

## **Applications of cyclodextrins in cosmetic products: A review**

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### **Synopsis**

Cyclodextrins are non-toxic cyclic polysaccharides. They form inclusion complexes with numerous organic molecules. The physical and chemical properties of the guest molecules change due to complex formation. Thus, for example, the stability of the complexed molecule against light and oxygen increases and the vapor pressure is reduced. The solubility of slightly soluble molecules increases in a cyclodextrin complex. All these and further advantages of cyclodextrins and their complexes can be used for the formulation of cosmetic products. As a result, effects are possible not realizable with common techniques.

### **INTRODUCTION**

The first reference to cyclodextrins was published in 1891 (1). Some years later Schar- dinger also observed the formation of cyclodextrins (2). At this time nothing was known about the structure of these molecules. Freudenberg continued in studying these com- pounds obtained from starch (3). He called them Schar- dinger dextrans. Further studies by him and Borchert showed the cyclic structure of Schar- dinger dextrans (Figure 1) (4,5). Beginning at that time, they were also called “cyclodextrins.” Cramer realized that these cyclodextrins were able to include neutral molecules within their cavities (6). From that time on, the interest in cyclodextrins increased. However, cyclodextrins were avail- able only in small quantities. Thus no practical applications seemed to be suitable for these molecules. However, in 1980 Saenger published a review article about cyclodex- trins (7) in which he mentioned some industrial applications. The First International Cyclodextrin Symposium organized by Szejtli took place in Budapest in 1981 (8). One year later the first cyclodextrin book written by Szejtli was published (9). Since then an increasing interest in cyclodextrins and their possible applications has existed.

Due to improvements in the production of cyclodextrins, their prices have dropped significantly during the last twenty years. As a result, more industrial applications have become possible and the increasing demand has caused a further reduction in production costs for cyclodextrins. Up to now mainly pharmaceutical applications have been de- scribed in the literature (10,11). Some further applications in analytical chemistry, food,

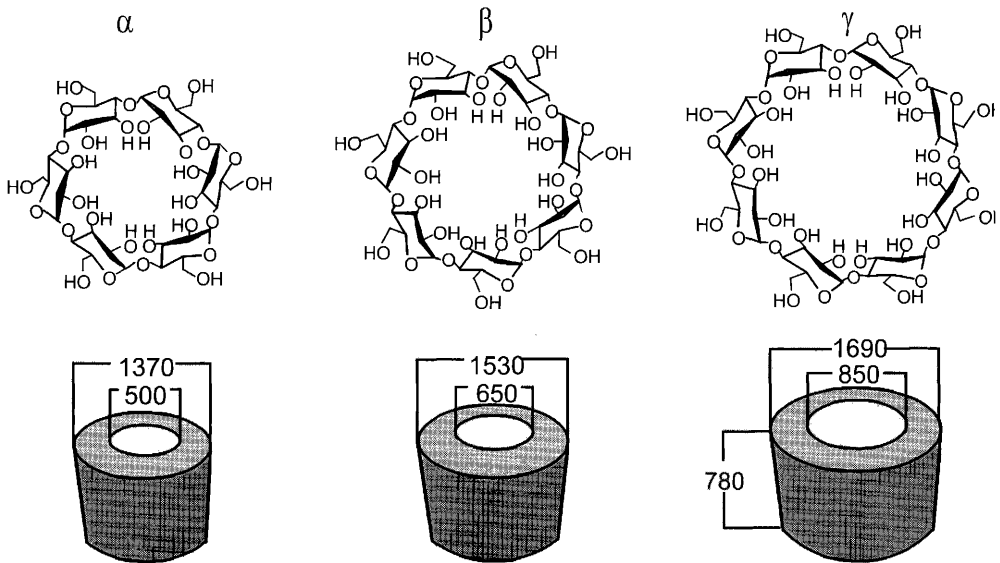


Figure 1. Structure of cyclodextrins (dimensions in pm).

and very recently textiles are known (12–14). Only a few applications of cyclodextrins in cosmetics have been published (12,13,15–17). Therefore, it seems to be worthwhile to discuss in general possible applications of cyclodextrins in cosmetic products and to give some examples of their present uses.

#### PROPERTIES OF CYCLODEXTRINS AND THEIR COMPLEXES

Cyclodextrins are formed during the enzymatic degradation of starch. They are polysaccharides built from six to eight ( $\alpha = 6$ ,  $\beta = 7$ ,  $\gamma = 8$ ) D-glucose units. The D-glucose units are covalently linked at the carbon atoms  $C_1$  and  $C_4$ . The radii of the rigid cavities vary from 0.50 to 0.85 nm. In these cavities guest molecules can be enclosed. For the complex formation between cyclodextrins and guest molecules, agreement between the size of the cavity and of the guest molecule is not essential. The complex formation takes place only if a part of the guest molecule is located inside the cavity.

