DOPA FOREVER!

Our industry offers no more delightful acronym than DOPA (DihydroxyPhenyl alanine), a key step in melanin synthesis. Since skin lightening and tanning products are high on the global product development docket, and melanin is the focal point of skin coloration, knowledge of DOPA and the reactions surrounding it should be part of every formulator’s arsenal.

Why would anyone want to lighten his or her skin? Most of the world’s population has significant skin coloration. A deeply rooted social consciousness in many cultures seems to deem “lighter is better” where skin tone is concerned. A likely explanation can be found in the traditional daily lives of the different classes. The common workers labored outside all day, and were consequently darker hued than the upper class, who spent their time indoors. Thus light skin is associated with economic and social superiority.

A contemporary reference to this phenomenon occurs in Tom Wolfe’s latest novel set in the American Southeast:

“He could still pass the Brown Paper Bag Test, as they used to call it here in the Black Beacon, which meant that so long as your skin was no darker than a brown paper bag from the grocery store, you were eligible for Black Society and black debs.”

In Asian nations, the primary use of skin lighteners is to make the skin whiter, lighter and brighter. More generally, the need for skin color modification extends far beyond cosmetic appearance. There are many serious skin disorders requiring treatment. In the West, skin lighteners are most frequently applied for the treatment of melasma, freckles (lentigo aestiva) or age spots (lentigo senilis).

There are many causes of hyperpigmentation. Expectant mothers can suffer chloasma (a blotchy, brownish pigmentation), which is thus referred to as “the mask of pregnancy.” It is also a side effect of taking contraceptive pills. Cosmetics, deodorant soaps and sun exposure are also implicated as causes.

Skin color is produced by melanin, which is produced in melanocytes. Melanocytes are present in many parts of the body, including the hair and eyes. Dermal coloration originates from those present in the basal layer of the epidermis. The melanocytes contain organelles called melanosomes, which have all the necessary components for melanin production. The melanosomes are transferred in the skin to keratinocytes, where the final distribution determines the skin tone.

The basic pathway of melanin synthesis is shown in Figure 1. The reaction from Tyrosine to DOPA to Dopaquinone is catalyzed by Tyrosinase. The pathway splits into two lines, one leading to eumelanin and the other to...

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*Greek kosmetikos, skilled in adornment or decorating.
pheomelanin. These two versions of melanin create different colors, eumelanin being brown or black, pheomelanin being red or yellow. Skin lightening actives must interfere with one or more steps in the synthesis reaction sequence.

From a formulation and regulatory perspective there are two geographic regions, the United States and Everywhere Else. The actives used in lightening products are hydroquinone (in the US) or Other Stuff (Everywhere Else). This makes lightening products an interesting challenge both domestically and internationally.

Hydroquinone (Figure 2) was accidentally discovered during World War II. Tanners wearing rubber gloves developed discolored areas on their hands and forearms. A search through every chemical involved in the process uncovered the culprit-hydroquinone, an intermediary in rubber synthesis. This accidental discovery was quickly applied to the consumer market.

There were lightening actives before hydroquinone-particularly mercurial peroxygenated derivatives, not high on the list of gentle additives. Thus hydroquinone became the standard lightening product in the US, and 2% active formulations are the only legal domestic OTC products. A 1982 ruling defined a skin bleaching active as “an agent designed to bleach or otherwise lighten limited areas of hyperpigmented skin through the suppression of melanin pigment formation within skin cells.”

The only ingredient deemed safe and effective in that ruling was hydroquinone. It can also be a cosmetic ingredient. Medical use in the US can combine hydroquinone with other materials. For example, a 1974 patent on skin depigmentation indicates up to 5% hydroquinone plus 0.1% retinoic acid and 0.1% dexamethasone. A product described on the internet uses 4% hydroquinone with sunscreens (padimate O, dioxybenzone, and oxybenzone) in a vanishing cream base.

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Hydroquinone has some deleterious properties, and it is illegal in much of the world. Some of the problems encountered in South Africa were recounted by Goldenberg, when hydroquinone was used as high as 8%, and later when hydroquinone monobenzyl ether was substituted. The problem was ochronosis, areas of hyperpigmentation developing in sun-exposed skin.

The global market is thus powered by a variety of other actives, such as arbutin, magnesium ascorbyl phosphate (MAP) and kojic acid. The structures of some of these actives are shown in Figure 3. These products can be used in the United States, but not listed as actives. The formulations must avoid the specific implication of skin bleaching, so phrases such as “brightening” or “even skin tone” must be employed.

Arbutin competes with DOPA on the reaction site on tyrosinase. Kojic acid inactivates tyrosinase by chelating a necessary copper ion. MAP acts as a reducing agent, interfering with some essential oxidative reactions in the melanin synthesis pathway. Kojic acid, arbutin and MAP are all water soluble. At a presentation made at the SCC Annual Scientific Seminar, the properties of kojic dipalmitate were discussed. As an oil soluble ester, kojic dipalmitate can act as an emollient. The likely mechanism of its activity is the action of esterases in the skin slowly releasing kojic acid from the ester. The claims were made that this product had superior stability in cosmetic formulations and compatibility with organic sunscreens.

Active ingredients often occur in natural products. For example, Melfade (Pentapharm, US Distributor Centerchem) has an INCI designation of water and Bearberry Extract. Bearberry, also known as Uva Ursi, contains about 18% arbutin. The product claims to not only disrupt melanin synthesis, but to also reduce existing pigmentation.

Some skin lightening actives are provided as mixtures to enhance their functionality. Gattuline(r) Whitening (Gattefossé) contains licoïce extract, aspergilus ferment and ethoxydicycloyl. The ferment contains kojic acid, and is thus the skin lightening component. The ferment also produces lactic acid, an AHA. The licoïce acts as a counter-irritant, and the ethoxydicycloyl is a carrier which improves delivery. Vanilla derivatives are another frequently used source of tyrosinase inhibitors. A recent Chesbrough Pond's patent claims a skin lightening composition which embraces vanillin and its C1 to C30 alkyl or aryl derivatives. Another product found in cyberspace is a wildberry extract combined with titanium dioxide. In this case, the wildberry contains kojic acid. Many websites, this one included, contain a detailed description of melanogenesis. Apparently many products are marketed to persons with deep interest in biochemistry.

We have looked at a number of lightening products, ranging from the only “legal” product, hydroquinone, to some alternate materials commonly used globally. Due to the many negative features of hydroquinone, and the benefit of using formulations on a multinationa scale, formulators and marketers would do well to consider alternate actives, positioning their products carefully to not conflict with regulatory restrictions.

References: