Prev. Nutr. Food Sci. 2020;25(4):440-448
https://doi.org/10.3746/pnf.2020.25.4.440
pISSN 2287-1098 · eISSN 2287-8602

Synthesis and Characterization of Phenolic Acid/Hydroxypropyl-β-Cyclodextrin Inclusion Complexes

Ji-Sang Kim

Department of Food and Nutrition, Kyungnam University, Gyeongnam 51767, Korea

ABSTRACT: The objective of this study was to synthesize and characterize inclusion complexes of phenolic acids with hydroxypropyl-β-cyclodextrin (HP-β-CD). The inclusion complexes were prepared by the freeze-drying method and characterized using a variety of analytical techniques, including ultraviolet-visible spectroscopy, Fourier transform infrared spectroscopy, differential scanning calorimetry, and X-ray diffractometry. The results of all these approaches indicated that phenolic acids were able to form an inclusion complex with HP-β-CD, and the phenolic acids/HP-β-CD inclusion compounds exhibited different spectroscopic features and properties based on the phenolic acids employed. The use of the HP-β-CD matrix allowed for higher encapsulation efficiency and afforded capsules with distinct shapes.

Keywords: hydroxypropyl-β-cyclodextrin, inclusion complex, phenolic acids

INTRODUCTION

Cyclodextrins (CDs) are cyclic (α-1,4)-linked oligosaccharides of α-D-glucopyranose units. CDs were identified over 100 years ago and have since been widely adopted in pharmaceutical agents. The three most studied CDs are the α-, β-, and γ-CDs containing six, seven, and eight D-glucopyranose units, respectively. The α-, β-, and γ-CDs have been used to incorporate drugs into aqueous vehicles. Their toxicity profiles have been studied extensively and have been shown to differ according to the route of administration. However, the application of CDs in the pharmaceutical field is limited by their relatively low aqueous solubility. Thus, numerous chemically modified CDs have been developed to counter the solubility limits and safety concerns of the parent CD. Hydroxypropyl-β-cyclodextrin (HP-β-CD), a hydroxyalkyl derivative, is a promising alternative to α-, β-, and γ-CDs as it displays improved water solubility and is more toxicologically benign (Gould and Scott, 2005). As the first approved CD derivative by the Food and Drug Administration, HP-β-CD is currently used in the food and agricultural industries (Szente and Szejtli, 2004; Yuan et al., 2008). It has been thoroughly investigated as a carrier for the delivery of drugs (Liu et al., 2010; Tsao et al., 2012). Furthermore, HP-β-CD has been widely used to improve the solubility of poorly water-soluble drugs (Liu et al., 2006; Ma et al., 2012). Inclusion within CDs has been shown to exert a profound improvement on the physicochemical properties of guest molecules as they are temporarily locked or caged within the host cavity (Schmid, 1989). This includes solubility enhancement of highly insoluble guests, stabilization of labile molecules against the degradative effects of oxidation, visible or ultraviolet (UV) light and heat, control of volatility and sublimation, physical isolation of incompatible compounds, chromatographic separation, taste modification by masking flavors or unpleasant odors, and controlled release of drugs and flavors. Therefore, CDs are used in the food (Fujishima et al., 2001), pharmaceutical (Bhardwaj et al., 2000), cosmetic (Holland et al., 1999), environment protection (Lezcano et al., 2002), bioconversion (Dufossé et al., 1999), and packaging and textile industries (Hedges, 1998).

Phenolic compounds exist in most plant tissues as secondary metabolites. The term 'phenolic' or 'polyphenol' can be defined as a substance that possesses an aromatic ring, bearing one or more hydroxyl substituents or functional derivatives, such as esters, methyl ethers, and glycosides (Harborne, 1989). Polyphenols are also important components of the human diet due to their potential antioxidant activity (Martin and Appel, 2010), their capacity to diminish oxidative stress-induced tissue damage resulting from chronic diseases (Bravo, 1998), and their anticancer activity (Harris et al., 2007). Similarly, phenol-

Received 23 July 2020; Accepted 8 September 2020; Published online 31 December 2020

Correspondence to Ji-Sang Kim, Tel: +82-55-249-2185, E-mail: jisangkim@kyungnam.ac.kr
Author information: Ji-Sang Kim (Professor)

ic acids act as functional ingredients in foods as they impart anticarcinogenic, antiviral, antibacterial, and potent antioxidant properties (Khadem and Marles, 2010; Park et al., 2014). However, simple phenolic acids such as cinnamic acids [e.g. ferulic acid (FA) and *p*-coumaric acid (PCA)] and benzoic acids [e.g. *p*-hydroxybenzoic acid (HBA) and vanillic acid (VA)] possess relatively low solubility in pure water. Thus, the encapsulation of polyphenols has been proposed to improve their stability and bioactivity for application in the abovementioned industries (Fang and Bhandari, 2010). The inclusion of phenolic acids within CDs is particularly relevant in the food industry because they are commonly found in cereals. The physicochemical properties of the included phenolic acids are modified by complexation. Properties such as solubility, durability, and stability are improved. Furthermore, the volatility and toxicity of the included phenolic acids are lowered, while bitter tastes and unpleasant odors are masked significantly. Upon complexation, the phenolic compounds are also stabilized against light, UV radiation, thermal decomposition, and oxidation (Roux et al., 2007; Tonelli, 2008; Chen et al., 2010; Singh et al., 2010).

Therefore, the objective of this study was to synthesize and characterize inclusion complexes of phenolic acids with HP-β-CD. The inclusion complexes were prepared by the freeze-drying method and characterized using a variety of analytical techniques, including UV-visible spectroscopy, Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and X-ray diffractometry (XRD).

MATERIALS AND METHODS

Chemicals and reagents

HP-β-CD, HBA, VA, PCA, and FA were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). All other chemicals were obtained from Merck KGaA (Darmstadt, Germany). All chemicals were of analytical grade and used without further purification, unless otherwise stated.

