Journal of Thermal Analysis and Calorimetry (2022) 147:347–353
https://doi.org/10.1007/s10973-020-10381-y

Phase solubility and thermoanalytical studies of the inclusion complex formation between curcumin and hydroxypropyl-β-cyclodextrin in hydroalcoholic solutions

Dzhovidon Kabirov[1] · Teresa Silvestri[2] · Marcella Niccoli[3] · Tatiana Usacheva[1] · Laura Mayol[2,4] · Marco Biondi[2,4] · Concetta Giancola[2]

Received: 26 June 2020 / Accepted: 21 October 2020 / Published online: 19 November 2020

Abstract
Curcumin (CURC) is endowed with many pharmacological properties, among these anti-inflammatory, antioxidant, antimicrobial, and anticancer activity. Unfortunately, CURC is basically water-insoluble and undergoes a rapid photodegradation, chemical degradation, and metabolism. CURC stability and solubility can be improved by the complexation with cyclodextrins, which are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic cavity. Thus, in this work, the formation of the inclusion complex between the semisynthetic hydroxypropyl-β-cyclodextrin (HPβCD) and CURC has been studied by means of phase solubility, differential scanning calorimetry and isothermal calorimetry experiments to assess the formation, stoichiometry and affinity constant of the obtained inclusion complexes. The thermodynamics of the complex formation has been studied in different hydroalcoholic solutions and the experiments have been performed at physiological and acidic pH to verify the effect of the ionization state on the efficacy of complex formation. Results show the relevance in the choice of the pH, solvent, and mixing time on the formation of the inclusion complex between active drug(s) and HPβCD.

Keywords Hydroxypropyl-β-cyclodextrin · Curcumin · Inclusion complex · DSC · Isothermal calorimetry · Phase solubility

Introduction

Curcumin (CURC) is the principal polyphenolic component of the rhizomes of *Curcuma Longa* plant, and is extensively used in food industry, cosmetics, and traditional Chinese medicine. Lately, a significant deal of research focus has been devoted to assess the possible applications of CURC in the pharmaceutical field [1–3]. Indeed, CURC is broadly acknowledged to be potentially able to exert numerous pharmacological effects such as: (i) a relevant antioxidant activity and scavenging of reactive oxygen (ROS) species [4]; (ii) inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which is a main signal transduction pathway involved in inflammatory processes [5]; antitumor and antimicrobial [3, 6]. Nowadays, the beneficial effects of CURC and its derivatives have been verified against an extensive array of cancer cells populations [2, 7–9], in wound healing [10, 11], Alzheimer's disease [12] and arthritis [13, 14], just to cite a few.

Regrettably, phase I trials have shown that the bioavailability of CURC administered orally is irrelevant [15]. Actually, CURC is inherently insoluble in water (saturation concentration is around 20 μg mL^{-1}, and the partition coefficient in < 2.5) [16], is unstable at neutral/slightly basic pH values and also undergoes an extensive and quick first-pass metabolism. Consequently, despite being a GRAS (Generally Regarded as Safe) molecule, the bioavailability profile of

Dzhovidon Kabirov and Teresa Silvestri have contributed equally to this work.

✉ Marco Biondi
mabiondi@unina.it

[1] Department of General Chemical Technology, Faculty of Inorganic Chemistry and Technology, Ivanovo State University of Chemistry and Technology, Sheremetevsky Avenue 7, Ivanovo, Russian Federation 153000

[2] Department of Pharmacy, University of Naples Federico II, Via Domenico Montesano 49, 80131 Naples, Italy

[3] Dipartimento di Scienze Chimiche, Università degli Studi di Napoli Federico II, Strada Comunale Cinthia 26, Naples, Italy

[4] Interdisciplinary Research Centre on Biomaterials – CRIB, Università di Napoli Federico II, P.le Tecchio, 80, Naples, Italy

orally administered CURC is unequivocally unsatisfactory, thus hindering its clinical use so far [15, 17, 18].

In this regard, the improvement of CURC solubility is fundamental to enhance its bioavailability. The solubility of CURC can be increased through numerous strategies, the most relevant being its encapsulation in liposomes [19, 20] or nanoparticles [21, 22]. Furthermore, the capacity of the active molecule to form host–guest complexes with cyclodextrins (CDs) have been studied so far [21–23]. CDs are regularly used in pharmaceutics to improve the solubility of water-insoluble compounds, thereby exploiting the preferential interaction of these molecules with the hydrophobic internal cavity of CDs. The hydrophilic external surface of CDs can bring lipophilic molecules in solution in aqueous media [24]. The formation of the complex between CURC and CD also proved to increase the bioavailability and stability of the guest molecule [25]. β-CD and semisynthetic β-CDs are widely used in the pharmaceutical industry due to their abundance and low cost [26]. This is of huge interest, considering that the formation of an inclusion complex between CURC and β-CD can result into a promoted cell uptake and higher half-life within tumor cells, and also into an augmented anti-inflammatory ability of the active molecule [27].

