Eur Food Res Technol (2008) 227:1001–1007
DOI 10.1007/s00217-007-0813-7

ORIGINAL PAPER

Inclusion interactions and molecular microcapsule of *Salvia sclarea* L. essential oil with β-cyclodextrin derivatives

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Received: 11 June 2007 / Accepted: 13 December 2007 / Published online: 9 January 2008

Abstract The inclusion interactions of β-cyclodextrin (β-CD), heptakis (2,6-di-methyl)-β-CD (DM-β-CD), mono[2-*O*-(2-hydroxyethyl)]-β-CD (2-HE-β-CD), and mono[2-*O*-(2-hydro-xypropyl)]-β-CD (2-HP-β-CD) with *Salvia sclarea* L. essential oil (SEO) were investigated by spectrofluorimetry, and the various factors affecting the inclusion process were examined in detail. At the same time, the formation constants at different temperatures and the thermodynamic parameters (ΔH, ΔS and ΔG) were calculated. The molecular microcapsule of SEO with β-CD was prepared by the method of saturated aqueous solution, and the stability of the microcapsule was determined. The results suggest that the stoichiometry of the SEO–CDs inclusion complexes was 1:1 (molar ratio), the formation constants of CDs with SEO decreased with the increasing of temperature, and the order that the capability associated with SEO was β-CD > DM-β-CD > 2-HE-β-CD > 2-HP-β-CD. The thermodynamic measurements showed that the inclusion process was an exothermic and enthalpy-driven process accompanied with a negative entropic contribution, and Van der Waals force plays an importance role in the process. In addition, the content of SEO in the microcapsule was 0.14 g/g and its stabilization was obviously improved.

Keywords *Salvia sclarea* L. essential oil · β-Cyclodextrin derivatives · Molecular microcapsule · Thermal stabilization

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Introduction

Cyclodextrins (CDs) are cyclic (α-1,4) linked oligosaccharides and β-cyclodextrin (β-CD) consists of 7α-D-glucopyranose molecules. The exterior side of CDs is hydrophilic due to the outward hydroxyl groups, while the interior cavity is hydrophobic, which can be a host to include many guest molecules of appropriate dimensions and properties to form inclusion complexes selectively. CDs are known to affect the spectral and chemical properties of some guests significantly and to increase the solubility, stability or bioavailability [1–2]. Furthermore, CDs can be used to separation of enantiomers in the essential oil, aroma and flavour fields as chiral selectors [3–4]. Thus, CDs had been widely used in pharmaceutical industry [5], foodstuff [6–7], chemistry [8–9] and agriculture [10–11].

Salvia sclarea L. (*S. sclarea*) [12–14] is a xerophytic biennial plant belonging to the family *Lamiaceae*. It is typical of the European Mediterranean basin and of Africa up to the Atlantic Ocean. It is widely cultivated for extractive purposes in France, Bulgaria, Russia, USA and China. The whole plant, mostly the inflorescences, possesses a very strong aromatic scent and the essential oil, characterized by a fresh floral and herbaceous odor. The essential oil has an economic value for the flavor and fragrance industries, where it is used as flavoring agent, in food and liquor preparations, in perfumery formulations and for cosmetic purposes [15–16]. Furthermore, the study showed that the essential oil is effective in decreasing the severity of menstrual cramps [17], and has antifungal activity [18–19]. However, *S. sclarea* essential oil (SEO) is labile for light, heat and oxygen, and insoluble in aqueous media. Its application is restricted within narrow fields. In order to expand the application fields of the representative

essential oil in food, medication and cosmetic industries, it is very necessary to study the inclusion interactions and molecular microcapsule of CDs with SEO [20–21].

