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ORIGINAL ARTICLE

Molecular inclusion of butylated hydroxyanisole (BHA) into alpha and beta cyclodextrins

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Abstract BHA (butylated hydroxyanisole) was complexed with α- and β-cyclodextrins with the objective of characterizing the thermal stability. From phase solubility diagrams, the association constants for the complexes of α-CD:BHA and β-CD:BHA were found as 49.3 and 585 L mol^{-1}, respectively. To increase the thermal stability of BHA, its molecular encapsulation in α-CD and β-CD, was tested using molar ratios of 1:1 and 1:2 (BHA:CD) and the complex preparation techniques of kneading and physical mixture. The products of complexation were characterized by differential scanning calorimetry and thermogravimetry, indicating the formation of a BHA:β-CD complex and showing that the release of the complexed BHA occurs in the temperature range of 280–350 °C, well above the temperature at which BHA sublimates. Dissolution tests have shown that the BHA: β-CD complex produced by kneading has high efficiency of dissolution and partition coefficient experiments demonstrated that the presence of β-CD leads to higher concentration of BHA in the organic phase.

Keywords Butylated hydroxyanisole · Cyclodextrins · Complex · Inclusion

Introduction

Butylated hydroxyanisole (BHA, Fig. 1) is an antioxidant and preservative applied in food, food packaging, animal feed, pharmaceutical preparations and cosmetic formulations, rubber and petroleum products. It is a common additive extensively applied to fat-containing foods, cookies, cereals, chewing gum, potato chips and vegetable oils. Due to its antioxidant activity, BHA was investigated as a possible cancer chemopreventive, because its conjugated aromatic ring is able to stabilize harmful free radicals and possibly intercepts reactive species of carcinogens, thus preventing cancer [1]. It can be concluded that BHA and butylated hydroxytoluene (BHT) pose no cancer hazard and, to the contrary, may be anticarcinogenic at current levels of food additive use [2].

Regarding the regulatory state, BHA is classified as Generally Recognized as Safe (GRAS) by FDA, for use in food when the total of antioxidants is not greater than 0.02% of fat or oil content. BHA also may be used as an antioxidant in flavoring substances whereby the additive does not exceed 0.5% of the essential oil content of the flavoring substance [1].

BHA has the chemical formula $C_{11}H_{16}O_2$ and molar mass of 180.24 g mol^{-1}. It is a white waxy solid, lightly yellow and has a faint characteristic odor. It melts at 45–63 °C, is flammable, with a flash point of 156 °C and has a boiling point of 264–270 °C. It is barely soluble in water and freely soluble in 50% ethanol, other alcohols, propylene glycol, petroleum ether, fats and oils. Commercial food-grade BHA is generally a mixture with >85% 3-*tert*-butyl-4-hydroxyanisole (3-BHA) and <15% 2-*tert*-butyl isomer (2-BHA). Food-grade BHA is >98% pure. As additive in food, it increases the shelf life of oils and fats, and it improves the quality of the product because it delays the oxidation of lipids [3], even showing low thermal stability.

Cyclodextrins (CDs, Fig. 2) have the ability to form inclusion complexes with organic and inorganic compounds which have numerous applications in biotechnology, food

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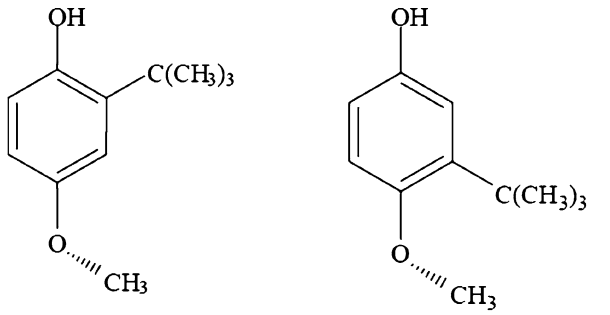

Fig. 1 Chemical structure of BHA isomers

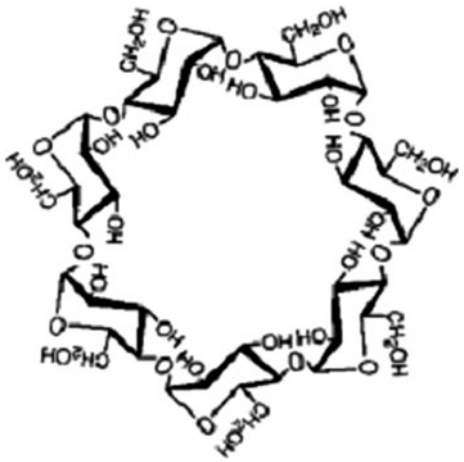

Fig. 2 Chemical structure of β-cyclodextrin

and pharmaceutical industries. The molecular encapsulation of lipophilic food ingredients with cyclodextrin improves the stability of flavors, vitamins, colorants and unsaturated fats [4].