In two previous works [28, 29], calorimetric studies were carried out to investigate the thermodynamics of the complexation between quercetin, that is another phytomolecule with a considerable therapeutic potential, and the semisynthetic hydroxypropyl-β-CD (HPβCD). These experiments also highlighted the importance of the choice of the appropriate solvent, pH, and temperature on the formation of host guest inclusion complex with active ingredient(s) and CDs. On the same research branch, the objective of this work was the study of the thermodynamics of the formation of the complex between CURC and HPβCD. To this aim, phase solubility, differential scanning calorimetry (DSC), and isothermal calorimetry experiments were employed to assess the stoichiometry, formation, and affinity constant of the obtained inclusion complexes. Therefore, herein the thermodynamics of the complex formation have been investigated in different hydroalcoholic solutions at physiological and acidic pH to verify the effect of the ionization state on the efficacy of complex formation, and also to study the effect of the cosolvent on the CURC solubility and on CURC encompassment.

Materials and methods

Materials

Curcumin (CURC) at a < 90% purity from Cayman Chemical Company, USA), and citric acid, Tween® 80 from Farmalabor (Italy) were employed. Ethanol (EtOH), 2-hydroxypropyl-b-cyclodextrin (HPβCD; degree of substitution (DS) = 4.2), dibasic sodium phosphate (Na_2HPO_4), sodium chloride (NaCl), and potassium chloride (KCl) were obtained from Sigma–Aldrich (USA). For calorimetric tests, the concentrations of CURC and HPβCD were $8{\cdot}10^{-6}$–$1.4{\cdot}10^{-4}$ mol·kg^{-1} and $1.2{\cdot}10^{-3}$–$1.2\cdot10^{-2}$ mol·kg^{-1}, respectively. The solutions in PBS (phosphate buffered saline) at pH 7.4 or 5.0 were prepared immediately before measurements. To increase CURC solubility in aqueous solutions, dimethylsulfoxide (DMSO; Sigma–Aldrich, USA) up to 2% v/v and EtOH up to 20% v/v to PBS buffer were also added.

Phase solubility experiments

Prior to phase solubility studies, PBS buffers were prepared as described in [28, 29]. Then, pH was adjusted 7.4 or 5.0 by adding 0.1 M HCl. In the case of the physiological pH, acid and citric acid 1:1 w/w, 0.1% w/v were added to prevent CURC degradation which was found to be negligible at pH = 5.0 [21]. In all cases, Ethanol (20% v/v) and Tween® 80 (0.5% w/v) were added to enhance CURC solubility. An excess amount of CURC (1 mg mL^{-1}) was suspended in 5 mL of PBS solutions at both pH values in the presence of HPβCD (3–15 mM). The suspensions were placed under stirring at room temperature (24 h, 100 rpm, in the dark) and, after that, filtered (0.22-μm membrane filter) and then analyzed by spectrophotometric assay (UV-1800, Shimadzu Laboratory World, Japan; λ = 426 nm) to quantify the solubilized CURC. In all cases, the linearity of the apparatus response was assessed in the 1–50 μM concentration range, with a $r^2 > 0.99$. Correspondingly, the CURC concentration versus HPβCD concentration was plotted and the constant of CURC-HPβCD complex formation, K_C, was obtained from the following equation:

$$K_c = \frac{\text{slope}}{S_0(1 - \text{slope})} \quad (1)$$

where S_0 is intrinsic CURC solubility.

Differential scanning calorimetry (DSC)

DSC tests were performed on freeze-dried solutions (24 h, 0.01 atm, − 83 °C; LyoQtest, Japan) recovered after phase solubility experiments to study CURC/HPβCD complex formation. The samples obtained at 15 mM HPβCD concentration were used for DSC experiments. The heats evolved during the thermal transitions of CURC, HPβCD and the recovered precipitate were detected by a Q20 differential scanning calorimeter (TA Instruments, USA; indium calibration). Each sample (around 5 mg) was subjected to a 20–200 °C ramp at 10 °C min^{-1} in hermetic aluminum pans, with a N_2

atmosphere (50.0 mL min^{-1}). Double scans were performed for all samples.

