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ORIGINAL ARTICLE

Release characteristics and antibacterial activity of solid state eugenol/β-cyclodextrin inclusion complex

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Abstract A solid state eugenol/β-cyclodextrin inclusion complex (EG/β-CD) was prepared by lyophilization method and characterized by Powder X-ray Diffraction (XRD) and Fourier Fransform Infrared Spectroscopy (FTIR). UV–Vis spectrometer was used to determine the EG content encapsulated in the complex. In order to estimate the release characteristics of the EG/β-CD powder, Avrami's equation and Thermogravimetric (TG) analyzer were, respectively, used. The loss percentage of EG was no more than 10 wt% for 4 week exposing at 25 °C and 75% humidity, and the release of EG is controlled by a combination mechanism of diffusion and first-order mode. TG results not only proved the thermo stability of the EG in EG/β-CD complex, but also clarified the thermal decomposition behaviors of the EG/β-CD. The antibacterial activity of the EG/β-CD complex was investigated using agar cup-plate diffusion method and bacterial strains of *Escherichia coli*, *Salmonella paratyphi* B, and *Staphylococcus aureus* were used. The results indicated that EG/β-CD had a selective antimicrobial active against *Escherichia coli*.

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Introduction

Eugenol (EG, 2-methoxy-4-(2-propenyl)phenol) is a natural flavor extract from plants and is usually used as a fragrant and flavoring agent in a variety of cosmetics and food products [1, 2]. It is well known to possess various biological activities such as notably antibacterial, antifungal [3], and antioxidant properties [2]. The role of such molecule in the prevention and therapy of diseases has received a great deal of attention [4]. Additionally, its antifungal and antibacterial inhabiting properties and applications have been shown in Food and Drug Administration [5, 6]. However, their low solubility in water limits its applications and bioavailability. Furthermore, the EG oil is easily oxidized, decomposed or evaporated when exposed to the air, light, or heat. One way to stabilize and use these substances is by inclusion in suitable host molecules.

Cyclodextrins (CDs) are torus-shaped cyclic oligosaccharides made up of α-1,4 linked D-glycopyranose with 6(α-),7(β-),8(γ-) units. They come from the decomposition of starch with cyclodextrin glucanotransferase (CGTase) and have non-toxicity which has been confirmed by Szejtli [7]. The inside cavity of β-CD is hydrophobic and the outside is hydrophilic. It is well know that CDs can effectively encapsulate some hydrophobic molecules to form molecular microcapsules, namely inclusion complexes or host–guest complexes, as the displacement of included water molecules by apolar substrates represents a thermodynamically favored process. The binding between the guest molecules and host CDs is not fixed or permanent

but rather is a dynamic equilibrium. Binding strength depends on how well the "host–guest" complex fits together and specific local interactions between the surface atoms. So, some hydrophobic drugs were encapsulated into the cavity of CDs in order to enhance the water solubility [8–12] or controlling release [13–15]. Moreover, an increase in solubility occurs in the guest molecules in water, so that their potential applications can be enlarged considerably. EG, a hydrophobic molecule, can be transferred into the cavity of cyclodextrins to obtain EG/CDs complex. Recently, such a purpose was reported by Yan Yang et al. [16] and Hao Zhan et al. [17], who prepared a series EG/CDs complex and was carefully characterized by the instrument of Fourier Fransform Infrared Spectroscopy (FTIR), NMR, UV, Thermogravimetric (TG) and X-ray Diffraction (XRD). However the releasing behaviors and germicidal activity of the encapsulated EG have not been studied yet. The aim of this work was to investigate the solid state eugenol/β-cyclodextrin inclusion complex (EG/β-CD) release characteristics and prove its antibacterial activity.

Experimental

Chemicals and bacterial strains

β-CD was purchased from TCI (Japan) and dried for 24 h at 105 °C. EG (>99) were purchased from Aladdin Co., Ltd. (Shanghai, China). Unless special notation, all the chemicals were analytical reagent grade and without further purification. Deionized water was prepared by Milli-Q century system (Millipore, American).