It was described the inclusion complexation of BHA and BHT with hydroxypropyl-β-CD (HPBCD) or, hydroxyethyl-β-CD (HEBCD) and their characterization by phase solubility analysis, X-ray diffraction and infrared spectroscopy. An increase on the solubility was more pronounced with BHA compared to that of BHT. According to these authors the association constant of BHA with hydroxypropyl-β-CD (HPBCD) or hydroxyethyl-β-CD (HEBCD) is 32,300 and 1,470 L mol^{-1}, respectively [5].

They report significant increase in aqueous solubilities, transformation of the crystalline BHA (or BHT) in an amorphous state and changes in IR spectra of the antioxidants that were indicative of the formation of complexes of BHA and BHT with the modified β-CDs.

The present work addresses the formation of inclusion complexes between BHA into α- and β-CD, which were studied by phase solubility diagrams for BHA and the CDs, yielding information on the association constants of these complexes. Data is presented here on the formation and thermal stability of the BHA:CD inclusion complex, using at the preparation stage, molar ratios of 1:1 and 1:2 (BHA:CD) as physical mixtures and kneaded products. In addition, the kinetics of dissolution for pure BHA and the product of complexation with the CD that gave the best results for complexation were compared. The partition coefficient of BHA that resulted from the same products was also determined, given its great importance in pharmaceutical applications.

Materials and methods

Materials

Butylated hydroxyanisole (MW 180.24 g mol^{-1}), 98% pure, β-cyclodextrin (MW 1,135 g mol^{-1}) and α-cyclodextrin (MW 972.85 g mol^{-1}) were acquired from Sigma Chemical Company Ltd-U.K. Analytical grade solvents and distilled water were used throughout this work.

Optimal conditions

For determination of the maximum BHA absorption wavelength, a sweeping of a 0.02 g L^{-1} BHA solution was carried out from 190 to 1,100 nm in a spectrophotometer. To verify if the solution was totally dissolved, it was filtered through a 0.22 μm Millipore membrane and new absorption spectra was obtained. After that, a suspension of 20 g L^{-1} was BHA was put in a shaker at 30 ± 0.5 °C and 150 rpm for 5 days to measure BHA solubility. The influence of α-CD and β-CD on the absorbance spectrum of a BHA solution was determined with different concentrations of the CDs, as fresh solutions and after 3 days.

Phase solubility studies

These tests were carried out according to the method reported by Higuchi and Connors [6]. Excess amounts of the BHA (100 mg) were weighted into 10 mL tubes, to which 10 mL of aqueous solutions containing various concentrations of α-CD (0–123 g L^{-1}), or β-CD (0–1.8 g L^{-1}) were added and shaken at 35 ± 0.5 °C. At the equilibrium after 3 days, an aliquot of the supernatant was filtered through a 0.22 μm Millipore membrane using vacuum. A portion of the sample was adequately diluted and analyzed spectrophotometrically to determine the concentration of BHA. The experiment was carried out in duplicate. The ratio of increase of BHA solubility (n) was calculated according Eq. 1 (where S_{max} is the BHA concentration with the highest concentration of CD and S_0 is

the BHA concentration in the absence of CD, calculated by phase solubility studies), and the apparent complex formation constant (K), was calculated from the straight-line portion of the phase solubility diagram (Eq. 2) [6].

$$n = \frac{S_{max}}{S_0} \quad (1)$$

$$K = \frac{Slope}{S_0(1 - slope)} \quad (2)$$

Preparation of the complexes

Kneading technique

The complex of BHA with α-CD or β-CD (1:1 and 1:2 molar ratio) by kneading technique was made kneading the CD with a 1 mL of water, at ambient temperature, until homogenization (approximately 5 min). Then, BHA was added to the paste and kneading followed for a further period of 20 min. The resulting paste was dried at ambient temperature (25 °C) for 48 h.

Physical mixture technique

BHA and cyclodextrins (for 1:1 and 1:2 molar ratio) dried at ambient temperature (25 °C) for 24 h and then were manually mixed, for a period of 10 min. A real physical mixture was prepared as above but without any drying or heating of the product, which served for comparison with the dried products.

Characterization methods for complexed products

Differential scanning calorimetry (DSC)

Aluminum capsules containing approximately 6 mg of samples were analyzed in a Shimadzu calorimeter, model DSC-50, under dynamic nitrogen atmosphere (20 mL min^{-1}) and heating rate of 10 °C min^{-1}, in the temperature range of 25–350 °C.

