A physicochemical, thermodynamical, structural and computational evaluation of kynurenic acid/cyclodextrin complexes

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Highlights

- The interaction of KYNA and several cyclodextrins (CDs) was studied.
- The modified HPβ-CD showed the strongest complexation constant (KF)
- The results showed high dependence on pH and temperature.

Abstract

In this work, the interaction between Kynurenic acid (KYNA) and several natural and modified cyclodextrins (CDs) is carried out. Among all the CD tested, HPβ-CD showed the strongest complexation constant (K_F), with a value of 270.94 ± 29.80 M^{-1}. Between natural (α- and β-) CDs, the complex of KYNA with β-CD was the most efficient. The inclusion complex of KYNA with CDs showed a strong influence of pH and temperature. The KF value decreased at high pH values, when the pKa was passed. Moreover, an increase of the temperature caused a decrease in the KF values. The thermodynamic parameters of the complexation (ΔH°, ΔS° and ΔG°) were studied with negative entropy, enthalpy and spontaneity of the process at 25 °C. Moreover, the inclusion complex was also characterized using FTIR and TGA. Finally, molecular docking calculations provided different interactions and their influence in the complexation constant.

Keywords

Kynurenic acid, Cyclodextrin, Inclusion complex, Physicochemical, Stability

1. Introduction

Kynurenic acid (KYNA, 4-Hydroxyquinoline-2-carboxylic acid, Fig. 1A) is a metabolite derived from tryptophan via kynurenine pathway found in some several foods like spices, potato, honey or broccoli (Turski et al., 2009, Turski et al., 2015). In recent years, its role as ionotropic glutamate and alpha 7-nicotinic receptor agonist has been investigated (Turski et al., 2013). Indeed, it was proposed as neuroprotective for cerebral ischemia, Parkinson's disease, schizophrenia, Huntington disease, epilepsy or depression (Campesan et al., 2011, Stone, 2000), and a potential overlapped biomarker between diagnosis and treatment response for depression (Erabi et al., 2020). Moreover, KYNA also presents an interesting antioxidant capacity (Lugo-Huitrón et al., 2011).

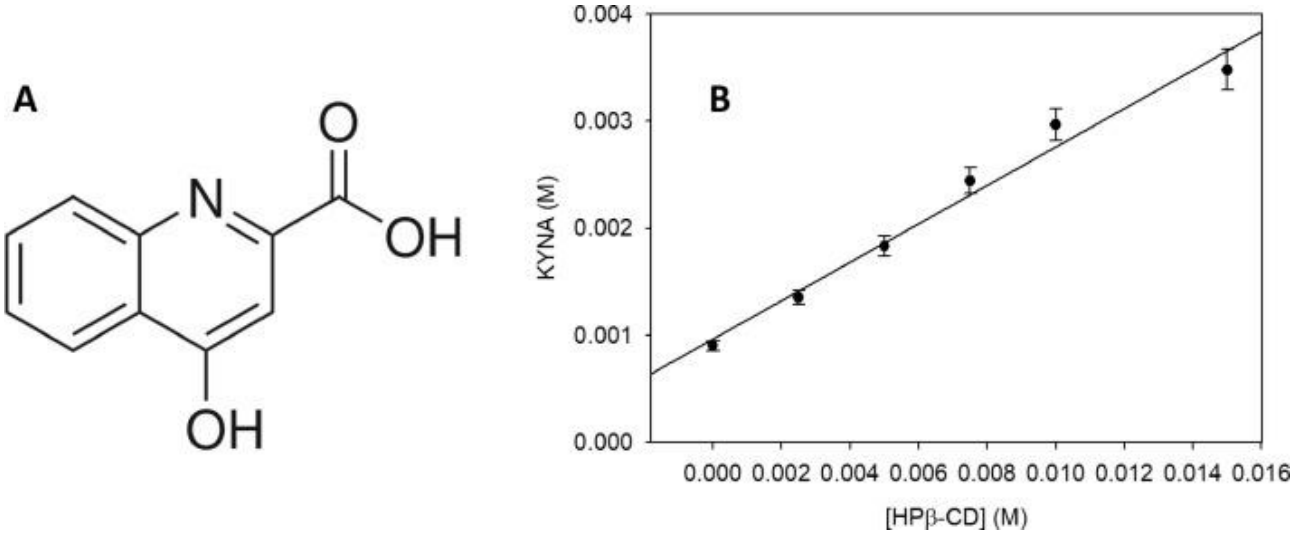

Fig. 1. (A) Structure of KYNA. (B) Higuchi and Connors plot, Effect of HPβ-CD on KNYA solubility (25 °C in water).