Isothermal calorimetry

Isothermal calorimetry equipment TAM was utilized to measure the heat involved in the encapsulation of CURC into HPβCD and heats of dilution of each compound, at constant room temperature. Details of calorimetric apparatus are described in a recent paper [28].

In isothermal calorimetry experiments, the heat of dilution ($\Delta_{dil}H$) from an initial to a final molality of aqueous solutions of HPβCD or CURC was detected. Moreover, heat of mixing ($\Delta_{mix}H$) of aqueous solutions of CURC and aqueous solutions of HPβCD, was also recorded.

The enthalpy of mixing, $\Delta_{mix}H$, is calculated by the enthalpy of formation of the complex, ΔH^*, and by the heats of dilution, $\Delta_{dil}H$, of CURC and HPβCD as follow:

$$\Delta_{mix}H\left[\left(m^{i}_{HP\beta CD}\right)\left(m^{i}_{CURC}\right) \rightarrow m^{f}_{HP\beta CD}, m^{f}_{CURC}\right] = \Delta H * + \Delta_{dil}H\left(m^{i}_{HP\beta CD} \rightarrow m^{f}_{HP\beta CD}\right) + \Delta_{dil}H\left(m^{i}_{CURC} \rightarrow m^{f}_{CURC}\right), \quad (2)$$

where m^{i} and m^{f} are the initial and final molality of HPβCD or CURC.

All the experimental ΔH values were derived from the well-known equation:

$$\Delta H = (dQ/dt)/P_{w} \quad (3)$$

where dQ/dt, expressed in Watt, is the heat flux, while P_w, expressed in kg s^{-1} is the total mass flow rate of the solvent. ΔH is expressed in J kg^{-1} of solvent in the final solution.

Results and discussion

In this work, we have studied the thermodynamics of the formation of the inclusion complex between the semisynthetic hydroxypropyl-β-cyclodextrin (HPβCD) and CURC. HPβCD has been chosen since it is approved by the FDA, and due to its enhanced solubility compared to native βCD and lack of toxicity, alongside its wide use as solubility enhancer in the pharmaceutical field. To this aim, phase solubility, differential scanning calorimetry (DSC) and isothermal microcalorimetry experiments were systematically carried out at pH = 5 and pH = 7.4 in hydroalcoholic solutions. Actually, it should be emphasized that all the experiments, except for DSC tests, were performed in hydroalcoholic solutions taking into account that the solubility of CURC in water and buffer solutions is irrelevant. Consequently, the determination of the heats involved in the complexation, as well as phase solubility tests, is not possible under such conditions.

Phase solubility

Phase solubility results, in the presence of 20% v/v EtOH, are depicted in Fig. 1 and have shown that, at pH = 7.4, the addition of HPβCD up to a 15 mM concentration has allowed a 20.5-fold increase in CURC solubility. At pH = 5.0 the solubility increase of CURC was 47-fold higher. The outcomes plainly point out that the formation of HPβCD-CURC inclusion complex is promoted at pH < pKa. Indeed, constants for the complex formation (K_c), obtained from phase solubility measurements, showed that K_c value (2285 ± 53 M^{-1}) at pH = 5.0 is about 1.4 times higher compared to K_c value (1679 ± 136 M^{-1}) at pH = 7.4. In addition, literature data show a K_c value of 424 M^{-1} in water and in the absence of

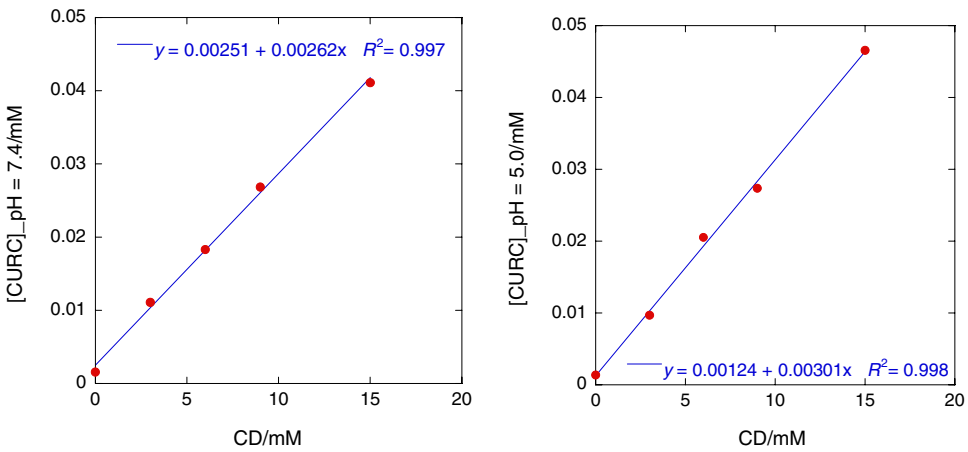

Fig. 1 Phase solubility diagrams of CURC/HPβCD inclusion complex formation at pH = 7.4 (left) and pH = 5.0 (right)

cosolvent, lower of almost one order of magnitude than in the presence of ethanol [29, 30].

