

Anti-aging Skin Care Formulations

Chapter 11

Textbook: Cosmetic Formulation of Skin Care Products; by Zoe Diana Draelos and Lauren A. Thaman; Taylor and Francis Group; 2006

Learning Objectives

By the end of this lecture, students will be able to:

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- Explain the purpose of anti-aging skin care formulations
- Identify common types of anti-aging skin care agents, their mechanism of action, and their efficacy.
- Discuss the formulation and product challenges of anti-aging skin care agents.

Introduction

Many cosmetic materials are claimed to have anti-aging effects when used topically. The term anti-aging is very broad (in terms of prevention vs. improvement and the wide array of possible benefit areas such as wrinkling, sagging, texture, sallowness, hyperpigmentation, etc.).

Vitamin A

Forms

Several forms of vitamin A are used cosmetically. The most widely utilized ones include retinol, retinyl esters (e.g., retinyl acetate, retinyl propionate, and retinyl palmitate), and retinaldehyde. Through endogenous enzymatic reactions, all of these are converted ultimately to trans-retinoic acid (trans-RA), which is the active form of vitamin A in skin.

Mechanisms

Trans-RA is the active form of vitamin A in skin. Trans-RA interacts with nuclear receptor proteins described as RA receptors and retinoid X receptors, which can form heterodimer complexes. These complexes then interact with specific DNA sequences to affect transcription, to either increase or decrease expression of specific proteins/enzymes.

Some specific changes induced by retinoid that are likely relevant to skin anti-wrinkle benefits are those that result in thicker skin to diminish the appearance of fine lines and wrinkles. For example, increased epidermal proliferation and differentiation (increased epidermal thickness), increased production of epidermal ground substance, which binds water, increasing epidermal hydration and thickness, and increased dermal production of extracellular matrix components such as collagen (increases dermal thickness).

In addition to stimulation of events in the skin, retinoids can also have an inhibitory effect on other tissue components. For example, retinoids are reported to inhibit the production of collagenase.

Efficacy

Since retinoids are irritating to the skin, and is better tolerated by the skin than trans-RA. Since retinoids tend to be fairly potent, topical doses of less than 1% are generally sufficient to obtain significant effects.

Product/Formulation Challenges

There are two primary challenges in working with retinoids:

1. Their tendency to induce skin irritation negatively affects skin barrier properties. While high doses will provide greater skin aging improvement, the associated irritation tends to define an upper concentration limit where they can be used practically.

Mitigation of the irritation may be managed to some extent with appropriate formulation to meter delivery into the skin, use of retinyl esters, which are less irritating than retinol, or inclusion of other ingredients (e.g., those with anti-inflammatory activity) to counter this issue.

2. Instability, especially to oxygen and light. Thus, to ensure stability of retinoid in the finished product, formulation and packaging must be done in an environment that minimizes exposure to oxygen and light.

The final product packaging also ideally needs to be opaque and oxygen impermeable, including the use of a small package orifice to reduce oxygen exposure once the container is opened. In addition, a variety of other strategies can be employed, e.g., encapsulation of the retinoid and inclusion of stabilizing antioxidants.

Vitamin B3

Forms

Three primary forms of vitamin B3 have found effective in skin care products: niacinamide (aka nicotinamide), nicotinic acid, and nicotinate esters (e.g., myristoyl nicotinate, benzyl nicotinate).

Mechanisms

Vitamin B3 serves as a precursor to a group of endogenous enzyme cofactors, specifically nicotinamide adenine dinucleotide (NAD), its phosphorylated derivative, and their reduced forms, which have antioxidant properties.

Efficacy

Topical niacinamide improves other aspects of aging skin, such as reduction in sebaceous lipids (oil control) and pore size, which likely contribute at least in part to improved skin texture. Additionally, niacinamide improves skin's elastic properties as demonstrated for two parameters of skin elasticity.

Beyond these effects, there is also improvement in the appearance of skin color (reduction in hyperpigmented spots and reduced skin yellowing) as noted above.