Although the compound present good solubility at pH 7, at pH 3–4 its solubility decreases dramatically complicating its administration in several food matrixes such as juice or similar. A recent study associates insufficient amount of KYNA in baby formulas as one of the factors involved in mass gain (Milart et al., 2019) or an effect as an immune-modulating agent (Małaczewska et al., 2014), so this type of products are particularly interesting as a fortifying nutraceutical specific for infants because children can easily drink these formulations. Although the interaction of KYNA with serum proteins as widely as the full thermodynamic characterization are well published to carrier the molecule (Hornok et al., 2020, Varga et al., 2016), some agent could be necessary before absorption. In this way, the complexation of this bioactive compound in cyclodextrins (CDs) could manage its introduction.

CDs are truncated cone-shaped oligosaccharides made up of α-(1 → 4) linked glucopyranoside units with six, seven and eight glucose units, α, β and γ-CD, respectively (Astray et al., 2020, Matencio et al., 2020, Szente and Szejtli, 2004). These natural CDs possess the E number E-457, E-459 and E-458 for α-, β- and γ-CD, respectively as member of the food additives list and have two GRAS status. Moreover, a derivative called 2-Hydroxypropyl-βCD (HPβ-CD) is used as orphan drug for Niemann Pick disease type C (Matencio et al., 2018, Matencio et al., 2020). Complexes formed of molecules and CDs are called “inclusion complexes” or nanoparticles (Lei et al., 2019, Nerome et al., 2013). Generally, CDs encapsulate poorly water-soluble compounds and hydrophobic moieties of amphiphilic molecules. Nevertheless, the solubility of these complexes not only depends on the CD used, but also of different factors such as pH or guess molecule (Matencio et al., 2016, Matencio et al., 2017, Matencio et al., 2017b, Matencio et al., 2018). The capacity of CDs to increase the solubility and protect several molecules, has increased its uses in the pharmaceutical and food industries (Fenyvesi et al., 2016, Jansook et al., 2018, Matencio et al., 2020).

Our research group has previously characterized the complex of KYNA with CD based nanosponges (Nilesh K. Dhakar et al., 2019), a CD-based material with interesting bioactivities tested also with bioactive compounds (Nilesh Kumar Dhakar et al., 2019, Krabicová et al., 2020, Matencio et al., 2020). However, thinking about the use of novel nanoparticles for food administration, CDs are more suitable because at least natural CDs and depending on the application several modified CDs such as HPβ-CD and Methyl-βCD (Mβ-CD) are already approved (Jansook et al., 2018).

In the light of the foregoing, the aim of this work were to study the complexation of KYNA with several CDs. Firstly, the complexation constant was obtained. Secondly, the strongest CD/KYNA complex was evaluated as model of the effect of temperature and pH on the complexation. Thirdly, FTIR and TGA analyses were carried out to characterize the inclusion complex. Finally, molecular docking was used to study the possible interactions that occur between KYNA and CDs.

2. Materials and methods

2.1. Material

CDs tested (α-, β-, 2-Hydroxypropyl-βCD [CIDs 44134771, DS 3] and Methyl-βCD [CID 10171019, DS 4]) were a kind gift from Roquette Frères (Lestrem, France). Kynurenic acid (KYNA, ≥ 98% purity, CID 3845) and remaining reactants were purchased from Sigma-Aldrich (Italy).

2.2. Equipment and experimental procedure

2.2.1. Preparation of KNYA/HPβ-CD inclusion complexes

KNYA with HPβ-CD inclusion complexes were prepared as follows: 5 mg of pure drug was added to 50 mL of milliQ water. After that, 50 mg of HPβ-CD were added and stirred for 12 h in darkness. This suspension was lyophilized using a LyoQuest (Telstar) and the powder was conserved in dry environment, in darkness and dried.

