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Studies of curcumin and curcuminoids. XXVII. Cyclodextrin complexation: solubility, chemical and photochemical stability

Hanne Hjorth Tønnesen [a,*], Már Másson [b], Thorsteinn Loftsson [b]

[a] *Institute of Pharmacy, University of Oslo, P.O. Box 1068 Blindern, 0316 Oslo, Norway*
[b] *Faculty of Pharmacy, University of Iceland, IS-107 Reykjavik, Iceland*

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Abstract

Cyclodextrin complexes of the natural compound curcumin were prepared in order to improve the water solubility and the hydrolytic and photochemical stability of the compound. Complex formation resulted in an increase in water solubility at pH 5 by a factor of at least 10^4. The hydrolytic stability of curcumin under alkaline conditions was strongly improved by complex formation, while the photodecomposition rate was increased compared to a curcumin solution in organic solvents. The cavity size and the charge and bulkiness of the cyclodextrin side-chains influenced the stability constant for complexation and the degradation rate of the curcumin molecule.

Keywords: Curcumin; Cyclodextrin; Solubility; Hydrolysis; Photostability

1. Introduction

Curcumin is a natural compound primarily used for food colouring. The substance further has a potential as a pharmaceutical excipient. It is known that curcumin has a stabilizing effect on certain photolabile drugs in solution and in topical preparations (Thoma, 1983; Spilgies, 1998). Curcumin can also be applied as a formulation aid to protect light-sensitive drugs in soft gelatine capsules (Tønnesen and Karlsen, 1987). Curcumin is further reported to have a number of pharmacological effects (Srimal, 1997). Discovery of antiviral, anticancer and antitumor properties are interesting, and curcumin undergoes systematic research to characterize its pharmacological potential and possibility for development into a modern drug. Curcumin is practically insoluble in water at acidic or neutral pH. The compound is, however, soluble in alkali. The pK_a values for the dissociation of the three acid protons in curcumin have previously been determined to 7.8, 8.5 and 9.0 respectively (Tønnesen and Karlsen, 1985a). At pH above neutral, i.e. when dissociation takes place, the compound undergoes a rapid hydrolytic degradation (Tønnesen and Karlsen, 1985a,b). The main decomposition products have previously been identified as feruloyl methane, ferulic acid

* Corresponding author. Tel.: +47-22-85-65-93; fax: +47-22-85-74-94
E-mail address: h.h.tonnesen@farmasi.uio.no (H.H. Tønnesen).

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and vanillin; the latter being a secondary degradation product formed by hydrolysis of feruolyl methane. The formation of coloured condensation products was also observed. In organic solvent, curcumin decomposes under exposure to light. A number of photolysis products have previously been identified (Tønnesen et al., 1986). The degradation mechanism has been discussed elsewhere (Tønnesen and Greenhill, 1992). The use of curcumin is thereby limited due to low water solubility under acidic or neutral conditions, high decomposition rate in alkaline media and photodegradation in organic solvents. Attempts to prepare water-soluble curcumin by complex formation or interaction with various macromolecules (e.g. gelatine, polysaccharides) have been reported (Maing and Miller, 1981; Leshik, 1981; Schranz, 1986; Todd, 1991). In these studies, complex formation with macromolecules was carried out under alkaline conditions, i.e. in a medium where curcumin is decomposed within minutes. The rapid degradation of curcumin clearly complicates the process. It is therefore of interest to study the possibility of forming a water-soluble curcumin complex at a pH where hydrolysis is at a minimum, and to investigate the stability of curcumin in such a complex.

