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Temperature-Dependent Spectroscopic Evidences of Curcumin in Aqueous Medium: A Mechanistic Study of Its Solubility and Stability

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Supporting Information

ABSTRACT: In curcumin, keto−enol−enolate equilibrium of the heptadiene-dione moiety determines its physiochemical and antioxidant properties. However, its poor solubility in water at neutral pH and room temperature decreases its bioavailability. Potential therapeutic applications have triggered an interest in manipulating the solubility of curcumin in water as its stability and solubility in water remains poorly understood. Here, the mechanism behind its solubility at various temperatures and the influence of interplay of temperature, intramolecular H-bonding, and intermolecular forces is reported, which leads to aggregation−disaggregation at various temperatures. Remarkable change is observed in temperature-dependent electronic transition behavior of curcumin, however, the absorption spectra after cooling and heating cycles remain unchanged, hinting much better thermal stability of curcumin in water than previously thought. This study indicates that it is perhaps the breaking of intramolecular hydrogen bonding which leads to exposure of polar groups and hence responsible for the dissolution of curcumin at higher temperature. The formation of intermolecular aggregates might be responsible behind a better room temperature stability of the molecules after cooling its aqueous suspension from 90 to 25 °C. These curcumin solubility studies have great application in biological research with reference to bioavailability and to understand target oriented mode of action of curcumin.

INTRODUCTION

After the advent of several synthetic drugs by the continued efforts of the synthetic chemists across the world with a broader objective to improve the overall health standards at an affordable cost, there is a rising concern about increasing cost to design newer drug molecules and their clinical trials, apart from other serious issues such as their solubility, environment hazards in their large scale productions, and long-term human safety records due to the unknown side effects.[1] Due to these reasons, researchers have turned their attention back on some of the natural products, timeworn traditional medicines, and the molecules responsible for their therapeutic activities where the efforts are required to scientifically validate their efficiency and other parameters.[2] Turmeric is one such wonder drug that has redrawn the attention of people from all over the world[1] for various ailments including wound healing, skin lightening (as a cosmetic), anti-inflammatory and antimicrobial effects since time-immemorial.[3] Curcumin or diferuloylmethane (1,7-bis [4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione) is a major functional component (2−5%) of turmeric, recognized as being responsible for most of its therapeutic effects.[4−6] Noting its curing abilities,[7−12] curcumin is studied for widespread clinical applications.[13] However, low aqueous solubility and, consequently, poor absorption and bioavailability, followed by rapid metabolism and systemic elimination[14,15] hinder the direct use of curcumin as a biomedicine. Though the hydrophobicity of the molecule helps in various molecular interactions, controlling the physiochemical properties,[16−20] it is poorly soluble in water at neutral pH due to strong hydrophobicity of the conjugated alkene chain, and the unavailability of a strong polar group renders the molecule insoluble or sparingly soluble in polar solvents. However, in slightly acidic media and possibly in the interior of cell membranes, it is likely to exist in the keto form. This form appears to favor H-atom transfer reactions,[21] thus, playing a crucial role in the antioxidant action of curcumin. Enhanced bioavailability of curcumin as a drug in the near future will definitely add a new dimension as a promising molecule to the forefront of therapeutic agents for the treatment of several diseases. Henceforth, several methods of conjugation have been adopted for enhancing the solubility and its bioavailability.[18,19,22−27]

A number of investigators have studied the structure of curcumin, solubility of curcumin in different organic solvents, predictions of the electronic and vibrational excitations, and their experimental data; however, a detailed study of curcumin in water at different temperatures is not reported. Keeping in mind the challenges in using this molecule as a potent drug, in

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the present study, in this article, the effect of temperature and dielectric environment on the solubility and structural stability of curcumin is investigated in detail and its mechanism is studied by performing detailed in situ UV visible spectroscopic measurements. It is observed that the spectrum of curcumin in water is complicated, uniquely temperature-dependent, and different from what is obtained in organic solvents. Below, the results on the spectroscopic study of solubility and stability of curcumin in varied environments are presented using UV−vis absorption spectroscopy, photoluminescence, NMR spectroscopy, and HPLC analysis.

EXPERIMENTAL SECTION

Materials. Purified curcumin was provided by CFTRI authors. The purity of as-received curcumin was verified by using various techniques such as UV−vis spectroscopy, FTIR spectroscopy, NMR spectroscopy, and HPLC (see Supporting Information). Unless mentioned in the manuscript, 2 mg of curcumin in 3 mL of deionized water (purified through a Millipore Milli-Q system with a resistivity of 18 MΩ/cm) at neutral pH was prepared by heating (>75 °C) for all tests.

In Situ Temperature-Dependent UV−Vis Absorption Spectroscopy. In situ temperature-dependent absorption spectroscopy up to 95 °C, with spectrum acquisition at an interval of every 5 °C rise in temperature, using a Cary 50 UV/vis spectrophotometer at a resolution of 1 nm, was performed.