2.2.2. Inclusion complex studies

The phase-solubility studies of Higuchi and Connors (Connors KA, 1965) were consulted. Different concentrations of CDs were prepared at a fix quantity of KYNA (2 mg/mL) at increasing concentration of an appropriate CD mixing for 24 h; after, the suspension was centrifuged at 2500 gx for 30 min, collecting the supernatant to measure its absorbance in an appropriate dilution of water using a UV–vis spectrophotometer (Perkin Elmer Lambda 25). A calibration curve was used to obtain KYNA concentration (R2 > 0.991) at 332 nm.

This method can evaluate a 1:1 stoichiometry (1CD per molecule).

(1)CD + KYNA ⇄ CD- KYNA

The following expression was used to evaluate the total solubility (St) of the drug:

$$S_t = S_0 + \frac{K_F S_0}{1+K_F S_0} \qquad (2)$$

where S0 is the intrinsic solubility of the drug, KF is the complexation constant and CD is the concentration of CD in the tube. The equation provides a slope that can be used to obtain KF using the Higuchi and Connors plot:

$$K_F = \frac{Slope}{S_0(1-Slope)} \qquad (3)$$

2.2.3. Temperature and pH

The effect of the temperature on KYNA complexation by CD was studied at different temperatures: 278, 298, 310 and 318 K (5, 25, 37 and 45 °C). To determine the standard thermodynamic parameters of enthalpy and entropy of KYNA transfer to the CD, the following equation was used:

$$LnK_F = -\frac{\Delta H^0}{RT} + \frac{\Delta S^0}{R} \qquad (4)$$

where KF is the complexation constant of the complex, T is the temperature (Kelvin), R is the gas constant, ΔH° and ΔS° are the standard enthalpy and entropy changes of complexes formed. For a linear plot of ln KF versus 1/T, the slope is –ΔH°/R and the intercept is ΔS°/R, respectively. The Gibbs free energy is determined using equation (5):

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 \qquad (5)$$

For the pH studies, the same method as that described in the previous section was followed at pH {2.5–4.5} 100 mM Acetate-Na at 25 °C.

2.2.4. Fourier-transform infrared spectroscopy

KYNA, HPβ-CD, physical mixture and KNYA/HPβ-CD nanopartilces were subjected to Fourier transform infrared (FTIR) spectroscopic studies in a Perkin-Elmer spectrum 100 FT-IR spectrophotometer (4000 to 650 cm−1).

2.2.5. Thermal gravimetric analysis

KYNA, HPβ-CD, physical mixture and KNYA/HPβ-CD were subjected to thermal gravimetric analysis using a Q500 thermogravimetric analyzer (TA instruments, USA) from 40 to 650 °C at 10 °C/min.

2.2.6. Molecular docking

The molecular structures used in this work were obtained from several databases or in house built. β-CD was obtained from Protein Data Bank (ID 4RER) and derivates were created by adding the correct quantity of radicals according to the DS to β-CD. KYNA was downloaded from the PubChem database (NCBI, USA). Using Autodock tools (version 1.5.6) with default parameters and charges, input files for docking were generated. Molecular docking was carried out using Autodock Vina (Trott & Olson, 2010). CDs were considered as flexible. Graphical representations of the docking results were prepared using PyMOL (Molecular GraphicsSystem, version 1.3, Schrödinger, LLC) with default parameters to display hydrogen bonds.

2.2.7. Data analysis

All experiments were carried out in triplicate with the exception of FTIR and TGA, which were carried out once. Regressions, a non-linear analysis and Graphics were made using Sigma-Plot (version 10.0.0.5). A t-test was carried out using Social Science Statistics website (https://www.socscistatistics.com/) with a significance of $P < 0.05$. Other mathematical operations were carried out using wxMaxima (version 12.04.0).

3. Results and discussion

3.1. Determination of the encapsulation constants between KNYA and different CDs

In order to calculate the KF with several CDs, we selected HPβ-CD as our first candidate. KYNA presents different keto-enol tautomerism, however the enol form of KYNA is predominant in aqueous solutions at low temperature (Pogoda et al., 2019) so, the presence of others was not consider. Different tubes were prepared with increasing concentrations of HPβ-CD and 2 mg/mL of KYNA and mixed for 24 h. The increase in solubility

of KYNA was in Fig. 1B showing a linear regression, which was used to obtain the slope for the KF calculation using eq. (3), with a value of 270.94 ± 29.80 M^{-1}.