Fairly high doses (2–5%) of vitamin B3 have been used to achieve desired benefits. However, since there is a very high tolerance of the skin to niacinamide, even with chronic usage, high doses can be used acceptably

Product/Formulation Challenges

- The key challenge for working with niacinamide and nicotinate esters is avoiding hydrolysis to nicotinic acid. Nicotinic acid, even at low doses, can induce an intense skin reddening (flushing) response. To avoid hydrolysis, formulating in the pH range of 5 to 7 is preferred.
- For the nicotinate esters, there are many commercial options. Many of them are readily hydrolyzed to nicotinic acid on or in the skin, such that flushing responses occur rapidly (within seconds/minutes) even at very low concentrations (1%).
- The longer chain esters (e.g., myristoyl-nicotinate) apparently are more resistant to this hydrolysis and thus appear to be more suitable for use topically.

Vitamin C

Forms

Of the many forms of this vitamin, some of the more commonly used are ascorbic acid, ascorbyl phosphate (typically as the magnesium and sodium salts), and other ascorbate derivatives (e.g., ascorbyl palmitate, ascorbyl glucoside).

Mechanisms

Vitamin C is well known as an antioxidant and has been utilized as a skin lightener (e.g., via tyrosinase inhibition and/or its antioxidant effect), and has anti-

inflammatory properties since it reduces the erythema associated with post-operative laser resurfacing. In addition also serves as an essential cofactor for the enzymes lysyl hydroxylase and prolyl hydroxylase, both of which are required for collagen (Types I and III) biosynthesis, increasing the production of collagen and hence wrinkle reduction.

Efficacy

The reported doses of vitamin C tested are fairly high. Some of the studies address ingredient oxidative stability, a particular challenge with this form of vitamin C. In an oil-in-water emulsion, loss of nearly half of the ascorbic acid in a month is typical. To achieve stability, an oxygen-impermeable aluminum tube was used for packaging, and ascorbic acid loss was reduced to less than 10%.

Product/Formulation Challenges

- The key challenge with vitamin C compounds in general is stability (oxygen sensitivity), particularly with ascorbic acid. Not only does oxidation lead to loss of the active material, but there is also rapid product yellowing (an aesthetic negative for the consumer).
- Various stabilization strategies can be attempted to address the issue, such as exclusion of oxygen during formulation, oxygen impermeable packaging, encapsulation, low pH, minimization of water, and inclusion of other antioxidants.
- Despite all those approaches, in general, ascorbate stability remains a challenge, and some of these approaches (e.g., very low pH) can lead to unwanted aesthetic skin effects as noted above.
- For the ascorbyl phosphates (Mg and Na salts), the resulting high content of salt in the product can dramatically impact the thickener system, requiring increased use of thickener ingredients. These ascorbate derivatives are also considerably more expensive than other ascorbate compounds.
- Another challenge is skin delivery. Ascorbic acid's penetration across skin is, in general, poor (typically less than 1% of the topical dose entering skin).

- For the phosphate derivatives of ascorbate, skin penetration can be an even greater challenge due to the negative charges on the phosphate moiety. Thus, the use of skin penetration enhancement approaches is desired.

Peptides

Forms

There is a limitless array of possible peptides, based on amino acid sequence, number of amino acid residues, and use of derivatives/isomers of these residues. Among them are a few that have received particular focus in the cosmetic industry. They are palmitoyl-lysine-threonine-threonine-lysine-serine (pal-KTTKS; Matrixyl^w), acetyl-glutamate-glutamate-methionine-glutamine-arginine-arginine (Ac-EEMQRR; Argireline^w), and the tripeptide copper glycine-histidine-lysine (Cu-GHK).

Mechanisms

Both KTTKS and GHK are fragments of dermal collagen and have been shown to stimulate the production of collagen and thus have been discussed in regard to wound healing. Incorporation of long-chain lipophilic residues such as palmitoyl onto peptides can dramatically improve their delivery into skin, e.g., the observed five- to six-fold increase in delivery of palmitoyl peptides versus their underivatized versions. Thus, pal-KTTKS was synthesized specifically for the topical use of this peptide.