Escherichia coli GIM 1.173 and *Salmonella paratyphi* B GIM1.224 were obtained from Microbial Culture Collection Center of Guang Dong Province (China). *Staphylococcus aureus* CICC 21600 were offered by China Center of Industrial Culture Collection. Nutrient broth (10.0 g of peptone, 3.0 g of beef extract powder, 5.0 g of sodium chloride, and 1.0 g of glucose were dissolved in 1,000 mL of sterile water) was purchased from Beijing Land Bridge Technology Co., Ltd. (China).

Preparation of solid state EG/β-CD complex

One gram of β-CD was dissolved completely in 30 mL of deionized water at 50 °C, and then added 135 μL of EG (molar ratio 1:1). The mixture was sealed by parafilm and stirred 6 h with magnetic stirrer for encapsulation completely. After stirring, the separated solid inclusion compounds were washed by 100 mL deionized water and 100 mL alcohol, respectively, and were frozen at −70 °C for 6 h in a freeze-dryer (LGJ-25C, Four-Ring Science Instrument Plant Beijing Co., Ltd), the lyophilization cycle was given in Table 1 and the lyophilization pressure was lower than 30 Pa. After removing the samples from the freeze-drier, they were stored in a gas-tight tube at 4 °C until testing.

FTIR spectra

FTIR samples were prepared in the form of potassium bromide pellets containing 8–10 mg samples and 400 mg potassium bromide, which were mixed and grounded in an agate mortar. The FTIR spectra were recorded by Avatar 360 spectrometer (Nicolet, USA). Thirty-two scans for each sample was operated at room temperature with resolution of 4 cm^{-1}, and the scan scope was in the range of 400–4,000 cm^{-1}.

XRD

X-ray powder diffraction of the solid samples was performed on D/Max2200. The samples were irradiated with monochromatised Cu-K and analyzed with $5° \leq 2\theta \leq 60°$. The voltage and current were 40 kV and 40 mA, respectively.

Quantification of EG content in the complex powder

The amount of EG in inclusion complexes was assayed as the following process. Firstly, a mixture of 8 mL alcohol and 25 mg the inclusion complexes powder was treated for 20 min in the ultrasonic oscillator. Secondly, the suspension was separated by centrifugation under 2,000 rpm for 10 min, and then diluted 20 times by alcohol for measuring the UV absorbance. The EG concentration of the dilution was calculated by the EG regression (Eq. 1), with a correction coefficient (r) 0.9994.

$$A = 6773c + 0.0156 \quad (1)$$

where A denotes the absorbance of the diluted supernatants and c (mol L^{-1}) the concentration of EG.

The absorption studies were performed using a UV–Vis dual-beam spectrophotometer (Persee 1901, China) with 1 cm thick quartz cuvette at the wavelength of 282 nm, and the EG content in the solid state complexes was calculated by Eq. 2

$$\text{EG content } (\%) = 26.27 \times \frac{c}{m} \times 100\% \quad (2)$$

Table 1 Lyophilization cycle

Sequence number	1	2	3	4	5	6	7	8
Temperature (°C)	−30	−25	−20	−15	−10	−5	0	10
Time (h)	1	1	1	1	1	1	2	2

where m denotes the weight of the complexes (g), and the factor of 26.27 is the product of molar mass of EG (164.2 g mol^{-1}), dilution factor (20), and the volume of the extracting solution (0.008 L) [17].

Release experiment of solid state EG/β-CD

Release of EG/β-CD by finite-time

The time stability of encapsulated EG during storage was investigated to determine the release characteristics at constant temperature and humidity. Five gram inclusion complex was precisely weighed and spread evenly in a thin layer in a 250 mL beaker. The beaker was stored in desiccators and protected from light. The relative humidity (RH) inside the desiccator was constant of 75% at 25 °C. Constant RH was created using saturated sodium chloride solution [18]. The desiccator was placed in thermostatic water-circulator bath at 25 °C for 24 h for the equilibrium. A thermo recorder (SHT10, Sensation, and Switzerland) was placed inside the desiccators to monitor the RH and temperature. At every prescribed time interval within the storage period, triplicate of 25 mg inclusion complexes were withdrawn from the desiccators for measurement of EG content.