Cyclodextrins are used as pharmaceutical excipients, mainly as solubilizing and stabilizing agents for lipophilic substances in aqueous preparations (Duchêne and Wouessidjewe, 1996; Loftsson and Brewster, 1996; Stella and Rajewski, 1997; Qi and Sikorski, 2001). A number of molecules are solubilized in cyclodextrin solutions through formation of an inclusion complex. The cyclodextrins are also known to affect the chemical stability of drug molecules. The observed effects have been extensively examined in the literature (Loftsson, 1995). The formation of an inclusion complex usually leads to retardation of the degradation process. However, in some cases, an increase in degradation rate is observed (Loftsson and Brewster, 1996). The effect of cyclodextrins on drug photostability is less investigated, although the number of publications in this field is rapidly increasing (Sortino et al., 2001). There seems, however, to be marked differences in photostabilizing effect between the various cyclodextrins (Ammar and El-Nahhas, 1995; Bortolus and Monti, 1996; Thoma and Kübler, 1997; Monti et al., 1998; Sortino et al., 1999; Lin et al., 2000). In some cases the complex formation has a destabilizing rather than a stabilizing effect on the photodegradation process (Mielcarek, 1996; Jiménez et al., 1997; Sortino et al., 1998; Lutka, 2000; Sortino et al., 2001). The cyclodextrin molecules have a hydrophilic outer surface and a less polar central cavity. The photochemical behaviour of a compound is strongly dependent on the microenvironment (e.g. polarity), and the photoreactivity of a drug molecule can therefore be altered by interactions with for instance macromolecules in a pharmaceutical preparation. Reformulation of a solution by adding a complexing agent (e.g. cyclodextrins) can therefore cause a dramatic change in product photostability. β-Cyclodextrin and its derivatives are the most commonly used compounds in pharmaceutical preparations. Substituents on the cyclodextrin molecules are likely to influence the interactions between drug and carrier by changing the shape of the cyclodextrin cavity or altering the charge–charge interactions (Másson et al., 1998). This can further influence the stability constant for complexation (K_c) and the degradation rate for the complexed drug. In the present work, we have investigated the effect of ionic and non-ionic cyclodextrins on the solubilization and the stability of curcumin in aqueous medium.

2. Materials and methods

2.1. Materials

The following cyclodextrins were used in this study: hydroxypropyl-α-cyclodextrin (Alfa-W6 HP 0.6, Wacker, $M_w \sim 1200$; HPαCD), hydroxypropyl-β-cyclodextrin (Encapsin HPB, Janssen, $M_w \sim 1400$; HPβCD), hydroxypropyl-γ-cyclodextrin (Cavasol WP8 HP Pharma, Wacker, $M_w \sim 1576$; HPγCD), randomly methylated β-cyclodextrin (Beta-W7 M1.8, Wacker, $M_w \sim 1310$; RMβCD), sulfobutylether-β-cyclodextrin (Captisol, Cydex Inc., $M_w \sim 2163$; SBβCD) and hydroxytrimethylammoniumpropyl-β-cyclodextrin (Wacker, $M_w \sim 1480$; HTAβCD). The cyclodextrin samples were

generously donated by the respective companies. The moisture content of the cyclodextrins was determined by use of a Scaltec SMO 01 Moisture Analyzer (Göttingen, Germany). Pure curcumin was synthesized using the procedure given by Pabon (Pabon, 1964). All other chemicals were commercially available substances of reagent or analytical grade. The buffers were prepared in total concentration of 0.05 M from potassium dihydrogen phosphate and disodium hydrogen phosphate. The ionic strength was adjusted to $\mu = 0.085$ by addition of sodium chloride.

2.2. Quantitation of curcumin

The concentration of curcumin was measured by reverse-phase HPLC. The separation was performed on a 15 cm × 3.9 mm Nova Pak® C_{18} column (Waters, Milford, MA). The mobile phase was composed of 0.5% citric acid adjusted to pH 3 with KOH and acetonitrile (60:40). A flow rate of 1.2 ml min^{-1} was used. Curcumin was detected at 350 nm. The retention time of curcumin was approximately 9 min.

Two chromatographic systems were applied. For the phase solubility and hydrolytic degradation studies, the system consisted of the following: a Merck-Hitachi L 6200A Intelligent pump, a Merck-Hitachi L 4250 UV–VIS detector, a Merck-Hitachi L 2000A auto injector and a Merck-Hitachi D 2500 integrator. For photochemical degradation studies the system consisted of a Shimadzu LC-9A pump, a Shimadzu SP D-10A UV–VIS detector, a Shimadzu SIL-10 DV auto sampler and a Shimadzu C-R3A integrator.