Due to the complex formation, the physical and chemical properties of the enclosed guest molecules change, e.g., the vapor pressure is reduced and the solubility in water increases. The most important advantages for the use of cyclodextrins in cosmetics are:

- (1) Protection of the guest molecules against:
  - decomposition reactions induced by light or heat
  - oxidation or hydrolysis
  - chemical reactions with other organic compounds
  - loss by evaporation
- (2) Solubilization of the guest molecules in water:
  - increase of solubility
  - increase of the rate of solubilization
  - avoidance of organic solvents
  - change of viscosity

- (3) Elimination of:
  - undesired odors or tastes
  - hygroscopicity
- (4) Improvement of handling:
  - of liquid or oily substances as powders
  - increase in the stability of emulsions

In contrast to starch, cyclodextrins and their derivatives are not a nutrient medium for microorganisms. As a result, the use of preservatives in formulations can be reduced. This is a further advantage of cyclodextrins.

Detailed studies on the toxicity, mutagenicity, teratogenicity, and carcinogenicity of cyclodextrins and some of their derivatives have been performed (18). These results indicate that cyclodextrins may be harmful to the human organism only at extremely high concentrations. No indication of acute toxicity was observed during animal experiments. Since November 2000,  $\beta$ -cyclodextrin has been licensed in Germany as an additive in food (19). This had already been done in Japan and in the USA some years earlier. Dermatological studies using cyclodextrins have been reported in the literature also (20).

The price of cyclodextrins was mainly responsible for the relatively low number of practical applications in different areas. Fortunately, during the last few years prices have decreased and, therefore, further and new applications of cyclodextrins have become possible.

## EXAMPLES OF THE USE OF CYCLODEXTRINS

The number of patent applications dealing with cyclodextrins in cosmetic and pharmaceutical applications is enormous. It is not the aim of this article to cite all of them. According to the above-cited advantages for the use of cyclodextrins, some examples will be given. There will be no special differentiation among the cyclodextrin derivatives used in cosmetic formulations. Due to the extremely large number of commercially available products, this information will be far from being complete. Only as examples will some trade names of cyclodextrin-containing cosmetic products be given.

### PROTECTION OF THE GUEST MOLECULES

*Protection against light and oxidation.* Tea tree oil shows antimicrobial properties. The pure oil is stable for a month in the absence of light and oxygen. Otherwise the terpenes present in the oil react with light and oxygen in the formation of the skin irritant p-cymene. As a cyclodextrin complex, tea tree oil is stable against light and oxygen and therefore the formation of undesired compounds is prevented. The antimicrobial and anti-inflammatory properties of tea tree oil are not affected by the complex formation (21). Some commercial products are Epicutin-TT<sup>®</sup> (Chem. Laboratorium Dr. Kurt Richter GmbH) and Pিকেlex<sup>®</sup> (Regena Ney Cosmetic).

Hydroquinone is used for skin whitening. In aqueous formulations hydroquinone is stable only in a limited-pH range. Therefore stabilizers are normally used. Due to the prevention of the oxidation of hydroquinone, the cyclodextrin complexes have a greater stability. They also show a greater depigmentation than the hydroquinone itself (22). Kojic acid is another substance used as a whitening agent in cosmetic creams. Its use is

limited because kojic acid is labile when exposed to light or heat. Due to decomposition it turns to a yellowish brown. The cyclodextrin complex has an improved stability against coloring in the lapse of time. The cyclodextrin complex of kojic acid also has an enhanced skin-whitening effect (23). Peroxyacetic acid is a liquid that is handled as an aqueous solution. It forms solid complexes with  $\alpha$ - and  $\beta$ -cyclodextrin. These stable powders are easy to handle and they can be used in cosmetic formulations as skin-lightening substances. These complexes also act as mild oxidants with disinfectant properties (24).

*Protection against loss by evaporation.* Volatile compounds like perfumes (25,26) or components of them (27) are stabilized against evaporation as cyclodextrin complexes. The complexes may be used in powders or liquid formulations. Even in solid form the perfume complexes are used in perfumes. Applying these suspensions on the skin assures a long-lasting effect by slow release of the perfumes. Long-acting perfumes are marked as Vivace® (Shiseido Co.).

#### SOLUBILIZATION OF THE GUEST MOLECULES

A large number of cosmetic components are nearly insoluble in water. Only a few examples, such as vegetable oils, hydrocarbons, higher fatty acids and their esters, vitamins, hormones, antiphlogistics, and preservatives are mentioned. All these chemical substances are able to form inclusion complexes with cyclodextrins. As a result, these complexes are more soluble compared to the pure compounds. This effect can be generally used for the formulation of cosmetics (28).

Salicylic acid is used for the cleaning of the skin. Its action is mainly antibacterial and keratolytic. The solubility of the acid or its derivatives in aqueous solution is low. The complex with cyclodextrins is much more soluble. Thus, possibly irritating reactions occurring with the free acid are prevented due to better homogeneity. Complexed with cyclodextrins, its disinfectant, bacteriostatic, and keratolytic properties also increase (29). The cyclodextrin complex of salicylic acid is already commercially available (Lipo Chemicals Inc.). It is used in Bioclin Sebo Care Impure Skin Cream® (Ganassini).