Photoluminescence Measurements. Curcumin was dissolved at high temperature and filtered through the Whatman filter paper (retention size > 11 μm) to remove large aggregates. The data was collected using a Cary Eclipse photoluminescence spectrophotometer from Varian equipped with a Xenon flash lamp.

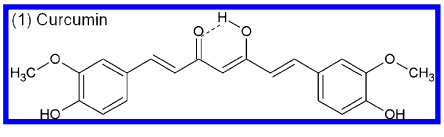
NMR Measurements. NMR spectroscopy was performed on the heat-treated curcumin dissolved in deuterated methanol. The ^{1}H NMR spectrum was taken using a 400 MHz Bruker AVANCE instrument using a broad band probe with a z-gradient coil. Chemical shifts (δ) are quoted in ppm and are referenced to solvent CD_3OD.

HPLC Measurements. The data were collected on the HPLC system Delta 600 series from Waters Corporation and a 425 nm wavelength was used for detection. For this purpose, the elution was carried out with gradient solvent systems with a flow rate of 1.0 mL/min at ambient temperature. The mobile phase consisted of methanol (A), water (B), and acetonitrile (C). The sample was determined using the above solvents programmed linearly from 45 to 65% acetonitrile in B for 0−15 min. The gradient then went from 65 to 45% acetonitrile in B for 15−20 min, with a constant of 5% A. The compounds were analyzed using HP ChemStation software.

RESULTS AND DISCUSSION

The structure of curcumin is represented in (1). Here, the β-diketone moiety undergoes keto−enol tautomerization[28] and

(1) Curcumin



the molecule exists in a planar, intramolecularly hydrogen-bonded form, both in solution as well as in the powder form.[29] As discussed earlier, at pH 7, curcumin is totally hydrophobic in nature due to the lack of any available polar groups in the molecule as well as due to the stretch of conjugated (heptadiene) backbone.[15,28,30,31] It is known that an isolated double bond or lone pair of electrons gives rise to a strong absorption about 190 nm,[32] whereas the presence of conjugation reduces the energy separation between the orbitals occasioned by absorption at longer wavelengths. In organic solvents, the enolization of the diketone group in curcumin allows conjugation between the π-electron clouds of the two vinylguaiacol parts. This leads to a common conjugated chromophore, resulting in reduction in energy. Due to the low-energy $\pi-\pi^*$ excitation of that chromophore, the solution of curcumin in organic solvents (primarily ethanol or methanol) typically absorbs around ∼420 nm, thus, exhibiting a bright yellow color. The $n-\pi^*$ transition, due to excitation of an oxygen lone-pair electron to the antibonding π-orbital of the carbonyl group in curcumin is observed around 262 nm in methanol (see red curve in Figure 1C).

In an aqueous medium, it is understood that, at alkaline pH, the acidic phenol group in curcumin donates its hydrogen, forming the phenolate ion that enables curcumin into dissolution in water. However, the molecule is not stable for long at neutral and alkaline pH and gets easily degraded into compounds like vanillin, ferulic acid, and so on.[33] Below pH 7, curcumin is stable, but parallel with the decreasing pH values, the dissociation equilibrium shifts toward the neutral form of very low aqueous solubility. Due to this process, significant change of the UV−vis absorption spectrum of curcumin can be observed at acidic pH values. However, in neutral pH, it is practically insoluble at room temperature.

Temperature-dependent reversible spectral changes have been observed previously in organic molecules.[34] Owing to the flat structure and hydrophobic nature of the curcumin molecule, $\pi-\pi$ interactions between the π-electron clouds of the aromatic molecules need to be considered in solvation as well as desolvation.[35] The possibility of stacking of curcumin molecules together into a supramolecular arrangement bound together by H-bonding reflects on the observations discussed below. Temperature-dependent UV−vis absorption spectroscopy of curcumin in water and effects of intramolecular H-bonding and intermolecular forces on the electronic transitions are discussed in this section. To check the effect of temperature on the solubility and stability of curcumin in water, an in situ temperature-dependent absorption spectroscopy up to 95 °C was carried out. The results are presented in Figure 1A, where it was observed that, as the temperature is increased, the peak intensity also increases around wavelengths 237, 345, and 419 nm and the color of the solution turns turmeric yellow. In Figure 1B, the increase in intensity of the peak situated above 400 nm is plotted as a function of temperature. Here, a solvatochromic shift was observed in the temperature-dependent absorption spectroscopy of curcumin in water. In general, the solvent effects on the $\pi-\pi^*$ and the $n-\pi^*$ transitions could be red-shifted or blue-shifted depending on the polarizabilities of the solute−solvent interactions and thereof their effects on the electron reorganization in both the solute and the solvent. Most transitions result in an increase in the polar nature in the excited state than the ground state. Distortions of the chromophore may also lead to red or blue shifts depending on the nature of the distortion. In the case of weak forbidden $n-\pi^*$ transitions of the oxygen lone-pair in ketones, the solvent effect is dependent on the extent to which the solvent can form H-bonds to the carbonyl group of curcumin in the excited state. In methanolic solution of curcumin, the absorption maxima of