Spectrofluorimetry has been widely used in the determination of the inclusion interactions of the guest with CDs [22–26], because it is highly sensitive, selective, easily operated and economic. The enhancement of the fluorescence intensity of essential oil due to its complexation with CDs might be very useful from an analytical point of view. To the best of our knowledge, the inclusion interactions of CDs with *S. sclarea* essential oil in the aqueous solution has not been reported. Therefore, in the present study, the host–guest complexation of *S. sclarea* essential oil with β-CD, heptakis (2,6-di-methyl)-β-CD (DM-β-CD), mono[2-*O*-(2-hydroxyethyl)]-β-CD (2-HE-β-CD), and mono[2-*O*-(2-hydro- xypropyl)]-β-CD (2-HP-β-CD) was investigated by using fluorescence spectroscopy. The stoichiometry and formation constants of the CDs–SEO complex were studied and their thermodynamic parameters were obtained. Furthermore, the molecular microcapsule of SEO with β-CD was prepared and the stabilization of essential oil in the microcapsule was determined.

Materials and methods

Materials

Salvia sclarea L. essential oil (SEO) was obtained from the Hengcheng Natural Flavor Factory (Ji'an, Jiangxi Province, China), containing up to 60% linalyl acetate. β-CD was purchased from Tianjin Chemical Factory (Tianjin, China). DM-β-CD, 2-HP-β-CD, and 2-HE-β-CD were purchased from Shandong Xinda Chemical Factory (Zibo, Shandong Province, China). Petroleum ether (60–90 °C), anhydrous ethanol, sodium hydroxide, sodium phosphate, sodium dihydrogen phosphate and sodium dibasic phosphate were purchased from Beijing Chemical Co. Ltd. (Beijing, China). Buffer solutions used for pH values in the range of 2.0–9.0 were prepared by mixing 0.1 mol/l sodium phosphate and 0.1 mol/l phosphoric acid solutions and by mixing 0.1 mol/l sodium dibasic phosphate and 0.1 mol/l sodium hydroxide for pH values in the range of 10.0–12.0, respectively. All reagents were of analytical reagent grade or much better. Doubly distilled water was used throughout.

All the fluorescence measurements were performed with a model Lengguang 970CRT spectrofluorimeter (Shanghai Precision and Scientific Instrument Co. Ltd., Shanghai, China). A Unico UV-2102 spectrophotometer (Shanghai Unico Co. Ltd., Shanghai, China) with matched 10-mm quartz cells was used to measure the absorbance and spectra. A model S-25 pH meter (Shanghai HongYi Instrumentation Co. Ltd) was used to measure pH values. A thermostatic shaker, model HZS-H (Haerbin Huaneng Company, Haerbin, China) was used to perform all inclusion procedures.

Determination of the equilibrium constants (K) and the thermodynamic parameters of the inclusion reactions of CDs with SEO

The 0, 1, 2, 3, 4, 5 and 6 ml of 0.01 mol/l β-CD solution (or 0.02 mol/l β-CD derivatives solutions) were added to each of seven 10 ml volumetric flasks containing 1 ml of 1.0×10^{-7} mol/l SEO solution, respectively. The mixed solution was diluted to the mark with phosphate buffer solution (pH 7.0), shaken mechanically. The experimental temperature was changed gradually from 25 to 45 °C. The spectra and fluorescence intensities were measured at intervals.

Preparation of molecular microcapsule of SEO in β-CD

The molecular microcapsules of SEO in β-CD were prepared according to following process: SEO was dispersed in 250 ml of β-CD aqueous solution in molar ratio of 1:1. The solution was shaken mechanically in a thermostatic shaker at 140 rpm and 25 °C for 3 h, and then kept at 4 °C in a refrigerator for 12 h. The solution was filtered and the precipitate was washed twice by petroleum ether to clear SEO on the surfaces of β-CD. The precipitate was air-dried at 40 °C for about 4 h until the weight keeps constant and then stored in a desiccator.

Determination of SEO in the microcapsule

A 20–30 mg of the microcapsules sample and 30 ml of ethanol were added to a 50 ml stoppered conical flask bathed in an ultrasonic wave rinser. SEO was extracted by ethanol from the microcapsules for 10 min in the ultrasonic condition. The supernatant containing SEO was obtained by centrifugation at 2,500 rpm for 10 min with a 2,250 g of centrifugal acceleration. The content of SEO in ethanol was determined using ultraviolet spectrophotometry at 285 nm maximal absorbance wavelength by the calibration curve of SEO.

Results and discussion

Excitation and emission spectra

The spectral characteristics of SEO were studied. Excitation and emission bandwidths were set both at 10 nm, and

the result showed that the wavelengths of maximum excitation and emission of SEO at pH 7.0 were 293 and 596 nm, respectively (Fig. 1).