2.3. Solubility studies and determination of stability constants

Solubilities were determined by adding an excess amount of curcumin to an aqueous buffer solution (pH 5) containing various amounts of different kinds of cyclodextrins. The suspension formed was equilibrated under continuous agitation for 1 week and then filtered through a Spartan 13/0.45RC filter (Schleicher & Schull, Germany) to form a clear cyclodextrin solution. An aliquot of the filtrate was diluted with the HPLC mobile phase before quantitation of curcumin. All studies were carried out in triplicate.

2.4. Hydrolytic degradation studies

A stock solution of curcumin (2×10^{-3} M) was prepared in methanol. A volume of 0.125 ml of the stock solution was added to the cyclodextrin solutions to make a final volume of 25 ml (1×10^{-5} M curcumin). Samples were prepared in phosphate buffer at pH 5 and 8, $\mu = 0.085$. The samples were kept in the dark at 30 ± 0.1 °C. The changes of curcumin concentration with time were monitored by HPLC. The observed first-order rate constants (k_{obs}) for the degradation was obtained from linear regression analysis of the logarithm of the curcumin concentration plotted against time. The K_c and k_c values where obtained by non-linear fitting of the k_{obs} data using the KALEIDAGRAPH software (Synergy Software). All studies were carried out in triplicate.

2.5. Absorption spectra

Absorption spectra were recorded on a Shimadzu UV-2101 PC UV–VIS scanning spectrophotometer.

2.6. Photodecomposition of curcumin–cyclodextrin complexes

A stock solution of curcumin (2×10^{-3} M) was prepared in methanol. A volume of 0.05 ml of the stock solution was added to the sample containing cyclodextrin (5% CD) or organic solvent to make a final volume of 10 ml (1×10^{-5} M curcumin). The aqueous samples were prepared in phosphate buffer at pH 5, $\mu = 0.085$. Irradiation was performed in a SUNTEST CPS (Heraeus GmbH, Hanau, Germany). The light source was a xenon lamp (1.8 kW) equipped with a glass filter, transmitting light corresponding to exposure behind window glass (cut-off approximately 310 nm). The light intensity was measured to 1.4×10^5 lux and 18.6 W m^{-2} in the visible and UV range, respectively, by using a lux meter in combination with a UV-filter radiometer (Hagner EC1 Digital luxmeter, Hagner EC1 UV-A). The

samples were exposed under continuous stirring. The changes of curcumin concentration with exposure time were monitored by HPLC. The observed first-order rate constants (k_{obs}) for the degradation was obtained from linear regression analysis of the logarithm of the curcumin concentration plotted against time. The calculated rate constants were corrected for the difference in absorbtivity (i.e. area under the absorption curve) between the various samples. The absorbtivity was measured on a Shimadzu UV-2101 PC UV–VIS scanning spectrophotometer. All studies were carried out in triplicate.

3. Results and discussion

The structures of curcumin and the cyclodextrin derivatives investigated in this study are given in Fig. 1. Commercially available curcumin is isolated from the plant *Curcuma longa* L. The 'pure curcumin' on the market consists of a mixture of three naturally occurring curcuminoids: curcumin, demethoxy- and bisdemethoxycurcumin, with curcumin as the main constituent. In the present work we have synthesized curcumin according to the method of Pabon (1964) in order to avoid interference from demethoxy- and bisdemethoxycurcumin.

3.1. Observed stability constants

The apparent stability constant (K_c) for a drug–cyclodextrin complex would normally be obtained from the slope of the phase–solubility diagram according to the following equation:

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

where S_0 is the saturation concentration of the drug substance in the solvent without cyclodextrin. Quantitation of curcumin in plain buffer at pH 5 was not possible because the saturation concentration was below the detection limit of the analytical system ($< 3 \times 10^{-8}$ M) and quantitation of the samples in plain buffer was therefore difficult. Due to the difficulties in determining S_0 for curcumin in

