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Complexation and physicochemical analysis of hydrophobic molecules of methyl jasmonate with Hydroxypropyl-β–Cyclodextrin

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ABSTRACT. In the present study, methyl jasmonate (MeJa) was included in 2-hydroxypropyl-β-cyclodextrin (HPβCD) by grinding (M_1), freeze drying (M_2), co-precipitation + freeze drying (M_3) and by applying supercritical carbon dioxide (M_4). FT-IR/ATR, FT-Raman, TGA, and DSC analyses of the complexation products confirmed that MeJa/HPβCD complexes were formed by the four different examined methods of inclusion. FT-IR/ATR supported the inclusion, mainly based on the reduction of intensity of absorption at the wavelength of maximum absorbance of free MeJa (1733 cm^{-1}), which was 27.69 au before inclusion. From these results, M_3 (2.29 au) and M_4 (0.90 au) were the most efficient techniques for complexation. TGA, and DSC analyses pointed out that the complexes formed by the methods M_3 and M_4 had the least loss of mass below approximately 305°C (the temperature that free HPβCD starts to decompose thermally). Except for M_1, the results of antioxidant activity (AA) based on the DPPH assay revealed that the AA of the inclusion compounds were higher than that of free MeJa ($\alpha = 0.05$). The best methods in terms of AA and thermal stability of the formed inclusion compounds were M_3 and M_4.

Kewwords: organic molecule; cyclodextrin; complexation; physicochemical characterization.

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Introduction

Methyl jasmonate (MeJa) is produced at various growth stages of plants, in general, in response to stresses, like those found in the soil by the growing seeds and roots, wind forces and herbivore attacks (Weiler et al., 1993). It is frequently referred to as volatile compound, likely because of its key odorant role at low levels on natural defense of plants against insect herbivores (Loftsson & Duchene, 2007), but its boiling point is approximately 220-225ºC at atmospheric pressure. Such a plant hormone has demonstrated to have an important anti-inflammatory (Dang et al., 2008), antioxidant (Wang, Bowman, & Ding, 2008), and antiparasitic activity (Ofer, Gold, & Flescher, 2008).

Despite the remarkable therapeutic properties of MeJa, its use as a drug in humans is limited by its low solubility in water; a drawback that has been at least partially solved by including MeJa in the central cavity of cyclodextrins (CDs) (Perassolo, Smith, Giulietti, & Talou, 2016). CDs are cyclic oligosaccharides comprised of 6, 7 (β-CD) or 8 glucose units that form a 3D toroidal structure with a hydrophobic cavity and an external surface that presents a hydrophilic nature (Alhassawi & Romero-Zerón, 2015; Loftsson & Duchene, 2007). The arrangement of hydroxyl groups and hydrogen/oxygen atoms are responsible for the opposed affinities of external and internal surfaces of CDs with water and make them especially attractive as hosts of non-polar drugs, as the MeJa. β-CD is cheap and commercially available with high purity, so it is usually preferred over the other CDs to form inclusion compounds with guest molecules for pharmaceutical purposes (Banchero, Ronchetti, & Manna, 2013). However, since it has relatively poor water solubility, modified β-CDs have been more extensively used as hosts to enhance the stability, aqueous solubility and bioavailability of the free guest (Yao et al., 2014).

2-hydroxypropyl β-cyclodextrin (HPβCD) is a water-soluble modified β-CD that presents low renal toxicity and hemolytic activity in humans. Based on these benefits, it is a Food and Drug Administration, FDA-regulated product that has been used to form inclusion compounds with ocular medications, for instance. As a host involved in the complexation of drugs, it also allows a controlled release of the bioactive guest to be achieved. Moreover, HPβCD is an additive that may increase the stability of thermolabile compounds in food or pharmaceutical products, as well as increase their shelf-life by protecting them against oxidation reactions that naturally take place during storage (Tan, Meng, Fan, Su, & Zhang, 2016). In summary, because of these many positive properties, HPβCD was chosen as the host to form inclusion compounds with MeJa in this study.