Influence of pH

Figure 2 shows that the effect of pH on the fluorescence emission of SEO in the absence or presence of CDs, in which SEO and CDs concentrations were held constant 1.0×10^{-8} and 4.0×10^{-8} mol/l, respectively. The fluorescence intensity of SEO itself in neutral media was stronger than in both acidic and basic media. With the introduction of different CDs, the SEO exhibited different fluorescence enhancement. In addition, the fluorescence intensities of SEO in four CDs in neutral media were always enhanced more remarkably than those in both acidic and basic media. Because the major components of SEO contains ester group, which is easy to react with an acid and a base, the SEO is more stable in neutral media than in both acidic and basic media. However, in any medium, it was noted that the fluorescence enhancement in four CDs followed the order: β-CD > DM-β-CD > 2-HE-β-CD > 2-HP-β-CD. This is because for the SEO–CDs systems, the effect of steric barriers becomes large after natural β-CD was modified by derivatization, which causes the guest molecules enter into the cavities of β-CD derivatives more difficultly than that of β-CD. Thus, we chose neutral media to study the inclusion interaction of SEO with CDs.

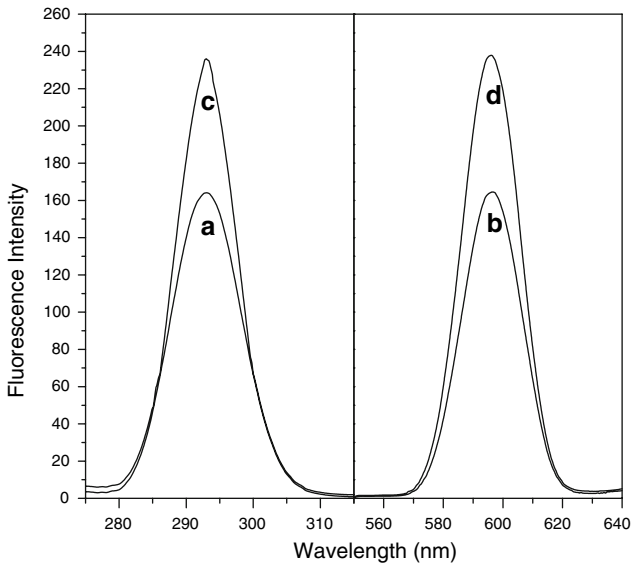

Fig. 1 Excitation and emission spectra of SEO: Excitation spectrum (*a*) and emission spectrum (*b*) of SEO in the absence of β-CD; and excitation spectrum (*c*) and emission spectrum (*d*) of SEO in the presence of β-CD. [SEO] = 1.0×10^{-8} mol/l, [β-CD] = 1.0×10^{-3} mol/l. EX 293 nm, EM 596 nm

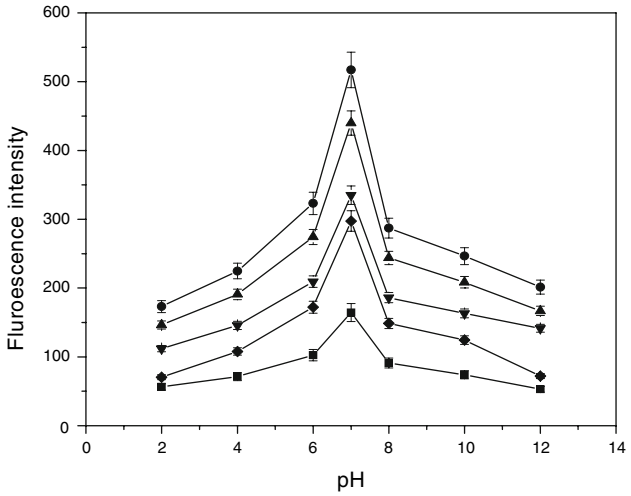

Fig. 2 Influence of the pH on the fluorescence intensity of SEO (*filled square*); SEO–β-CD complex (*closed circle*); SEO–DM-β-CD complex (*filled triangle*); SEO–2-HE-β-CD complex (*filled inverted triangle*); SEO–2-HP-β-CD complex (*open square*); [SEO] = 1.0×10^{-8} mol/l, and [CDs] = 4.0×10^{-3} mol/l. Each value represents the mean ± SD ($n = 3$)