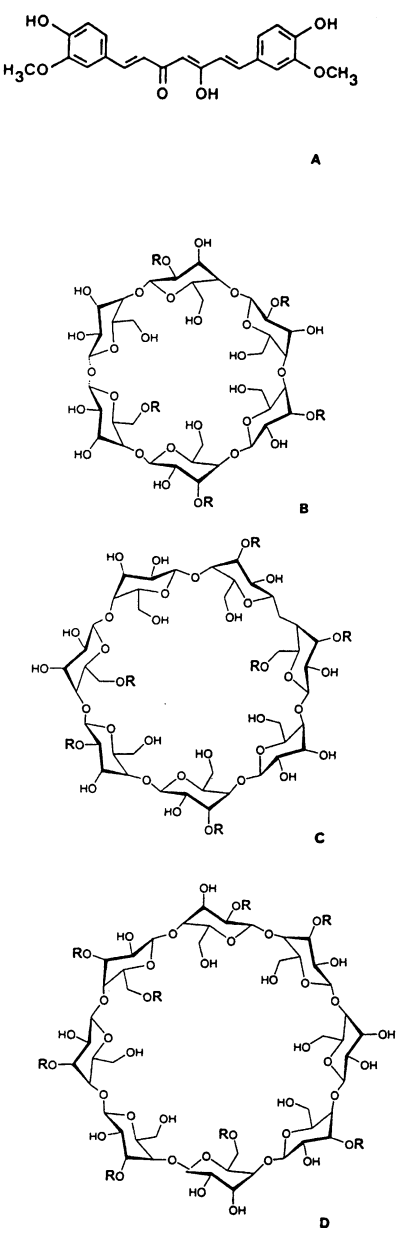

Fig. 1. Structure of curcumin and the cyclodextrin derivatives. **A**: curcumin; **B**: α-cyclodextrin; **C**: β-cyclodextrin; **D**: γ-cyclodextrin; HPαCD: hydroxypropyl-α-cyclodextrin—R, $-CH_2CH(OH)CH_3$; HPβCD: hydroxypropyl-β-cyclodextrin—R, $-CH_2CH(OH)CH_3$; HPγCD: hydroxypropyl-γ-cyclodextrin—R, $-CH_2CH(OH)CH_3$; RMβCD: randomly methylated β-cyclodextrin—R, $-CH_3$; SBβCD: sulfobutylether-β-cyclodextrin—R, $-(CH_2)_4SO_3^-$; HTAβCD: hydroxytrimethylamoniumpropyl-β-cyclodextrin—R, $-CH_2CH(OH)-CH_2N(CH_3)_3^+$.

this system, the apparent stability constant (K_c) for the curcumin–cyclodextrin complexes could not be determined from the phase–solubility diagram. An estimate of the minimum stability constant (K_{cmin}) was therefore made using the analytical detection limit as the highest possible value for S_0 (i.e. $S_0 = 3 \times 10^{-8}$ M). The slopes in the phase–solubility diagrams were linear ($R \geq 0.99$ with the exception of RMβCD; $R \leq 0.98$), which was consistent with 1:1 complex formation. The observation of two isobestic points in the spectrophotometric titration of HPβCD was also consistent with this stoichiometry of the complex (data not shown). The differences in slope showed the relative affinity for the different cyclodextrin derivatives. Curcumin had the highest affinity for the relatively hydrophobic cavity of RMβCD and the large cavity of HPγCD (Table 1). The affinity for the anionic SBβCD was fourfold the affinity for the cationic HTAβCD. The increase in curcumin solubility at pH 5 after addition of cyclodextrins to the solution was in the order of 10^4 or more which is a factor of 10 higher than reported previously for this substance (Jicsinszky et al., 1998). The highest concentration, approximately 8×10^{-4} M or approximately 290 μg ml^{-1} of curcumin, was measured in 11% solutions of RMβCD. Solutions with a higher concentration of cyclodextrin were not investigated. The observed increase in solubility from the maximum solubility in plain buffer (i.e. 3×10^{-8} or 11 ng ml^{-1}) was higher than what has been reported for most substances (Stella and Rajewski, 1997). The value of K_{cmin} exceeded the normal range reported for βCD, which is between 10^1 and 10^5 M^{-1} (Conners, 1997). Values higher than 10^5 M^{-1} are rarely reported. However, curcumin demonstrates the difficulties in determining the K_c values for compounds with high affinity for the cyclodextrin cavity. Such compounds are often very lipophilic and will have extremely low water solubility.