Many methods of complexation are available in the literature, such as grinding and co-precipitation with a variety of solvents (Junior et al., 2016), and freeze drying (Moyano et al., 1997). However, all these procedures are high energy-demanding operations that mostly use organic solvents. A promising alternative is the complexation by applying supercritical carbon dioxide ($scCO_2$). The $scCO_2$ method have some advantages and particular characteristics (i.e. liquid-like solvent power, gas-like viscosity and diffusivity, tunable physical properties, no traces of solvent in the final product, etc.) in comparison with the conventional chemical methods of complexation (Banchero & Manna, 2012; Banchero et al., 2013; Huang et al., 2016). It is not only believed to be a more efficient method when compared to the above mentioned ones (Rudrangi et al., 2015), but it also involves the use of a non-toxic solvent (CO_2), which can be easily removed from drugs or drug/cyclodextrin complexes after processing (Banchero & Manna, 2012; Banchero et al., 2013; Nerome et al., 2013), in addition it is an environmentally acceptable method because it uses a cheap substance as solvent (Banchero et al., 2013; Junior et al., 2017).

In this context, the present study aimed to evaluate the formation of inclusion compounds of MeJa with HPβCD by applying supercritical CO_2 (M_4) in comparison with the typical complexation methods of kneading (M_1), freeze drying (M_2) and co-precipitation + freeze drying (M_3). Spectral (H-NMR, FT-IR/ATR, FT-Raman, PAS) and thermal (TGA, and DSC) analyses were performed to confirm complexation. The 2,2 - diphenyl-1-picrylhydrazyl (DPPH) assay was also applied to determine the antioxidant activity of the free and complexed MeJa.

Material and methods

Chemicals

MeJa (purity ≥ 94.5%, MW = 224.3 g moL^{-1}) and HPβCD (MW = 1380 g moL^{-1}) were purchased from Wacker Chemie AG (Burghaunsen, Germany). DPPH, and 6-hydroxy-2,5,7,8-tetramethylch-roman-2-carboxylic acid (Trolox) were from Sigma-Aldrich (purity ≥ 90.0, Saint Louis, MO, USA). Ethanol 98% purity was from Anidrol (Diadema, State São Paulo, Brazil), and CO_2 technical grade from White Martins (Rio de Janeiro, State Rio de Janeiro, Brazil). All of them were used as received.

Complexation

M_1 (grinding method of complexation) is the simplest among the investigated methods of complexation. It basically consisted of grinding a dry mixture of MeJa (formed inclusion compounds) and HPβCD in a crucible for 15 min at ambient temperature and atmospheric pressure. The molar ratio of the guest to the host was unity (Junior et al., 2017).

To include MeJa in HPβCD by freeze-drying (M_2 - freeze drying method of complexation), a 1:1 molar mixture and 50 mL distilled water were initially added in a beaker, kept under agitation for 30 min. The dispersion was transferred to a freeze-dryer (L 101, Liotop, São Carlos, Brazil) to be lyophilized at 1.3 Pa and –54ºC (temperature of the condenser) for 36 hours. M_2 was according to the procedure of complexation by freeze-drying suggested by da Rosa et al., (2013); Vajna et al., (2011).

M_3 (co-precipitation + freeze drying method of complexation) was carried out at the same molar ratio between the guest and host already assumed for M_1 and M_2 (Mangolim et al., 2014). HPβCD was diluted in distilled water, while separately, MeJa was diluted in ethanol (98% purity), making two different solutions, respectively. Both solutions were prepared under stirring at a controlled temperature of 40°C and a concentration of 1 M. Thereafter, still under stirring and separately, the solutions were cooled in a controlled manner to 25°C for 4 hours in order to visually inspect the formation of precipitates. In the rotary evaporator, the two solutions were then mixed under a stirring condition of 120 rpm and a temperature of

≈78°C (the boiling point of ethanol at the atmospheric pressure) for approximately 90 min. This operation promotes the formation of the MeJa/HPβCD complex. Then the complex formed is frozen and lyophilized at 1.3 Pa and -54°C for 36 hours.