Preparation of the phenolic acid/HP-β-CD complexes

The complex was prepared by mixing the phenolic acid and HP-β-CD (in a 1:1 M ratio) according to the freeze-drying method described by Pralhad and Rajendrakumar (2004). A mixture of HP-β-CD (4 mmol) and phenolic acid (4 mmol) was diluted in water (50 mL). The mixture was incubated at 30°C for 24 h at 150 rpm in the dark at room temperature, and then filtered through a 0.45 μm membrane (Acrodisc® syringe filters GHP membrane, Pall Corporation, Ann Arbor, MI, USA) to remove the excess drug. The resulting solution was frozen at −80°C and then subjected to lyophilization in a freeze-drier (FDU-1200, EYELA, Tokyo, Japan) for 24 h to obtain the product in the form of a powder.

Efficiency of encapsulation (EE)

The EE was determined as described by Sansone et al. (2011). Each encapsulated sample (10 mg) was dissolved in MeOH (4 mL), sonicated for 5 min, and centrifuged for 10 min at 3,000 rpm. The phenolic acid concentration in the supernatant solution was determined using high performance liquid chromatography (HPLC). HPLC analysis was performed using an Agilent 1260 Infinity Quaternary LC (Hewlett Packard, Wilmington, NC, USA), equipped with a multiple wavelength diode-array detector operating at 280 nm. Chromatographic separations were achieved using an Agilent Zorbax RRHD SB-C18 threaded column (2.1 mm i.d.×100 mm, 1.8 μm particle size; Agilent Technologies, Inc., Santa Clara, CA, USA). The column temperature and flow rate were set at 30°C and 0.3 mL/min, respectively. Two solvents (solutions A and B) were used to achieve a gradient elution. Solution A was composed of water containing 0.1% formic acid, while solution B was composed of acetonitrile containing 0.1% formic acid, and the following gradient was employed: 0% B (0 min), 5% B (0～3.5 min), 15% B (3.5～7.1 min), 40% B (7.1～25 min), 40% B (25～26 min), 100% B (26～27 min), 100% B (27～29 min), and 0% B (29～35 min). The standards employed for analysis were HBA, VA, PCA, and FA.

The phenolic acid was identified and quantified based on analytical standard curves, using the following equation:

$$\text{EE (\%)} = \frac{\text{ADC}}{\text{TDC}}$$

where ADC is the actual drug content and TDC is the theoretical drug content.

UV-visible spectroscopy

The UV-visible absorption spectra for phenolic acids, HP-β-CD, and inclusion complexes were recorded by using a Synergy™ HTX spectrophotometer (BioTek Instruments Inc., Winooski, VT, USA). Each sample (50 mmol) was dissolved in water (mL) at room temperature. The aqueous solutions were scanned in the range of 200 nm to 400 nm to obtain the UV-visible absorption spectra.

FT-IR

The FT-IR spectra of the phenolic acids, HP-β-CD, and inclusion complexes were recorded between 5,000 cm^{-1} and 550 cm^{-1} (mid-infrared region) on an FT-IR spectrometer (FT/IR-6300, JASCO Corporation, Tokyo, Japan) with 250 scans at a resolution of 2 cm^{-1}. Each sample was ground with spectroscopic grade potassium bromide

(KBr) powder and then pressed into 1 mm pellets (2 mg of sample per 200 mg dry KBr). A blank KBr disk was used as the background. FT-IR spectra were smoothed, and the baseline was corrected automatically using JASCO's exclusive built-in software (Spectra Manager™ II, JASCO Corporation).

DSC

DSC analysis was carried out for the phenolic acids, HP-β-CD, and inclusion complexes using a Q10 differential calorimeter calibrated with indium (TA Instruments, New Castle, DE, USA). All samples were freeze-dried prior to DSC analysis. Each dried powder (2~3 mg) was heated in a crimped aluminum pan at a scanning rate of 5°C/min, and temperature range of 25°C to 400°C, under a nitrogen flow of 40 mL/min. An empty pan that was sealed in the same manner was used as reference. Each sample was measured thrice to ensure reproducibility.

XRD

The X-ray powder diffraction patterns were obtained using a PANalytical X'Pert PRO MPD X-ray diffractometer (PANalytical Inc., Almelo, The Netherlands) with a Ni-filter, Cu-Kα radiation, a voltage of 40 kV, and a current of 30 mA. Analyses were performed on the same samples prepared for the DSC studies. Data were collected in the range of $2\theta=5.00^{\circ}$ to 50.00° (θ being the angle of diffraction), with the following parameters at room temperature: step width: 0.02°, step time: 0.4 s, scanning speed: 5°/min, divergence slit width: 0.2 mm, scatter slit width: 0.6 mm, and receiving slit width: 0.2 mm. Samples were freeze-dried and then transferred (10 mg samples) onto the slide for packing prior to X-ray scanning.

Statistical analysis

The experimental data were subjected to analysis of variance (ANOVA). The significant differences between the mean values, as determined from measurements carried out in five replicate tests (i.e., $P<0.05$), were obtained by Duncan's multiple range test using statistical analysis software (SPSS 20.0, IBM Inc., Armonk, NY, USA).

RESULTS AND DISCUSSION

Encapsulation efficiency of phenolic compounds with HP-β-CD

The EE is defined as the concentration of the incorporated material (such as active ingredients, drugs, fragrances, proteins, pesticides, antimicrobial agents, etc.) detected in the formulation relative to the initial concentration used to make the formulation. A high EE means that substrates were successfully entrapped within the micelle or nanoparticle. The EE of encapsulated HBA/HP-β-CD, VA/HP-β-CD, PCA/HP-β-CD, and FA/HP-β-CD are shown in Table 1. The HBA/HP-β-CD complex exhibited the highest EE (91.34%), followed by VA/HP-β-CD (89.31%), PCA/HP-β-CD (88.71%), and FA/HP-β-CD (87.74%). HP-β-CD has gained appreciable acceptance among the various types of CDs. The inclusion complexes of HP-β-CD have been successfully used to improve the solubility, chemical stability, and bioavailability of several poorly soluble compounds. Various known laboratory methods used for the formation of the inclusion complexes have been widely reported, including coprecipitation, neutralization, kneading, spray-drying, freeze-drying, solvent evaporation, ball-milling, and sealed-heating techniques (Yamada et al., 2000). Simple phenolic acids such as cinnamic acids (e.g. FA and PCA) and benzoic acids (e.g. HBA and VA) have relatively low solubility in pure water (pH<4); however, these can form intramolecular as well as intermolecular hydrogen bonds, due to the polarizable hydroxyl moiety of the phenolic and carboxylic groups (Carvalho et al., 2004). Thus, it has been suggested that the interaction between phenolic acids and HP-β-CD polymers occurs via hydrogen bonds. As HP-β-CD forms inclusion complexes with molecules, which enter partly or entirely into the relatively hydrophobic cavity of the CD, several high-energy water molecules are simultaneously expelled (Karathanos et al., 2007). In addition, the proposed driving forces that allow for complex formation between CDs and drugs are hydrogen bonds, van der Waals forces, hydrophobic interactions, and the release of high-energy water molecules from the cavity (Salústio et al., 2009). Thus, it has been suggested that in the formation of the inclusion complex, the more polar water molecules present in the cavity of the CD are replaced by phenolic acids of lower polarity. According to the literature, the encapsulation efficiency is related to the encapsulated compound and the coating used.