3.2. Hydrolytic stability of curcumin

As discussed above curcumin is rapidly decomposed in buffer at pH above 7 with a half-life in the range of few minutes. At lower pH (e.g. pH 5) an accurate measurement of the degradation rate in plain buffer is difficult to obtain due to the low solubility of curcumin in the reaction medium. The influence of various β-cyclodextrin derivatives in the concentration range 0.1–5% on the hydrolytic degradation of curcumin in buffer at pH 8.0 was studied. The effects of both charged and neutral cyclodextrins were investigated. When no cyclodextrin was present the pseudo first-order rate constant (k_0) was 22.4 h^{-1}. Even at the lowest cyclodextrin concentration (0.1%) a more than 50-fold increase in stability was observed (Fig. 2), which indicated that more than 98% of the curcumin molecules were included in the cyclodextrin cavity. More than a 500-fold increase in stability could be obtained by further addition of some of the cyclodextrins. In order to obtain the

Table 1
The effect of cyclodextrin charge and cavity size on the minimum and estimated stability constants (average ± min/max, $n = 3$) and the k_c value

Cyclodextrin	Phase solubility (pH 5)		K_{cmin} (M^{-1}) × 10^4	Degradation studies[a]	
	Slope × 10^{-3}	Solubility (10^{-4} M) at 11% CD		Estimated K_c (M^{-1}) × 10^5	k_c (h^{-1})
HPαCD	1.1 ± 0.1	1.15 ± 0.02	> 3.7	–	–
RMβCD	9.4 ± 0.1	8.10 ± 0.60	> 32.0	3.6 ± 0.5	0.09
HPβCD	1.5 ± 0.09	1.22 ± 0.08	> 5.0	2.1 ± 0.4	0.04
SBβCD	2.5 ± 0.2	1.23 ± 0.07[b]	> 8.3	4.7 ± 0.9	0.15
HTAβCD	0.6 ± 0.04	0.41 ± 0.03[b]	> 1.9	–	–
HPγCD	4.9 ± 0.3	3.82 ± 0.52	> 16.0	–	–

K_{cmin} was estimated by using the analytical detection limit as the highest possible value for S_0.
[a] The K_c estimates and the k_c values were obtained by fitting the data in Fig. 2 into Eq. (2).
[b] Determined at 10% CD.

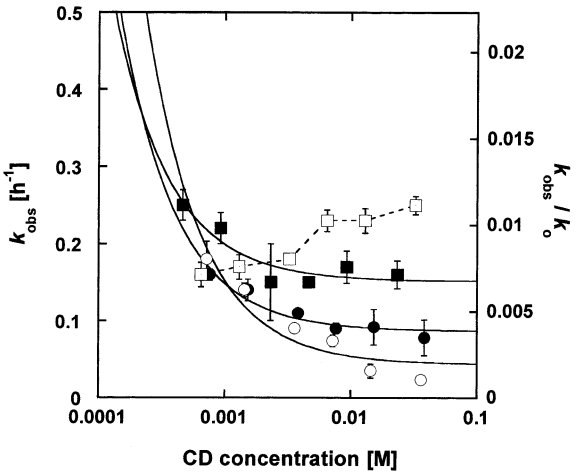

Fig. 2. The effect of RMβCD (●), HPβCD (○), SBβCD (■) and HTAβCD (□) on the hydrolysis of curcumin in phosphate buffer solutions, pH 8.0. The degradation rate relative to k_0 (22.4 h^{-1}) is shown on the right axis. The solid lines show fitting to Eq. (2).