3.1.1. Evaluation of different CDs for the optimum encapsulation of KYNA

Different natural (α- and β-, with GRAS status and approved food additives, due to the size of the molecule and the cavity of γ-CD it was not considered) and modified (HPβ-CD and Mβ-CD, useful excipients which present methyl or 2-hydroxypropyl radicals) were used in order to increase the number of CDs evaluated, the results of which (Table 1) showed great variability.

Table 1. KF vals, SD and docking scores of different CD/KYNA inclusion complexes.

Type of CD	**HPβ-CD**	**β-CD**	**Mβ-CD**	**α-CD**
K_F (M^{-1})	270.94	204.52	145.27	15.05
SD (±)	29.80	22.50	15.98	1.66
Docking Score	−7.20	−6.60	−6.10	−5.80

The highest KF value (KF = 270.94 ± 29.80 M^{-1}) was for HPβ-CD, followed by β-CD (KF = 204.52 ± 22.50 M^{-1}), Mβ-CD (KF = 145.27 ± 15.98 M^{-1}) and, finally, α-CD (KF = 15.05 ± 1.66 M^{-1}). As the results show, the inner cavity of β-CD: (6.0–6.4 Å) fitted KNYA better than α-CD: (4.7–5.2 Å).

For this reason, β-CD and their derivatives HPβ-CD and Mβ-CD were considered the most interesting CD to continue the investigation. In Table 1 it is observed that HPβ-CD showed the highest KF value, followed by natural β-CD. It seems that the extra polarity of the substituent enhance the KYNA complexation; indeed, Mβ-CD obtained less KF than β-CD. The differences observed in the KF value for the complexes with modified CDs could be due to the different hydrophobic nature due to the substituents, the one bearing the methyl or hydroxypropyl groups), as occurs with other molecules (Matencio et al., 2016, Matencio et al., 2019, Matencio et al., 2017a). Additionally, these results were corroborated using a t-test ($P < 0.05$), showing significative differences between the KF values. For this reason, HPβ-CD was chosen as host CD for the following sections of the paper.

3.2. Effect of pH on the complexation of KYNA by HPβ-CD

The pH of the medium could affect the activity and stability of molecules, being an important factor to consider. Depending on the product (e.g. juice or milk), the stability of the complexes may be different (Matencio, Navarro-Orcajada, Conesa, et al., 2020). Indeed, several authors have shown that the protonation state has a great influence on the encapsulation constants (López-Nicolás et al., 2009, Matencio et al., 2017b, Samuelsen et al., 2020). Fig. 2A shows a substantial influence of KF on pH, passing from an average value of 1384 ± 73 M^{-1} (when the medium pH is between 2.5 and 3) to about 220 ± 103 M^{-1} (when the medium pH is between 3.5 and 4.5), possibly by the titration of a ionizable group. These results suggest that the introduction of this bioactive compound is some food matrixes such as juice (pH around 3–5.5) or soft drinks would be improved in presence of CDs (Matencio, Navarro-Orcajada, Conesa, et al., 2020).