To better understand these results, it is necessary to consider that CURC exists in different forms according to the pH. In fact, as reported in [31], the CURC solutions are red at pH < 1, and this is associated with the protonated form of the CURC while, at pH > 7.5 the color changes to orange red and this is associated with the pKa value for the dissociation of the enolic group. It should also be added that at pH > 7 the CURC is extremely unstable and undergoes a rapid hydrolytic degradation, with a half-life in the order of minutes, as also reported in [24].

In the pH range 1–7, the neutral form of CURC prevails, and this is associated with a minimum solubility of the active molecule. These considerations corroborate the results whereby a weakly acidic pH, far from the neutral pH to which the stability of the CURC is seriously at risk, is more favorable for the formation of the inclusion complexes between CURC and HPβCD, as hypothesized in this paper.

DSC

DSC tests were taken on the recovered precipitate from phase solubility experiments to verify the formation of the inclusion complex between HPβCD and CURC, which results into the disappearance and/or the shift of endothermic peaks of DSC curves, thereby pointing at a modification occurring in the crystal lattice. To ensure that the DSC trace reported in Fig. 2d is representative of the thermal behavior of the HPβCD/CURC inclusion complex, thermoanalytical tests were performed on the dried salts used to produce PBS and on Tween 80. No thermal events were detected in the temperature range considered (data not shown). As a consequence, DSC traces of the samples are displayed in Fig. 2a–d and summarized in Table 1. First scans are here reported since second scans did not show any thermal event.

CURC exhibited a clear endothermic melting peak at 183 °C, corresponding to the fusion of CURC crystals (Fig. 2a). In the case of HPβCD, a single and very broad peak with an onset at 95.5 °C and peaking around 128 °C, was found out (Fig. 2b). This endothermic event is attributed to the release of bound water in the cavity. The DSC