UV-visible spectroscopic analysis of encapsulated HP-b-CD/phenolic complexes

UV-visible spectroscopy is an important tool used to

Table 1. Encapsulation efficiency of inclusion complexes of phenolic acids with HP-β-CD (unit: %)

Sample	Efficiency of encapsulation
HBA/HP-β-CD	91.34±0.17[a]
VA/HP-β-CD	89.31±0.16[b]
PCA/HP-β-CD	88.71±0.20[b]
FA/HP-β-CD	87.74±0.29[c]

Data represent the mean values for each sample±standard deviation (n=5).
Different letters (a-c) indicate a significant difference at $P<0.05$.
HP-β-CD, hydroxypropyl-β-cyclodextrin; HBA, *p*-hydroxybenzoic acid; VA, vanillic acid; PCA, *p*-coumaric acid; FA, ferulic acid.

study the complexation of phenolic acids with HP-β-CD. The encapsulation process involving CDs alters the physicochemical properties of the guest molecule (phenolic acids). The absorption spectra of HBA/HP-β-CD, VA/HP-β-CD, PCA/HP-β-CD, and FA/HP-β-CD complexes are presented in Fig. 1. HP-β-CD displayed no absorbance in the UV-visible spectrum. The λ_{max} values of HBA, VA, PCA, and FA were 251 nm, 255 nm and 289 nm, 288 nm, and 321 nm, respectively. The UV absorbance of HP-β-CD was very low and it did not exhibit any appreciable peak within the 200∼400 nm range; this was expected as the molecule does not contain π-electrons (double bonds) that can absorb UV energy. Moreover, the phenolic acid/HP-β-CD complexes displayed a decrease in the absorption and a small shift (≈2 nm) in the λ_{max} values, although they were similar to the characteristic absorption peaks for the polyphenols. Zhao et al. (2010) reported that a blue shift of ca. 2 nm for chlorogenic acid was detected after inclusion with β-CD. However, Górnas et al. (2009) reported a bathochromic shift in the absorption peaks of chlorogenic and caffeic acids in the presence of β-CD. Therefore, these results suggested that interactions between the phenolic acids and HP-β-CD existed due to partial shielding of the chromophore electrons in the HP-β-CD cavity, indicating that the phenolic acids were capable of forming inclusion complexes with HP-β-CD.

FT-IR analysis of encapsulated HP-b-CD/phenolic complexes

FT-IR is a useful technique that can be used to confirm the formation of an inclusion complex. The FT-IR spectra of the encapsulated HBA/HP-β-CD, VA/HP-β-CD, PCA/HP-β-CD, and FA/HP-β-CD are presented in Fig. 2. In the spectrum of HBA (Fig. 2A), there were strong absorption bands in the range of 1,675∼1,101 cm^{-1}. The O−H group gave rise to three vibrations (stretching, in-plane bending, and out-of-plane bending). The strong band at 3,390 cm^{-1} was attributed to the O−H group. The sharp absorption band at 1,675 cm^{-1} corresponded to the carbonyl C=O stretching vibration. The intense absorption at 1,168 cm^{-1} was attributed to the C−O stretching vibration. In the spectrum of VA (Fig. 2B), there were strong absorption bands in the range of 1,683∼1,205 cm^{-1}. The IR spectrum of VA showed the characteristic bands at 3,484 cm^{-1} for the O−H group, 1,683 cm^{-1} for the C=O group, 1,299 cm^{-1} for the C−O group, and 3,100∼2,778 cm^{-1} for the CH_3 group. The IR data obtained for VA agreed with previous reports (González-Baró et al., 2008). In the spectrum of PCA (Fig. 2C), there were strong absorption bands in the range of 1,671∼1,105 cm^{-1}. The IR spectrum of PCA showed the characteristic bands at 3,378 cm^{-1} for the O−H group, 1,671 cm^{-1} for the C=O group, and 1,245 cm^{-1} for the C−O group. In the spectrum of FA (Fig. 2D), there were strong absorption bands in the range of 1,691∼1,112 cm^{-1}. The IR spectrum of FA showed the characteristic bands at 3,436 cm^{-1} for the O−H group, 3,016 cm^{-1} for the C−H group, 1,691 cm^{-1} for the C=O group, 1,666 cm^{-1} for the alkene group, and 1,619∼1,432 cm^{-1} for the C=C group. The IR data obtained for

