J Incl Phenom Macrocycl Chem (2007) 57:109–112
DOI 10.1007/s10847-006-9212-0

ORIGINAL ARTICLE

Cyclodextrins as cosmetic delivery systems

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Received: 15 May 2006 / Accepted: 20 October 2006 / Published online: 18 January 2007
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Abstract Aim of this work was the study of ferulic acid/cyclodextrin (CD) association complexes. Ferulic acid (FA) is a compound well-known as antioxidant and photoprotective agent (approved in Japan as sunscreen). Notwithstanding this, it is poorly suited for cosmetic applications because it undergoes functional and organoleptic modifications, when it is exposed to air, UV-light and heat. For this reason we prepared a set of FA/CD complexes with the aim to improve its physico-chemical stability. The inclusion complexes were characterized by differential scanning calorimetry (DSC), X-ray diffraction (XRD), and nuclear magnetic resonance (^{1}H-NMR). The FA/α-CD complex showed the most promising properties (high association constant, high degree of photostability, slower FA release) as sunscreen delivery system.

Keywords CDs inclusion complexes · Ferulic acid · Photostability · Radical scavenging activity · Release

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Introduction

In the formulation of cosmetic products [1], active ingredients and a variety of other compounds give to the products their physical form and may control the delivery of the active ingredient(s). The cosmetic industry is constantly looking for new and effective products endowed with a satisfactory biological activity and an efficient delivery on the skin. In this context, several technological advances have been made in the development of new formulations for cosmetic delivery. These new technologies control the rate and target of delivery and the duration of activity.

The cosmetic delivery systems can be divided into three classes: vesicular (liposomes and niosomes), molecular (cyclodextrins), and particulate (microcapsules and matrix particles) [2].

Aim of the study was to improve the physico-chemical stability of the well-known phenolic compound ferulic acid (FA) [3–7] using different cyclodextrins (α-, β-, γ-CD) at the light of its possible use as sunscreen. FA is a polyphenolic derivative with interesting sunscreen properties but it is poorly suited for cosmetic use since it undergoes degradation when exposed to light, air and heat [3].

In this paper, we report the results relative to different FA/CD inclusion complexes, with particular emphasis on the FA/α-CD inclusion complex, since in a previous thermodynamic study [8] it has been shown to possess a high degree of stability. In addition, we have tested the release and the Oxygen Radical Antioxidant Capacity (ORAC assay) of this promising inclusion complex in respect to free FA.

Experimental section

All complexes were prepared by mixing at various molar ratios FA and CDs according to the co-precipitation method [9]. We used α-, β-, Hp-β-, γ-, Hp-γ-cyclodextrins and the inclusion complexes were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) and NMR analyses. The inclusion percentage of FA was determined by HPLC. FA/α-CD complex stoichiometry and its association constant were determined by ^{1}H-NMR. The photostability evaluation was performed on all complexes in comparison to free FA. FA/CDs complexes were tested in a non-ionic oil-in-water (O/W) emulsions irradiated at 10 MED (Minimal Erithemal Dose, UVB, 300 mJ/cm^2) and analysed by HPLC before and after irradiation. The sunscreen release was studied using the Strainer cell model. Delivery tests were performed on FA/α-CD complex in a non-ionic O/W emulsion. Quantitation has been made by HPLC.

The radical scavenging activity of the FA/α-CD complex was evaluated by the ORAC assay in comparison to free FA and α-CD.

Results and discussion

FA/Hp-γ-CD complex showed the highest degree of inclusion (18%). The inclusion order was: FA/Hp-γ-CD > FA/α-CD > FA/γ-CD > FA/Hp-β-CD > FA/β-CD.

^{1}H-NMR analyses demonstrated that in all the CDs complexes, FA was embedded inside the cavity of the host [10]. Anyway, in the case of the FA/α-CD inclusion complex there was a peculiar ^{1}H-NMR behaviour. In fact, while the inclusion of FA in the other CDs led to marked changes in the chemical shift of the vinyl group protons of FA, these signals were not affected when FA was included in α-CD. In this case, a significant change was observed in the chemical shift of the proton f (Fig. 1 and Tables 1, 2) of FA and of the proton H4 in the CD molecule, thus to suggest a different interaction of FA with the protons of the α-CD cavity in respect to that of other sets of cyclodextrins (β, γ), where, as demonstrated by us, the hydroxyl-, methoxyl- and carboxyl- groups are projected outside [10].

An ^{1}H-NMR study was performed to define the stoichiometry and the association constant of this complex [11]. The stoichiometry was investigated at 298 K at pH 4: the proton spectra exhibited only one set of signals, whose chemical shifts were significantly different from those of FA and α-CD. This indicates that the FA and α-CD association/dissociation equilibrium is more rapid than the ^{1}H-NMR time-scale. Hence the stoichiometry of the complex can be calculated by the Jobs' continuous variation analysis [12]. At pH 4, maximal change in chemical shift is obtained at an r value of 0.5 (Fig. 2); $r = m/(m + n)$, m and n = proportions of FA, and α-CD in the complex. This indicates a 1:1 stoichiometry, (see the profile of the plot of $r\Delta\delta$ of the H(f)-hydrogen versus the molar fraction of FA, Fig. 2).