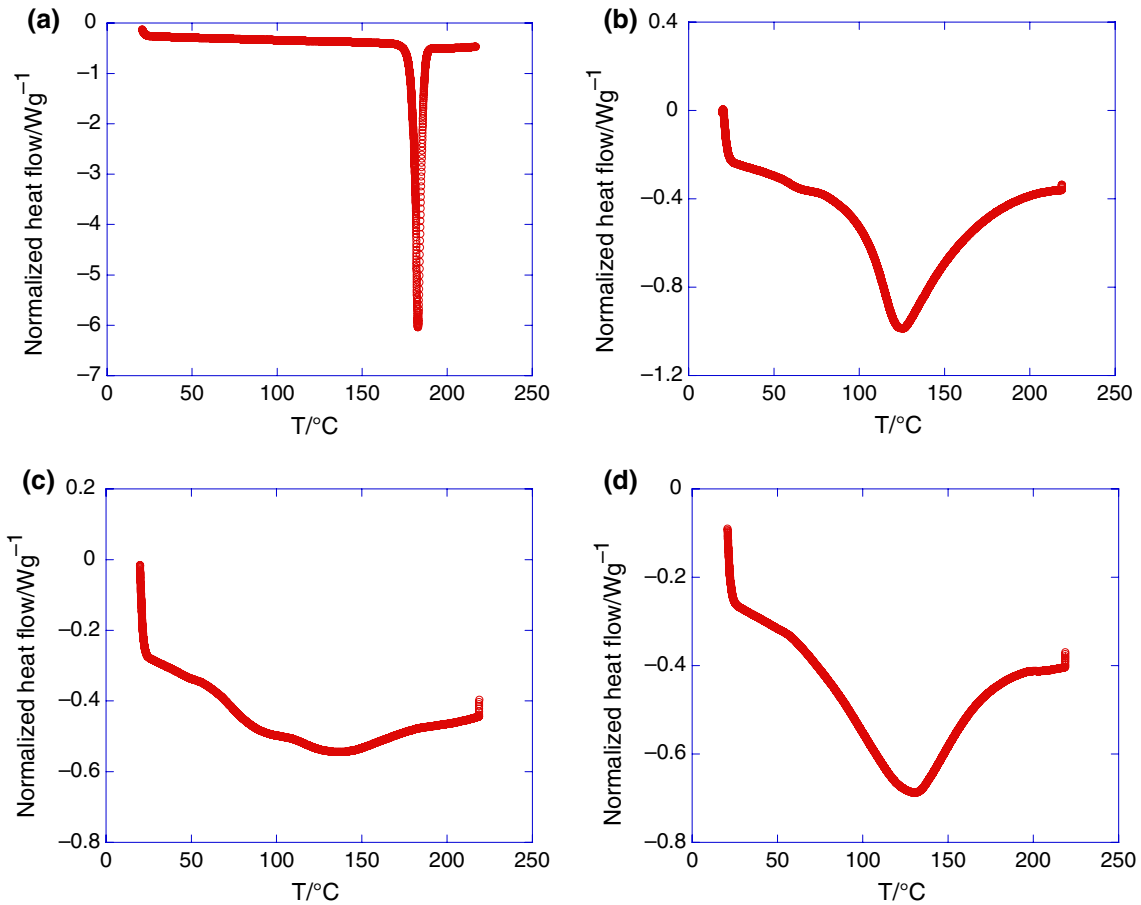

Fig. 2 DSC traces of CURC (**a**), HPβCD (**b**), HPβCD-CURC inclusion complex at pH = 7.4 (**c**) and at pH = 5.0 (**d**)

Table 1 Onset and peak temperatures of raw materials and HPβCD/CURC complexes in 20% EtOH at pH = 7.4 and pH = 5.0 at 298.15 K

	T_{onset}/ °C	T_{peak}/°C
CURC	181.2 ± 0.1	182.9 ± 0.3
HPβCD	95.5 ± 3.0	128.2 ± 6.2
Complex at pH = 7.4	57.4 ± 5.1	120.8 ± 10.8
Complex at pH = 5.0	64.9 ± 0.3	129.5 ± 0.3

curve of the inclusion complex obtained at pH = 7.4 showed a shoulder (Fig. 2c), which suggests the occurrence of multiple endothermic events. In particular, the neutral pH is very close to the lowest of the three pK_a values of CURC (pK_a = 7.8, 8.5, and 9.0, corresponding to three acidic protons [24]). As a consequence, the DSC trace reported in Fig. 2b can be realistically associated to the occurrence of both charged and non-charged CURC molecules, which are supposed to interact differently with HPβCD, therefore evoking two distinct, and partially overlapped, endothermic phenomena. Moreover, the melting peak of CURC was not observed, thereby indicating the formation of the complex and the successful displacement of water molecules in solution [32]. This observation was further confirmed when the complex was formed at acidic pH. In particular, the DSC trace in this case qualitatively and closely resembled the features of HPβCD alone (Fig. 2d). However, it must be underlined that at pH = 7.4 the endothermic peak was found at a lower temperature while at pH = 5.0, it was found approximately at the same temperature of bare HPβCD, while the onset was about 30 °C lower compared to HPβCD alone. This was attributed to a complete inclusion and masking of CURC, and also to strong interactions of HPβCD and CURC in the solid state.

Isothermal calorimetry

To gain further information on thermodynamic parameters of the inclusion complex formation, isothermal calorimetric measurements were performed. Results showed that the heat of mixing at pH = 7.4 and pH = 5.0 without ethanol was too small to be measured. In the presence of 20% v/v EtOH, a small but measurable heat of complex formation was recorded at both the pH values. The calorimetric data did not show the typical rectangular hyperbolic shape, in the range of concentrations we were able to explore (Fig. 3), and this did not allow the determination of constants for the complex formation. The cyclodextrin was in strong excess over the CURC during the whole titration experiment, therefore CURC was completely bound to HPβCD. Each injection produces the same heat providing the complex formation enthalpy when divided by molarity of CURC. Consequently, we were able to determine the standard molar enthalpy for the formation of HPβCD-CURC complex: $\Delta H^0 = -4.67 \pm 0.06$ kJ mol^{-1} at pH = 7.4 and $\Delta H^0 = -8.11 \pm 0.06$ kJ mol^{-1} at pH = 5.0. These values show very slight differences between the two pHs, although beyond the experimental errors.