degradation rate constant (k_0) for curcumin within the CD cavity the data for RMβCD, HPβCD and SBβCD (Fig. 2) was fitted to the following equation:

$$k_{obs} = \frac{k_0 + k_c K_c[CD]}{1 + K_c[CD]}, \quad (2)$$

where k_0 is the pseudo first-order rate constant in the absence of cyclodextrin, k_c is the degradation rate of the complexed substance, K_c is the stability constant and CD is the molar concentration of cyclodextrin. The difference in k_c values showed that there was better shielding from hydrolytic reactions in the cavity of the neutral RMβCD and HPβCD than in the cavity of the anionic SBβCD. Eq. (2) can also be used to obtain the K_c value. However, the accuracy of this method is limited when the K_c value is higher than 10^4 M^{-1} (Másson and Loftsson, 1998), and therefore the K_c values presented in Table 1 can only be regarded as estimates. The K_c values obtained from the degradation studies did, however, emphasize the high value for the stability constant, all values being in the 10^5 M^{-1} range. The observed differences in the K_c values obtained by the two methods could partly be ascribed to a difference in ionisation form of curcumin in the two experiments, inducing a change the aqueous solubility of the molecule. Taking this into account in addition to the fact that the K_c values obtained at pH 5 are only minimum values, the results from the two methods seem to be fairly consistent. The minimum values obtained from the phase–solubility method are two–four times lower than K_c estimated from the degradation studies. The data for HTAβCD could not be fitted into Eq. (2). Although this cationic cyclodextrin also demonstrated a stabilizing effect on curcumin, k_{obs} increased with increasing CD concentration in the concentration range 0.1–5%. Some secondary effects, possibly an increase in ionic strength by an increase in HTAβCD concentration, apparently influenced the degradation rate. Such secondary effects have previously been observed in samples containing this cyclodextrin derivative (Másson et al., 1998). The sample found to be most stable at pH 8, i.e. curcumin in 5% HPβCD, was further studied at pH 5. The first-order rate constant for the degradation in this medium was determined to be 0.035 per day ($n = 3$) leading to a half-life of 19.8 days.

3.3. Photostability of curcumin in cyclodextrin complexes

The influence of complexation by various cyclodextrin molecules on curcumin photostability was investigated. The CD concentration and the curcumin concentration were kept constant at 5% and 10^{-5} M, respectively. The degradation rate was compared to the photochemical degradation of curcumin in a hydrogen-bonding organic solvent (methanol) and in an aqueous system (ethanol–phosphate buffer pH 5 (40:60)). The degradation in pure water or plain buffer at pH 5 could not be studied due to the low curcumin solubility in these solvents. The first-order rate constant (k_{obs}) of a direct photochemical reaction is proportional to the reaction quantum yield (φ) of the compound, the molar absorbtivity (ε) of the compound at a specific wavelength (λ) and irradiance (I) of the light-source at a specific wavelength, i.e. $k_{obs} = \varphi \Sigma \varepsilon_\lambda I_\lambda$. In most cases the reaction quantum yield is independent of the wavelength, while I and ε vary with wavelength. For a continuous irradia-

tion source like the xenon lamp, the expression $I \times \varepsilon$ has to be integrated over the relevant wavelength range where each has a non-zero value. This integral represents the overlap integral for the combination of the particular irradiation source and the actual sample (Tønnesen and Moore, 1993). The variation in the overlap integral between the emission spectrum of the irradiation source and the absorption spectrum of the various samples was therefore taken into account in the calculation of the rate constants in the present study. The results are presented in Table 2. The formation of an inclusion complex had a destabilizing effect on curcumin with respect to photodecomposition compared to that of the "free" molecule in solution. The cyclodextrin charge seemed to have a minor influence on the photostability of curcumin included in the complex. The cavity size did, however, seem to influence the degradation process. The α- and γ-derivatives of HP-CD had a lesser destabilizing effect than the β-derivative. The polarity inside the cavity, the orientation of the curcumin molecule and the extent of inter- and intramolecular hydrogen bonding in α- and γ-cyclodextrin may be different from β-cyclodextrin. This is likely to influence the photochemical stability of the curcumin molecule. Cyclodextrin-catalyzed reactions can either be classified as covalent or non-covalent catalysis (Bender and Komiyama, 1978). In the first case, the cyclodextrin complex can catalyze a reaction via the formation of covalent intermediates, while in the latter case the apolar environment or sterically restricted reaction field inside the cavity is of major importance. Both mechanisms may influence the photodegradation of curcumin. The polarity of a 10^{-2} M aqueous solution of β-CD is reported to correspond with approximately a 40% ethanol–water mixture (Frömming and Szejtli, 1994). Assumed that this approximation applies to the β-cyclodextrin derivatives investigated in this work, the photolysis of curcumin was studied in ethanol–phosphate buffer pH 5 (40:60). The observed photodecomposition rate of curcumin in ethanol–phosphate buffer was, however, much lower than the observed photodecomposition rate in the various β-cyclodextrin complexes (Table 2). It has previously been reported that addition of alcohol to cyclodextrin samples increases the hydrophobicity of the CD cavity (Warner and Nelson, 1988). Photodegradation studies of curcumin were therefore also carried out in HPβCD solutions (5%) to which 1% alcohol (ethanol or butanol) was added. The observed degradation rate decreased by addition of alcohol to the system but was still much higher than the degradation rate in ethanol–phosphate buffer (40:60) or in pure organic solvent (methanol) (Table 2). This indicated that the polarity might be of less importance than interactions (e.g. hydrogen bond formation, formation of covalent intermediates) between curcumin and the medium with respect to photochemical reactivity. It has previously been demonstrated that the excited