From the data fitting (Fig. 3) resulting from ^{1}H-NMR titration experiments, we calculated a $K_{1:1}$ of 1162 ± 139 M^{-1}, of the same order of magnitude of the inclusion complex between Eugenol (a phenol structurally-related to FA) and α-CD [13].

The FA/α-CD complex formulated in O/W emulsion showed the best photostability after irradiation at 10 MED, in respect to the emulsions containing the other CDs. By contrast, after irradiation of the emulsion containing free FA, we observed in the HPLC chromatogram a sharp peak due to the formation of the cis-FA isomer.

In the Strainer cell test, a slower FA release was observed from the FA/a-CD complex: 20% FA/α-CD vs 50% for FA alone.

Finally in physiomimetic conditions (phosphate buffer solution, pH 7.4) the complex (5–20 μM) showed an antioxidant activity significantly lower than that of free FA (approximately 15%, ORAC assay).

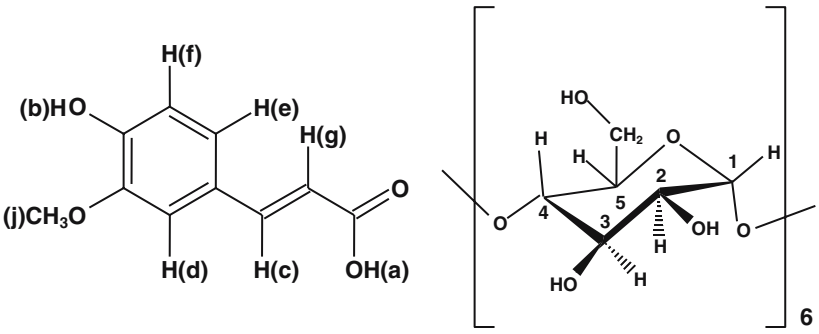

Fig. 1 Ferulic acid and α-Cyclodextrin formulae and numbering

Table 1 ^{1}H-NMR chemical shifts of the protons of ferulic acid free or complexed with α-CD in D_2O

	δ free (ppm) in D_2O	δ bound (ppm) in D_2O	$\Delta\delta = \delta$ bound-δfree (ppm)
H(f)	6.950	7.064	0.114

Table 2 ^{1}H-NMR chemical shifts of the protons of α-CD free or complexed with ferulic acid in D_2O

	δ free (ppm) in D_2O	δ bound (ppm) in D_2O	$\Delta\delta = \delta$ bound-δfree (ppm)
H4	3.530	3.613	0.083

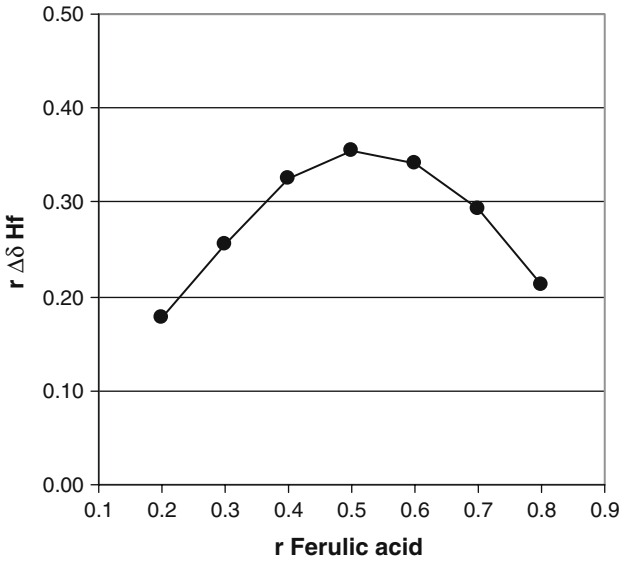

Fig. 2 Job plot of proton H(f) at pH 4

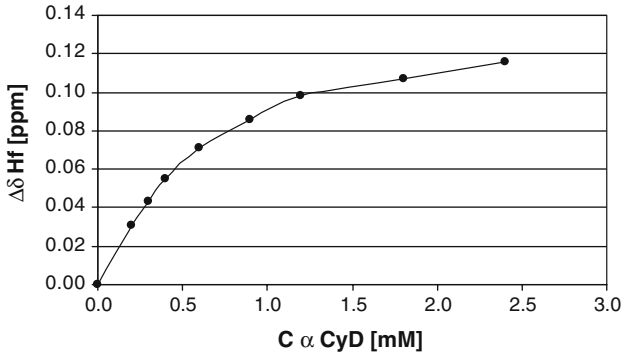

Fig. 3 Graphical data fitting for the H(f) proton of FA

The deep embedding of FA inside the cavity makes the phenol group, responsible for the antioxidant activity, less close to the wider rim of α-CD and less able to quench the free radicals promoted by the radical initiator 2,2′-azobis-(2-amidinopropane)-dihydrochloride (AAPH). This results in a decrease in the antioxidant activity of FA against peroxyl-radicals.

Conclusions

In conclusion, the results of this study evidence that among the different FA/CD inclusion complexes, the FA/α-CD complex shows a 1:1 stoichiometry and an high association constant. This complex exhibits the best photostability: no degradation products are present in the HPLC chromatogram after irradiation. In addition, it possesses a slower release capacity of FA in respect to the free compound, and a lower degree of antioxidant potency. All these findings point to an FA/α-CD complex endowed with a strong UV-light stability, to demonstrate an effective intervention of α-CD as a reservoir/delivery system for cosmetic purposes.

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