Figure 4 displays the thermodynamic parameters of HPβCD-CURC formation at both the investigated pHs are shown. The Gibbs energy changes, $\Delta G°$, were calculated from the K_c values obtained by phase solubility measurements. The entropy changes were obtained from the well-known thermodynamic relation: $\Delta S° = (\Delta H° - \Delta G°)/T$. The overall thermodynamic parameters of complexation of active compounds with cyclodextrins are often obtained by phase solubility experiments (references). Enthalpy changes are indirectly determined by van't Hoff enthalpy plots with higher errors with respect to the direct enthalpy determinations. In this work, we were able to directly measure the

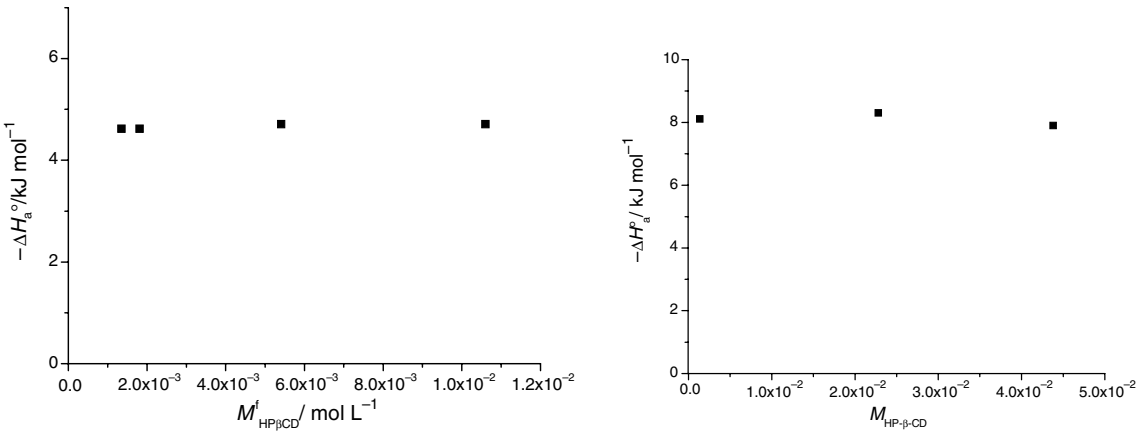

Fig. 3 Enthalpies of binding, ΔH^*, normalized to the total molality of the guest, m_{curc}, as a function of the final molality of cyclodextrin, in buffer PBS + 20% EtOH at pH = 7.4 (left panel) and pH = 5.0 (right panel) at 298.15 K. The experimental points are indicated by squares

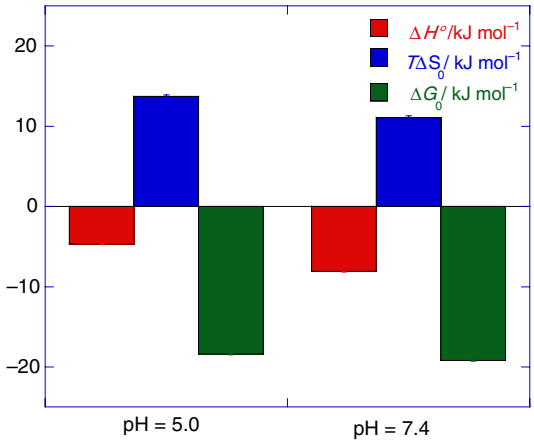

Fig. 4 Thermodynamic parameters for the inclusion complex formation between HPβCD and CURC in 20% EtOH at pH = 7.4 and pH = 5.0 at 298.15 K

Table 2 Thermodynamic parameters for the inclusion complex formation between HPβCD and CURC in 20% EtOH at pH = 7.4 and pH = 5.0 at 298.15 K

	K_c/M^{-1}	$\Delta H°$/kJ mol^{-1}	$T\Delta S^0$/kJ mol^{-1}	ΔG^0/kJ mol^{-1}
pH = 7.4	1679 ± 136	− 4.67 ± 0.06	13.7 ± 0.2	− 18.4 ± 0.1
pH = 5.0	2285 ± 53	− 8.11 ± 0.06	11.1 ± 0.2	− 19.2 ± 0.1

calorimetric enthalpies of complex formation at both the pHs and used them to obtain the entropy changes.

An inspection of Table 2 and Fig. 4 shows that the inclusion complex formation between HPβCD and CURC is enthalpically (exothermic process) and entropically (increased entropy) favored at both the pH values. This behavior is in line with results previously obtained for the inclusion complex between HPβCD and quercetin [29]. Actually, both the enthalpic and entropic contributions to Gibbs energy arise from a delicate balance among different processes, such as desolvation of HPβCD and CURC molecules, hydrophobic interaction between CURC and the cavity of HPβCD, and the competition between ethanol and water for the cavity when the content of ethanol is too high. The pH contributes to this balance, the CURC solubility increases at pH = 5.0 with a slightly better affinity for HPβCD. Overall, the combination of the hydroalcoholic solvent (2:8 v/v) and a slightly acid pH contribute to a better encapsulation of CURC in the cavity of HPβCD [33–35].

