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ORIGINAL ARTICLE

Solubilization of ultraviolet absorbers by cyclodextrin and their potential application in cosmetics

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Abstract

Conventionally, synthetic organic ultraviolet (UV) absorbers, such as octylmethoxy cinnamate (OMC) and avobenzone, have been formulated into cosmetic sunscreens. However, because of their high skin stimulus, alternative products made from natural compounds are required. Although some botanical flavonoids and ferulic acid derived from rice bran are candidates for natural UV absorbers, because of their poor solubility, it has been difficult to formulate these natural compounds into cosmetics. In this work, we confirmed by screening tests that cyclodextrins could make an inclusion complex with the UV absorbers in aqueous solutions. We found by a phase solubility test and Job plot that hydroxypropylated-γ-cyclodextrin (HP-γ-CD) made an inclusion complex with ferulic acid in a stoichiometry of 1:2. In cosmetic applications, the formulation containing the ferulic acid/HP-γ-CD inclusion complex showed a higher sun-cut effect than that containing OMC. Notably, the ferulic acid/HP-γ-CD inclusion complex showed extraordinarily high protection values for UVA, which will be useful for preparing effective and safe sunscreen formulations.

Keywords Ferulic acid · Hydroxypropylated-γ-cyclodextrin · Phase solubility · Cosmetics · Sunscreens · Sun protection factor

Introduction

To keep our skin healthy and beautiful, protection from ultraviolet (UV) rays is very important. Basically, UV rays are divided into three types by their wavelength; UVA (400–320 nm), UVB (320–280 nm), and UVC (280–200 nm) [1]. UVC is absorbed by the ozone layer, but both UVA and UVB reach the surface of the earth and damage our skin. Because of the relatively short wavelength of UVB, it stimulates our skin strongly. Therefore, even a short irradiation time of UVB will cause sunburns. On the other hand, the stimulus of UVA is milder than that of UVB because of its longer wavelength. However, in recent years, protection from UVA has been studied intensively in the cosmetic industry, because UVA can penetrate our skins deeper than UVB and can cause accumulated damage to our skin and bring about photoaging, such as wrinkling and freckling [2]. Synthetic organic UV absorbers and inorganic UV scattering agents are formulated into basic cosmetic sunscreens. Although synthetic UV absorbers, such as octylmethoxy cinnamate (OMC) have a high sun-cut effect and transparency, because of their strong stimulus and low photostability [3], some manufacturers avoid formulating them into sunscreens. On the other hand, UV scattering agents, such as TiO_2 and ZnO, show relatively high photostability compared with UV absorbers. Conventionally, to reduce their white color, nano-sized TiO_2 and ZnO have been formulated into sunscreen products. However, some concerns about the harm to health of nanoparticles via percutaneous absorption have been reported [4]. Using natural ingredients is now a popular trend in the cosmetic market. Ferulic acid (FA) derived from rice bran [5] and some kinds of botanical flavonoids [6] have been reported as candidates for natural UV absorbers. However, because of their poor solubility, they have not been formulated into cosmetic products. Although, recently, the inclusion complexes of FA and rutin with several kinds of cyclodextrin (CD) in aqueous solutions were reported [7–10], there are only few reports concerning about the usage of inclusion complexes with various UV absorbers in cosmetic field. In this work, we confirmed which kinds of CDs, such as α-CD, β-CD, γ-CD, and modified CD,

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could make inclusion complexes with different organic UV absorbers and investigated the properties of these inclusion complexes by UV–Vis spectroscopy, phase solubility studies, and methods of continuous variation. In addition, the application of these inclusion complexes to cosmetics is also reported.

Materials and methods

Materials and chemicals

trans-Ferulic acid (*t*FA) was purchased from TOKYO CHEMICAL INDUSTRY CO., LTD. (Japan). Rutin was purchased from ALPS PHARMACEUTICAL IND. CO., LTD. (Japan). OMC, ethtlhexyl triazone, and bis-ethylhexyloxyphenol methoxyphenyl triazone were obtained from BASF (Germany). Homosalate, avobenzone, octcrylene, and ethtlhexyl salicylate were obtained from DSM (The Netherlands). Ethylhexyl dimethyl PABA and benzophenone-3 were obtained from ASHLAND (USA). α-CD, methylated-β-cyclodextrin (Me-β-CD), hydroxypropylated-β-cyclodextrin (HP-β-CD), γ-CD, and hydroxypropylated-γ-cyclodextrin (HP-γ-CD) were purchased from NIHON SHOKUHIN KAKO CO., LTD (Japan).