In many personal care products triclosan acts as a topical antiseptic and disinfectant. It is nearly insoluble in water, moderately soluble in alkaline solutions, and quite soluble in organic solvents. The cyclodextrin complex (Lipo Chemicals Inc.) is soluble in water, giving a clear solution.

Menthol has an effect as a cooling agent in different cosmetic products. Menthol is only slightly soluble in water. To increase the solubility, alcohol is normally added. The cyclodextrin complex is freely soluble in water, giving a clear solution without the presence of alcohols (Lipo Chemicals Inc.).

In topical anti-aging formulations, retinol is used. It reduced wrinkles and supports the restoration of UV-damaged tissues. Unfortunately, UV light and oxygen initiate chemical reactions of retinol. Thus, during oxidation some peroxidic toxic intermediates are formed. Also, the solubility of retinol is low in aqueous media. Retinol forms complexes with cyclodextrins that are stable in the presence of light and oxygen. Complexes of retinol acetate and retinol palmitate with  $\beta$ -cyclodextrin are well known. Also, retinoic acid and some of its derivatives form complexes with cyclodextrins (30). Just recently the formation of complexes with  $\gamma$ -cyclodextrin have been reported (31). Retinol-

cyclodextrin complexes are used in the following products: Eucerin Vital Retinol® (Beiersdorf), Nutrients & Anti-aging Agents® (Efal), and Dexol A® (Collaborative Laboratories).

Cyclodextrins are also used to increase the solubility of substances secreted by the skin, and thus they are used in products for skin cleaning. They are able to complex and to dissolve skin fat. The formed fat complex with cyclodextrins can be easily removed from the skin. Therefore cyclodextrins, together with other ingredients, are in a product named Gesichtstonic® (Annemarie Börlind).

#### ELIMINATION OF UNDESIRE ODORS

Dihydroxyacetone is used as tanning agent. It is not stable in aqueous solution. More important is the unpleasant odor of dihydroxyacetone, which is difficult to mask by perfumes. This odor vanishes using the cyclodextrin complex. The slow release of dihydroxyacetone from the complex results in a more uniform tanning of the skin. This cyclodextrin complex is used in Ultrasun Selftan® (Ultrasun) and in Self-Action Super Tan For Face® (Estée Lauder).

Glutathione shows various physiological activities. For example, it inhibits melanin pigment formation. Thus it may be used for skin whitening and skin-improving effects. Unfortunately, glutathione generates an offensive odor upon use in cosmetic formulations. The glutathione complex with cyclodextrin is free of the odor of glutathione and has the same effect on the skin as glutathione (32).

Mercapto compounds are often used in waving lotions. Due to the presence of mercapto derivatives, an extremely unpleasant odor is generated during application. This odor is often masked in part by the addition of perfumes to the lotion. A more efficient possibility is the use of cyclodextrins. Due to complex formation with the mercapto compounds, the unpleasant odor is eliminated (33).

Chamomile extracts or oil have an antiphlogistic, bacteriostatic, and wound-healing effect. These formulations often have an intense and unpleasant odor. This odor is reduced by complexation with cyclodextrins. The anti-inflammatory activity of chamomile extracts remains unaffected (34).

Deodorants are used to control malodors formed by microbial degradation of sweat. Cyclodextrins and mixtures of cyclodextrins can be used in deodorant sticks. The cyclodextrins are able to complex perspiration malodors (35).

#### IMPROVEMENT OF HANDLING

*Liquid or oily substances as powders.* The oily  $\alpha$ -tocopherol acts as an antioxidant. It is used in many personal care products to protect the surface of the stratum corneum from damage caused by free radicals. As a cyclodextrin complex it is not soluble in water or oil. It should be used as a powder or suspended in lotions and creams (Lipo Chemicals Inc.). The formation of complexes with cyclodextrins serves to enhance the stability of tocopherol (36,37).

Octyl methoxycinnamate is used as an oil-soluble sunscreen. As a cyclodextrin complex it is also not soluble in water or oil. The complex can be used in formulations as a powder

or suspended in appropriate cream and lotion vehicles. In these formulations a slow release of octyl methoxycinnamate from the complex takes place, resulting in a long-lasting protection of the skin (Lipo Chemicals Inc.).

*Stability of emulsions.* In a simple three-component system of paraffin oil, water, and  $\beta$ -cyclodextrin, stable emulsions are formed. The formed emulsions are stable under various storage conditions. However, the origin of this stabilization effect can not be given at present (38). The apparent viscosity of these emulsions strongly depends on the cyclodextrin concentration. The stabilization effect of  $\beta$ -cyclodextrin on emulsions formed from triglyceride and water has also been reported (39).

## CONCLUSION

Cyclodextrins are already used in cosmetic products. They offer many advantages. For example, the discussed effects of the stabilization of substances, reducing their vapor pressure, and increasing their solubility cannot be easily achieved with other formulation techniques. Due to further decreases in their prices, more applications will become possible in the near future. The use of textiles with permanently fixed cyclodextrins offers new applications for cosmetic formulations (14). These textiles may act as depots for cosmetic compounds. They will be released from the cyclodextrins only in contact with the skin.

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