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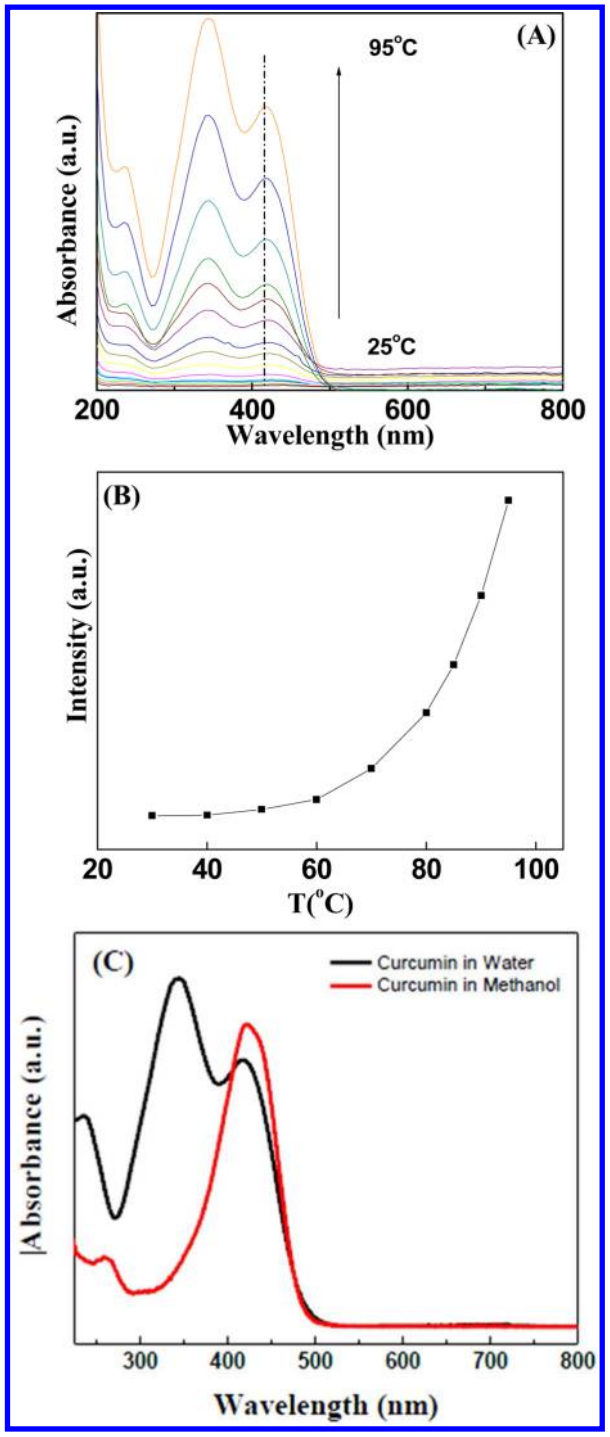

Figure 1. (A) Temperature-dependent UV−visible spectra of curcumin in water; (B) Change in the peak intensity (of absorption at $\lambda_{max} \sim 420$ nm) vs temperature; (C) UV−visible spectra of curcumin in water (black curve) and methanol (red curve).

the $n-\pi^*$ transition is at 262 nm (see red curve in Figure 1C), whereas in aqueous solution, this transition is situated at around 237 nm. A comparison of the spectrum of curcumin in water and the spectrum of curcumin in methanol is shown in Figure 1C. This will help in understanding the following explanation. Clearly, the $n-\pi^*$ transition is blue-shifted from methanol to water, a more polar solvent. Here, the effect of temperature does not seem to affect this blue-shift caused by the solvent effect as expected. However, the $\pi-\pi^*$ transitions of curcumin in water, unlike the $n-\pi^*$ transition, is quite complicated. In this case, generally the opposite effect occurs where the dipole−dipole interactions with the polar solvent molecules will lower the energy of the excited state than that of the ground state. Thus, a red shift for the $\pi-\pi^*$ transition was expected while changing methanol to water. However, the absorption peak for the $\pi-\pi^*$ transition in methanol is situated at 420 nm and in water, two peaks at about 345 and 419 nm are observed where the intensity of the peak at 345 nm is prominent in comparison to the peak at 419 nm. The evolution of these two absorption peaks for the $\pi-\pi^*$ transitions of curcumin in water indicates change in the tautomeric form of the keto−enol−enolate group in curcumin where the role of the solvent effect and the temperature might be significant. In contrast to these results, it is important to confirm that the absorption spectrum of curcumin in methanol does not change with varying temperature. It was observed that there is a mild "decrease" in intensity with increase in temperature due to the Boltzmann distribution of the populations at ground state at different temperatures (see Supporting Information, S2). It thus appears that the resonance stability in the keto−enol−enolate in water is changed sharply as the temperature is increased. The thermal energy provided by heating could be responsible in breaking the intramolecular H-bonding of the keto−enol−enolate group in curcumin exposing the polar groups to the solvent. However, instead of a red-shift caused by more dipole−dipole interactions between curcumin and water molecules, a remarkable blue-shift in the peak at 345 nm was observed (Figure 1A). The blue-shift could be due to these two factors: (1) the increased thermal activation energy of the solution could hinder the interaction between the solute and the solvent, preventing them to form stable intermolecular H-bonding or $\pi-\pi$ interactions and, hence, reducing the dipole−dipole interactions and increasing the energy of the transition, and (2) the opening of the cyclic moiety (keto−enol−enolate group) in curcumin has lowered the conjugation effect of the molecule and thus increasing the energy. Thus, as the temperature of the sample is increased, it is observed that the positions of the uncoupled absorption peaks of the $\pi-\pi^*$ transition moves to higher frequency. This is considered to result from a decrease in the H-bond strength between the water molecules and curcumin, at high temperatures, where the keto−enol groups of curcumin could have been available for interaction with water molecules (due to breakage of intramolecular H-bonding). As the temperature increases, the H-bond strengths become progressively weaker as a result of increased distortion and elongation of the H-bonds. With respect to the absorption characteristics of the molecule, it is evident that there are environmental changes caused by the breakdown of the intramolecular H-bond in the keto−enol tautomer as the temperature is raised, leading to the change in the electronic transition energy. Moreover, as the conjugation decreases, the wavelength of the maximum absorption also decreases. Both nonspecific dipolar interaction and specific H-bonding interaction play an important role in the position of the absorption and fluorescence maxima of any sample. As stated before, the large spectroscopic shifts observed could also be explained based on $\pi-\pi$ stacking interactions which cannot be overlooked in the absence of evidence of a direct probe into the forces playing between the molecules.