Thermogravimetric analysis (TGA)

Samples (approximately 6 mg) were analyzed in a Shimadzu thermobalance, model TGA-50, under dynamic nitrogen atmosphere (20 mL min^{-1}) and heating rate of 10 °C min^{-1} using platinum crucibles. The temperature range was from 25 to 500 °C.

Dissolution tests

Dissolution tests were performed for the pure substance and for the complexes obtained in the best preparations with cyclodextrins, using the dissolution tester Erweka DT 808 LH. HCl 0.01 mol L^{-1} was employed as dissolution medium, for a volume of 500 mL, at 37 °C, with agitation system (paddle) and stirring speed of 75 rpm. The absorbance of the medium was determined after 1, 5, 10, 20, 30, 45, and 60 min. The samples were filtered and then subjected to spectrophotometric reading at 287 nm. The obtained values were transformed into BHA concentration using the previously determined calibration curve. Dissolution kinetics was determined based on concentration, dissolved percentage, and dissolution efficiency, for pure BHA and for the different complexation products.

The percentage of dissolved BHA was calculated relative to the maximum concentration obtained after the 60 min dissolution test, while the dissolution efficiency, expressed as a percentage, was calculated as the ratio between the area under the curve of percentage of dissolved BHA and the total area for the elapsed time of test [7]. As the molar ratio in the preparation of the complexes was variable, a fixed mass of 600 mg of product was taken for the dissolution tests.

Partition coefficient

The partition coefficient was determined using water and, as organic phase, *n*-octanol. Samples of the products under analysis were dissolved in the aqueous phase and their initial concentrations were determined by UV spectrophotometry at 287 nm. The phases were mixed by stirring with magnetic bar (700 rpm) for 2 h at room temperature and then subjected to centrifugation (3,000 rpm/10 min). Final BHA concentration in aqueous phase was also determined by spectrophotometry for all the samples. The concentration of BHA in the organic phase was calculated by the difference between initial and final concentration in the aqueous phase.

Results and discussion

UV/visible analysis

The UV/Visible spectrophotometric sweeping of the diluted BHA solution showed no differences on the absorption as a function of the wavelength, when comparing the solutions before and after filtering. The peak absorbance of 0.3350 observed at the wavelength of 287 nm for a 0.02 g L^{-1} BHA solution was used to derive Eq. 3, which relates the BHA concentration with the absorbance and dilution. An aliquot of a filtered suspension with excess BHA (20 g L^{-1}) was analyzed spectrophotometrically to determine the BHA solubility, giving by application of Eq. 3, 0.1415 g L^{-1} at 30 °C.

$$C_{BHA} = 0.0597 \times \text{absorbance} \times \text{dilution} \quad (3)$$

Some substances after inclusion in cyclodextrins pass through physicochemical changes, which may alter their UV/VIS spectra, causing changes to the peak wavelengths and increase or reduction of the maximum absorbance. These modifications are akin to that caused by solvents of different polarities, suggesting that the complexed molecule in solution was transferred from a polar mean to the non polar cavity of the cyclodextrins. These changes can originate from perturbations of the included molecule electron cloud, caused by direct interactions with the CD cavity, exclusion of water molecules from the cavity or by a combination of both effects [8].

From the absorbance spectra of BHA in α- and β-CD solutions, we concluded that the addition of α- or β-CD does not influence the BHA absorbance spectrum. These solutions were prepared with 0.002 g L^{-1} BHA and 0.54 g L^{-1} α- or β-CD, respectively.

It is rare to observe detectable changes in the UV/VIS absorbance spectrum of complexed active principles, but they are seen in some cases [9].

Phase solubility analysis

The phase solubility diagrams corresponding to the BHA:α-CD and BHA:β-CD systems are shown at the Figs. 3 and 4. The solubility of BHA increases linearly as a function of the α- and β-CD concentrations and the solubility curve can be classified as type A_L at the temperature of 35 °C. According to Higuchi–Connors [6], AL type complexes can be accepted as complexes containing one cyclodextrin molecule. Moreover, straight lines for systems classified as A_L, Higuchi type curves, clearly indicate the formation of a stoichiometric 1:1 complex in solution [10]. The good quality fit shown at Figs. 3 and 4 warrants the conclusion of a 1:1 molar ratio complex.