Influence of reaction time

The effect of reaction time was studied and the results are shown in Fig. 3. As can be seen that the fluorescence intensity reached a maximum after the reagents had been added for 20 min and remains constant for at least 1 h. We measure the fluorescence intensity until the reaction time is up to 120 min, the fluorescence intensity is decrease slightly. Hence, after inclusive reaction was carried out for 20 min, the subsequent fluorescence intensities were measured within 1 h.

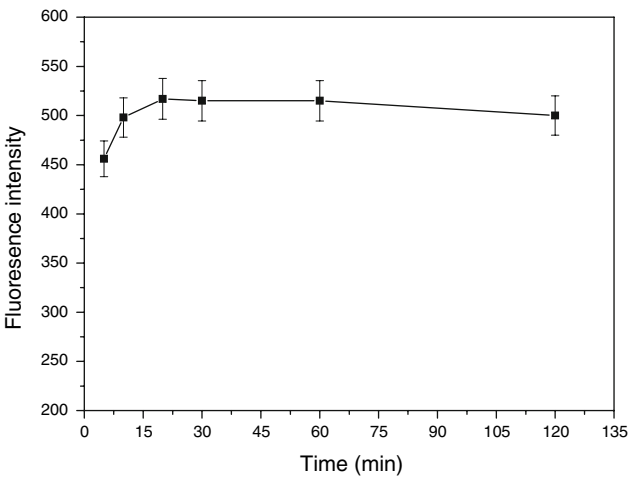

Fig. 3 Effect of reaction time on fluorescence intensity of the complex [SEO] = 1.0×10^{-8} mol/l, and [β-CD] = 4.0×10^{-3} mol/l

Influence of CDs concentration

The effect of CDs concentration on the fluorescence intensity of SEO was examined at pH 7.0. The concentration of SEO was fixed at 1.0×10^{-8} mol/l and the concentrations of β-CD were 0, 1, 2, 3, 4, 5 and 6.0×10^{-3} mol/l, for β-CD derivatives were 0, 2, 4, 6, 8, 10 and 12.0×10^{-3} mol/l, respectively. The fluorescence spectra of SEO in the presence of β-CD, DM-β-CD, 2-HE-β-CD and 2-HP-β-CD are given in Fig. 4. Introduction of CDs to an aqueous solution of SEO resulted in the change of fluorescence signals. As can be seen that the fluorescence intensities of SEO were dramatically enhanced in β-CD media, while weak enhancement of fluorescence was observed for the three other CDs.

Figure 5 illustrates the effect of CDs concentrations on the fluorescence intensity of SEO at pH 7.0. With the increase of CDs concentration, the fluorescence intensity of SEO gradually enhanced until the stable inclusion complex formed. It was noted that the fluorescence intensity of SEO in β-CD media enhanced dramatically, which implies that the most effective host molecule of the four CDs was β-CD. The enhanced fluorescence intensity of SEO in CDs media followed the order: β-CD > DM-β-CD > 2-HE-β-CD > 2-HP-β-CD.

Stoichiometry and formation constants of the inclusion complex

The stoichiometry and formation constants of the inclusion complex were studied under the established experimental conditions by the following method: assuming that the composition of the complex was 1:1, the following expression can be written as:

$$[G] + [CD] = [G - CD], \quad (1)$$

wherein [CD], [G] and [G–CD] are the concentration of CDs, SEO and the inclusion complexation, respectively.

K_α can be calculated from CDs–SEO system by Hildebrand–Benesi equation [27]:

$$\frac{1}{\Delta F} = \frac{1}{[SEO]\ [CD]\ K_\alpha \alpha} + \frac{1}{[SEO]\alpha}, \quad (2)$$

wherein ΔF was the change in the fluorescence intensity of the SEO by the addition of CDs, α was the fluorescence measure coefficient, K_α was the formation constant of the SEO–CD complex , and [SEO], [CD] were the concentration of SEO and CDs, respectively.