M_4 (complexation of MeJa with HPβCD by applying supercritical CO_2) was based on analogous procedures available in the literature (Banchero et al., 2013). The pressure of the employed $scCO_2$ apparatus can be set up to 200 bar and enables the temperature control of the sample. In this work, the chosen operating conditions were 90 bar, 40°C, and 60 min. To avoid degradation of MeJa, the temperature of M_4 methodology was fixed at 40°C. Pressure condition set to 90 bar resulted in low density (e.g., 0.29 g cm^{-3}). The most soluble compounds present the essential oils are extracted using these operational conditions (Reverchon & De Marco, 2006). Such conditions were tested in a previous work and revealed to be very satisfactory in complexation of drugs with cyclodextrins (Junior et al., 2017). In summary was fed into a packed bed formed by a 1:1 molar mixture of MeJa and HPβCD. Stagnant CO_2 at the desired temperature and pressure was left in the bed for further 60 min. before removal by simple system depressurisation.

Spectral analyses (FT-IR/ATR, FT-Raman)

Spectroscopy techniques (FT-IR/ATR, FT-Raman) were also applied, requiring no procedure of sample preparation, to analyze the guest, host and products of complexation (i.e.; dry powder was used in these cases). FT-IR/ATR and FT-Raman spectra were recorded from commercial spectrometers, so the procedures of absorbance reading are presented in a summarized way. In particular, FT-IR/ATR spectra with 128 scans each were monitored in the wavelength range between 4000 and 400 cm^{-1} at a resolution of 2 cm^{-1} by using a spectrometer (model Vertex 70v, Bruker, Ettlingen, Germany) coupled to an attenuated total reflectance (ATR) cell (model Platinum, Bruker, Ettlingen, Germany). FT-Raman absorbances with 500 scans per sample at wavelengths from 4000 to 4 cm^{-1} (resolution = 4 cm^{-1}) were instead measured with the same Vertex 70 v spectrometer equipped with a Raman module and a Germanium detector. The excitation source was a 1064 nm laser whose power could be varied from 5 to 200 mW.

Thermal analyses (DSC and TGA)

Both the responses emerged from thermal treatments of 2 mg powder samples placed in platinum crucibles taken to the furnace of a thermogravimetric analyzer (model STA 409 PC, Netzsch, Selb, Germany). The temperature of the sample was increased from 25 to 600°C at a constant heating rate of 10°C $min.^{-1}$ and under a N_2 stream of 50 mL $min.^{-1}$, respectively.

Antioxidant activity

The measured antioxidant activity (*AA* - antioxidant activity [%]) of MeJa in the free- and in the complexed forms (from different tested methodologies of complexation) was based on the well-known DPPH assay (Brand-Williams, Cuvelier, & Berset, 1995). It is a standard assay that involves a homogeneous reaction between DPPH as a stable free radical (0.004 mM) and the examined samples (3×10^{-3} M) with ethanol as solvent. In the current case, it took place in a glass vessel, involving a mixture of 3.6 mL of the first solution and 0.4 mL of the second, under dark room conditions for approximately 1 hour. The AA of the samples was given absorbance of the reaction products was measured at 517 nm with a spectrophotometer (model UV-1203, Shimadzu, Kyoto, Japan). The control was a mixture of 3.6 mL of a DPPH ethanol solution (0.004 mM) and 0.4 mL of a Trolox ethanol solution (0.05 mM). The *AA* of the samples were given by Equation 1:

$$AA = 100\left[\frac{A - A_c}{A_c}\right] \quad (1)$$

where:

*A (*absorbance of solutions of ethanol and MeJa, in a free and complexed form) and A_c (absorbance of control) are the absorbances of the samples and that of the control, respectively. All the experiments were performed in triplicate.

Results and discussion

Spectral analyses (FT-IR/ATR, FT-Raman)

The similarities between the FT-IR/ATR spectra of free HPβCD and those of the formed inclusion compounds observed in Figure 1a. is another indication of complexation of MeJa with HPβCD by the four different methods of inclusion (Sambasevam, Mohamad, Sarih, & Ismail, 2013; Yuan, Lu, & Jin, 2014).

Changes in intensity and wavenumber of some peaks in the complexes when compared to the same ones found in the free MeJa spectrum (e.g., at 1733, 2960, 1436 cm^{-1}), as well as the identification of absorption peaks characteristic of free MeJa in all the formed complexes (e.g.; at 1733 cm^{-1}) also support that the guest was included into the cavity of the HPβCD.