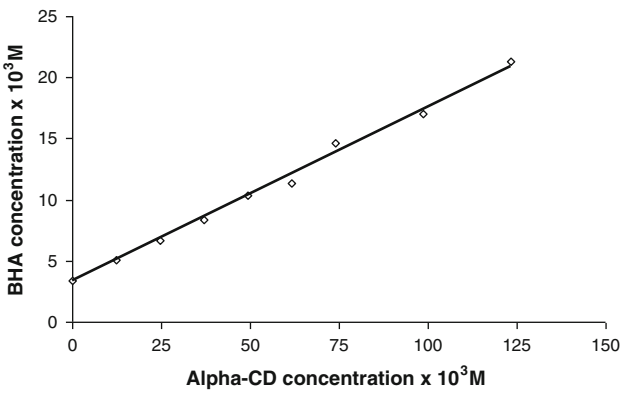

Fig. 3 Phase solubility diagram for BHA with α-CD at 35 °C

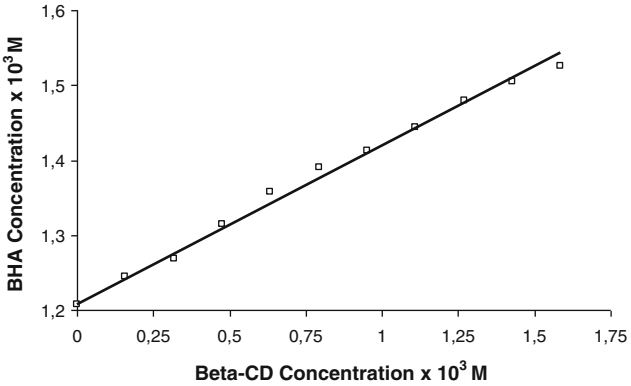

Fig. 4 Phase solubility diagram for BHA with β-CD at 35 °C

The apparent association constant with α-CD at 35 °C was calculated from the slope and intercept of the A_L solubility diagram as 49.3 L mol^{-1} according to Eq. 3, which was fit with a correlation coefficient of $r^2 = 0.9946$. The ratio of increase of BHA solubility with α-CD addition was 621% as calculated by Eq. 1. The value of the association constant for the complex BHA:β-CD was 585.0 L mol^{-1}, with $r^2 = 0.9919$ and the ratio of BHA solubility increase was 126% compared to the solution without β-CD. The maximum solubility enhancement obtained with β-CD was smaller than that determined for α-CD, because in spite of BHA:β-CD association constant being greater, the maximum concentration that a solution of β-CD can be made is much lower than with α-CD, i.e. the lower solubility of β-CD in comparison to α-CD, hinders making more concentrated solutions of BHA. The values of the association constants determined [5] for the complexes HPBCD:BHA and HEBCD:BHA (see Introduction) are 55.7 and 2.5 times greater than that for BHA:β-CD, possibly because the hydroxyl external substituents in HPBCD and HEBCD help to stabilize the complex. In solid or powder products that contain the complex, an intermediary value for the association constant, such as the case of BHA:β-CD in our work, is beneficial because during shelf life the active included substance is slowly but constinuously released to the product giving its protection.

Other parameters resulting from the analysis of Figs. 3 and 4 are shown at Table 1. The increase in BHA solubility by mmol of CD added is faster for β-CD addition than for α-CD, as can be seen by the slopes of the fitted straight lines (Table 1). This result is related to the value of the association constant, which is greater for the BHA:β-CD complex than for BHA:α-CD. However, the maximum solubility ratio increase observed with β-CD is smaller, because of its lower solubility. Figure 4 shows a much smaller span at the x axis than Fig. 3, consequently the maximum BHA solubility achieved with α-CD addition is about 21 mmol L^{-1}, while for β-CD is 5 mmol L^{-1}.

Table 1 Phase solubility diagram parameters for BHA complexation with α- and β-cyclodextrins

Cyclodextrin	α-CD	β-CD
S_0 (mmol L^{-1})	3.72 ± 0.05	3.72 ± 0.05
S_{max} (mmol L^{-1})	21.28 ± 0.05	5.05 ± 0.05
Slope (mmol L^{-1} BHA $mmol^{-1}$ L CD)	0.1446	0.7005
R^2	0.9946	0.9919
K (L mol^{-1})	49.31 ± 0.05	585.03 ± 0.05
Solubility enhancement	621%	126%

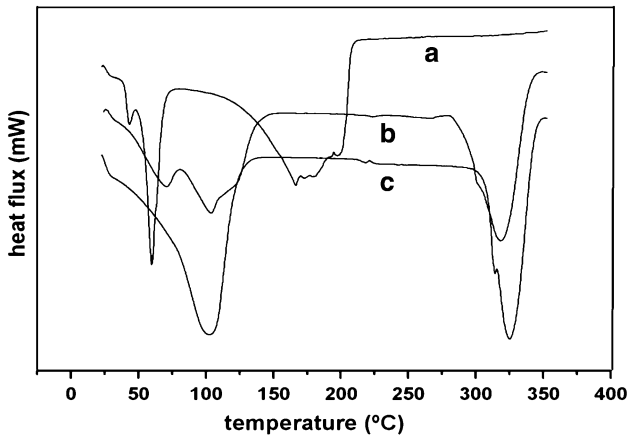

Fig. 5 DSC thermogram for (*a*) BHA, (*b*) β-cyclodextrin and (*c*) α-cyclodextrin