Figure 6 showed the double reciprocal plots of $1/\Delta F$ versus 1/[CD] for SEO complexed with CDs at pH 7.0. The plot exhibited good linearity, which implies the formation of inclusion complexes with a 1:1 stoichiometry, and the formation constant (K) were obtained from the ratio of the intercept to the slope a different temperatures (Table 1). From Table 1, the four CDs showed different inclusion capacity to SEO. The inclusion interaction of SEO with β-CD was far stronger than that with the three other CDs. The inclusion complex interaction, expressed by the formation constant, followed the order: β-CD > DM-β-CD > 2-HE-β-CD > 2-HP-β-CD. For the SEO–CDs systems, the effect of the steric barrier becomes large after natural β-CD was modified, what causes the guest enter into the β-CD derivatives cavity more difficultly than β-CD. In addition, the formation constant K decrease with

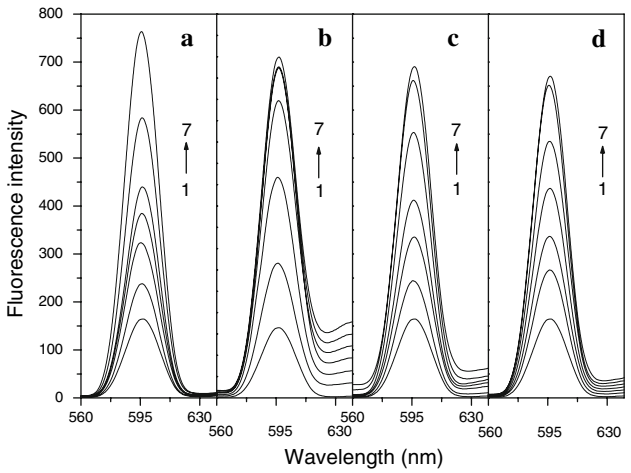

Fig. 4 Fluorescence spectra of SEO in the present of different concentrations of CDs [SEO] = 1.0×10^{-8} mol/l, pH 7.0. *a* β-CD: from (1) to (7): (1) 0.0, (2) 1.0, (3) 2.0, (4) 3.0, (5) 4.0, (6) 5.0 and (7) 6.0×10^{-3} mol/l. *b* DM-β-CD: from (1) to (7): (1) 0.0, (2) 2.0, (3) 4.0, (4) 6.0, (5) 8.0, (6) 10.0 and (7) 12.0×10^{-3} mol/l. *c* 2-HE-β-CD: from (1) to (7): (1) 0.0, (2) 2.0, (3) 4.0, (4) 6.0, (5) 8.0, (6) 10.0 and (7) 12.0×10^{-3} mol/l. *d* 2-HP-β-CD: from (1) to (7): (1) 0.0, (2) 2.0, (3) 4.0, (4) 6.0, (5) 8.0, (6) 10.0 and (7) 12.0×10^{-3} mol/l

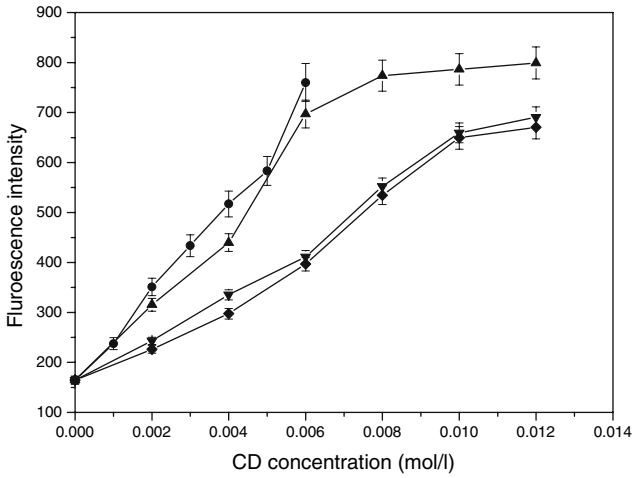

Fig. 5 Effect of CDs concentration on the fluorescence intensity of SEO (pH 7.0). SEO–β-CD complex (*closed circle*), SEO–DM-β-CD complex (*filled triangle*), SEO–2-HE-β-CD complex (*filled inverted triangle*), SEO–2-HP-β-CD complex (*open square*). Each value represents the mean ± SD ($n = 3$)