Conclusions

Herein, the encapsulation of CURC into HPβCD has been studied through phase solubility, DSC and isothermal calorimetry, at physiological and acidic pH and in hydroalcoholic solvent (2:8 v/v).

Results of the thermal analyses of CURC, HPβCD, and HPβCD-CURC showed that the melting peak of CURC at 183 °C was not detected, therefore confirming the inclusion complex formation. Phase solubility outcomes have shown that at pH = 7.4 the addition of HPβCD up to a 15 mM concentration has allowed a 20.5-fold increase in CURC solubility. On the other side, at pH = 5, the solubility increase of CURC was 47-fold higher. Results of isothermal calorimetric measurements allow to derive the enthalpy changes of the encapsulation of CURC in the cavity of HPβCD complex in showed that the hydroalcoholic solvent (2:8 v/v) and at both the pHs. Taken all together, results clearly indicate that the formation of the HPβCD-CURC inclusion complex is strongly promoted at pH < pK_a of CURC and hold promise for the optimization of complex loading within conventional and/or advanced pharmaceutical dosage forms.

Acknowledgements This work was funded by Ministry of Foreign Affairs and International Cooperation of Italy [grants in favor of foreign citizens not residing in Italy and Italian citizens living abroad, № 946-22/10/2018], by RFBR and VAST according to the research project № 19-53-54004] and State Assignment of the Ministry of Science and Higher Education and the Russian Federation (project FZZW-2020-0009).

References

1. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. J Pharm Sci. 1996;85(10):1017–25.
2. Mahran RI, Hagras MM, Sun D, Brenner DE. Bringing curcumin to the clinic in cancer prevention: a review of strategies to enhance bioavailability and efficacy. AAPS J. 2017;19(1):54–81.
3. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS J. 2013;15(1):195–218.
4. Mishra B, Priyadarsini KI, Bhide MK, Kadam RM, Mohan H. Reactions of superoxide radicals with curcumin: probable mechanisms by optical spectroscopy and EPR. Free Radic Res. 2004;38(4):355–62.
5. Jobin C, Bradham CA, Russo MP, Juma B, Narula AS, Brenner DA, et al. Curcumin blocks cytokine-mediated NF-kappa B activation and proinflammatory gene expression by inhibiting inhibitory factor I-kappa B kinase activity. J Immunol. 1999;163(6):3474–83.
6. Chignell CF, Bilskj P, Reszka KJ, Motten AG, Sik RH, Dahl TA. Spectral and photochemical properties of curcumin. Photochem Photobiol. 1994;59(3):295–302.
7. Wong KE, Ngai SC, Chan KG, Lee LH, Goh BH, Chuah LH. Curcumin nanoformulations for colorectal cancer: a review. Front Pharmacol. 2019;10:152.
8. Gianfredi V, Nucci D, Vannini S, Villarini M, Moretti M. In vitro biological effects of sulforaphane (SFN), epigallocatechin-3-gallate (EGCG), and curcumin on breast cancer cells: a systematic review of the literature. Nutr Cancer. 2017;69(7):969–78.
9. Feng T, Wei Y, Lee RJ, Zhao L. Liposomal curcumin and its application in cancer. Int. J. Nanomed. 2017;12:6027–44.