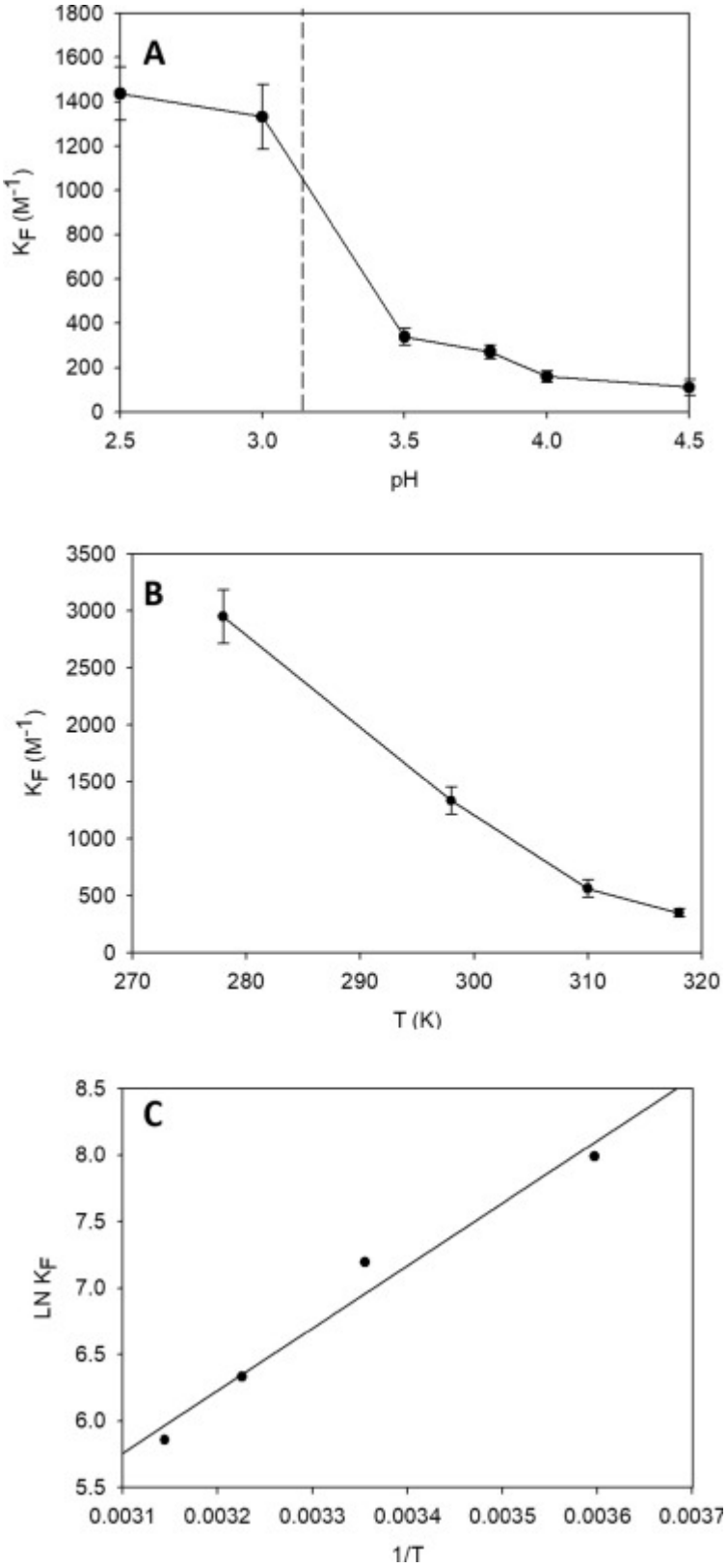

Fig. 2. (A) Effect of different pH values on KF values (25 °C). (B) Effect of different temperatures (5, 25, 37 and 45 °C) on KF values (pH 3). (C) Van't Hoff plot of temperature data.

The same effect has been described with other molecules when the effect of pH is studied (López-Nicolás et al., 2009, Matencio et al., 2017, Matencio et al., 2020). Indeed, the decrease in the KF value coincides with the region where the KNYA begins deprotonation of its acid group (pKa = 3.17, drugbank). The possible

formation of some hydrogen bond between KNYA and the hydrophilic part of CD at pH values above the pka (3.17) may justify the dependence, because hydrogen bonding is one of the most important types of interaction in the stabilization of inclusion complexes (Bru et al., 1996, Saenger, 1980). Moreover, making the second derivatives (data not shown) to a polynomial fit (Matencio et al., 2016) an apparent pKa of 3.37 was obtained, very close to the reported value. The fact that the complexes between HPβ-CD and the protonated form of KYNA were more stable at acid pHs might be of great interest for the food industry, because the protonated form of molecules, which is usually less soluble, presents different properties such as antioxidant capacity (Lemańska et al., 2001, Rodríguez-Bonilla et al., 2017) and CDs are able to increase the total quantity of antioxidant increasing the total capacity of the solution (Matencio, Navarro-Orcajada, Conesa, et al., 2020).