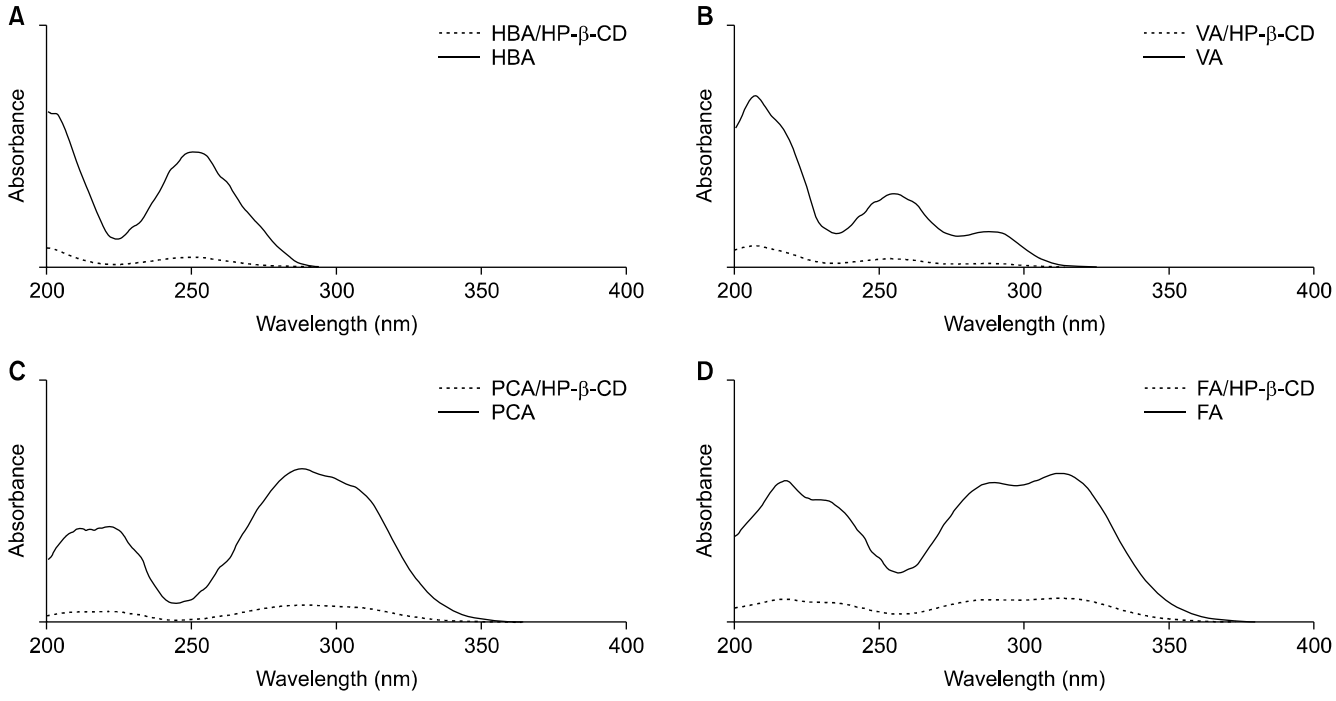

Fig. 1. Ultraviolet-visible absorption spectra of (A) HBA and HBA/HP-β-CD, (B) VA and VA/HP-β-CD, (C) PCA and PCA/HP-β-CD, and (D) FA and FA/HP-β-CD. HBA, *p*-hydroxybenzoic acid; VA, vanillic acid; PCA, *p*-coumaric acid; FA, ferulic acid; HP-β-CD, hydroxypropyl-β-cyclodextrin.

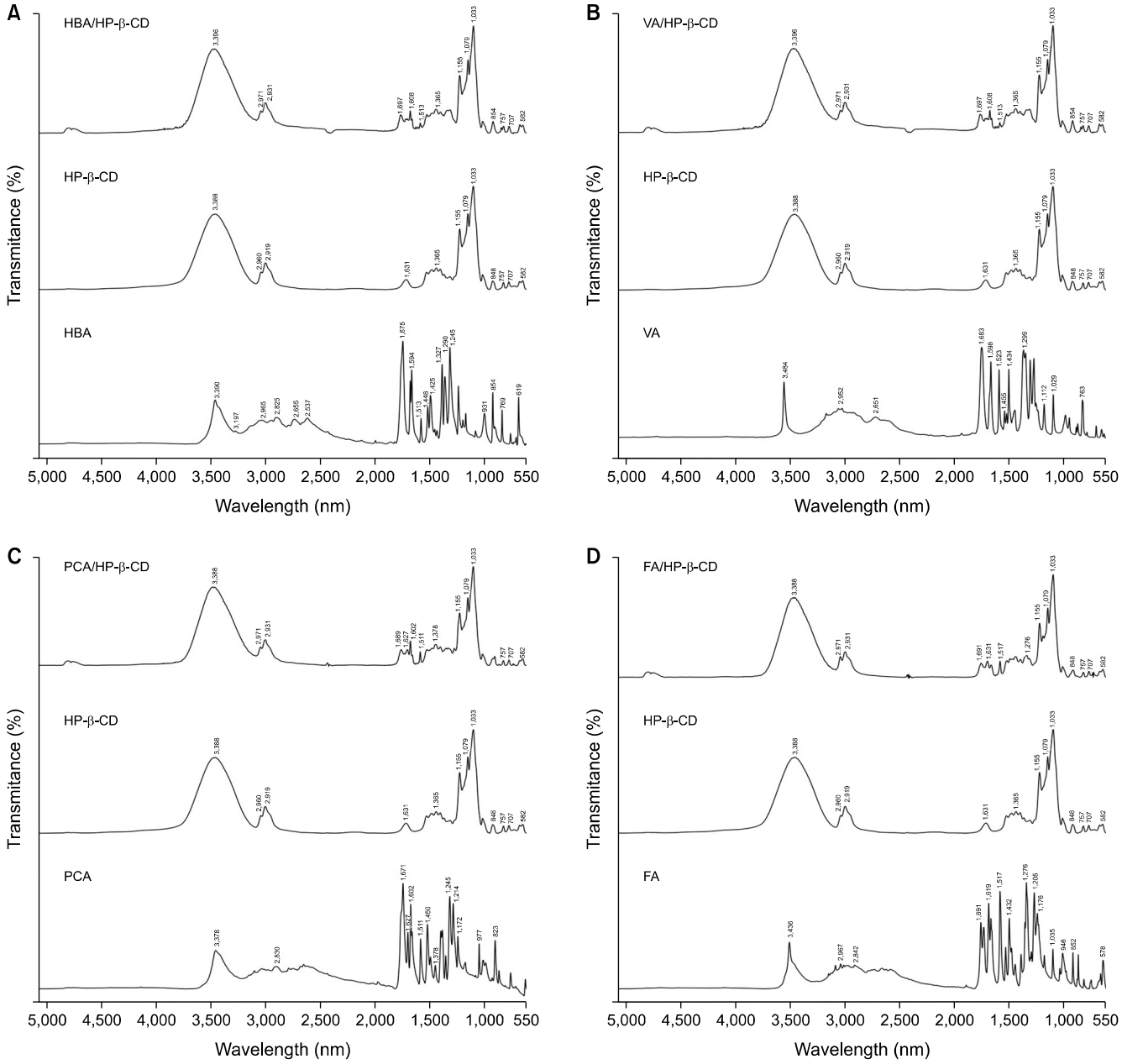

Fig. 2. Fourier transform infrared spectroscopy spectra of (A) HBA and HBA/HP-β-CD, (B) VA and VA/HP-β-CD, (C) PCA and PCA/HP-β-CD, and (D) FA and FA/HP-β-CD. HBA, *p*-hydroxybenzoic acid; VA, vanillic acid; PCA, *p*-coumaric acid; FA, ferulic acid; HP-β-CD, hydroxypropyl-β-cyclodextrin.