Screening test

The screening test was conducted as follows: 15 mg of each organic UV absorber was added to 3 mL of 10 wt% solutions of α-CD, Me-β-CD, HP-β-CD, γ-CD, and HP-γ-CD. The test tubes were then shaken in a water bath for 72 h at 25 °C or for 8 h at 75 °C. These solutions were assessed to see whether the UV absorbers had dissolved.

UV–Vis spectroscopy

The UV–Vis absorption spectra were recorded on a V-730 spectrophotometer (JASCO, Japan) using a 1 cm quartz cuvette. Each inclusion complex sample was dissolved in water at 25 °C.

Phase solubility study

We referred to the method of Higuchi and Connors [11]; which is that the excess amounts of *t*FA were added to 3 mL solutions of α-CD, Me-β-CD, HP-β-CD, and HP-γ-CD with concentrations ranging from 0 to 16 mM, the test tubes were shaken in a water bath for 72 h at 25 °C, after that, the suspensions were filtered through 0.45 μm membrane filters to eliminate undissolved *t*FA, the concentrations of *t*FA in the filtrates were determined by HPLC using a CAPCELL PAK C18 column (75 mm × 4.6 mm i.d., Japan), a sample volume of 10 μL was injected into the HPLC column, and *t*FA was eluted with acetonitrile/water/acetic acid (19.00:79.38:1.62) at a flow rate of 1.0 mL/min in an isocratic program for 5 min. The absorbance of the eluate was monitored continuously at 313 nm.

The methods of continuous variation

The methods of continuous variation were conducted according to a Job plot [12]. Aqueous solutions (50 mM) of the total *t*FA and CDs (α-CD and HP-γ-CD) were prepared. The molar fractions [*t*FA]/([*t*FA] + [CD]) were varied from 0 to 1. The samples were shaken in a water bath for 72 h at 25 °C and filtered through 0.45 μm membrane filters to eliminate undissolved *t*FA. The UV spectra were recorded on a V-730 spectrophotometer (JASCO, Japan) using 1 cm quartz cuvette, and ΔA was plotted to create a Job plot. The absorbance difference $\Delta A = A - A_0$ was determined by measuring the absorbance of *t*FA with (A) and without (A_0) cyclodextrins at λ_{max}.

Sun protection factor (SPF) and ultraviolet A protection factor (UVA-PF) measurement of oil in water (O/W) sunscreens

SPF and UVA-PF measurements of the *t*FA/CDs inclusion complexes were performed as follows: first, samples of the O/W sunscreens were prepared by the predetermined formulations shown in Table 1. The sample sunscreen was then applied to a glass plate (approximately 2.4 mg/cm^2) and spread evenly by finger. After drying for 15 min at room temperature, the SPF and UVA-PF values were measured on a Model SPF-290AS Automated UV Transmittance/SPF Analyzer (SOLAR LIGHT, USA).

Results and discussion

Screening test

Figure 1 shows molecular structures of candidates of natural UV absorbers and OMC. Moreover, Table 2 shows that *t*FA, alloxazine, and rutin could make inclusion complexes with some of the CD solutions (*t*FA with α, Me-β, HP-β, HP-γ; alloxazine with Me-β, HP-β, HP-γ; and rutin with Me-β, HP-β). These results also indicated that the process of making the inclusion complex was greatly affected by temperature. For example, rutin dissolved in Me-β and HP-β-CD solutions at 75 °C, whereas it did not form any inclusion complexes with CDs at 25 °C.

Table 1 Formulations of O/W emulsions for SPF and UVA-PF analysis

Phase	Ingredient	Test 1 (w/w%)	Test 2 (w/w%)	Test 3 (w/w%)	Test 4 (w/w%)	Test 5 (w/w%)
A	De-ionized water	34.14	38.14	33.14	38.14	33.14
A	*trans*-Ferulic acid	–	1.00	–	–	–
A	HP-γ-cyclodextrin	5.00	–	–	–	–
A	FA/HP-γ-cyclodextrin inclusion complex FA/HP-γ-CD = 1.0/5.0	–	–	6.00	–	–
A	1,3-Butylene glycol	1.99	1.99	1.99	1.99	1.99
A	Preservative	0.30	0.30	0.30	0.30	0.30
B	60% surface treated TiO_2 BG paste	28.57	28.57	28.57	28.57	28.57
B	Pentylene glycol	1.00	1.00	1.00	1.00	1.00
B	1,2-Hexandiol	0.75	0.75	0.75	0.75	0.75
B	Isopentyldiol	3.25	3.25	3.25	3.25	3.25
C	Squalane	20.00	20.00	20.00	20.00	20.00
C	Octylmethoxy cinnamate	–	–	–	1.00	6.00
D	Cellulose beads powder	5.00	5.00	5.00	5.00	5.00
Total		100.00	100.00	100.00	100.00	100.00