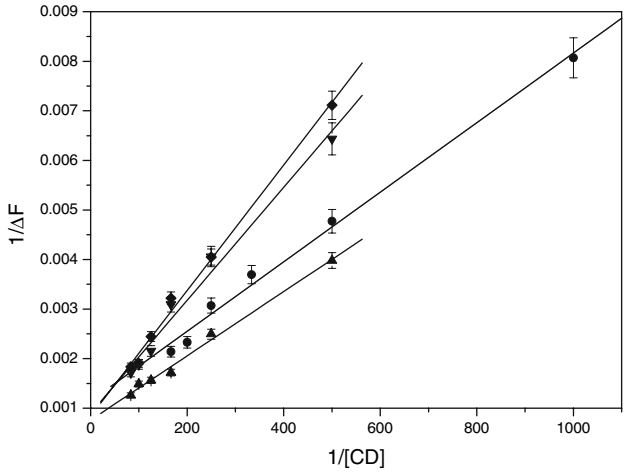

Fig. 6 Double reciprocal plots for SEO complex to CDs at pH 7.0. SEO–β-CD complex (*closed circle*); SEO–DM-β-CD complex (*filled triangle*); SEO–2-HE-β-CD complex (*filled inverted triangle*), SEO–2-HP-β-CD (*open square*) complex. Each value represents the mean ± SD ($n = 3$)

increasing temperature, indicating that the affinity of CDs to SEO decreased as expected for an exothermic process. Similar result was also gotten by Karathanos [28] and by Tommasini [29].

Inclusion complex thermodynamics

The study of thermodynamics conduced to analyzing the interactions between CDs and SEO. It has been generally accepted that the main driving forces for complexation are hydrogen binding between the hydroxyl groups of CDs and the guest, Van der Waals force interactions between host and guest molecules, hydrophobic interaction, and the release of "high energy water" molecules from the cavities of CDs to bulk water. Hydrophobic interaction essentially involves favorable positive entropy together with a slightly positive enthalpy change, while the other forces involve negative ΔH and ΔS [30].

The thermodynamic parameters (ΔH, ΔS and ΔG) for the formation of inclusion complex were determined from temperature dependence of apparent formation constants, by using classical Van't Hoff equation [Eq. (3)], and plotting ln K versus $1/T$ [30]

$$\ln K = -\Delta H/\mathrm{RT} + \Delta S/R. \quad (3)$$

The corresponding enthalpy and entropy can be obtained from the slop and intercept, respectively. The results are shown in Table 2, which indicate the marked tendency of SEO to complex with CDs in water. The negative values of enthalpy changes indicate that the interaction processes of SEO with CDs are exothermic. The enthalpy of the system was largely decreased, which implied that the main driving forces of inclusion reaction were Van der Waals force and the extrusion of "high energy water" molecules from the cavities of CDs. The changes of entropy are also negative in these processes. This behavior can be explained considering that the complexation causes a decrease in translational and rotational degrees of freedom of the complexed molecule as compared with the free ones, giving a more ordered system. These results indicate that the complexation of SEO with CDs has occurred [30]. The Gibbs free energy change for the interactions that take place during the inclusion process may be found by the following Eq. (4):

$$\Delta G = -\mathrm{RT} \ln K. \quad (4)$$

The Gibbs free energy at temperature 298 K is calculated as a negative value (Table 2), indicating that the inclusion process is a spontaneous one.

Content of SEO in(β-CD microcapsules

Figure 7 show that SEO had a maximum absorption peak at 285 nm in ethanol medium. The standard curve of SEO was made at 285 nm and the equation was $Y = 0.6393X - 0.02677$ (Fig. 8). The correlation was 0.9998, wherein X was the concentration of SEO (mg/ml), and Y was the absorbance at 285 nm.