FA agreed with previous reports (Yu et al., 2010; Yang et al., 2013). The FT-IR spectrum of pure HP-β-CD illustrated intense broad absorption bands at 3,600∼3,000 cm^{-1}, which corresponded to the free stretching vibrations. The CH_3 and CH vibrations were at 2,960 cm^{-1}. The large band in region 1,155∼1,033 cm^{-1} was ascribed to the C−O stretching vibration. However, the FT-IR spectra of the phenolic acid/HP-β-CD inclusion complexes did not display any features that were similar to the pure phenolic acids, although the spectra were very similar to that of HP-β-CD. Changes in the FT-IR spectra were also observed by Wang et al. (2011) when evaluating the encapsulation of FA in HP-β-CD. The authors observed displacement, reduction, and disappearance of the peaks relating to FA in the matrix of HP-β-CD. Therefore, these results suggested that the characteristic stretching bands of the phenolic acids were masked by the intense band corresponding to the OH bending vibration of HP-β-CD. It can therefore be deduced that the inclusion complexes were successfully formed.

DSC analysis of encapsulated HP-β-CD/phenolic complexes

DSC can be used for the identification of inclusion complexes. When guest molecules are embedded in HP-β-CD cavities, their melting, boiling, or sublimating points gen-

eral shift to different temperatures or disappear (Marques et al., 1990). The DSC curves for HBA/HP-β-CD, VA/HP-β-CD, PCA/HP-β-CD, and FA/HP-β-CD complexes are presented in Fig. 3. The DSC curve of HBA (Fig. 3A) showed a sharp endothermic peak at 214°C. The DSC curves of VA (Fig. 3B) and PCA (Fig. 3C) showed sharp endothermic peaks at 210°C and 216°C, respectively. The DSC curve of FA (Fig. 3D) displayed one sharp endothermic peak at 172°C, corresponding to the melting point of the crystalline form of the drug, followed by an exothermic effect due to decomposition at higher temperatures. The DSC curve of HP-β-CD showed a broad endothermic peak at approximately 294°C. This peak was related to dehydration by the removal of water molecules that were bound to CD (Kohata et al., 1993; Marini et al., 1996). The DSC curve of the inclusion complex showed the complete disappearance of HBA, VA, PCA, and FA peaks. This indicated that complex formation had successfully occurred, because the reduction in intensity and /or expansion and the endothermic peak shift to lower temperatures indicates partial complexation (Naidu et al., 2004). Also, the exothermic peaks emerging after 300°C were possibly due to melting and thermal decomposition of HP-β-CD (Hedges et al., 1995). The melting points of the phenolic acids disappeared, and the thermal properties of HP-β-CD were altered following the formation of