Differential scanning calorimetry (DSC)

Figure 5 shows the DSC curves for BHA, α-CD and β-CD. The thermogram of BHA presents three endothermic peaks: the first at 43.24 °C, without any mass loss, the second at 59.22 °C that corresponds to the melting point of BHA and the third at 165.45 °C corresponding to the sublimation of BHA. For α-CD, there are three endothermic peaks: the first at 69.57 °C is a small endothermic peak that occurs without any mass loss and it is thought to be associated to the anhydrous α-CD behavior, the second peak at 103.41 °C is associated with the loss of humidity and the third peak at 317.74 °C is caused by thermal degradation of α-CD. For β-CD, there are two stronger endothermic peaks at 102 and 324.78 °C associated with the loss of humidity and thermal degradation of β-CD, respectively. In addition, at 218.32 °C there is a small endothermic peak that occurs without any mass loss, and it is thought to be associated with a reversible molecular transformation of an unknown nature [11].

The products obtained with the different complex preparation techniques were characterized by DSC and the resulting thermograms are shown in Figs. 6 and 7 for BHA:α-CD and BHA:β-CD, respectively.

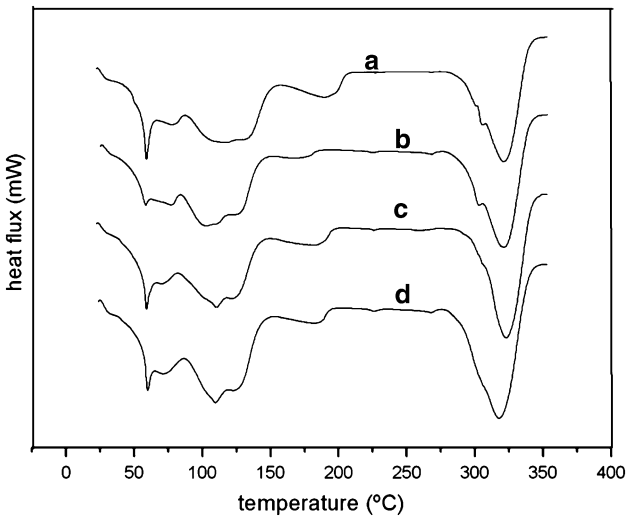

Fig. 6 DSC curves for the products obtained by the complex preparation techniques with BHA and α-cyclodextrin at different molar ratios: (*a*) kneading (1:1), (*b*) kneading (1:2), (*c*) physical mixture (1:1), (*d*) physical mixture (1:2)

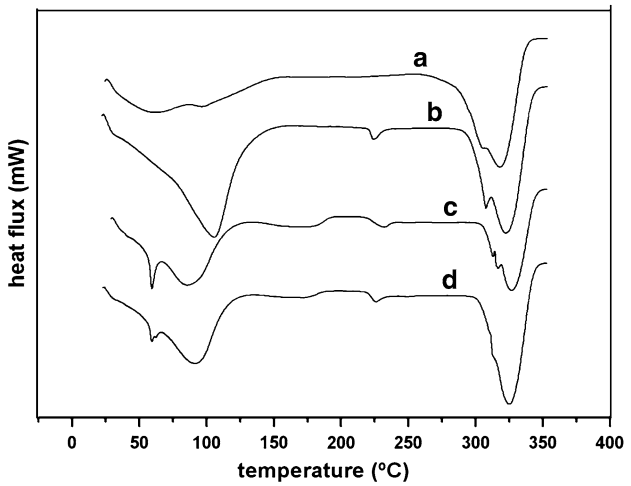

Fig. 7 DSC curves for the products obtained by the complex preparation techniques with BHA and β-cyclodextrin at different molar ratios: (*a*) kneading (1:1), (*b*) kneading (1:2), (*c*) physical mixture (1:1), (*d*) physical mixture (1:2)

From Fig. 6 it can be observed that the thermograms are quite similar and only for the product obtained by kneading with the molar ratio 1:2 there was a reduction of the BHA fusion peak. This is an indication that there is a small interaction between BHA and α-CD and this is a consequence of the BHA molecule being too large to be included inside the α-CD cavity.

For the products with molar ratio 1:1, obtained either by kneading or physical mixture of BHA and α-CD, the peaks associated with fusion and boiling of BHA are clearly visible in their normally expected temperature ranges, showing little interaction between BHA and α-CD (Fig. 6).