Methods

1. Mixed Phase A and B. And then Phase C was added into the mixture gradually to obtain homogenous emulsions
2. Added Phase D into the mixture and mixed well

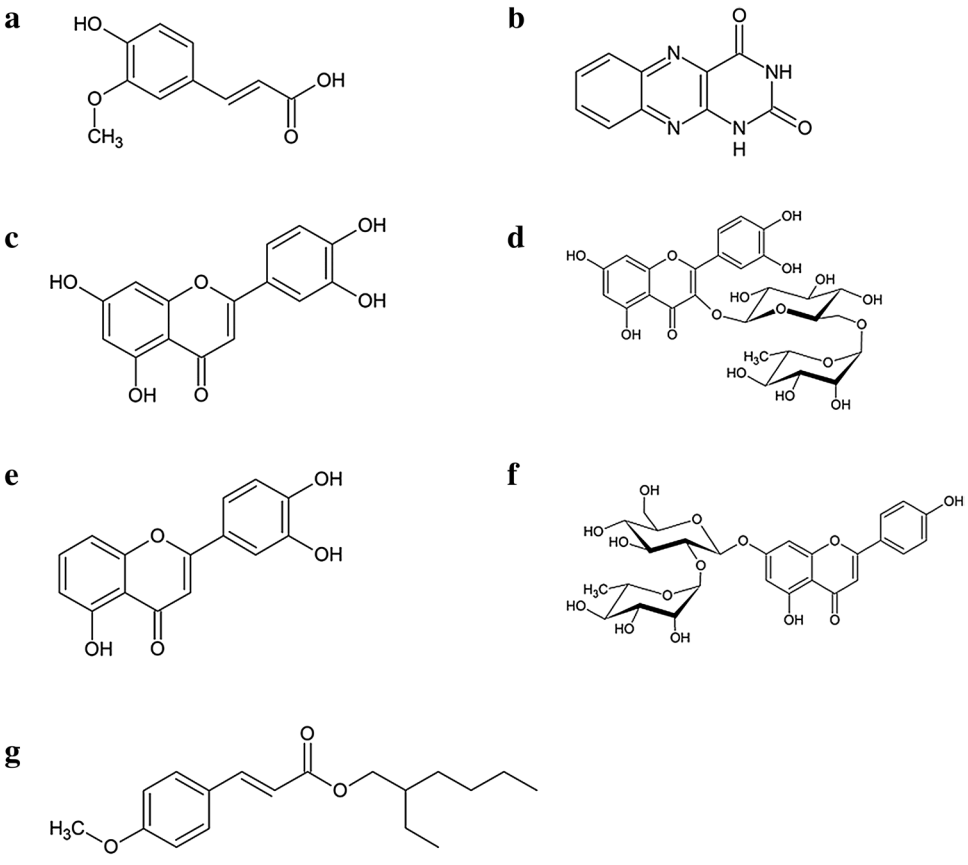


Fig. 1 The molecular structures of candidates for natural UV absorbers and OMC. **a** *trans*-Ferulic acid, **b** alloxazine, **c** luteolin, **d** rutin, **e** apigenin, **f** rhoifolin and **g** OMC

Table 2 The results of the screening test of the solubility of the UV absorbers by temperature and type of CD

	25 °C					75 °C				
	α-CD	Me-β-CD	HP-β-CD	γ-CD	HP-γ-CD	α-CD	Me-β-CD	HP-β-CD	γ-CD	HP-γ-CD
Natural										
trans-Ferulic acid	O	O	O	X	O	O	O	O	X	O
Alloxazine	X	O	O	X	X	X	O	O	X	O
Luteolin	X	X	X	X	X	X	X	X	X	X
Rutin	X	X	X	X	X	X	O	O	X	X
Apigenin	X	X	X	X	X	X	X	X	X	X
Rhoifolin	X	X	X	X	X	X	X	X	X	X
Synthetic										
Octyl methoxycinnamate	X	X	X	X	X	X	X	X	X	X
Homosalate	X	X	X	X	X	X	X	X	X	X
Avobenzone	X	X	X	X	X	X	X	X	X	X
Octocrylene	X	X	X	X	X	X	O	X	X	X
bis-Ethylhexyloxyphenol methoxyphenyl triazine	X	X	X	X	X	X	X	X	X	X
Ethylhexyl dimethyl PABA	X	X	X	X	X	X	X	X	X	X
Benzophenone-3	X	X	X	X	X	X	O	X	X	X
Ethylhexyl salicylate	X	X	X	X	X	X	X	X	X	X
Ethylhexyl triazone	X	X	X	X	X	X	X	X	X	X