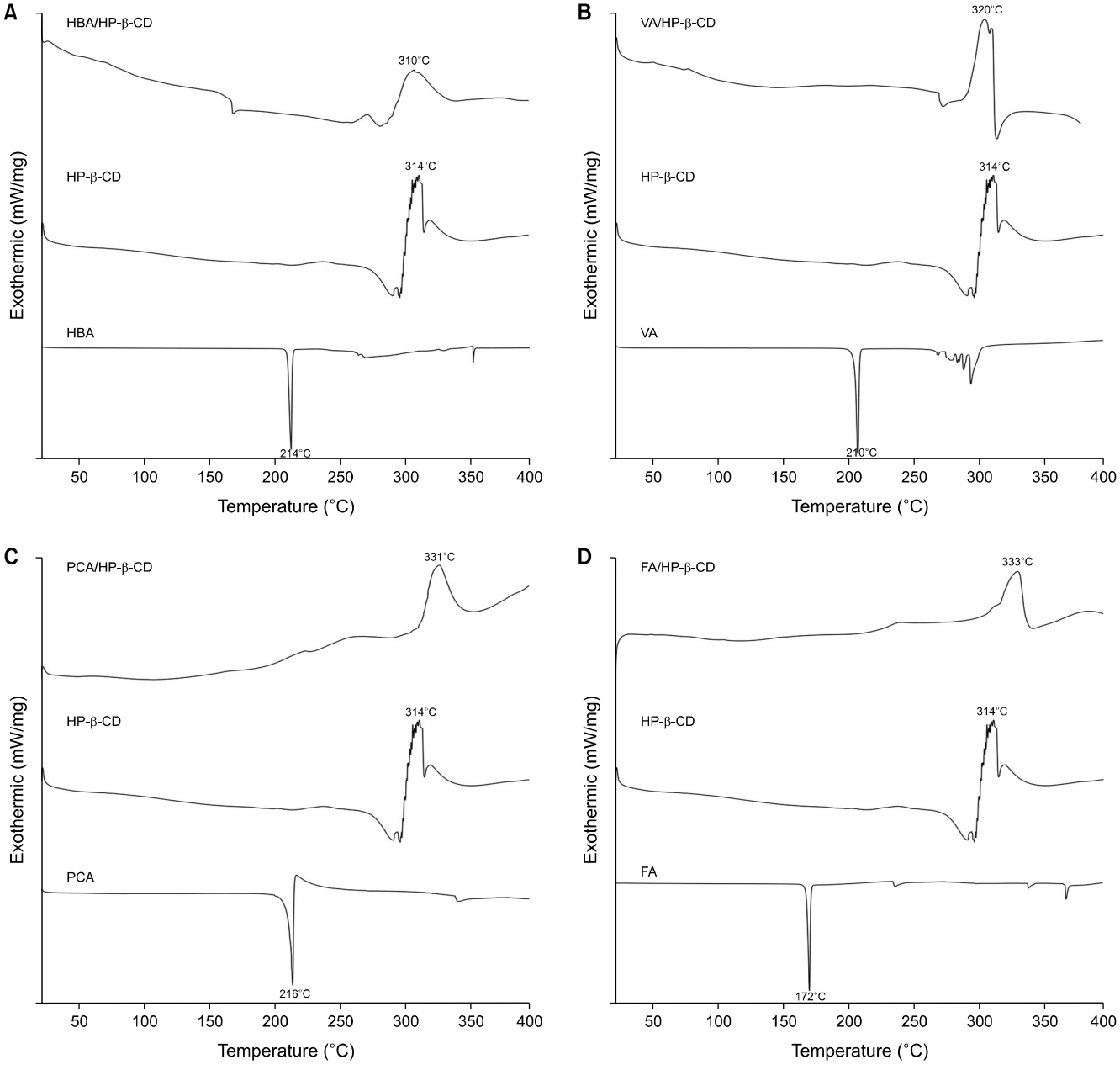

Fig. 3. Differential scanning calorimetry thermograms of (A) HBA and HBA/HP-β-CD, (B) VA and VA/HP-β-CD, (C) PCA and PCA/HP-β-CD, and (D) FA and FA/HP-β-CD. HBA, *p*-hydroxybenzoic acid; VA, vanillic acid; PCA, *p*-coumaric acid; FA, ferulic acid; HP-β-CD, hydroxypropyl-β-cyclodextrin.

the phenolic acid/HP-β-CD inclusion complexes, seen as a shift in the melting points. DSC analysis provided exhaustive data relating to the physical changes that accompanied complex formation (Patel et al., 2019). The disappearance of thermal peaks due to the presence of the guest molecule further indicated the successful preparation of the inclusion complex (Amiri and Nalbandi, 2018; Suvarna et al., 2018).

XRD analysis of encapsulated HP-β-CD/phenolic complexes

Powder X-ray diffractometry is a useful method for the detection of CD complexation in powder or microcrystalline states. Should the inclusion complex form, the resulting diffraction pattern of the complex is clearly distinct from the superimposed diffraction patterns of the components (Veiga et al., 1996). As shown in Fig. 4, the XRD pattern of HBA (Fig. 4A), VA (Fig. 4B), PCA (Fig. 4C), and FA (Fig. 4D) showed intense, sharp peaks, due to the crystalline nature of the compound. HBA had strong crystallinity peaks at 2θ of 17.2°, 18.6°, 24.1°, 26.1°, 26.5°, 28.6°, 29.6°, and 31.9°. VA had strong crystallinity peaks at 2θ of 9.3°, 10.1°, 12.8°, 16.5°, 21.9°, 24.0°, 25.7°, 27.0°, and 29.1°. PCA had strong crystallinity peaks at 2θ of 17.6°, 18.9°, 19.8°, 24.9°, 26.4°, 26.8°, and 30.2°. FA had strong crystallinity peaks at 2θ of 8.9°, 9.7°, 12.8°,

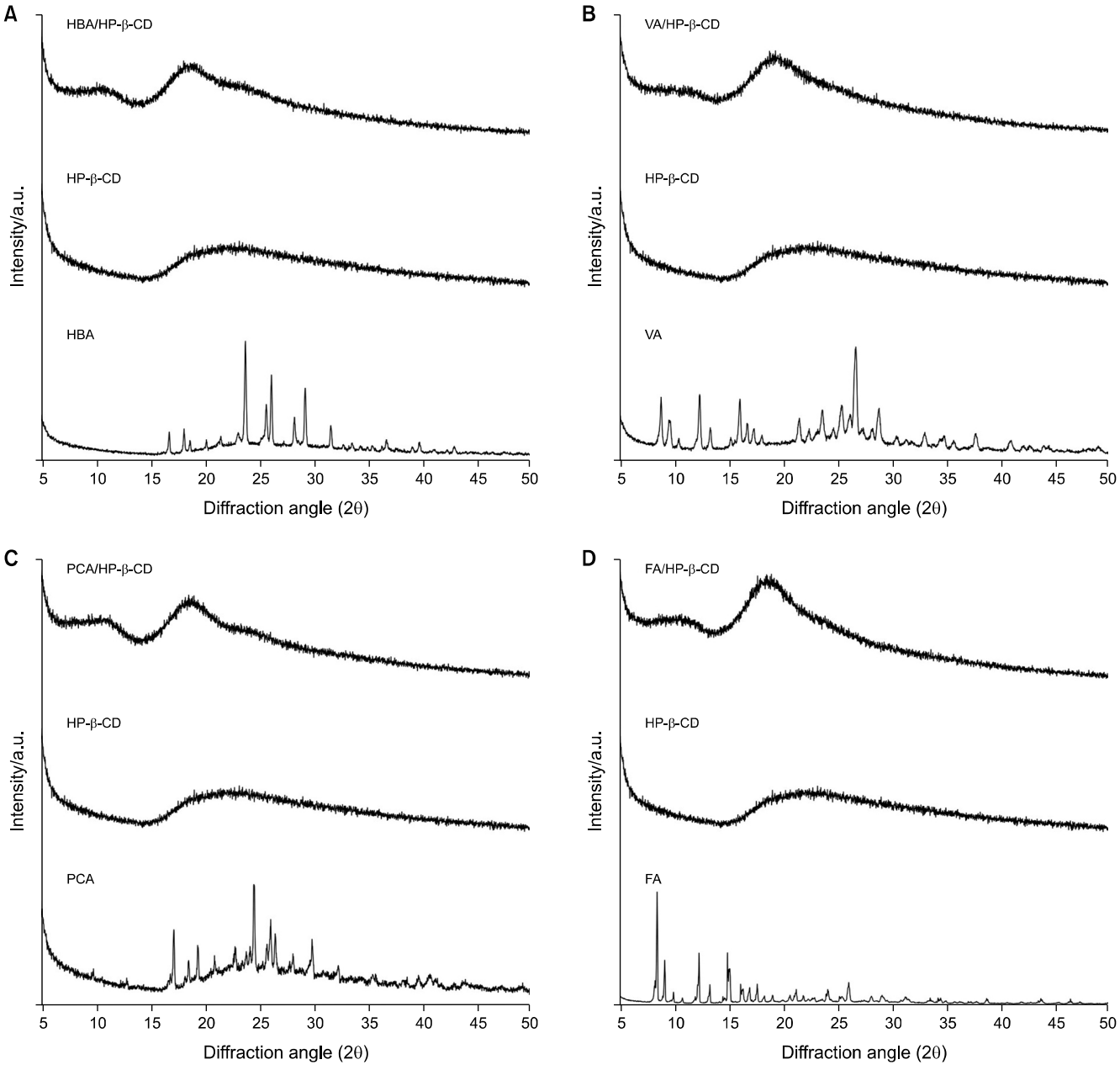

Fig. 4. Powder X-ray diffraction patterns of (A) HBA and HBA/HP-β-CD, (B) VA and VA/HP-β-CD, (C) PCA and PCA/HP-β-CD, and (D) FA and FA/HP-β-CD. HBA, *p*-hydroxybenzoic acid; VA, vanillic acid; PCA, *p*-coumaric acid; FA, ferulic acid; HP-β-CD, hydroxypropyl-β-cyclodextrin.

