

Cyclodextrins against Skin Aging

With age the skin's natural rejuvenation process slows down and the skin becomes drier, thinner, and less elastic [1]. Skin aging is influenced by several factors including genetics, environmental exposure (UV radiation, xenobiotics, and mechanical stress), hormonal changes and metabolic processes (generation of reactive oxygen species, sugars and aldehydes). All factors have a role in the alterations of skin structure, function and appearance [2].

There have been a lot of papers and patents published on the CD-stabilized or CD-solubilized compounds having anti-aging effect on the skin. It has been proved that complexation protects these compounds by preventing decomposition on light and heat, improving the compatibility with the other components of the cosmetic formulations, decreasing irritation, masking smell and influencing the release properties. For example, the light stability of vitamin E is improved [3], the aqueous solubility of lipids (oils, fats, and higher fatty acids) is enhanced [4]. The components of Vitamin A (retinol, retinal and retinoic acid) are both solubilized and stabilized meanwhile the skin irritation is reduced when GCD is used and even the penetration into each skin layer is increased when DIMEB is applied [5]. Retinoic acid/HPBCD had similar effect as retinoic acid itself on wrinkle scores and skin elasticity during skin treatment, meanwhile the cutaneous irritation was reduced [6]. HPBCD also improved the penetration of milk thistle extract containing flavonoids, such as sylimarine [7].

Some further examples of anti-aging compounds formulated with CDs are listed in Table 1.

Table 1: Examples of antiaging compounds formulated with CDs

Anti-aging compound	CD	Effect	Formulation	Ref.
L-ascorbic acid	BCD	combating formation of free radicals	face mask	[8]
Retinyl palmitate	BCD	increasing the thickness and elasticity of the skin	creams	[9]
Retinol	GCD	protecting skin	cream	[10]
Retinol + Ubiquinone	GCD	preventing skin aging	cosmetic formulations	[11]
Tretinoin (all trans-retinoic acid)	HPBCD	anti-wrinkle effect	topical formulation	[12]
Tocopherol acetate	GCD	suppressing the cytotoxic effect of UV irradiation	creams	[13,14]
Isoflavonoid ext.	HPBCD	inhibiting skin aging and acne	O/W cream	[15]
Saccharomyces cerevisiae extract	not specified	stimulating the formation of chondroitin sulfate, keratin sulfate, elastin and collagen	soft creams	[16]
Vitamin C, retinol, linoleic acid, rutin, etc.	CD-polypeptide copolymer	rejuvenation of skin	cosmetic formulations	[17]

Prodrug systems, such as retinal-GCD hemiacetal against skin pigmentation have been also patented [18].

Recently, Korean researchers have found a novel effect of methyl BCD (RAMEB): it proved to be a collagen-modulating agent [19]. It is well known that methyl CDs remove cholesterol from cell membrane and disrupt the lipid rafts [20]. Depletion of cholesterol abolishes the majority of caveolae [21] inhibiting caveolins, the membrane proteins having various functions especially in signaling. Caveolin-1 was found to play a role also in cell senescence [22]. One of the possible mechanisms is that Caveolin-1 acts against collagen expression in the skin. The idea of Lee et al. was to inhibit Caveolin-1 by methyl BCD and thus improving the collagen expression [19]. As the age-related reduced collagen levels result in thinning the dermis, the anti-aging techniques should focus on enhancing the skin volume by up-regulating collagen expression. Methyl BCD enhanced collagen expression especially when injected to mice intradermally twice weekly in 2.5% concentration.

Another Korean group studied the effects of cholesterol modulation on pigmentation of skin using methyl BCD [23]. Jin *et al.* reported that the methyl BCD treatment resulted in the decrease of pigmentation in human melanocyte and cultured skin. The mechanism standing behind this observation was assumed to be in relation to the inhibition of the expression of tyrosinase enzyme and microphthalmia-associated transcription factor of melanocytes, as well as triggering a cell signaling process. These results suggest that cholesterol reduction achieved by methyl BCD treatment is capable of inhibiting melanin biosynthesis by affecting tyrosinase expression and by a special cell signaling process.

Taking the safety of CDs into account (no adverse reactions, such as skin fibrosis, allergy were observed) the methyl BCD as an anti-aging agent in human skin has a great potential. On the other hand, it is a new example for the CD itself as an active agent and not as a carrier.

Fortunately, the methylated CDs are among the 11 cyclodextrin derivatives listed in the European Commission database with information on cosmetic substances and ingredients (CosIng) in addition to the parent, the acetylated, hydroxypropylated, sulfated, maltosylated, hydroxyethylated, dimaltosyl, quaternary ammonium, laurate and the polymerized cyclodextrins.

Although this large number of derivatives are accepted as cosmetic ingredient, mainly three of them are used most of the time: the parent cyclodextrins in solid formulations and for emulsion stabilization, the hydroxypropylated BCD for water solubility issues and the methylated BCD for extended release of perfume ingredients. According to our knowledge cosmetic formulation with methyl CD as active agent has not been marketed as yet.



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Amyloglucosidase, Micelle, α -Cyclodextrin, β -Glucosidase

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β -CD, γ -CD, Head-to-head configuration, Head-to-head + tail-to-head triplet, Diphenylpolyenes, Styrene

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Cyclodextrins, Lipid bilayers, Vectorization

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Aerodynamic assessment, Pulmonary delivery

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2-Hydroxypropyl- β -cyclodextrin, β -cyclodextrin, Oral administration, Prolonged plasma profile

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Polycarboxymethyl- β -cyclodextrin, Polyetherimide, Orfloxacin, Self-assemble procedure

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Benzimidazole-graft-dextran, Multifunctional cyclodextrins, Doxorubicin, Modular multifunctional drug delivery, Tumor therapy

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Kneading, Freeze-drying, Physical mixture

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Complexation with β -cyclodextrin, Improve solubility and gastrointestinal adsorption, Schistosomiasis, Drug discovery

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Co-spray drying with β CD, Isothermal microcalorimetry

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Cancer cells capture/release, Biomedical application

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Solubility, Partition, Permeation, Stability, β -cyclodextrin

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ROS-sensitivity, ROS-responsiveness, Cyclodextrin, Nanomedicine, Tumor targeting

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Post-injection precipitation, Phlebitis, Sulfobutylether- β -cyclodextrin, Rabbit ear vein, PEGylated liposomes, Drug retention

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Cholesterol accumulation, Improved liver status, Cellular models of NPC, Induced pluripotent stem cells, Transgene-free

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Freezing damage, Cryopreservation, Sperm

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Cationic polymer, Nanoparticle formation, Cytotoxicity, Transfection efficiency

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Maltooligosaccharides, Microdochium nivale, Glucose oxidase, Bread making

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Enzymic and nonenzymic browning, Food drying

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β -Cyclodextrin-acrylamide, Rheological properties, Isothermal adsorption, Aspergillus niger

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