3.3. Effect of temperature on the complexation of KYNA by HPβ-CD

Different results can be obtained for the effect of temperature on the inclusion complex formation. Normally, inclusion complexes are less stable at high temperatures (Armstrong et al., 1987, Matencio et al., 2017, Saenger, 1980). However, the encapsulation of some polyunsaturated fatty acids by CDs is favoured by an increase in temperature (López-Nicolás et al., 1995, Matencio et al., 2017a). For this reason, the next step was to study the effect of temperature on the KF values for the complex interactions at four different temperatures: 5, 25, 37 and 45 °C at pH 3, where the value KF were large enough to detect changes.

As shown in Fig. 2B, an increase in temperature led to a strong decrease in the encapsulation constant values, while the intrinsic solubility of KYNA was increased in the range tested (supplementary Fig. 1). One of the most important interaction between a CD and a guess, hydrogen bonds are usually weakened by heating. This fact, with the increase in the intrinsic solubility, could be a possible explanation to this effect (Matencio et al., 2016).

3.4. Thermodynamic parameters for the HPβ-CD/KYNA complexation

The complexation of KNYA by HPβ-CD produces some changes in the thermodynamic parameters (ΔH°, ΔS° and ΔG° at 25 °C), so these parameters were obtained to gain information on mechanistic aspects of the affinity. Fig. 2C shows that the ln KF vs 1/T plot is linear, with a correlation coefficient higher than 0.97. From these data, different conclusions may be obtained:

During the complexation, the entropy undergoes negative changes (-73.28 ± 6.66 J $mol^{-1}K^{-1}$). This can be because i) a decrease in the translational and rotational degrees of freedom of the complexed KYNA, leading to more ordered system and ii) the complexation decreases the number of species in solution.

Moreover, the exothermic nature (-39.42 ± 1.95 kJ mol^{-1}) is typical of hydrophobic interactions (e.g. van der Waals), due to i) the displacement of water molecules from the cavity of HPβ-CD and ii) the formation of hydrogen bonds and other interactions (Ravelet et al., 2002). Indeed, an exothermic nature in the exothermic formation is a common situation (Schönbeck & Holm, 2019). Concerning the spontaneity of the encapsulation process, our data show that the inclusion process is spontaneous (–17.24 ± 0.87 kJ mol^{-1}).

3.5. Characterization of HPβ-CD/KYNA inclusion complexs: FTIR and TGA studies

The next step was to characterize our novel inclusion complex. After obtaining the lyophilized, FTIR analysis was carried out (Fig. 3A), the characteristic peaks of KYNA (Dhakar et al., 2019) at, for example, 3095 cm^{-1} (-Nsingle bondH stretching) or 1660 cm^{-1} (-Cdouble bondC stretching) disappeared, indicating the interaction of HPβ-CD with KYNA like occurred with CD-based nanosponges (Dhakar et al., 2019). Moreover, the physical

mixture showed several peaks of KYNA that were not found in the inclusion complex. In addition, the ratio between 1150 cm^{-1} (C-OH stretching) and 1024 (Csingle bondH) is increased from 2.5 for HPβ-CD to 2.69 when the inclusion complex is formed.