Then, the DSC results corroborate the low equilibrium constant for the formation of the BHA:α-CD complex, shown at Table 1.

The thermograms obtained for BHA and β-CD complexation products presented at Fig. 7 clearly show that the BHA fusion peak is absent for the kneading preparations with molar ratios 1:1 and 1:2, BHA: β-CD, while for the physical mixtures at both molar ratios, this peak is well defined. The striking absence of the fusion peak after kneading is an indication that an inclusion complex was formed between the BHA and β-CD. This result is in accord with the larger equilibrium constant for the formation of the BHA:β-CD complex, shown at Table 1. In addition, the lower temperature and enthalpy of dehydration of the 1:1 kneading complexation product compared to that of the pure β-CD, indicate that the inclusion of BHA in the β-CD cavity reduces the binding strength of the water remaining water molecules.

Thermogravimetric analysis (TGA)

Figure 8 shows the thermogravimetric analysis of BHA, α-cyclodextrin and β-cyclodextrin. For pure β-cyclodextrin, the first stage of weight loss in the thermogravimetric curve occurs in the temperature range of 28–92 °C and corresponds to the dehydration of the β-CD molecule. The weight loss in this stage was 4.4%. The second weight loss stage for β-CD occurs in the range of 280–500 °C, with a mass reduction of 87%, and is related to the thermal decomposition of β-CD. α-CD thermogravimetric curve shows three mass loss stages, the first from 21.56 to 60.02 °C, corresponding to a structural rearrangement that can be attributed to a change of phase to α-CD anhydro form, based on the very low mass loss (2.7%), the second from 60.02 to 114.22 °C, with a reduction of 6.2% in mass and third, from 269.8 to 500 °C, related to the decomposition of the α-CD molecular structure and 81.1% mass loss. With pure BHA, Fig. 8 shows that at 180 °C, the entire BHA sample has been totally volatilized.

The thermogravimetric curves presented at Fig. 9 show little difference for the kneading or physical mixtures preparations of the same BHA:α-CD molar ratio, indicating that little quantity of complex could have been formed. This result is in accord with the previous DSC results and phase solubility analyses.

Figure 10, differently from Fig. 9, does show that for β-CD, BHA kneading products do not present the BHA volatilization stage, as show the physical mixtures, confirming complex formation for the kneaded compounds. BHA is liberated from the β-CD cavity at the same

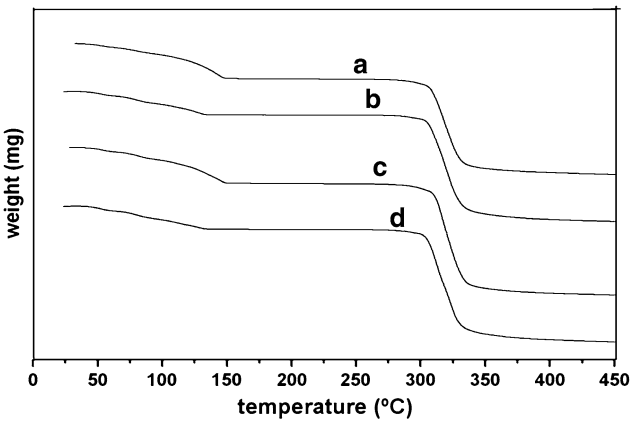

Fig. 9 Thermogravimetric curves of products obtained by the complex preparation techniques at different BHA and α-cyclodextrin molar ratios: (*a*) kneading (1:1), (*b*) kneading (1:2), (*c*) physical mixture (1:1), (*d*) physical mixture (1:2)

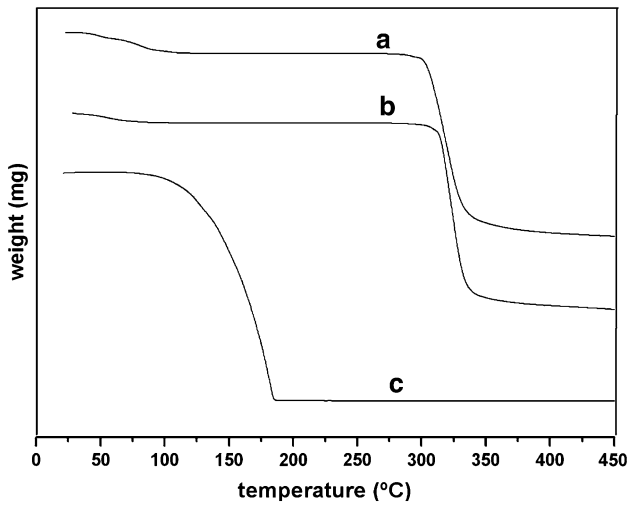

Fig. 8 Thermogravimetric curves of the pure substances: (*a*) α-cyclodextrin, (*b*) β-cyclodextrin and (*c*) BHA