However, there are some differences between the FT-IR/ATR spectra of the inclusion compounds obtained by applying M_1-M_2 and M_3-M_4. For instance, from Figure 1a it is clear that the intensity of absorption at 3006 and 2960 cm^{-1}, characteristics of vibrations of = C–H and –C–H groups in the MeJa structure, are observed in the complexes obtained by applying the methods M_1 and M_2. However, they were no longer found (the one at 3006 cm^{-1}), or were shifted (the one at 2960 cm^{-1}), in the spectra of the inclusion compounds formed by applying co-precipitation + freeze-drying (M_3) and $scCO_2$ (M_4). This indicates the difference in the complexation mechanism between the methods M_1-M_2 and M_3-M_4.

The FT-Raman spectra of all the examined samples of free and inclusion compounds are illustrated in Figure 1b. To support complexation from these data, attention was given to changes in absorbance intensity and position of characteristics bands of MeJa at 1737, 1656 and 1272 cm^{-1} also detected in the spectra of MeJa/HPβCD complexes.

A reliable quantitative procedure to verify whether inclusion took place, still based on FT-IR/ATR spectroscopy, involves the estimation of absorbance band areas characteristics of functional groups of the guest (Aigner, Berkesi, Farkas, & Szabó-Révész, 2012; Valentini et al., 2015). In other words, such groups are those whose bands are exhibited in the spectrum of MeJa, but not in the one of HPβCD. In this case, the Gaussian function (dashed lines in Figure 2) with parameters tuned on the recorded absorbance (solid lines in Figure 2) was used to describe the absorbance bands of these particular groups at 1734 and 1701 cm^{-1}.

Coefficients of determination (R^2) close to unity corroborated the reliability of such a model, thus, in order to compute the areas, the Gaussian curves (dashed lines in Figure 2) were simply integrated. The sum of the computed areas from the MeJa spectrum (23.76 + 3.93 = 27.69 au) (Figure 2b) and those from the spectra of MeJa/HPβCD complexes close to the aforementioned frequencies (4.52 + 2.24 = 6.76 au; 0.85 + 0.67 = 1.52 au; 1.39 + 0.32 + 0.58 = 2.29 au; 0.41 + 0.38 + 0.11 = 0.90 au) (Figure 2, c to f) are markedly diverse. In summary, such an analysis also supports the formation of inclusion compounds of MeJa with HPβCD.