Release of EG by different temperatures

TG curves were recorded on Perkin-Elmer Pyirs1 thermo gravimetric analyzer between 25 and 550 °C at a constant heating rate of 5.0 °C min^{-1} under pure nitrogen gas. The solid samples were EG/β-CD inclusion complex and β-CD.

Preparation of standard bacterial suspensions and antibacterial solutions

E. coli, *S. paratyphi* B, and *S. aureus*, which were inoculated three time for activation, were added to 5 mL of sterile buffer solutions (pH = 7) respectively. These bacterial suspensions were tested and adjusted to 10^5 cfu mL^{-1} (cfu = colony-forming units) by blood counting chamber and must inoculated within 1 h.

1.0, 0.5, and 0.25 g of EG/β-CD powder were dissolved in 100 mL of sterile water, respectively, to obtain 10, 5, and 2.5 mg mL^{-1} antibacterial solutions. The average EG content in EG/β-CD powder was 10 wt%, so the EG controls were prepared by mixing 96, 48, 24 μL of pure EG (density = 1.06 g mL^{-1}) into 100 mL of sterile water, respectively, to obtain 1, 0.5, and 0.25 mg mL^{-1} mixtures. CD controls were dissolved 0.9, 0.45, and 0.22 g of β-CD powder into 100 mL of sterile water, respectively, to obtain 9, 4.5, and 2.2 mg mL^{-1} solutions.

Antibacterial activity testing-agar cup-plate diffusion method

A layer of nutrient agar (20 mL) seeded with *E. coli, S. paratyphi* B, and *S. aureus* bacterial suspension (2 mL) was allowed to solidify in the Petri plate, and holes of 6 mm in diameter were cut into the solidified agar layer with a sterile Oxford cylinder. Then, equal volumes of EG/β-CD solutions, EG controls, and CD controls were placed directly into the holes, and the plates were incubated at 37 °C for 24 h. The zone of inhibition developed for each concentration was measured and the readings were taken thrice.

Results and discussion

X-ray analysis

Because EG is an oil liquid, there is no X-ray powder diffraction data available. In Fig. 1, the XRD diffraction spectrum of EG/β-CD inclusion compound shows considerable diversity when comparing with XRD diffraction of pure β-CD. The peaks of 22.98, 19.64, and 12.54 in β-CD shifted to lower 2θ angle of 20.90, 17.96, and 11.58 in EG/β-CD inclusion compound. And the different location of XRD diffraction peaks between EG/β-CD inclusion complex and β-CD indicated that the crystalline pattern of the β-CD probably changed when EG molecule was in the cavity of the host molecule [16]. Moreover two peaks at 10.68, 9.08 in β-CD were absent in EG/β-CD inclusion compound. Besides, it is important also to remark that the

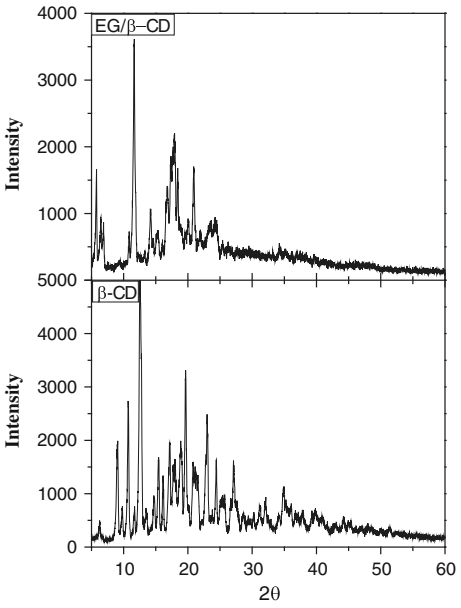

Fig. 1 XRD spectra of EG/β-CD and β-CD

peaks intensities in EG/β-CD were decreased with respect to the spectrum of the β-CD, indicating a lower degree of crystallinity for the complex. This fact may be attributed to the relative rapid precipitation of the complex during the lyophilization preparation which is insufficient for a regular crystal growth and spatial order at higher ranges.