O: dissolved; X: precipitated

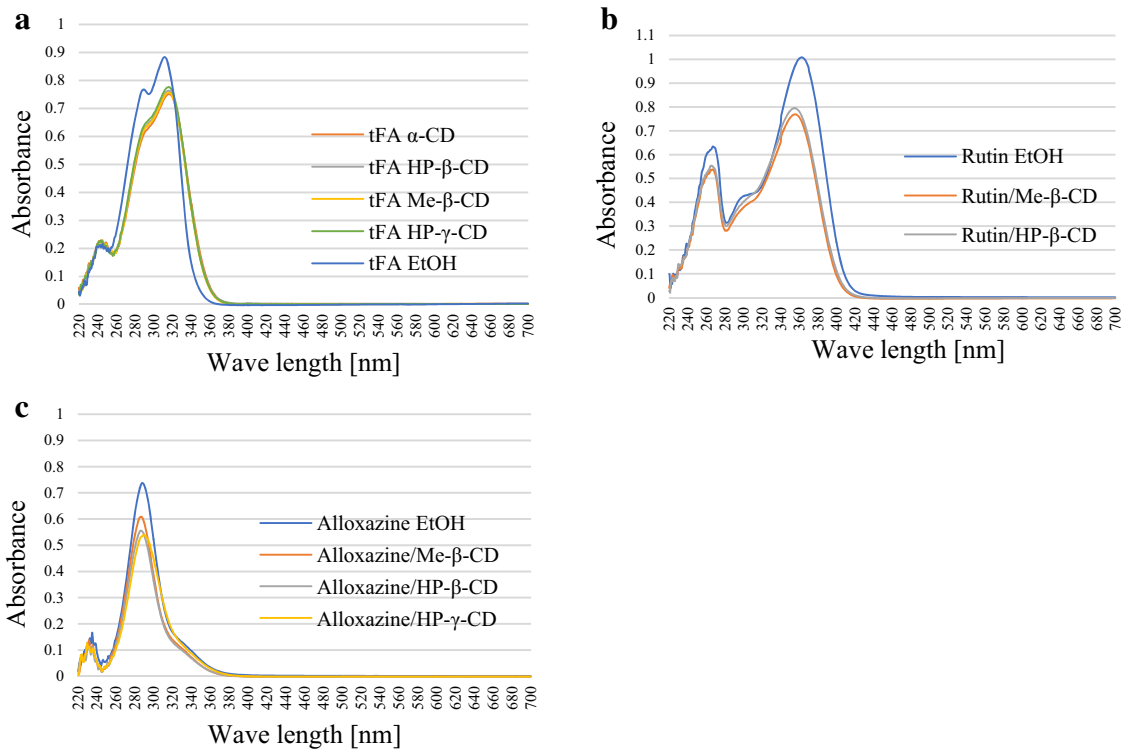


Fig. 2 UV–Vis absorption spectra of *t*FA (**a**), rutin (**b**), and alloxazine (**c**) upon complexation with CDs. Solutions of each sample (0.05 mM) were scanned at 25 °C to obtain these spectra

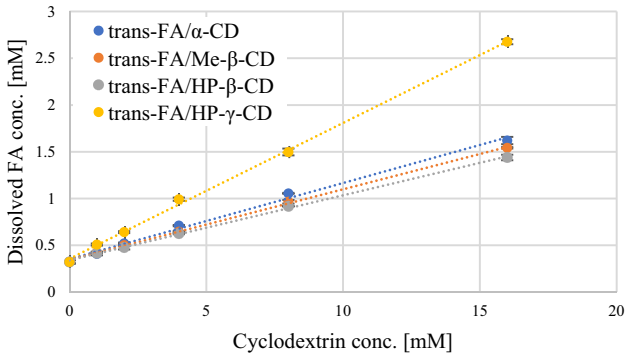


Fig. 3 Phase-solubility diagrams of the inclusion complexes between *t*FA and various CDs