10. Shao M, Hussain Z, Thu HE, Khan S, de Matas M, Silkstone V, et al. Emerging trends in therapeutic algorithm of chronic wound healers: Recent advances in drug delivery systems, concepts-to-clinical application and future prospects. Crit Rev Ther Drug Carr Syst. 2017;34(5):387–452.
11. Mohanty C, Sahoo SK. Curcumin and its topical formulations for wound healing applications. Drug Discov. Today. 2017;22(10):1582–92.
12. Chen M, Du ZY, Zheng X, Li DL, Zhou RP, Zhang K. Use of curcumin in diagnosis, prevention, and treatment of Alzheimer's disease. Neural Regen. Res. 2018;13(4):742–52.
13. Dudics S, Langan D, Meka RR, Venkatesha SH, Berman BM, Che CT, et al. Natural products for the treatment of autoimmune arthritis: their mechanisms of action, targeted delivery, and interplay with the host microbiome. Int J Mol Sci. 2018;19(9):2508.
14. Rahman M, Beg S, Verma A, Al Abbasi FA, Anwar F, Saini S, et al. Phytoconstituents as pharmacotherapeutics in rheumatoid arthritis: challenges and scope of nano/submicromedicine in its effective delivery. J Pharm Pharmacol. 2017;69(1):1–14.
15. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PSSR. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998;64:353–6.
16. Prasad S, Tyagi AK, Aggarwal BB. Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. Cancer Res. Treat. 2014;46(1):2–18.
17. Anand P, Thomas SG, Kunnumakkara AB, Sundaram C, Harikumar KB, Sung B, et al. Biological activities of curcumin and its analogues (Congeners) made by man and mother nature. Biochem Pharmacol. 2008;76(11):1590–611.
18. Pan MH, Huang TM, Lin JK. Biotransformation of curcumin through reduction and glucuronidation in mice. Drug Metab Dispos. 1999;27(4):486–94.
19. Campani V, Scotti L, Silvestri T, Biondi M, De Rosa G. Skin permeation and thermodynamic features of curcumin-loaded liposomes. J Mater Sci Mater Med. 2020;31(2):18.
20. Rogers NM, Stephenson MD, Kitching AR, Horowitz JD, Coates PTH. Amelioration of renal ischaemia-reperfusion injury by liposomal delivery of curcumin to renal tubular epithelial and antigen-presenting cells. Br J Pharmacol. 2012;166(1):194–209.
21. Mayol L, Serri C, Menale C, Crispi S, Piccolo MT, Mita L, et al. Curcumin loaded PLGA-poloxamer blend nanoparticles induce cell cycle arrest in mesothelioma cells. Eur J Pharm Biopharm. 2015;93:37–45.
22. Serri C, Argirò M, Piras L, Mita DG, Saija A, Mita L, et al. Nanoprecipitated curcumin loaded particles: effect of carrier size and drug complexation with (2-hydroxypropyl)-β-cyclodextrin on their biological performances. Int J Pharm. 2017;520(1–2):21–8.
23. Yallapu MM, Jaggi M, Chauhan SC. β-Cyclodextrin-curcumin self-assembly enhances curcumin delivery in prostate cancer cells. Colloids Surfaces B Biointerfaces. 2010;79(1):113–25.
24. Tønnesen HH, Másson M, Loftsson T. Studies of curcumin and curcuminoids. XXVII. Cyclodextrin complexation: solubility, chemical and photochemical stability. Int J Pharm. 2002;244(1–2):127–35.
25. Suvarna V, Gujar P, Murahari M. Complexation of phytochemicals with cyclodextrin derivatives—an insight. Biomed Pharmacother. 2017;88:1122–44.
26. Loftsson T, Másson M, Brewster ME. Self-association of cyclodextrins and cyclodextrin complexes. J Pharm Sci. 2004;93(5):1091–9.
27. Ma Z, Wang N, He H, Tang X. Pharmaceutical strategies of improving oral systemic bioavailability of curcumin for clinical application. J Control Release. 2019;359–80.
28. D'Aria F, Serri C, Niccoli M, Mayol L, Quagliariello V, Iaffaioli RV, et al. Host–guest inclusion complex of quercetin and hydroxypropyl-β-cyclodextrin: a calorimetric study. J Therm Anal Calorim. 2017;130(1):451–6.
29. Usacheva T, Kabirov D, Beregova D, Gamov G, Sharnin V, Biondi M, et al. Thermodynamics of complex formation between hydroxypropyl-β-cyclodextrin and quercetin in water–ethanol solvents at T = 298.15 K. J Therm Anal Calorim. 2019;138(1):417–24.
30. Yadav VR, Suresh S, Devi K, Yadav S. Effect of cyclodextrin complexation of curcumin on its solubility and antiangiogenic and anti-inflammatory activity in rat colitis model. AAPS PharmSciTech. 2009;10(3):752.
31. Tønnesen HH, Karlsen J. Studies on curcumin and curcuminoids—VI. Kinetics of curcumin degradation in aqueous solution. Z Lebensm Unters Forsch. 1985;180(5):402–4.
32. Al Hagbani T, Nazzal S. Curcumin complexation with cyclodextrins by the autoclave process: method development and characterization of complex formation. Int J Pharm. 2017;520(1–2):173–80.
33. Charumanee S, Weiss-Greiler P, Wolschann P, Viernstein H, Titwan A, Sirithunyalug J, et al. Thermodynamic investigations on the inclusion complexation of piroxicam with cyclodextrin derivatives. Sci Pharm. 2005;73(3):147–61.
34. Charumanee S, Titwan A, Sirithunyalug J, Weiss-Greiler P, Wolschann P, Viemstein H, et al. Thermodynamics of the encapsulation by cyclodextrins. J Chem Technol Biotechnol. 2006;81(4):523–9.
35. Chen A, Liu M, Dong L, Sun D. Study on the effect of solvent on the inclusion interaction of hydroxypropyl-β-cyclodextrin with three kinds of coumarins by phase solubility method. Fluid Phase Equilib. 2013;341:42–7.