The content of SEO in β-CD microcapsule was determined in aqueous solution (pH 7.0) and the result was 0.14 g/g. According to stoichiometry, the maximum

Table 1 The formation constants (K) value of SEO/CDs under different temperatures $(\mathrm{mol/l})^{-1}$

Temperature (°C)	25	35	45
β-CD	164.5 ± 7.2	138.4 ± 5.5	114.6 ± 3.4
DM-β-CD	116.6 ± 3.9	89.7 ± 2.7	75.6 ± 1.9
2-HE-β-CD	85.2 ± 2.4	68.1 ± 1.8	57.6 ± 1.7
2-HP-β-CD	64.6 ± 2.6	52.8 ± 2.1	41.4 ± 1.4

Table 2 Thermodynamic parameters of SEO/CDs complexes

Host	$-\Delta G_{25}$ (KJ mol^{-1})	$-\Delta H$ (KJ mol^{-1})	$-\Delta S$ (JK^{-1} mol^{-1})
β-CD	12.63 ± 0.12	14.29 ± 0.5	5.57 ± 1.1
DM-β-CD	11.75 ± 0.1	17.18 ± 0.2	18.26 ± 0.42
2-HE-β-CD	10.99 ± 0.08	15.73 ± 0.37	15.77 ± 1.3
2-HP-β-CD	10.29 ± 0.14	17.49 ± 0.22	24.07 ± 0.01

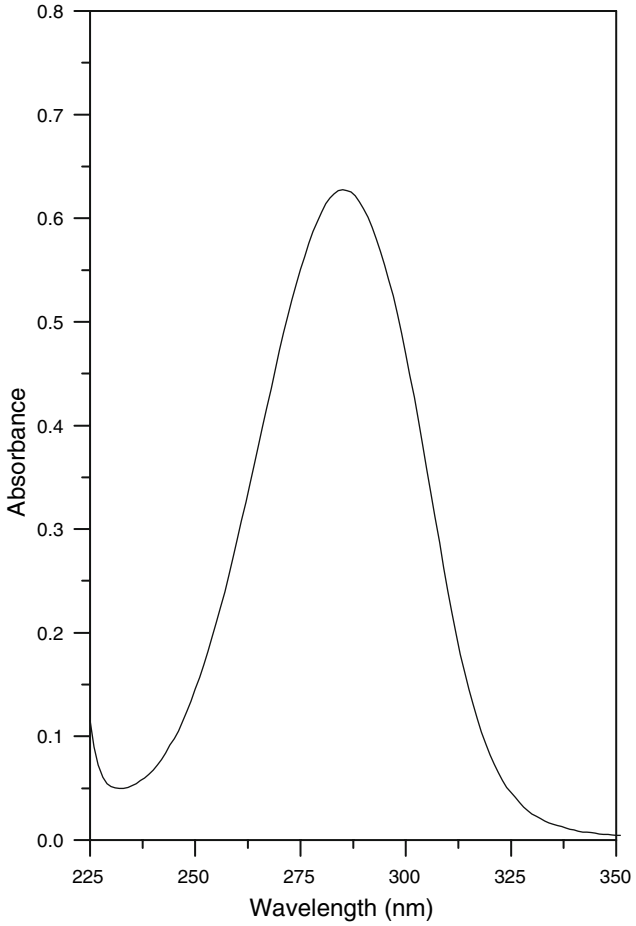

Fig. 7 UV–vis spectra of SEO in aqueous solution. [SEO] = 5×10^{-3} mol/l

theoretical load of SEO in β-CD microcapsule is 0.17 g/g. The relative higher content of SEO in the microcapsules also reflects the high affinity of β-CD with SEO.

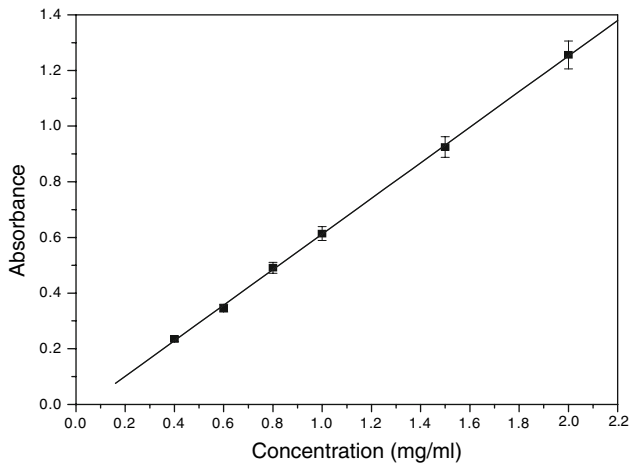

Fig. 8 The standard curve of SEO in aqueous solution. Each value represents the mean ± SD ($n = 3$)