IR spectra analysis

The IR spectra of β-CD, EG and their inclusion compounds are shown in Fig. 2. The prominent peak assignments are listed in Table 2. From Table 2, the encapsulation of EG did not cause significant shifts of the FTIR bands as compared with β-CD. These results indicate that no strong interaction existed between EG and C–C, C–O–C, OH groups of β-CD. Nevertheless, the FTIR spectra of EG/β-CD and β-CD show small differences. Firstly, the bands at 1,513 and 1,267 cm^{-1}, which are respectively attributed to aromatic υC=C stretching and phenols υ(C–O) stretching of EG, were only observed in the spectrum of EG/β-CD. However, they gave a very lower strength in the spectrum of EG/β-CD, we presume that it is due to no more than 10% (w/w) EG in its inclusion compound, and it is easily covered up by the peaks of β-CD [16]. Secondly, the O–H stretching band at 3,421 cm^{-1} in EG/β-CD increased of 14 cm^{-1} as compared with that of β-CD, besides, the band also changed narrow. This phenomenon indicates a change of hydration bonds structure, which is probably associated with a reorganization of the intramolecular hydrogen bonds formed between these O–H groups of β-CD in the presence of EG. These results all indicate that the EG is encapsulated into the hydrophobic cavity of β-CD.

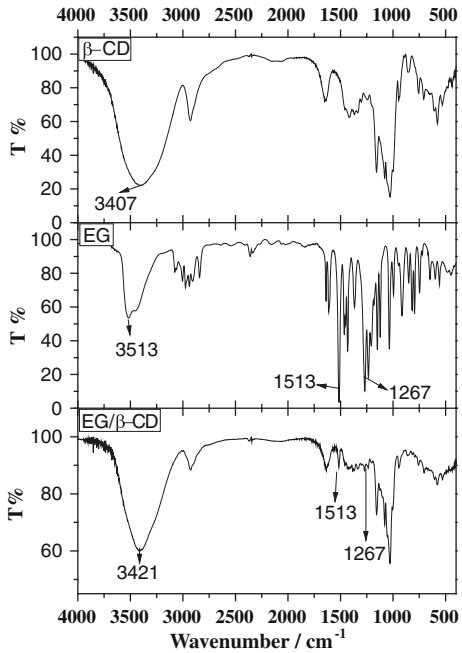

Fig. 2 FTIR spectra of β-CD, EG, and EG/β-CD

Time stability and release behavior analysis of solid state EG/β-CD

The release characteristics of the encapsulated flavors from the powder are quite important for estimating the storage period, as well as the controlled release applications. So, the time stability of the inclusion complex of EG/β-CD was investigated by Avrami's equation (Eqs. 3, 4).

$$R = \exp(-[kt]^n) \tag{3}$$

$$R = \frac{\text{Amount of EG remained after prescribed time}}{\text{Initial amount of EG}} \tag{4}$$

Then, Eq. 5 could be leaded out by the Eq. 3

$$\ln(-\ln R) = \ln k + n \ln t \tag{5}$$

where R is the retention of the EG during release, t is time, n a parameter representing the release mechanism, and k the release rate constant.

Figure 3 shows time stability of EG/β-CD complex prepared by the lyophilization. The EG lost percentage was no more than 10 wt% when it was placed for 4 week under 25 °C and 75% humidity. By regression analysis of the Eq. 5, $n = 0.882$ and $k = 3.4 \times 10^{-4}$ h^{-1} was obtained. Theoretically, the parameter $n = 0.54$ corresponds to diffusive release and $n = 1$ to a first-order release kinetics which generally occurs when the guest compound is actually a solution [18]. We performed this release experiment at a relative high humidity (75%), $n = 0.882$ indicated that the EG encapsulated by β-CD was released in a combination mechanism of diffusion and first-order mode [21]. As suggestions by Whorton and Reineccius [22], the release of the entrapped flavoring materials is closely related with the adsorption of water in the wall materials and hydration of the powder. The water begins to penetrate the surface wall of the dried particle, followed by cracks appearing near the surface of the particle and subsequent release of the flavor. Besides, the release rate constant k (3.4×10^{-4} h^{-1}) showed highly flavor retention which demonstrates that the encapsulation of EG with β-CD could control the releasing of EG flavor.