To understand the mechanism further as well as to examine the thermal stability of the molecule, the in situ UV/vis spectra of curcumin in water was acquired during a cycle of heating,

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cooling and reheating (Figure 2A). The absorption curve after the first round of heating (measurements taken at 90 °C and

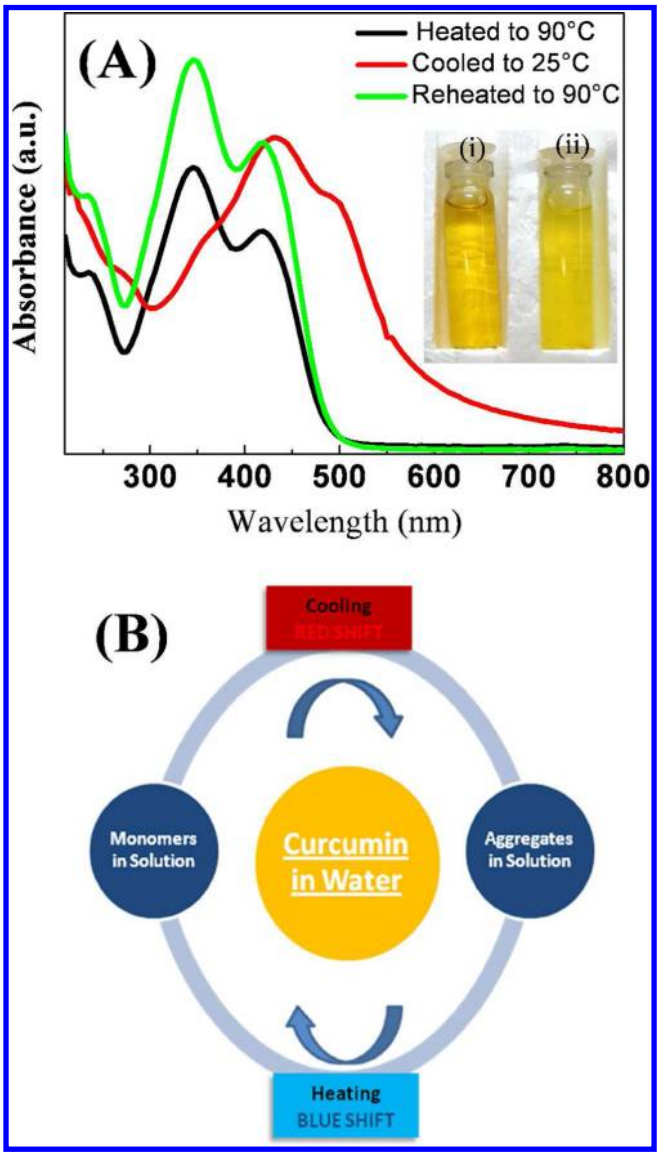

Figure 2. (A) UV−visible spectroscopy of curcumin in water; the graph shows spectra taken at 90 °C, cooled back to room temperature, ∼25 °C, and reheated to 90 °C. Inset: (i) optical transmission of curcumin in water at 90 °C and (ii) turbid solution of curcumin in water at 25 °C. (B) Schematic picture of dissolution of curcumin in water upon heating and cooling and its corresponding blue shift and red shift in its absorption spectra.