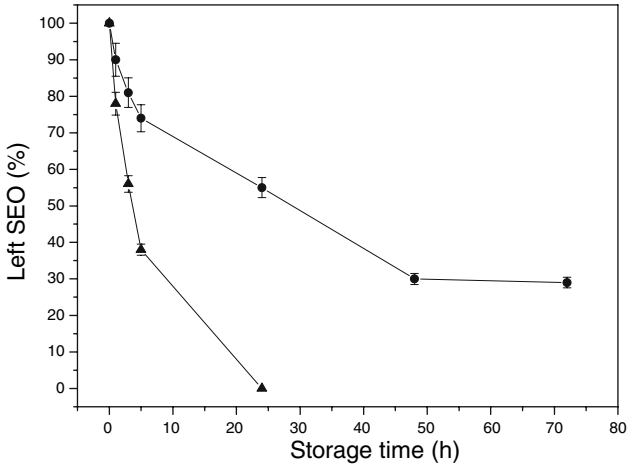

Fig. 9 Changes in SEO content in the microcapsules at 85 °C, microcapsules (*closed circle*); physical mixture (*filled triangle*). Each value represents the mean ± SD ($n = 3$)

Stability of SEO in the microcapsules

The stability of SEO in β-CD microcapsules was determined at room temperature and 85 °C, respectively. Figure 9 is the plot of residual SEO versus time at 85 °C. Although SEO was a volatile oil, more than 30% of SEO was left in the microcapsules after 48 h. Comparing with the physical mixture of β-CD and SEO, just after 5 h the content of SEO has decreased to 37% and after 24 h SEO was unable to be determined. The results suggested that the steric hindrance of β-CD torus gave good protection against evaporation after SEO was included in the cavities of β-CD. The conclusion was also confirmed by the stability of SEO in the microcapsules at room temperature. It can be seen from Fig. 10 that the content of SEO was

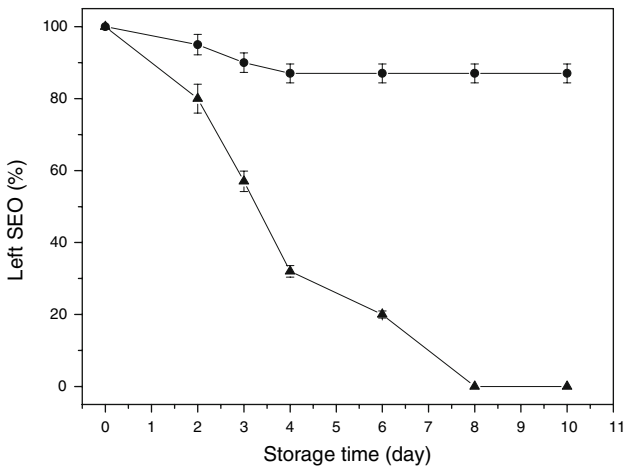

Fig. 10 Changes in SEO content in the microcapsules at room temperature (25 °C), microcapsules (*closed circle*); physical mixture (*filled triangle*). Each value represents the mean ± SD ($n = 3$)

almost unchanged in 10 days. However, the content of SEO in the physical mixture decreased to zero in 8 days.

Conclusion

It has been demonstrated that β-CD and its derivatives can react with SEO to form the complexes i.e., molecular microcapsules, and the inclusion interactions of β-CD with SEO were far stronger than three other CDs. Microencapsulations of SEO in β-CDs are very stable and the application of the essential oil should be expanded. Moreover, it may be concluded that the molecules of SEO inside the CDs cavities were protected. Therefore, the microcapsules of SEO in β-CDs can be used as an additive in foods that the SEO is normally added as a flavor, and as a new formulation to optimize its pharmacological profile.

Acknowledgments The authors acknowledge Natural Science Foundation of Tianjin and Tianjin Key Laboratory of Food Technology for financial support.

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