Solubility of Quercetin in Water + Methanol and Water + Ethanol from (292.8 to 333.8) K

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The solubilities of quercetin in water + methanol and water + ethanol mixtures were measured over the temperature range of (292.8 to 333.8) K. The concentrations of quercetin in different solvent mixtures were analyzed by the UV/vis spectrophotometric method. The experimental solubility data were correlated with the modified Apelblat equation. The calculated solubilities show good agreement with the experimental solubility data.

Introduction

Flavonoids are natural polyphenolic compounds and are widely present in plants and foods. These compounds have anti-inflammatory and anticancer effects. Quercetin (3,5,7,3′,4′-pentahydroxyflavone, QCT) is a member of flavonoids. This compound is one of the most abundant flavonoids in the human diet.[1-4] The solubility of organic compounds in different solvents plays an important role in their separation and purification applications.[5,6] To determine proper solvents and to design an optimized production process, it is necessary to know the solubility of quercetin in different solvents.

In the present study, solubilities of quercetin in water + methanol and water + ethanol mixtures over a temperature range of (292.8 to 333.8) K were measured by a static method. The results can be used in the crystallization and purification of quercetin. The experimental solubility data were correlated with the modified Apelblat equation.

Experimental Section

Materials. Quercetin hydrate (3,5,7,3′,4′-pentahydroxyflavone, QCT) with a purity of > 99 % (by mass) was supplied by Across (Geel, Belgium). Ethanol and methanol were HPLC grade with purity of 99.9 % (by mass) and purchased from Merck (Darmstadt, Germany). Double-distilled water was used for all the experiments.

Apparatus and Procedure. Saturated solutions of quercetin were prepared in a spherical, 10 mL Pyrex glass flask. The flask was maintained at the desired temperature through circulating water. The water temperature was controlled by a thermostat within ± 0.1 K that was provided from a constant-temperature water bath. For each measurement, an excess amount of quercetin was added to a known volume of solvent. The solutions were constantly stirred using a Teflon-coated magnetic stirring bar running at (400 to 500) rpm and allowed to mix for 2 h. Then, the solution was allowed to settle for at least 3 h before sampling. The upper portion was taken, filtered, and poured into a volumetric flask preweighed by using an analytical balance (Sartorius, model BP 221s, Germany) with a resolution of ± 0.1 mg and diluted with ethanol to a certain volume. The prepared samples were finally analyzed by a UV/vis spectrpho-

tometric method at 374 nm using a CECIL UV/vis spectrophotometer (model 3000, UK).

The external calibration curve was obtained in ethanol and used for quantification of quercetin in different solvents. The solubility was expressed as mole fraction and calculated as moles of solute to the sum of moles of solute and solvents. The experimental solubility data were fitted to the modified Apelblat equation and the parameters of the model were calculated. Each data point reported is at least an average of three measurements at each condition.

Results and Discussion

To find the suitable equilibrium condition, different dissolution times were tested. The results indicated that the dissolution increased with an increase of dissolution time from (30 to 240) min and reached equilibrium at 120 min at 298.2 K where the solubility can be measured (data not shown). Constant and reproducible solubility data after 2 h were taken as an indication of reaching equilibrium conditions.

The experimental and calculated mole fraction solubility data of quercetin in water + methanol and water + ethanol mixtures are listed in Table 1 and graphically shown in Figures 1 and 2. The experimental data show that: (1) the solubilities of quercetin in water + methanol and water + ethanol mixtures increase smoothly with increasing temperature, (2) at a constant temperature, the solubilities of quercetin in water + methanol and water + ethanol mixtures increase with increasing methanol and ethanol contents, and (3) the highest solubilities were obtained when a water + ethanol mixture was used as solvent.

The temperature dependence of the solubilities of quercetin in water + methanol and water + ethanol mixtures at different temperatures can be well-correlated by the modified Apelblat equation[7]

$$\ln(x) = A + B/(T/K) + C \ln(T/K) \tag{1}$$

in which x is the mole fraction solubility and T is the absolute temperature (K). The equation parameters A, B, and C were obtained by fitting the experimental solubility data and are presented in Table 2 together with the corresponding root-mean-square deviations (rmsd). The rmsd is defined as follows

$$\text{rmsd} = \left[\frac{1}{n} \sum_{i=1}^{n} (x_i^{\text{cal}} - x_i^{\text{exp}})^2 \right]^{1/2} \tag{2}$$