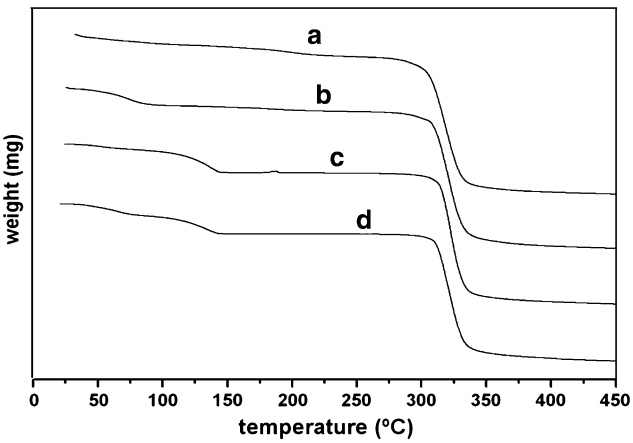

Fig. 10 TGA thermograms of products obtained by the complex preparation techniques: (*a*) kneading (1:1), (*b*) kneading (1:2), (*c*) physical mixture (1:1), (*d*) physical mixture (1:2), with BHA: β-cyclodextrin molar ratio

temperature range, 280–350 °C, in which this CD decomposes, making it hard to distinguish the decomposition of the guest and host molecules.

For the subsequent experiments, only the pure substance and the complexes obtained between BHA and β-CD were tested, because they were more stable than the complex obtained with α-CD.

Dissolution tests

Table 2 displays data concerning the dissolution tests, with a total sample mass of 600 mg.

Figures 11, 12, and 13 present the kinetics of dissolution as a function of time, based respectively on concentration, dissolved percentage, and dissolution efficiency, for pure BHA and for the different complexation products.

Comparing the results in Table 2 and Figs. 11, 12 and 13, it can be observed that the CDs increase the dissolution rate of BHA, as is also true for other drugs [12]. Additionally, BHA complexed by the kneading technique presented higher dissolution efficiency than that of pure BHA. BHA produced by physical mixture showed high dissolution efficiency, but the total amount of BHA dissolved in this case was lower.

Table 2 Data concerning the dissolution tests

Samples	BHA (mg)	β-CD (mg)	BHA dissolved after 60 min (mg)
Pure BHA	600	0	98.45
Kneading (1:1)	95.28	504.72	64.00
Kneading (1:2)	47.64	552.36	36.60
Physical mixture (1:1)	95.28	504.72	5.00
Physical m ixture (1:2)	47.64	552.36	9.50

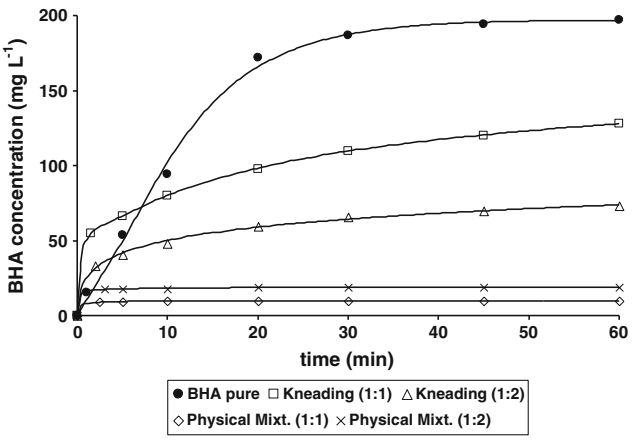

Fig. 11 Concentration of BHA obtained in the dissolution tests

Partition coefficient

The values of the apparent partition coefficients (P) and log P obtained in the tests are presented in Table 3.

As verified by previous DSC and TGA analyses, values of the partition coefficient obtained in preparations with kneading were lower when compared with the preparation