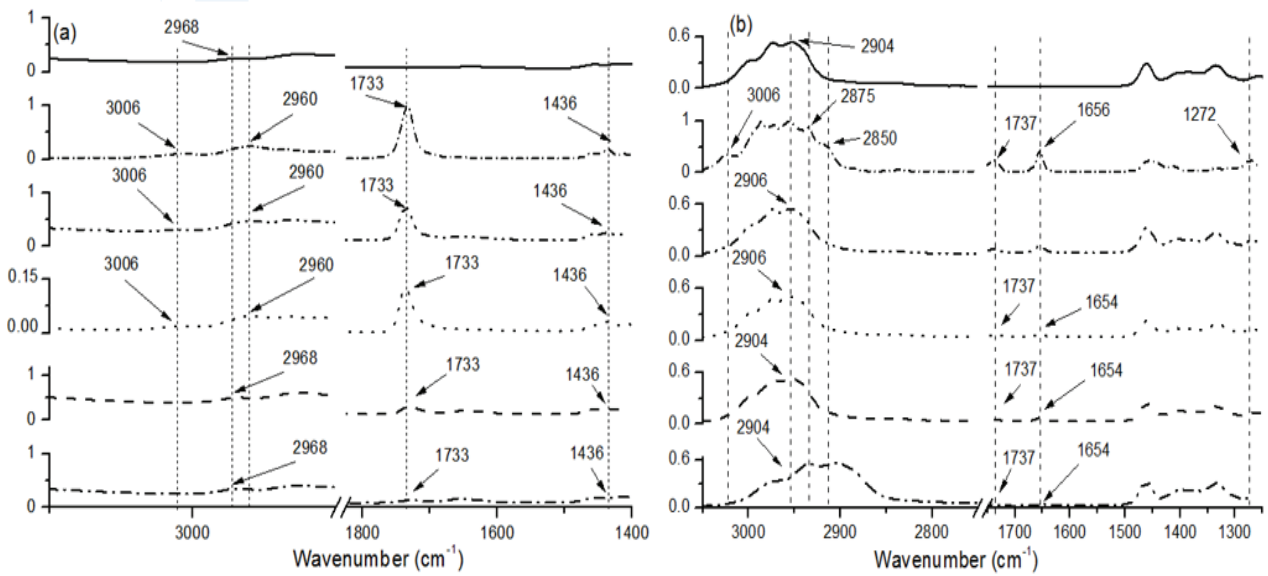

Figure 1. FT-IR/ATR (a), and FT-RAMAN (b) spectroscopy. Free HPβCD (solid line), free MeJa (short dash dot line), and MeJa/HPβCD complexes obtained by M_1 (dash dot dot line), M_2 (dot line), M_3 (dash line), M_4 (long dash dot line) (1:1 molar ratio).

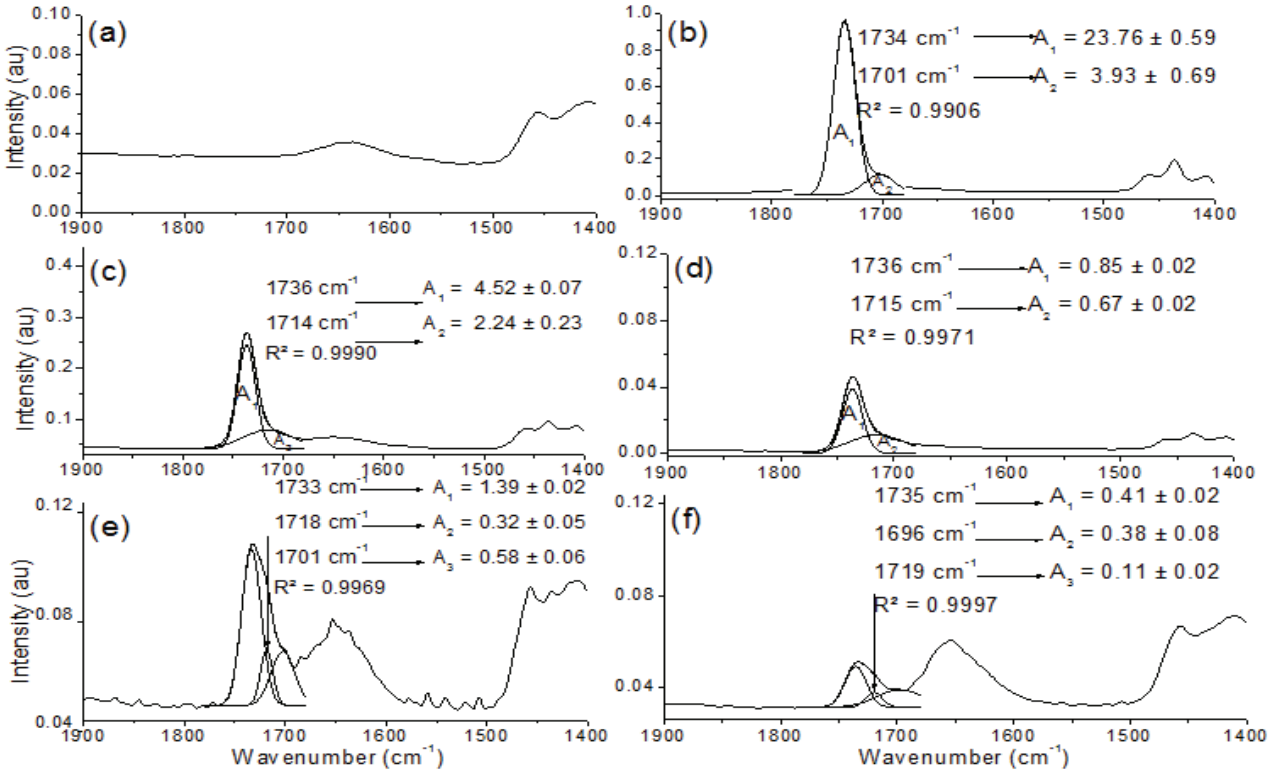

Figure 2. FT-IR/ATR of free HPβCD (a), free MeJa (b), MeJa/HPβCD from M_1 (c), MeJa/HPβCD from M_2 (d), MeJa/HPβCD from M_3 (e), and MeJa/HPβCD from M_4 (f). (1:1, molar ratio). Solid lines: experimental measurements; Dashed lines: calculated with the Gaussian function.