15.4°, 15.6°, and 26.4°. In contrast, the XRD pattern of HP-β-CD revealed a broad peak in the range of 15∼25° (2θ), confirming its amorphous character. However, the phenolic acid/HP-β-CD inclusion complexes displayed a large, broad background signal below the crystalline peaks, which was like that of the amorphous HP-β-CD. Furthermore, the characteristic peaks of the phenolic acids were absent, indicating the formation of a significant amount of amorphous material. These results were consistent with those of the FT-IR spectroscopy.

In conclusion, the results of this study clearly demonstrated that phenolic acids could be efficiently complexed with HP-β-CD for the formation of an inclusion complex. This was achieved using the freeze-drying method in a phenolic acid/HP-β-CD molar ratio of 1:1. The encapsulated phenolic acids displayed different characteristics to the pure phenolic acids, as confirmed by UV-visible spectroscopy, FT-IR, DSC, and XRD. The HP-β-CD matrix displayed a higher encapsulation efficiency, and capsules with characteristic shape were obtained. Further studies should be performed to measure the release of phenolic acids from the capsules, to determine if the encapsulating material increases the efficiency of delivery.

AUTHOR DISCLOSURE STATEMENT

The author declares no conflict of interest.

REFERENCES

Amiri S, Nalbandi B. Improve solubility and bioavailability of silver sulfadiazine via formation of inclusion complex by cyclodextrin. J Inorg Organomet Polym. 2018. 28:1764-1774.

Bhardwaj R, Dorr RT, Blanchard J. Approaches to reducing toxicity of parenteral anticancer drug formulations using cyclodextrins. PDA J Pharm Sci Technol. 2000. 54:233-239.

Bravo L. Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. Nutr Rev. 1998. 56:317-333.

Carvalho JCT, Gosmann G, Schenkel EP. Compostos fenólicos simples e heterosídicos. In: Simões CMO, Schenkel EP, Gosmann G, de Mello JCP, Mentz LA, Petrovick PR, editors. Farmacognosia da Planta ao Medicamento. 5th ed. Editora da UFSC-Florianópolis, Editora da UFRGS-Porto Alegre, Brazil. 2004. p 519-535.

Chen Q, Liu C, Liu F. Application of cyclodextrins in polymerization. Prog Chem. 2010. 22:927-937.

Dufossé L, Souchon I, Feron G, Latrasse A, Spinnler HE. *In situ* detoxification of the fermentation medium during γ-decalactone production with the yeast *Sporidiobolus salmonicolor*. Biotechnol Prog. 1999. 15:135-139.

Fang Z, Bhandari B. Encapsulation of polyphenols—a review. Trends Food Sci Technol. 2010. 21:510-523.

Fujishima N, Kusaka K, Umino T, Urushinata T, Terumi K. Flour based foods containing highly branched cyclodextrins. JP Patent 136,898. 2001.

González-Baró AC, Parajón-Costa BS, Franca CA, Pis-Diez R. Theoretical and spectroscopic study of vanillic acid. J Mol Struct. 2008. 889:204-210.

Górnas P, Neunert G, Baczyński K, Polewski K. Beta-cyclodextrin complexes with chlorogenic and caffeic acids from coffee brew: spectroscopic, thermodynamic and molecular modelling study. Food Chem. 2009. 114:190-196.

Gould S, Scott RC. 2-Hydroxypropyl-β-cyclodextrin (HP-β-CD): a toxicology review. Food Chem Toxicol. 2005. 43:1451-1459.

Harborne JB. General procedures and measurement of total phenolics. In: Harborne JB, editor. Methods in Plant Biochemistry: Plant Phenolics. Academic Press, London, UK. 1989. Vol 1, p 1-28.

Harris CS, Mo F, Migahed L, Chepelev L, Haddad PS, Wright JS, et al. Plant phenolics regulate neoplastic cell growth and survival: a quantitative structure-activity and biochemical analysis. Can J Physiol Pharmacol. 2007. 85:1124-1138.

Hedges AR, Shieh WJ, Sikorski CT. Use of cyclodextrins for encapsulation in the use and treatment of food products. In: Risch SJ, Reineccius GA, editors. Encapsulation and Controlled Release of Food Ingredients. American Chemical Society, Washington, DC, USA. 1995. p 60-71.

Hedges AR. Industrial applications of cyclodextrins. Chem Rev. 1998. 98:2035-2044.

Holland L, Rizzi G, Malton P. Cosmetic compositions comprising cyclic oligosaccharide and fragrance. US Patent 99,009907. 1999.

Karathanos VT, Mourtzinos I, Yannakopoulou K, Andrikopoulos NK. Study of the solubility, antioxidant activity and structure of inclusion complex of vanillin with β-cyclodextrin. Food Chem. 2007. 101:652-658.

Khadem S, Marles RJ. Monocyclic phenolic acids; hydroxy- and polyhydroxybenzoic acids: occurrence and recent bioactivity studies. Molecules. 2010. 15:7985-8005.

Kohata S, Jyodoi K, Ohyoshi A. Thermal decomposition of cyclodextrins (α-, β-, γ-, and modified β-CyD) and of metal-(β-CyD) complexes in the solid phase. Thermochim Acta. 1993. 217: 187-198.

Lezcano M, Al-Soufi W, Novo M, Rodríguez-Núñez E, Tato JV. Complexation of several benzimidazole-type fungicides with α- and β-cyclodextrins. J Agric Food Chem. 2002. 50:108-112.