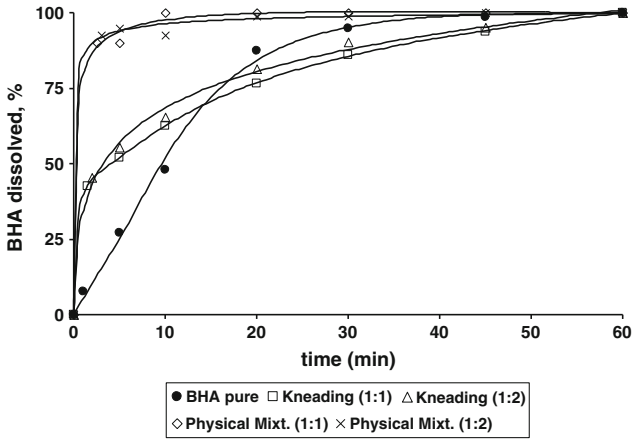

Fig. 12 Percentage of BHA dissolved as a function of time

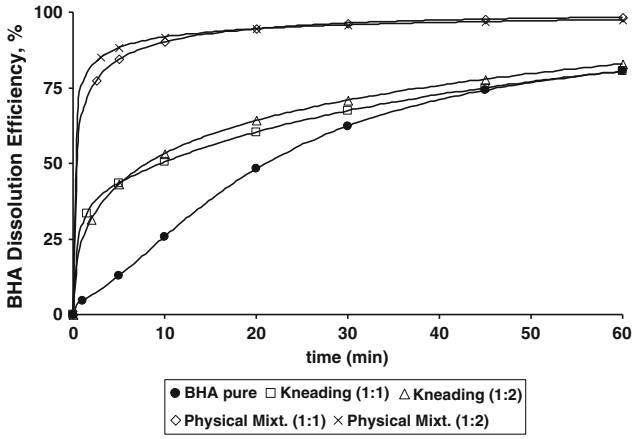

Fig. 13 BHA dissolution efficiency for the different preparations

Table 3 Apparent partition coefficients (P) of the complexes formed with β-CD

Samples	P values	Log P
Pure BHA	0.2519 ± 0.05	−0.599
Kneading (1:1)	1.373 ± 0.05	0.1377
Kneading (1:2)	1.565 ± 0.05	0.1945
Physical mixture (1:1)	3.073 ± 0.05	0.4876
Physical mixture (1:2)	1.596 ± 0.05	0.2032

with physical mixture, especially for the molar ratio 1:1. The results were analyzed based on the assumption that the CDs and the inclusion complexes do not move from the aqueous phase, due to their hydrophilic character, which was confirmed by the results. Higher values of P indicate that the substance tends to migrate to the organic phase (in the present case, *n*-octanol), and the obtained values show that the presence of β-CD favor migration of BHA to the organic phase. The largest P value was obtained for the physical mixture of BHA and β-CD, with molar ratio of 1:2.

Polarity studies of inclusion complexes with CDs, dissolved in aqueous phase, are based on distribution models between both phases. Experiments carried out by some authors showed that the addition of CD to a biphasic system of solvents with lipophilic drugs results in a process that is different from that which exists in the absence of CD. Within the aqueous phase, concentration of the free drug will be low due to complexation with the CD. Near the interface, however, the concentration of free drug will be relatively high due to the displacement of the drug from the complex by the organic solvent. The mass transfer of the drug from the aqueous phase to the organic phase will be mainly determined by the total concentration of complexed and free drug in the aqueous phase, and not only the free fraction. As the organic solvent enters the aqueous phase, the capacity of CDs to increase the drug dissolution decreases, due to competition between the solvent and the drug to complex with the CD. The partition coefficient will thus be modified with the addition of CDs [13–15].

Conclusion

This study shows that increasing concentrations of α-CD and β-CD cause the solubility of BHA to increase. The rate of solubility enhancement is higher in the presence of β-CD, but the highest concentration achieved in the presence of α-CD is greater, because with this latter CD, a much higher CD concentration can be achieved.

In addition, it was shown that there is formation of the α-CD:BHA and β-CD:BHA complexes in aqueous solution. The association constant of these complexes has been calculated by phase solubility study as 49.3 and 585.0 L mol^{-1}, respectively, and the stoichiometric molar ratio is 1:1.

The aqueous solubility of BHA can be significantly increased by forming the inclusion complexes with α-CD and β-CD, reaching a value 1.26 times greater in the presence of β-CD, that is 5 mmol L^{-1} BHA, and 6.21 times with α-CD, which is about 21 mmol L^{-1}.

From the DSC results of BHA and α-CD complexation products, it was verified that there was little interaction between these compounds, while from the DSC thermograms of the inclusion complex involving BHA and the β-CD (in both preparations with molar ratios 1:1 and 1:2), it was observed the disappearance of the melting peak of pure BHA. On the contrary, for the DSC thermograms of the physical mixtures of BHA and both CDs, this peak appears well defined (particularly in the preparation 1:1).

Thermogravimetric analyses involving α-CD and BHA also showed little interaction between these compounds, but for BHA and β-CD it was verified that the product from the kneading complexation tests does not present the volatilization stage of free BHA (more visible in the 1:1 complex), demonstrating the formation of the inclusion complex.

The dissolution kinetics studies demonstrated that the product of complexation BHA:β-CD has high dissolution efficiency and the cyclodextrins increase the BHA partition coefficient in an water/*n*-octanol mixture.

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