Ac-EEMQRR is described as a mimic of botulinum neurotoxin (Botox), which functions by inhibiting neurotransmitter release, thus “relaxing” the muscles involved in defining facial wrinkles (53).

Efficacy

The peptide pal-KTTKS is quite potent clinically, providing effects from very low topical doses, and it does not induce skin irritation responses (no redness, dryness, burn, sting, or itch responses).

In contrast to the potency of pal-KTTKS, the reported effects of other peptides require much higher doses, such as 2% for Cu-GHK and as high as 10% for Ac-EEMQRR.

Product/Formulation Challenges

- An important challenge is delivery into the skin since peptides are poorly penetrating, especially as the number of amino acid residues increases. An approach to that problem is the addition of a lipophilic chain (e.g., palmitate), which in the case of KTTKS increased skin penetration several-fold over the underivatized peptide.
- An additional challenge is the cost. As the number of amino acid residues increases, the cost of the peptide can increase dramatically. The consequences are that only low levels of peptide can be used in the product (which is acceptable if the peptide is potent, as in the case of pal-KTTKS) or the finished product cost to the consumer must be very high.

Dimethylaminoethanol (DMAE)

Mechanism

DMAE (also known as deanol) is a precursor to acetylcholine, a neurotransmitter involved in increased muscle tone. There could be firming of the skin via effects on the facial musculature. In addition, acetylcholine may affect the keratinocytes (specifically their proliferation, adhesion, and motility), leading to “epidermal contractility,” leading to a firming/tightening effect on the skin. DMAE also has antioxidant properties, which may contribute to its anti-aging effects.

Product/Formulation Challenge

- DMAE, a base, has historically been used as a formula pH-adjusting agent. Its pH is approximately 10. Thus, pH adjustment to the desired value appears to be sufficient.

Kinetin (N6-Furfuryladenine)

Mechanisms

Kinetin is a plant hormone. It is a powerful natural antioxidant with effects in protecting DNA and protein from oxidative damage. Even very low levels (ppm) delay the onset of changes associated with cell aging, e.g., appearance of lipofuscin, appearance of multinucleate cells, and microtubule disorganization.

Efficacy

Topical 0.1% kinetin was reported to improve several aging skin problems, such as wrinkling, poor texture, and hyperpigmentation. The 0.1% dose is well tolerated by the skin, with no significant irritation issues described.

Product/Formulation Challenge

- The limitation with kinetin is its fairly low solubility in formulation. This restricts the upper dose to approximately 0.1% for an aesthetically elegant formulation. This also impacts delivery into skin, although even from this relatively low dose, sufficient material does enter skin to provide clinical effects.

Triterpenoids

Forms

There are numerous plant-derived triterpenoid compounds and derivatives of them, with a few receiving attention in the cosmetic area, e.g., asiatic acid, ursolic acid, medacassic acid, oleanolic acid, betulinic acid, and boswellic acid. There are also naturally occurring saccharide esters of these, such as asiaticoside, which is the ester of asiatic acid.

Mechanisms

There are many reported mechanisms for triterpenoids, for example, antioxidant, anti-inflammatory, elastase inhibition, wound healing, and promotion of collagen and ceramide production. Since triterpenoids share some structural similarity to steroidal compounds such as hydrocortisone, they may also share some of the mechanistic properties and potency of such compounds (e.g., anti-inflammatory effects).

Product/Formulation Challenge

- The key issue with triterpenoids is poor solubility, which also results in limited skin delivery. Formulation in liposomes has been employed to improve both delivery and formula solubility, although the resulting increase in oil content of the formulations may negatively impact the aesthetics.

Ubiquinone (co-enzyme Q10)

Mechanism

Ubiquinone is an endogenous antioxidant present throughout the body, including the skin. The levels decrease with age. Topical ubiquinone replenishes the skin.

Efficacy

The skin care benefits of topical ubiquinone address only the antioxidant properties of this ingredient.

Product/Formulation Challenge

- Ubiquinone is yellow-orange in color. Thus, only low doses (1%) can be used in topical cosmetic skin care products to avoid aesthetic color concerns. This low dose likely limits the benefit potential of this ingredient.