Thermal stability and decomposition behaviors analysis of solid state EG/β-CD

Figure 4 illustrates TG curves of β-CD and EG/β-CD. The weight loss processes of β-CD could be divided into two stages. The first weight loss in the range of 25–82 °C is attributed to the release of water molecule combined on the β-CD powder. The second weight loss began at the

Table 2 Wavenumbers (cm^{-1}) and assignments for the bands observed in the FTIR spectra (Fig. 2) of EG, β-CD and their inclusion complex EG/β-CD

Chemical functional groups	Wave number cm^{-1}		
Vibration mode	β-CD	EG	EG/β-CD
ν(O–H)	3407	3513	3421
ν(Ar–H) or ν(C=H)	–	3078, 3008	–
Methyl and methylene ν(C–H)	2925	2973, 2937, and 2960, 2842	2,925
Vinyl ν(C=C)	–	1637	Overlapped
Aromatic ν(C=C)	–	1612, 1513	1513
Methylene δ_s(C–H)	Overlapped	1463	Overlapped
Methyl δ_s(C–H) and δ_{as}(C–H)		1450, 1365	Overlapped
ν(C–O) and ν(C–O–C)	1157, 1027	1267, 1230	1267, 1157, 1025
δ(O–H), methylene δ_s(C–H) [19, 20]	1458–1338	Overlapped	1458–1338

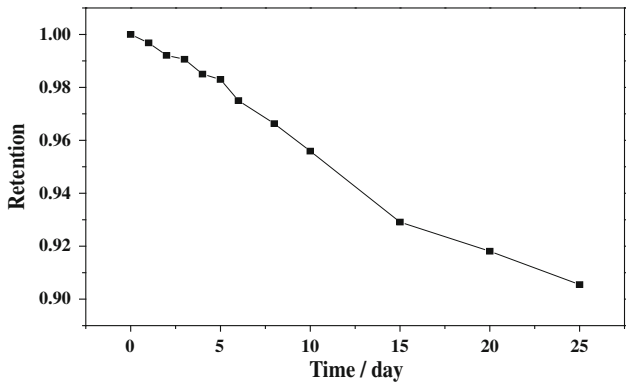

Fig. 3 Curve of solid state EG/β-CD stability versus time

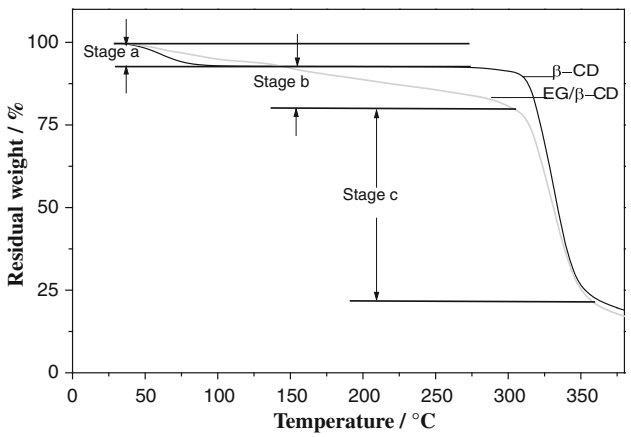

Fig. 4 TG curves of β-CD and EG/β-CD

temperature of 305 °C, which is due to the decomposition of β-CD [23].

Compared with the TG curve of β-CD, the weight loss processes of EG/β-CD complex could be divided into three stages. The first weight loss in the range of 25–145 °C is attributed to the release of water molecule. The second weight loss in the range of 145–305 °C is attributed to the collapse of the complex channel crystal lattice, and the release of the EG from the cavity of β-CD. The well combination of the EG/β-CD complex protects the EG molecule from volatilizing early. Since the EG oil is easy to volatilize at room temperature, the encapsulation of EG in β-CD cavity demonstrates an enhancement of the thermal stability. The third weight loss which starts at the temperature of 305 °C is attributed to decomposition of β-CD.