shown by black curve) is similar to the results shown earlier in Figure 1A, however, after cooling the sample back to ∼25 °C, there is a remarkable change in the absorption spectra (shown by red curve) where the absorption peaks after the first heating are situated at 237, 345, and 420 nm (at 90 °C) and after the cooling, the peaks are observed at 275, 431, and 500 nm (at 25 °C). It is believed that the $n-\pi^*$ transition is red-shifted during the cooling owing to reaggregation (by formation of hydrogen bonding) and less polar microenvironment caused due to aggregation. The green curve which corresponds to reheating the aqueous suspension of curcumin shows that during the reheating, peaks reappear at their original positions (237, 345, and 420 nm). This process is described in the schematic presented in Figure 2B. The picture in the inset of Figure 2A shows two vials with curcumin in water at 90 °C, which is quite clear transparent solution (left) and 25 °C which is relatively turbid (right), represent the agglomeration−deagglomeration cycle of the molecule. Also, the shift from 431 to 420 nm upon heating indicates breaking of the interactions therein. As proposed earlier in this paper, upon heating, the breaking of the intramolecular H-bond possibly leads to the absorption maximum at 345 nm and enhanced solubility at 90 °C. The peak at 420 nm is also characteristic of curcumin in almost all organic solvents (except like ethyl amine, which is highly basic). During the cooling process, nonspecific dipolar or hydrophobic interactions take place which leads to the strong peak at 345 nm (seen in the heating cycle) reducing to a small shoulder after cooling to room temperature.

It is imperative to note that the solid packing state of the molecule also plays a role in the energetics and, hence, the solubility at different temperatures. The H-bond formation, $\pi-\pi$ interactions, and molecular packing[36] may conform to the physical process of aggregation and disaggregation observed. More proof of the proposed hypothesis is shown in the inset of Figure 2A, where the optical transmission of the sample is exhibited. Sample vial (i) is that of curcumin in water at 90 °C and it is an optically transparent solution. The same sample is cooled to room temperature (ii), and it is observed that there is turbidity in the sample. Here, as seen in the picture, owing to the hazy appearance of the sample, it is suspected that the spectroscopy of this turbid suspension of curcumin particles in water involves a large scattering contribution. It can be inferred from this temperature-dependent behavior of the sample that the aggregation of the molecules takes place upon cooling. It is also important to note that curcumin dissolved in other solvents obey Lambert−Beer's law, suggesting the absence of aggregation of molecules; however, in water, curcumin spectroscopy fails to obey the law.

Additionally, to better understand the unique absorption behavior shown for the first time in this study on curcumin in water (the emergence of three sharp peaks) a detailed temperature dependent study of UV−vis absorption was carried out to study the influence of the change in the dielectric environment by comparing three different composition percentage of solvent mixture: (1) 50% methanol, (2) 20% methanol, and (3) 10% methanol in water. In each case, the amount of curcumin was kept same. The absorption spectra of these three samples with varied dielectric environment is shown in Figure 3, where, in contrast to the absorption spectra shown in Figure 1A, at 50% of methanol and water mixture (top panel), the principle peak is situated at 420 nm followed by a quite weak shoulder around 350 nm. However, as the percentage of water is increased then it is observed that the intensity of the absorption peak at 350 nm increases, reducing the ratio of peak intensity at 420 and 350 nm as the temperature increases (Compare with Figure 1A). Further analysis shows that the peak which was observed at 345 nm in pure water at higher temperature (Figure 1A) is now shifted at around 350 nm for the water−methanol mixtures, in accordance with the fact that the mixture is less polar than water. Though the presence of methanol in water reduces the solvation energy required for curcumin to dissolve in the mixture, water molecules being highly miscible with methanol easily forms strong H-bonds with methanol and hence it does not reduce the energy required for the $\pi-\pi^*$ transition resulting into the blue-shift. This implies that the peak observed