Table 3 The stability constants of inclusion complexes of *t*FA and various CDs

	trans-FA/α-CD	*trans*-FA/Me-β-CD	*trans*-FA/HP-β-CD	*trans*-FA/HP-γ-CD
K_s (M^{-1})	250.0	238.0	218.5	477.5

UV–Vis spectroscopy

As shown in Fig. 2, upon complexation with the CDs, a bathochromic shift of *t*FA and a hypsochromic shift of rutin were detected, whereas no shifts were observed in the spectra of alloxazine. The absorbance maximum of FA was slightly shifted, from 312 to 316 nm, upon formation of an inclusion complex. Some researchers have reported that these shifts in the UV–Vis spectra are induced by interactions between the guest compound and host CD. According to Wang et al. [13], a partial shielding of the chromophore electrons derived from a π–π^* transition of the double bond of FA might be the cause of the bathochromic shift of FA/HP-β-CD. Furthermore, because of this bathochromic shift of the *t*FA/CD inclusion complexes, the UV absorption abilities between 320 and 370 nm were greatly increased. This property might be useful for preparing effective cosmetic sunscreens, because UV rays between 320 and 400 nm (UVA) cause wrinkling and aging.

Phase-solubility study

Phase-solubility analysis of *t*FA/CD was carried out in aqueous solutions at 25 °C using four kinds of CD, namely, α-CD, Me-β-CD, HP-β-CD, and HP-γ-CD. Figure 3 shows the phase-solubility diagrams of these *t*FA/CDs inclusion complexes. According to Higuchi and Connors [11], all diagrams were categorized as A_L type diagrams (i.e., linear increases in *t*FA solubility with increasing CD concentrations). As shown in Table 3, the stability constants (K_s) of *t*FA/α-CD, *t*FA/Me-β-CD, and *t*FA/HP-β-CD were calculated to be 250.0, 238.0, and 218.5 M^{-1}, respectively, whereas for the *t*FA/HP-γ-CD inclusion complex, it was calculated to be 477.5 M^{-1}. Furthermore, the 16 mM solutions of α-CD, Me-β-CD, HP-β-CD, and HP-γ-CD could dissolve 5.0-, 4.8-, 4.5-, and 8.3-fold, respectively, higher amounts of *t*FA than a solution without any CD. These results suggested that the stoichiometry of the *t*FA/HP-γ-CD inclusion complex was 2:1.

The methods of continuous variation

The Job method, known as a continuous variation method, is one of the best methods to recognize the stoichiometry of host–guest inclusion complexes (i.e., the ratio of guest and host is 1:2 if R = 0.33; 1:1 if R = 0.5; 2:1 if R = 0.67). Figure 4 shows the Job plots for *t*FA/α-CD (a) and *t*FA/HP-γ-CD (b). In Fig. 4a, the inflection point was detected close to R = 0.5. This result suggested that the *t*FA/α-CD

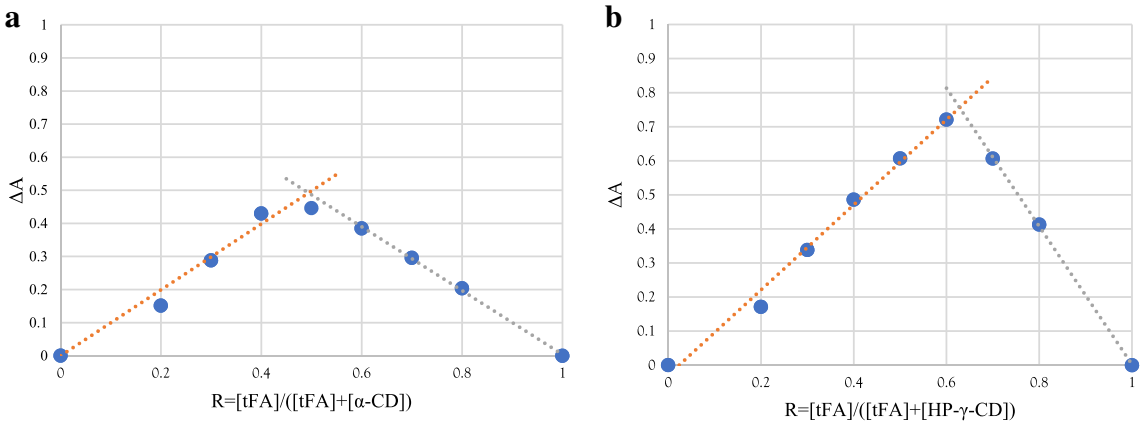
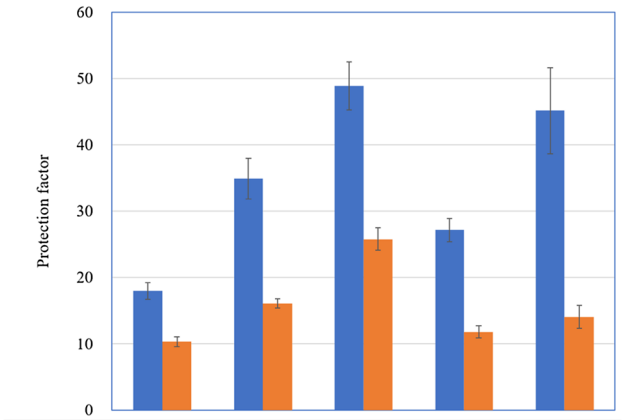