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Table 1. Mole Fraction Solubility of Quercetin (A) in Water + Methanol and Water + Ethanol Mixtures from $T = $ (292.8 to 333.8) K

T/K	$10^5 x_A^{exp} \pm SD^a$	T/K	$10^5 x_A^{exp} \pm SD^a$
Water (B) + Methanol (C)			
$x_C^o = 0.0000$		$x_C^o = 0.1031$	
292.8	5.04 ± 0.20	292.8	7.34 ± 0.16
298.6	5.51 ± 0.11	298.6	9.21 ± 0.31
303.2	5.85 ± 0.13	303.2	9.65 ± 0.83
308.6	6.18 ± 0.06	308.6	10.04 ± 0.24
314.1	6.53 ± 0.09	314.1	12.42 ± 0.16
318.8	6.70 ± 0.14	318.8	13.67 ± 1.11
322.2	6.91 ± 0.40	322.2	14.34 ± 0.86
325.6	7.13 ± 0.15	325.6	15.41 ± 0.93
331.2	7.38 ± 0.30	331.2	18.23 ± 0.86
333.8	7.53 ± 0.09	333.8	19.16 ± 0.86
$x_C^o = 0.2042$		$x_C^o = 0.3054$	
292.8	10.65 ± 0.13	292.8	18.76 ± 0.96
298.6	14.76 ± 0.20	298.6	22.44 ± 0.83
303.2	15.46 ± 1.03	303.2	23.78 ± 1.33
308.6	16.10 ± 0.17	308.6	25.85 ± 2.03
314.1	21.19 ± 1.81	314.1	32.23 ± 2.40
318.8	23.15 ± 1.17	318.8	33.04 ± 1.23
322.2	25.87 ± 1.92	322.2	35.61 ± 1.26
325.6	27.13 ± 1.05	325.6	37.19 ± 1.46
331.2	30.61 ± 1.05	331.2	44.63 ± 1.38
333.8	31.84 ± 1.15	333.8	46.13 ± 1.25
$x_C^o = 0.4039$		$x_C^o = 0.5024$	
292.8	28.21 ± 2.32	292.8	33.53 ± 1.66
298.6	34.79 ± 1.26	298.6	39.68 ± 1.52
303.2	37.56 ± 1.43	303.2	44.42 ± 1.81
308.6	40.61 ± 1.10	308.6	47.31 ± 1.07
314.1	48.37 ± 3.03	314.1	55.95 ± 1.61
318.8	48.74 ± 1.38	318.8	56.43 ± 2.14
322.2	49.03 ± 1.31	322.2	57.82 ± 1.48
325.6	53.36 ± 2.11	325.6	61.51 ± 1.63
331.2	62.12 ± 1.41	331.2	70.52 ± 1.59
333.8	64.38 ± 1.45	333.8	71.93 ± 2.02
$x_C^o = 0.6010$		$x_C^o = 0.7022$	
292.8	43.24 ± 1.78	292.8	52.18 ± 2.41
298.6	49.39 ± 1.37	298.6	60.28 ± 1.74
303.2	53.40 ± 2.10	303.2	64.83 ± 1.39
308.6	57.83 ± 1.46	308.6	68.71 ± 2.13
314.1	67.58 ± 1.91	314.1	80.77 ± 2.27
318.8	73.65 ± 1.67	318.8	85.30 ± 2.51
322.2	79.25 ± 1.82	322.2	90.51 ± 2.61
325.6	80.48 ± 2.31	325.6	93.16 ± 1.73
331.2	85.05 ± 2.42	331.2	102.71 ± 2.74
333.8	87.15 ± 1.65	333.8	108.34 ± 2.24
$x_C^o = 0.8080$		$x_C^o = 0.9330$	
292.8	62.25 ± 1.43	292.8	75.76 ± 1.71
298.6	71.22 ± 2.43	298.6	82.62 ± 2.24
303.2	76.27 ± 2.52	303.2	88.15 ± 2.20
308.6	80.72 ± 2.62	308.6	93.38 ± 1.95
314.1	89.92 ± 1.71	314.1	102.71 ± 1.15
318.8	100.72 ± 3.31	318.8	113.51 ± 3.53
322.2	111.45 ± 2.41	322.2	127.93 ± 1.17
325.6	114.74 ± 2.23	325.6	132.84 ± 3.18
331.2	120.85 ± 1.94	331.2	142.20 ± 1.68
333.8	129.06 ± 2.71	333.8	150.30 ± 2.37
$x_C^o = 1.0000$			
292.8	84.50 ± 2.05		
298.6	91.90 ± 2.38		
303.2	95.70 ± 2.46		
308.6	103.62 ± 1.77		
314.1	112.80 ± 2.74		
318.8	126.87 ± 1.90		
322.2	132.58 ± 1.40		
325.6	142.07 ± 2.11		
331.2	158.93 ± 2.53		
333.8	162.84 ± 2.53		
Water (B) + Ethanol (D)			
$x_D^o = 0.1031$		$x_D^o = 0.2042$	
292.8	14.47 ± 1.26	292.8	23.61 ± 1.01
298.6	16.38 ± 0.95	298.6	25.71 ± 1.12
303.2	17.28 ± 1.01	303.2	26.48 ± 0.96