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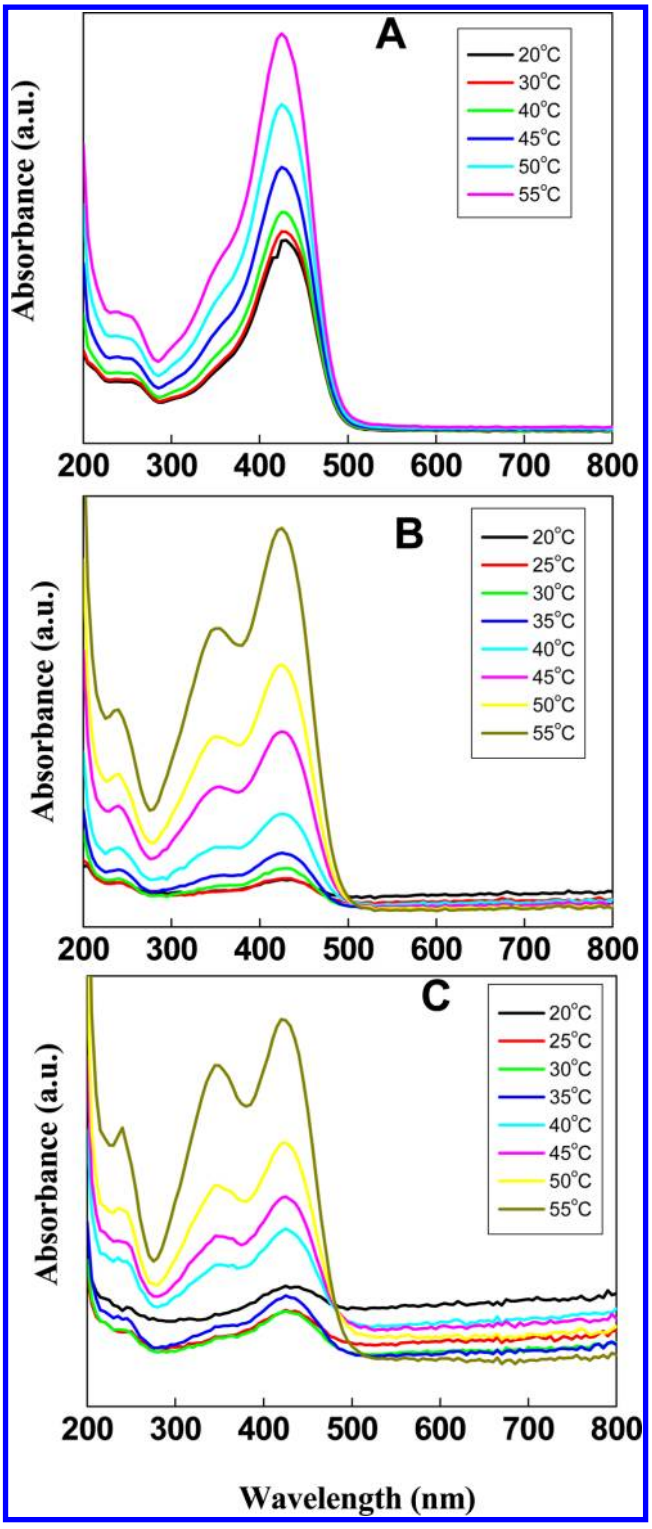

Figure 3. UV−visible spectroscopy of curcumin in water and methanol at increasing temperatures and at different vol % (A, 50% methanol; B, 20% methanol; C, 10% methanol in water). The comparison clearly shows that the structure of the peak in water is dependent on the change in the dielectric environment.

in water around 345 nm is solely due to the change in the dielectric environment, wherein the structure of the curcumin molecule in that state gives rise to this signature.

In Figure 4, the room temperature photoluminescence spectrum taken on curcumin in water is compared with

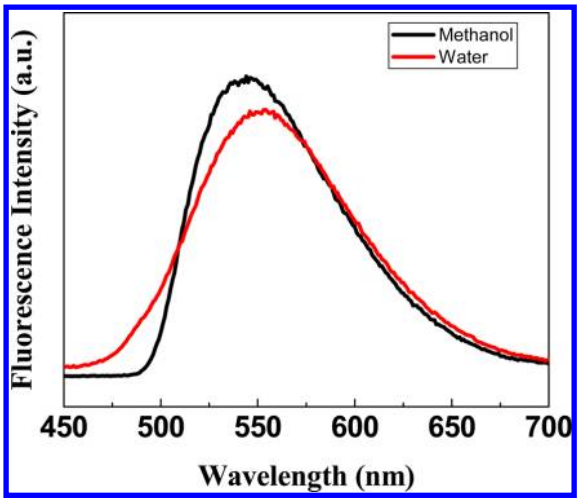

Figure 4. Comparison between the photoluminescence spectra of curcumin in water and methanol at the excitation wavelength of 420 nm.

curcumin in methanol at the excitation wavelength of 420 nm. In both the media, curcumin shows a quite broad emission peak centered at around 540 nm for methanol and at 550 nm for water. These results are in consistent to the absorption data where the dependence of electronic absorption of curcumin on its dielectric environment was shown. Moreover, there is remarkable change in the shape of the emission curve which might have its origin in the change in the absorption peak profile (Figures 1A and 3) thereby emitting at varied wavelengths with different intensities for water and methanol. A careful photoluminescence excitation study and deconvolution of the spectra will be able to give more information about the relative contribution of various emission peaks in the broad peaks as seen in the figure.

It is quite challenging to exactly quantify the solubility of curcumin in water due to its poor solubility and varied range of size of the agglomerates which explains the lack of any previous report on it. Half a gram of curcumin in 325 mL water was dispersed and large agglomerates were filtered out by using Whatman filter paper (retention size > 11 μm) after heating it up to 95 °C, where much of the insoluble curcumin (in form of large agglomerates) could be filtered out and the filtrate is a stable yellow suspension/solution of in water. The stability of this suspension was checked and it was found to be stable (no change in the electronic absorption) for more than a month. In the next step, this suspension was filtered at 95 °C using 220 nm syringe filter to remove very small agglomerates. The picture of the vial is shown in the inset of Figure 5I (vial on left). When it is filtered after cooling to 25 °C, most of the color in the vial is lost (vial on right), indicating that, after cooling back to 25 °C, a significant proportion of curcumin molecules (though still in suspension) aggregate back to form clusters larger than the pore size of the filter paper, which is consistent with our earlier hypothesis based on the absorption study which indicated that with decrease in the temperature, a large part of curcumin molecules precipitates back to its stable form of keto−enol−enolate tautomer forming large aggregates. This is an important observation, in accordance with our absorption data, revealing that as the temperature begins to reduce, curcumin mostly precipitates back to its stable form of keto−enol−enolate tautomer, recrystallizing into few monomer units. The more intriguing observation is the fact that not all of