Liu HK, Lo YK, Tsai TR, Cham TM. Physicochemical characterizations of ostholehydroxypropyl-β-cyclodextrin inclusion complexes with high-pressure homogenization method. J Food Drug Anal. 2010. 18:391-397.

Liu J, Qiu L, Gao J, Jin Y. Preparation, characterization and *in vivo* evaluation of formulation of baicalein with hydroxypropyl-β-cyclodextrin. Int J Pharm. 2006. 312:137-143.

Ma SX, Chen W, Yang XD, Zhang N, Wang SJ, Liu L, et al. Alpinetin/hydroxypropyl-β-cyclodextrin host-guest system: preparation, characterization, inclusion mode, solubilization and stability. J Pharm Biomed Anal. 2012. 67-68:193-200.

Marini A, Berbenni V, Bruni G, Giordano F, Villa M. Dehydration of β-cyclodextrin: facts and opinions. Thermochim Acta. 1996. 279:27-33.

Marques HMC, Hadgraft J, Kellaway IW. Studies of cyclodextrin inclusion complexes. I. The salbutamol-cyclodextrin complex as studied by phase solubility and DSC. Int J Pharm. 1990. 63: 259-266.

Martin KR, Appel CL. Polyphenols as dietary supplements: a double-edged sword. Nutr Diet Suppl. 2010. 2:1-12.

Naidu NB, Chowdary KP, Murthy KV, Satyanarayana V, Hayman AR, Becket G. Physicochemical characterization and dissolution properties of meloxicam-cyclodextrin binary systems. J Pharm Biomed Anal. 2004. 35:75-86.

Park EK, Ahn SR, Kim DH, Lee EW, Kwon HJ, Kim BW, et al. Effects of unripe apple polyphenols on the expression of matrix metalloproteinase-1 and type-1 procollagen in ultraviolet irradiated human skin fibroblasts. J Korean Soc Appl Biol Chem. 2014. 57:449-455.

Patel KK, Gade S, Anjum MM, Singh SK, Maiti P, Agrawal AK, et al. Effect of penetration enhancers and amorphization on transdermal permeation flux of raloxifene-encapsulated solid lipid nanoparticles: an *ex vivo* study on human skin. Appl Nanosci. 2019. 9:1383-1394.

Pralhad T, Rajendrakumar K. Study of freeze-dried quercetin-cyclodextrin binary systems by DSC, FT-IR, X-ray diffraction and SEM analysis. J Pharm Biomed Anal. 2004. 34:333-339.

Roux M, Perly B, Djedaïni-Pilard F. Self-assemblies of amphiphilic cyclodextrins. Eur Biophys J. 2007. 36:861-867.

Salústio PJ, Feio G, Figueirinhas JL, Pinto JF, Cabral Marques HM. The influence of the preparation methods on the inclusion of model drugs in a β-cyclodextrin cavity. Eur J Pharm Biopharm. 2009. 71:377-386.

Sansone F, Picerno P, Mencherini T, Villecco F, D'Ursi AM, Aquino RP, et al. Flavonoid microparticles by spray-drying: Influence of enhancers of the dissolution rate on properties and stability. J Food Eng. 2011. 103:188-196.

Schmid G. Cyclodextrin glycosyltransferase production: yield enhancement by overexpression of cloned genes. Trends Biotechnol. 1989. 7:244-248.

Singh J, Dartois A, Kaur L. Starch digestibility in food matrix: a review. Trends Food Sci Technol. 2010. 21:168-180.

Suvarna V, Thorat S, Nayak U, Sherje A, Murahari M. Host-guest interaction study of Efavirenz with hydroxypropyl-β-cyclodextrin and L-arginine by computational simulation studies: preparation and characterization of supramolecular complexes. J Mol Liq. 2018. 259:55-64.

Szente L, Szejtli J. Cyclodextrins as food ingredients. Trends Food Sci Technol. 2004. 15:137-142.

Tonelli AE. Cyclodextrins as a means to nanostructure and functionalize polymers. J Incl Phenom Macrocycl Chem. 2008. 60: 197-202.

Tsao JY, Wu CP, Tsai HH, Peng KC, Lin PY, Su SY, et al. Effect of hydroxypropyl-β-cyclodextrin complexation on the aqueous solubility, structure, thermal stability, antioxidant activity, and tyrosinase inhibition of paeonol. J Incl Phenom Macrocycl Chem. 2012. 72:405-411.

Veiga F, Teixeira-Dias JJC, Kedzierewicz F, Sousa A, Maincent P. Inclusion complexation of tolbutamide with β-cyclodextrin and hydroxypropyl-β-cyclodextrin. Int J Pharm. 1996. 129:63-71.

Wang J, Cao Y, Sun B, Wang C. Characterisation of inclusion complex of *trans*-ferulic acid and hydroxypropyl-β-cyclodextrin. Food Chem. 2011. 124:1069-1075.

Yamada T, Imai T, Ouchi K, Otagiri M, Hirayama F, Uekama K. Inclusion complex of 3,9-bis(*N*,*N*-dimethylcarbamoyloxy)-5H-benzofuro[3,2-c]quinoline-6-one (KCA-098) with heptakis (2,6-di-*O*-methyl)-β-cyclodextrin: interaction and dissolution properties. Chem Pharm Bull. 2000. 48:1264-1269.

Yang JM, Zha LS, Yu DG, Liu J. Coaxial electrospinning with acetic acid for preparing ferulic acid/zein composite fibers with improved drug release profiles. Colloids Surf B Biointerfaces. 2013. 102:737-743.

Yu D, Nie W, Zhu L, Branford-White C. Fast dissolution nanofiber membrane of ferulic acid prepared using electrospinning. Proceedings of the 4th International Conference on Bioinformatics and Biomedical Engineering. 2010 June 18-20. Chengdu, China. https://doi.org/10.1109/ICBBE.2010.5516130

Yuan C, Jin Z, Li X. Evaluation of complex forming ability of hydroxypropyl-β-cyclodextrins. Food Chem. 2008. 106:50-55.

Zhao M, Wang H, Yang B, Tao H. Identification of cyclodextrin inclusion complex of chlorogenic acid and its antimicrobial activity. Food Chem. 2010. 120:1138-1142.