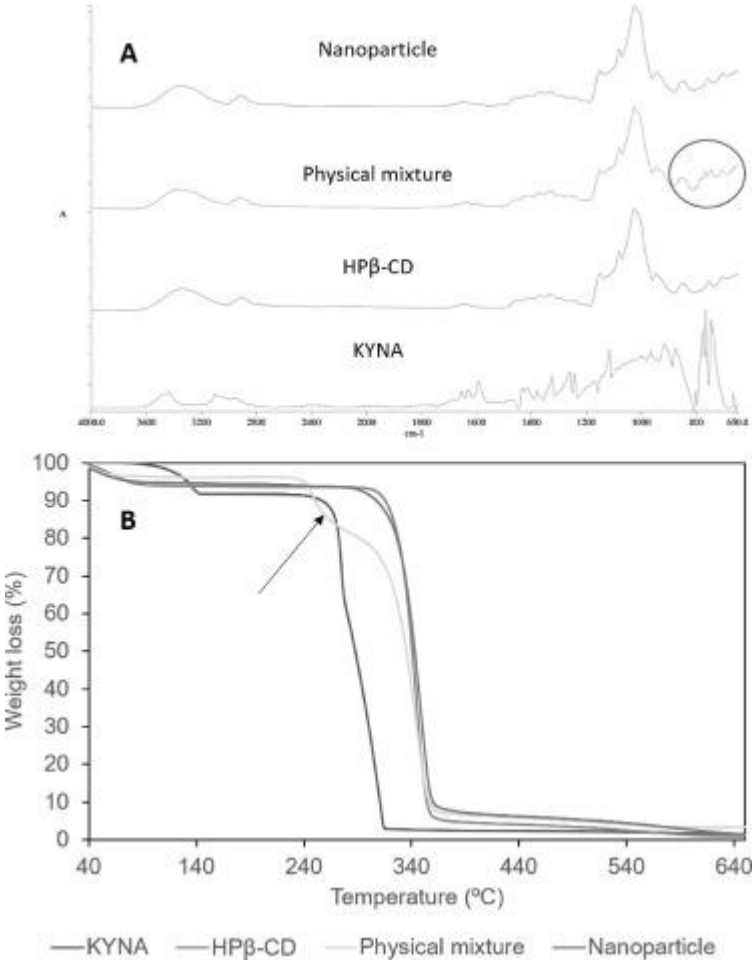

Fig. 3. (A) FTIR spectrum of KYNA, HPβ-CD, physical mixture and the inclusion complex. Indicated, the KYNA peaks in the physical mixture. (B) TGA results of KYNA, HPβ-CD, physical mixture and the inclusion complex. Arrow: the degradation of KYNA in the physical mixture.

Additionally, TGA studies were carried out (Fig. 3B). While HPβ-CD presented a degradation step at 341 °C (starting degradation at 278 °C), the presence of KYNA in the inclusion complex reduce the temperature to 335 °C (starting degradation at 269 °C), possibly to the presence of the degradation steps of KYNA at 275 and 307 °C. Moreover, the physical mixture showed the combinatorial degradation of KYNA and HPβ-CD separately, which is homogeneous with inclusion complex formation. On the other hand, there is a mass reduction of 95% in HPβ-CD, in comparison with the inclusion complex (91%). Such observations lend weight to the complexation.

3.6. Molecular docking of the CD/ KYNA complexes

To better understand how KYNA interacts with CDs, a good approximation are docking simulations (Abril-Sánchez et al., 2019, Tao et al., 2020, Vázquez et al., 2019). Table 1 shows that the docking scores were directly proportional to the KF values. This great ordination suggests that the simulated complexes get the essentials interactions between the host and the guest.

The poses obtained were analysed trying to get more details (Fig. 4). As regards the ring size of the different CDs, the weakest interaction corresponds to the complex with α-CD, as depicted in Fig. 4.A. Although it seems to fit well, the inner cavity might be not optimal for KNYA complexation. In general terms, the stability of the complexation increases with β-CD and its derivatives Mβ-CD, HPβ-CD (Figs. 4.B, 4.C and 4.D).