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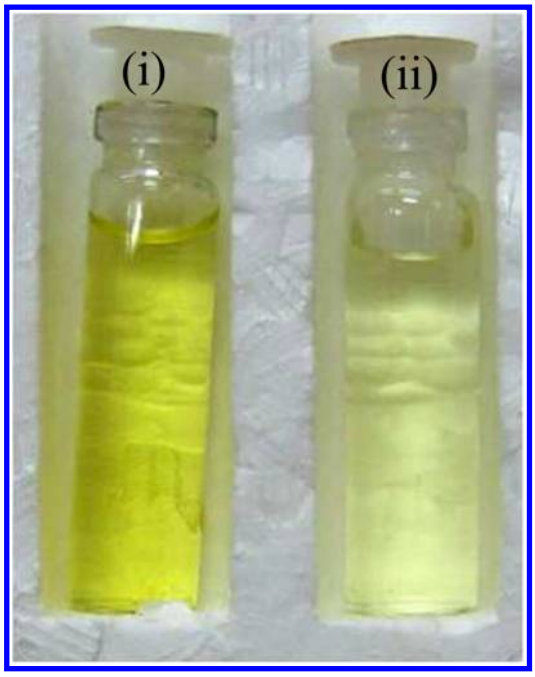

Figure 5. Picture of curcumin in water after filtering through a 0.22 μ filter at different temperatures. (i) Color of solution filtered immediately after dissolution by heating and (ii) color of solution filtered after cooling.

the curcumin precipitates back immediately. It is observed that for more than a month's time, the curcumin in water remains stable in suspension, which can be used for any further assays or applications. Hence, it is noted that the curcumin gets into the water phase and remains stable without the use of a cosolvent, or other chemical means to modify the molecule and, thus, affecting its activity.

For further quantification, solubility of curcumin in water upon heating is an ambiguous term to use in this study. As observed and established in the above explanations, the tests reveal that curcumin is more dispersed in the solvent (water) than dissolved, though it is readily available for biochemical reactions and drug actions. Moreover, the amount of curcumin in the solvent is extremely low even after heating it in water. Establishing the amount of curcumin that goes into the solution phase with acceptable accuracy is difficult. That explains the lack of any work relating to research on curcumin alone in water so far in literature, except a study where the researchers have quantified using the standard graph of curcumin concentration in "methanol" to show a 10-fold increase of curcumin concentration in "water".[31] After repeated tests to estimate the amount of curcumin that is in water, this value was found to be in the range of 1−10 μg/mL, using gravimetric analysis. However, since decrease in temperature could lead to the molecule precipitating out of water to form aggregates of solid curcumin, ensuring the level of curcumin in solution phase could be erroneous. Hence, it was not possible to accurately calculate the molar extinction coefficient of curcumin in water, as reported in some previous studies; aggregates are formed and, thus, Lambert−Beer's law cannot be applied. Moreover, for conjugated dienes, ε_{max} cannot be predicted with accuracy.

Further, to determine the stability of curcumin in water, UV−vis spectroscopy, FTIR spectroscopy, NMR spectroscopy and HPLC techniques were used. The aqueous sample of curcumin after heating was filtered through a Whatman filter paper (retention size > 11 μm) to obtain a homogeneous sol, which was further dried completely to remove the water and redispersed in the desired solvent for all the techniques.

Figure 2, where the absorption spectra of curcumin in water was compared after repeated heating cycles, indicated the robustness of curcumin. To further check its thermal stability, in Figure 6, the UV−visible absorption spectra of curcumin

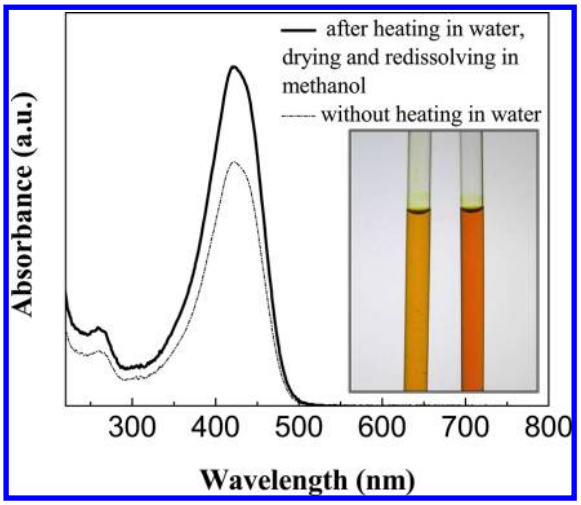

Figure 6. UV−vis spectra of curcumin in methanol. The solid curve shows the absorption spectra taken after dissolution of curcumin in water (up to 100 °C) and thereafter drying it and resuspending in methanol. The broken curve shows the absorption spectra of curcumin in methanol without heat treatment. The picture in inset shows the color of the curcumin in methanol. Two different cases are shown where the darker contrast in the second tube is due to higher amount of dissolved curcumin in methanol.