Fig. 4 Job plots of **a** *t*FA/α-CD and **b** *t*FA/HP-γ-CD inclusion complexes



	TEST1 (HP-γ-CD 5%)	TEST2 (tFA 1%)	TEST3 (tFA/HP-γ-CD = 1.0/5.0 6%)	TEST4 (OMC 1%)	TEST5 (OMC 6%)
SPF	17.98	34.90	48.91	27.17	45.16
UVA PF	10.32	16.11	25.80	11.80	14.03

Fig. 5 SPF and UVA-PF values of each O/W sunscreen

inclusion complex existed in a 1:1 stoichiometry in aqueous solution. On the other hand, in Fig. 4b, the inflection point of the *t*FA/HP-γ-CD inclusion complex appeared at around R = 0.67. This result indicated that the *t*FA could make an inclusion complex with HP-γ-CD in a stoichiometric ratio of 2:1; that is, this supported the result of phase-solubility study. These results suggested that making *t*FA/HP-γ-CD inclusion complex in a 2:1 stoichiometry could stabilize twice higher amount of *t*FA in HP-γ-CD solution, compared with using other CDs.

Applications for cosmetics

Figure 5 shows the results of the SPF and UVA-PF analysis of each sunscreen emulsion. TEST 3 in Table 1 showed the highest SPF and UVA-PF values among the five kinds of sample sunscreens. In case of comparing TEST 2–3, sample sunscreen containing *t*FA/HP-γ-CD inclusion complex (TEST3) showed higher SPF and UVA-PF values than that containing *t*FA alone (TEST2). It is highly probable that this result stems from the increase in the solubility of *t*FA in water solution. In addition, the SPF and UVA-PF values in TEST 3 showed 1.4- and 1.6-fold higher values, respectively, than in TEST 2. This result indicated that the UVA-PF value of the sample sunscreen was more strongly affected than the SPF value by making an inclusion complex. The measurement results suggested that the bathochromic shift of the *t*FA/CD inclusion complexes induced the improvement of UVA-PF value. From the above results, it is promising that the *t*FA/CD inclusion complex could be applied to cosmetic sunscreens. Moreover, since FA has been reported as an antioxidant protection product [14] and an antitumor activity product [15], cosmetics containing *t*FA/CD inclusion complex could be significantly effective for keeping our skin health and beauty.

Conclusions

The screening test revealed that some CDs made inclusion complexes with different kinds of natural UV absorbers. In particular, *t*FA was dissolved in α, Me-β, HP-β, and HP-γ-CD aqueous solutions at 25 °C, and its UVA absorption ability was improved by making an inclusion complex with the CDs. In addition, the phase-solubility analysis and Job plot indicated that HP-γ-CD made an inclusion complex with *t*FA in a molecular ratio of 1:2. However, further studies using 1D or 2D NMR spectroscopies will be needed to clarify the precise structure of the inclusion complex of *t*FA/HP-γ-CD in aqueous solution.

These above results indicated that making inclusion complex with HP-γ-CD could dramatically improve the water solubility of *t*FA. Regarding applications in cosmetics, we succeeded to prepare very high effective sunscreens using *t*FA/HP-γ-CD inclusion complex. The O/W sunscreen containing the *t*FA/HP-γ-CD inclusion complex showed much higher SPF values than that containing OMC. In recent year, due to the safety, healthy and ecological problems, natural cosmetics without using any synthetic ingredients are being required by consumers. Therefore, this result will make a great contribution to the development of natural cosmetic field.

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