Table 2
Photochemical degradation of curcumin in the presence and absence of cyclodextrin according to first-order kinetics (average ± min/max, $n = 3$)

Cyclodextrin	Concentration CD (%)	k'_{obs} (min^{-1})	$t_{1/2}$ (min)
RMβCD	5.0	$3.4 \times 10^{-2} \pm 0.003$	20.4
HPαCD	5.0	$1.5 \times 10^{-2} \pm 0.001$	46.2
HPβCD	5.0	$2.4 \times 10^{-2} \pm 0.002$	28.9
HPγCD	5.0	$1.6 \times 10^{-2} \pm 0.001$	43.3
SBβCD	5.0	$2.7 \times 10^{-2} \pm 0.003$	25.7
HTAβCD	5.0	$3.2 \times 10^{-2} \pm 0.001$	21.7
Ethanol–phosphate buffer pH 5 (40:60)	5.0	$9.8 \times 10^{-3} \pm 0.003$	70.7
Hydroxypropyl-β-CD + 1% EtOH	5.0	$1.7 \times 10^{-2} \pm 0.003$	40.8
Hydroxypropyl-β-CD + 1% BuOH	5.0	$1.8 \times 10^{-2} \pm 0.003$	38.5
Methanol		$5.2 \times 10^{-3} \pm 0.0004$	133.3

k'_{obs} is the observed first-order rate constant for the total degradation of curcumin (complexed and free form).

state of the curcumin molecule will be stabilized if the unpaired electrons of the phenolic OH is given to the ring, i.e. acting as a charge-transfer donor to the excited state (Tønnesen et al., 1995). Destabilization of the excited state will occur when the non-bonding electrons on the oxygen atom of the OH-group become engaged in intermolecular hydrogen bonding instead of being given to the ring. In general, this would lead to an increase in destabilization of the excited state by an increase in hydrogen-bonding donor capacity of the medium. Thus, the destabilization in the CD cavity could be explained by intermolecular hydrogen bond formation. The photochemical and photophysical properties of curcumin in the presence of cyclodextrins are now under further investigation.

4. Conclusion

Complexes between curcumin and cyclodextrins can be formed under slightly acidic conditions (pH 5) at room temperature. The complex formation leads to an increase in the water solubility of curcumin by a factor of approximately 10^4. Curcumin had the highest affinity for the relatively hydrophobic cavity of RMβCD and the large cavity of HPγCD, while the least affinity was observed for the cationic HTAβCD. The observed increase in solubility was high compared to what is reported for most substances, and the value of K_c exceeded the normal range reported for βCD, which is between 10^1 and 10^5 M^{-1}. The hydrolytic stability of curcumin under alkaline conditions was dramatically improved by complex formation. The neutral cyclodextrins offer better protection than the charged cyclodextrins. On the other hand, a decrease in photostability is observed by complex formation with cyclodextrins compared to solutions of curcumin in organic solvent systems. The substituents on the CD molecule seem to have little influence on the photodegradation, while the interior of the cavity may be of some importance. The mechanism of interactions between curcumin and cyclodextrins is under further investigation, as this is essential for the development of a water-soluble and stable curcumin product.

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