phenylalanine (which blocks alpha-MSH *in vitro*) both significantly increase the skin appearance benefits of topical formulations containing niacinamide (Figure 10.3).



**Figure 10.2** Topical regimen of niacinamide, peptide (pal-KTTKS), and retinyl propionate significantly reduces the appearance of facial fine lines and wrinkles (baseline vs. week 8).



**Figure 10.3** Topical niacinamide in combination with N-undecyl-10-enoyl-L-phenylalanine significantly reduces the appearance of facial hyperpigmented spots (baseline vs. week 8).

### UV-induced immunosuppression and actinic keratosis

Continued research assessing the impact of both topical and oral niacinamide on preventing UV-induced immunosuppression establishes the ability of this vitamin to block this critical pathway in cancer onset, as exemplified through the reduction in the onset of actinic keratosis. While the effect appears to be more notable in the male population, this is an important finding for both genders.

### Uses

Niacinamide is used topically in cosmetic skin care products for the facial appearance benefit effects discussed above. Topical niacinamide has also been used dermatologically for the treatment of acne in some countries and more recently to provide appearance benefits in rosacea patients and as an adjunct skin care with topical retinoids. Facial appearance benefits in a rosacea patient after four weeks of topical niacinamide are shown in Figure 10.4.

### Possible side effects

Niacinamide can be used at high doses topically (at least up to 5%, the dose used in several commercial cosmetic products) and is generally well tolerated; however, in some rare cases mild skin irritation has been observed. The nicotinic acid form of Vitamin B3 can be problematic for topical use due to a skin reddening (vasodilation) response that can occur



**Figure 10.4** Topical niacinamide provides facial appearance benefits in rosacea patients (baseline vs. week 4).

at doses less than 1%. Often irritation and itching can accompany this response. Some nicotinic acid esters, even at doses much lower than 1%, can be difficult to use in cosmetic skin care products due to skin hydrolysis to free nicotinic acid, resulting in the reddening and irritation/itch effects. One ester (myristoyl nicotinate) has been reported to lack these effects, while still providing chronic skin benefits.

## Conclusion

This chapter illustrates the myriad dermatological and topical uses of niacinamide in cosmetic formulas, from simple moisturization to providing appearance benefits in patients with dermatological skin disorders such as rosacea via improvement in skin barrier integrity. Since many of the skin appearance issues improved with this vitamin are encountered by dermatologists in their daily practices, having a cost-effective, skin-friendly material such as niacinamide is a welcome addition to the skin care options available for dermatologists to recommend to their patients.

While in vitro-based mechanistic understanding is a critically important component of selecting ingredients for cosmetic formulations, the importance of clinical proof of effectiveness cannot be over-emphasized to demonstrate real-world utility. Clinical studies demonstrating ingredient effectiveness must involve the following key design elements: statistically powered, double-blinded, vehicle-controlled, randomized, utilizing state-of-the-art objective measures (e.g. computer image analysis), and peer review of the study design and its results. These clinical efforts, which support the studies reported here for topical niacinamide, should provide the basis for recommending ingredients, and the products that contain those ingredients, to improve skin appearance in a noticeable and patient-relevant manner.

As laboratory and clinical research continues, additional skin care benefits of niacinamide and its combinations with other ingredients are likely to be found for this versatile, yet potent, water-soluble vitamin. Those



new discoveries are expected to broaden even further the clinical utility of topical niacinamide.

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