An additional remarkable finding from Figure 2 is that $A_1 + A_2$ for the free MeJa minus $A_1 + A_2$ for the MeJa/HPβCD complex by M_1 gives the lowest variation of area (≈20.93 au) among those computed. Such a change is associated with a minor degree of complexation by grinding. Because M_1 is the only inclusion method performed at mild conditions of temperature and pressure, it is naturally supposed that complexation at *T* and *P* close to normal ambient conditions does not contribute positively to include the guest into the host. The presence of a new absorbance band in the FT-IR/ATR spectra shown in Figure 2 (e and f) between 1600 and 1700 cm^{-1} confirms that the more drastic conditions of *T* and *P* by M_3 and M_4 favor inclusion.

Thermal analyses (TGA and DSC)

The results of loss of mass from the TG analyses in Figure 3a are discussed in view of three endothermic energy phenomena observed in Figure 3b (DSC data) in the temperature ranges 20-110, 110-305 and 305-700°C.

For instance, the decrease in mass between 20 and 110°C is an endothermic transition due to the evaporation of compounds with low boiling point (Bruylants, Wouters, & Michaux, 2005). Water is often the most common, so such a stage is usually referred to as dehydration (Yang et al., 2013). The free CD's are often produced by crystallization with water as solvent, so their cavities present a high content of water (≈ 8.56 %) that was completely removed when the HPβCD was thermally treated up to 110°C (Frijlink, Eissens, Schoonen, & Lerk, 1990). The differences of water loss among the complexes obtained by the different methods of inclusion are basically attributed to the distinct temperature and pressures at which they were produced. For example, M_1 involved a *T* close to 25°C and a *P* that was the atmospheric one, so almost all the water naturally found in the HPβCD was not removed during inclusion (≈ 8.54%), but only when heated in the oven of the thermogravimetric analyzer.

From a rapid analysis of the loss of mass in Figure 3a from 110 to 305°C, it is possible to infer that the free HPβCD is thermally stable at this temperature range, that is, the loss of mass for HPβCD was only 0.57%. Therefore, the higher decay of mass of formed complexes may be only associated with the boiling point of MeJa (220-225°C). This suggests that M3 and M4 are the best methods in terms of formation of thermally stable complexes. The highest temperature of the endothermic peak for the MeJa/HPβCΔ complex by M_4 (311.11 °C) supports it (see Figure 3b).