Antibacterial activity of EG/β-CD

The antibacterial activity of EG/β-CD complex was determined by a agar cup-plate method using three organisms such as *E. coli*, S. *paratyphi* B, and *S. aureus* in aqueous. Three different concentration of EG/β-CD water solution were performed in this experiment, including 10 (saturated solution of EG/β-CD powder at room temperature), 5, and 2.5 mg mL^{-1}. The results are listed in Table 3. In Table 3, EG/β-CD water solution showed a clear inhibitory effect against *E. coli* but no prominent inhibitory effect against *S. paratyphi* B and *S. aureus*. These phenomena indicate that EG/β-CD have a selective antimicrobial active against bacterial strains.

The inhibitory effect against *E. coli* does not relate to β-CD, because all the β-CD controls presented no prominent inhibition zone. However, EG controls also gave no inhibitory effect. These results are probably attributed to two main reasons. One is EG liquid cannot dissolve into the water; therefore, it can hardly diffuses through the agar media, resulting in no inhibitory effect. The other reason is that EG is of easy volatility, especially, EG floating on the surface of water is lost more easily, this still results in the decrease of the inhibitory effect. However, the EG/β-CD can solve the above two problems due to its controlling release and good water solubility.

Table 3 Inhibitory effect of EG/β-CD, EG controls, and β-CD controls against *E. coli*, *S. paratyphi* B, and *S. aureus*

Bacterial strain	EG/β-CD			EG controls			β-CD controls		
	Concentration of EG/β-CD (mg mL^{-1})			Concentration of EG (mg mL^{-1})			Concentration of β-CD (mg mL^{-1})		
	10	5	2.5	1	0.5	0.25	9	4.5	2.2
E. coli	++	+	−	−	−	−	−	−	−
S. paratyphi B	−	−	−	−	−	−	−	−	−
S. aureus	−	−	−	−	−	−	−	−	−

++ hypersensitivity, the average diameters of inhibitory zone >15 mm

+ sensitivity, 15 mm > the average diameters of inhibitory zone >10 mm

− no prominent inhibitory effect, the average diameters of inhibitory zone <10 mm

The release of the EG from the EG/β-CD powder leads to the decrease of the inhabitation ability. Take *E. coli* for example, 10 mg of EG/β-CD powder (EG content = 10 wt%) dissolving in 1 mL of sterile water had an obvious antibacterial effect (Table 3). If EG releases from the EG/β-CD powder until the amount of EG remained half of the initial value (Now, EG content = 5 wt%), then the powder also dissolves in 1 mL of sterile water, here the concentration of the later EG/β-CD solution equals 5 mg mL^{-1} compared to the initial EG/β-CD solution. In this process, $R = 0.5$. By calculating of the Avrami's equation, $n = 0.882$ and $k = 3.4 \times 10^{-4}$ h^{-1}, this process will take 236 days under 25 °C and 75% humidity. However, the later EG/β-CD solution could also have an antibacterial effect against *E. coli* (Table 3). Thus, by our preparation, EG could be stored in a state of solid powder and will possess the antibacterial effect against *E. coli* for a long-acting.

Conclusion

The solid state of EG/β-CD was prepared by the lyophilization method. The inclusion phenomenon of EG with β-CD were successfully characterized by XRD and FTIR spectroscopy. Based on results from UV–Vis spectrometer and TG analyzer, the time and thermal stability of the EG/β-CD complex were enhanced, and EG release mechanism of diffusion combined with first-order mode was suggested. By dissolving the EG/β-CD into water and according the results of the agar cup-plate diffusion method, the complex of EG/β-CD showed a good antibacterial activity against *E. coli* with 10 mg mL^{-1} solution, however, no prominent actions were given against *S. paratyphi* B and *S. aureus*.

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