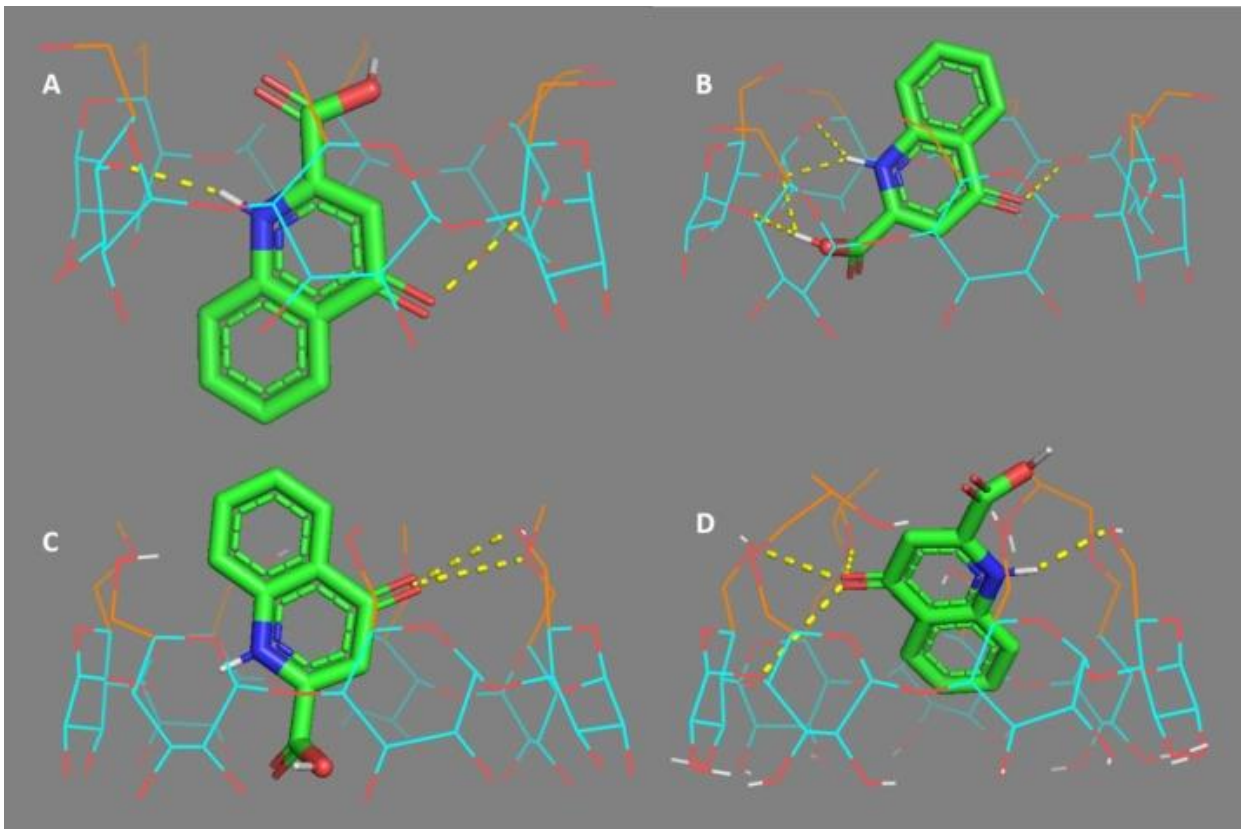

Fig. 4. Molecular docking poses of KNYA for (A) α-CD, (B) β-CD, (C) Mβ-CD and (D) HPβ-CD inclusion complexes. In yellow, hydrogen bonds. Flexible parts of CDs are indicated in orange.

For CDs with seven sugar rings, the most stable combination corresponds to HPβ-CD followed by the natural β-CD and the derivative HPβ-CD, though Mβ-CD was lower than β-CD. The Mβ-CD complex has fewer hydrogen bonds than the β-CD complex, which might explain the lower KF obtained. In the case of HPβ-CD, although it presents less polar interactions, the reason of the higher stability could be due to the additional accommodation that KYNA finds between the substituents, as well as the increased polarity of the CD (curiously, the extra hydrophobicity of methyl substituent decreases the values of KF and the score).

4. Conclusions

In the present study, we studied the complexation of KYNA in several CDs to obtain a possible carrier for functional foods. Between all the CDs tested, HPβ-CD and β-CD presented the best KF values (270.94 ± 29.80 M^{-1} and 204.52 ± 22.50 M^{-1} respectively). HPβ-CD/KYNA inclusion complex was selected as model for the remaining study. The effect of pH demonstrated a decrease of KF value at high pH values due to the pKa of the molecule. In similar way, the increase of temperature decreased the value of KF. The thermodynamic parameters demonstrated that the encapsulation is exothermic (-31.42 ± 1.57 kJ mol^{-1}), with negative entropy (-46.63 ± 2.33 J mol−1 K^{-1}) and endergonic at 25 °C (–17.52 ± 0.87 kJ mol^{-1}). The inclusion complex was confirmed using FTIR and TGA, where the characteristic peaks of KYNA disappeared after inclusion

complex formation. A computational study carried out using molecular docking calculations showing essential details about complexation. The findings represent a new opportunity to obtain results that support the use of KYNA as an ingredient of new foods.

Credit authorship contribution statement

Adrián Matencio: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Visualization. Fabrizio Caldera: Methodology, Validation, Formal analysis, Writing - review & editing. Alberto Rubin-Pedrazzo: Conceptualization, Methodology, Validation, Formal analysis. Yousef Khazaei Monfared: Conceptualization, Validation. Nilesh Kumar-Dhakar: Conceptualization, Validation. Francesco Trotta: Conceptualization, Resources, Writing - review & editing, Formal analysis, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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