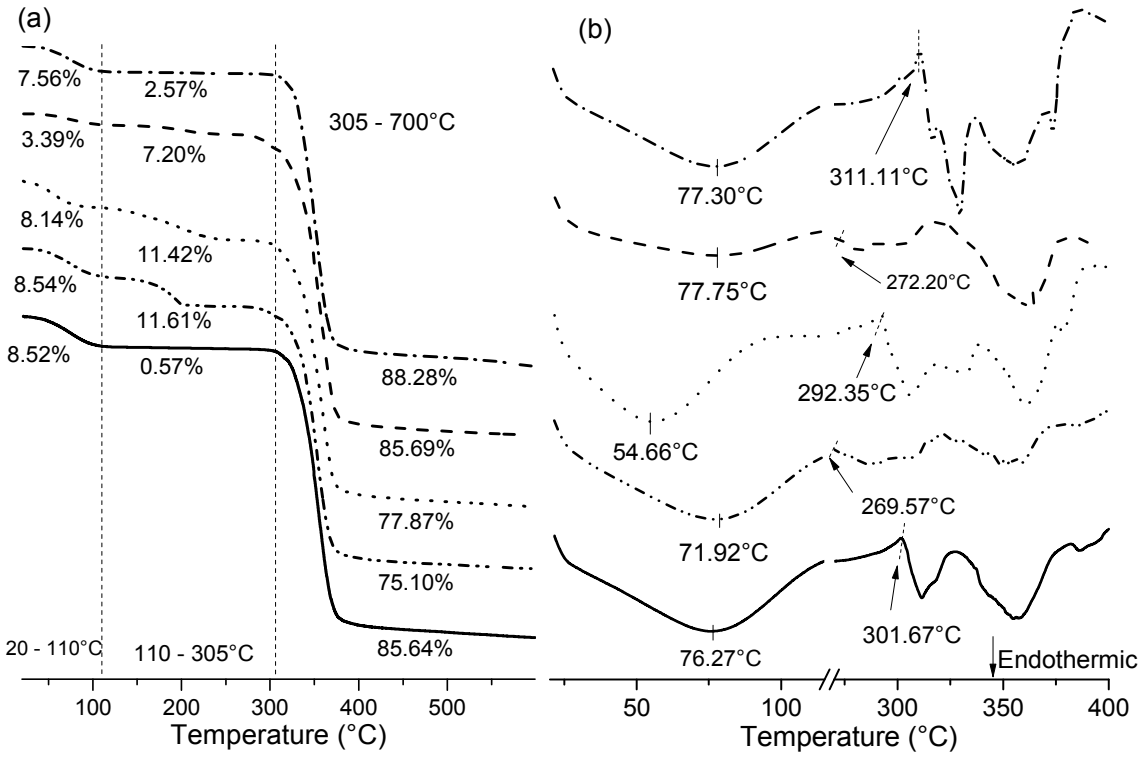

Figure 3. (a) TGA curves; (b) DSC curves. Free HPβCD (solid line), and MeJa/HPβCD complexes obtained by M_1 (dash dot dot line), M_2 (dot line), M_3 (dash line), M_4 (dash dot dot line), (1:1, molar ratio).

A sharp fall of mass of all the examined compounds is observed in Figure 3a by increasing the temperature of the samples above 305°C. According to Udrescu et al., (2014), the endothermic peak for free HPβCD at 301.67°C in Figure 3b could be the melting point of the host. However, the loss of mass of HPβCD started at this temperature, in Figure 3a, may not be explained by this phenomenon, but only by the evaporation or thermal decomposition of this compound, as it was already inferred for another cyclodextrin (Junior et al., 2017).

Antioxidant activity

Figure 4 illustrates the variation of measured *AA* of free MeJa and of formed complexes over time.

A first-order kinetic model given by Equation 2 was able to describe correctly the experimental results at all the examined circumstances ($R^2 \geq 0.97$).

$$AA = AA_e\left[1 - exp\left(-kt\right)\right] \quad (2)$$

Such a model allows a simplified and clear view of the kinetic results because it summarizes the several kinetic data per method of inclusion in only two model parameters (k and AA_e). k is the antioxidant activity constant rate of the examined sample ($min.^{-1}$), while AA_e represents the antioxidant activity at equilibrium (%). These parameters were tuned on the measured *AA* reported in Figure 4 to minimize the sum of the squared residues by applying the Levenberg-Marquardt method.

A comparison among the parameters of this model for the different kinetic curves shown in Figure 4 is an accurate procedure to evaluate the effect of complexation and inclusion methods on *AA* in terms of kinetics and equilibrium. As may be more explicitly noticed in Table 1 than in Figure 4, there is no difference among the kinetics of *AA* of all the examined samples (free MeJa or complexes formed by M_1 to M_4) for a confidence level equal to 0.05.

However, except for M_1, the influence of complexation on *AA* at equilibrium is noticeable (Stražišar, Andrenšek, & Šmidovnik, 2008). The negligible role of complexation by grinding on AA is in accordance with previous evidences reported in the literature (Folch-Cano, Jullian, Speisky, & Olea-Azar, 2010; Stražišar, Andrenšek, & Šmidovnik, 2008). In terms of results of AA_e, Table 1 reveals that M_3 and M_4 are the best methods of inclusion among those currently considered.