dissolved at room temperature in methanol is compared with that of curcumin dissolved in methanol after boiling it in water, drying it, and resuspending this heat-treated powder in methanol. No change in the absorption spectra was observed (other than small change in the intensity). To have a closer look in any change in the chemical nature of heat-treated curcumin, NMR spectroscopy was performed on the heat-treated curcumin dissolved in deuterated methanol. In Table 1,

Table 1. ^{1}H NMR Data for Curcumin in CD_3OH

No.	δ_H (J in Hz)	
	1	2
1	3.31, t	3.33, t
2	3.91, s (6.0)	3.91, s (6.0)
3	6.65, dd (2.16)	6.65, dd (2.16)
4	6.83, d (2.65)	6.83, d (2.68)
5	7.12, d (1.83)	7.12, d (1.91)
6	7.21, d (2.00)	7.23, d (1.92)
7	7.55, dd (3.18)	7.55, dd (3.24)

the NMR spectra of curcumin in deuterated methanol is compared with heat-treated curcumin taken in deuterated methanol, which reconfirms that there is no change in the chemical structure of curcumin, even after boiling in water for a long time. Finally, to confirm any partial degradation in curcumin, HPLC was performed on as-received curcumin and heat-treated curcumin. The results are compared in Figure 7. The HPLC analysis of as-received curcumin in methanol shows

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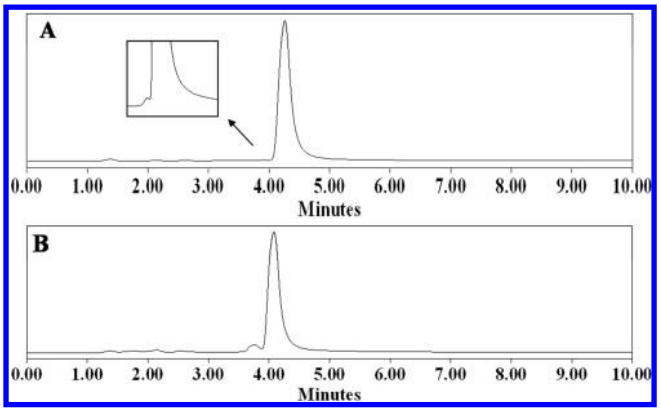
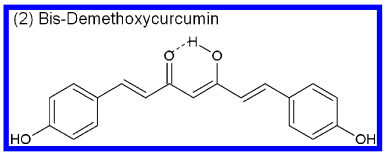


Figure 7. HPLC chromatograms of curcumin (A) before heating and (B) after heating in water, drying, and redissolving in methanol. Inset of (A) is the zoomed view.

a peak at retention time of 4.3 min, which corresponds to curcumin (Figure 7A).[37] Additionally, there is a negligible peak around 3.75 min that corresponds to bisdemethoxycurcumin (2) (1*E*,6*E*)-1,7-bis(4-hydroxyphenyl)hepta-1,6-diene-3,5-



dione) (zoomed view). Bisdemethoxycurcumin is another curcuminoid present in turmeric whose structure is similar to that of curcumin (1). Because these two curcuminoids are equally important for the therapeutic applications, even the presence of a trace amount of bisdemethoxycurcumin along with curcumin is not undesirable and often unavoidable even after purification.[30] The HPLC analysis of heat treated curcumin (Figure 7B) shows that curcumin has not undergone any chemical change or degradation because of heat treatment. However, the intensity of the peak corresponding to bisdemethoxycurcumin is enhanced little bit which can be explained by the absence of nonpolar methoxy group in the molecule. The absence of nonpolar methoxy group in this molecule enhances its availability in polar water as compared to curcumin, which has two methoxy groups.

CONCLUSION

In summary, this article presents an in-depth spectroscopic study to understand the role of temperature and dielectric environment of the molecule curcumin with respect to its solubility. It is observed that the solvent and temperature play a major role in the absorption spectrum of curcumin which was found to be important to understand the process of dissolution. It is also shown that curcumin is dispersed in water at high temperatures and aggregates upon cooling, with some precipitation out of the solvent. Based on these detailed spectroscopic measurements at various temperature conditions, it is proposed that it is the breakage of intramolecular H-bonding that probably leads to the increased availability of curcumin molecule in water at high temperature. As the temperature is increased, the thermal energy helps in breaking the bonds and exposes the polar hydroxyl (−OH) and keto (>C═O) group, which enhances the solubility of the ampiphilic molecule. Due to temperature-dependent dispersion of curcumin in water, it is not possible to estimate its solubility or the molar absorbance with accuracy. Possible enhancement in its bioavailability cannot be overlooked, considering the promising utility of this report.

ASSOCIATED CONTENT

Supporting Information

UV−visible and temperature-dependent UV−visible, temperature-dependent FTIR, ^{1}H NMR, and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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