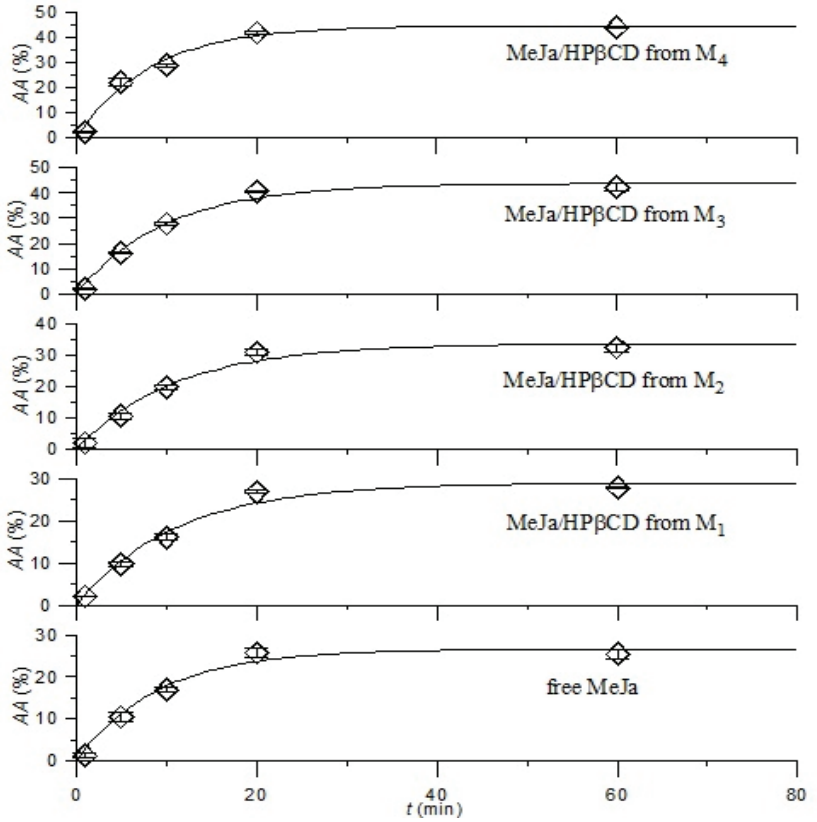

Figure 4. Experimental (symbols) and calculated (solid lines, Equation 2) kinetic results of antioxidant activity of free and complexed MeJa.

Table 1. Tuned parameters of Equation 2 for the examined antioxidant samples. U_k (uncertainty in k for $\alpha = 0.05$ [% min.$^{-1}$]) and U_{AAe} (uncertainty in AA_e for $\alpha = 0.05$ [%]) are the uncertainties in k and AA_e for $\alpha = 0.05$, respectively.

Sample	R^2	$k \pm U_k$ (% min.$^{-1}$)	$AA_e \pm U_{AAe}$ (%)
MeJa	0.97	0.11 ± 0.22^a	26.6 ± 1.9^a
MeJa/HPβCD from M_1	0.98	0.09 ± 0.02^a	29.1 ± 1.9^a
MeJa/HPβCD from M_2	0.98	0.09 ± 0.02^a	33.6 ± 2.4^b
MeJa/HPβCD from M_3	0.99	0.10 ± 0.02^a	43.8 ± 2.4^c
MeJa/HPβCD from M_4	0.98	0.12 ± 0.02^a	44.6 ± 2.4^c

k or AA_e followed by different letters, in the same column, are significantly different by t-test at $\alpha = 0.05$.

Conclusion

The spectroscopy measurements demonstrated that inclusion compounds were obtained by all the considered methods, but the inclusion took place in a different way by M_3-M_4 and M_1-M_2. Because of this, the positive effect of complexation on thermal stability and *AA* of MeJa (analyses TGA/DSC and DPPH assay) was more markedly noticed when the complexes were formed by combining (M_3) and by applying (M_4). Although M_3 being similar to M_4, concludes that the use of cheap, non-toxic and low energy-demanding method of inclusion with $scCO_2$ is more advantageous than those currently considered to form complexes of MeJa with HPβCD.

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