Table 1. Continued

T/K	$10^5 x_A^{exp} \pm SD^a$	T/K	$10^5 x_A^{exp} \pm SD^a$
308.6	18.83 ± 1.29	308.6	27.32 ± 1.38
314.1	20.32 ± 1.38	314.1	31.95 ± 1.31
318.8	21.73 ± 1.96	318.8	34.16 ± 1.27
322.2	23.72 ± 1.43	322.2	38.62 ± 1.22
325.6	24.58 ± 1.27	325.6	39.16 ± 1.14
331.2	26.39 ± 1.35	331.2	41.23 ± 1.81
333.8	28.27 ± 1.12	333.8	44.16 ± 1.21
$x_D^o = 0.3054$		$x_D^o = 0.4039$	
292.8	32.21 ± 2.22	292.8	48.02 ± 1.47
298.6	35.04 ± 1.23	298.6	50.92 ± 1.44
303.2	36.12 ± 1.20	303.2	52.08 ± 2.08
308.6	37.06 ± 1.42	308.6	53.16 ± 2.58
314.1	41.11 ± 1.48	314.1	60.67 ± 2.34
318.8	47.27 ± 1.17	318.8	65.73 ± 1.36
322.2	52.17 ± 2.17	322.2	70.43 ± 2.25
325.6	55.41 ± 1.43	325.6	73.36 ± 1.68
331.2	58.73 ± 2.90	331.2	80.86 ± 2.84
333.8	63.41 ± 2.15	333.8	83.63 ± 1.51
$x_D^o = 0.5024$		$x_D^o = 0.6010$	
292.8	57.41 ± 2.93	292.8	68.31 ± 3.21
298.6	59.82 ± 2.19	298.6	70.73 ± 2.74
303.2	61.96 ± 1.32	303.2	73.64 ± 1.15
308.6	63.38 ± 2.15	308.6	76.92 ± 1.27
314.1	69.95 ± 2.18	314.1	88.83 ± 3.23
318.8	76.48 ± 1.66	318.8	93.55 ± 2.00
322.2	82.37 ± 1.89	322.2	99.04 ± 3.20
325.6	85.73 ± 2.01	325.6	104.23 ± 2.54
331.2	94.18 ± 3.76	331.2	116.42 ± 2.17
333.8	96.38 ± 1.44	333.8	120.33 ± 2.38
$x_D^o = 0.7022$		$x_D^o = 0.8080$	
292.8	80.49 ± 2.16	292.8	99.52 ± 2.19
298.6	88.36 ± 3.35	298.6	110.83 ± 2.63
303.2	91.16 ± 1.09	303.2	116.38 ± 1.57
308.6	94.34 ± 2.61	308.6	121.21 ± 3.30
314.1	113.21 ± 2.57	314.1	138.24 ± 1.87
318.8	116.62 ± 3.03	318.8	145.57 ± 2.43
322.2	120.49 ± 2.67	322.2	152.73 ± 2.38
325.6	128.83 ± 1.94	325.6	161.71 ± 1.06
331.2	142.20 ± 3.31	331.2	175.46 ± 2.62
333.8	149.13 ± 1.76	333.8	183.96 ± 1.19
$x_D^o = 0.9330$		$x_D^o = 1.0000$	
292.8	120.71 ± 2.43	292.8	135.00 ± 4.04
298.6	134.52 ± 2.78	298.6	153.00 ± 3.77
303.2	143.14 ± 2.31	303.2	165.00 ± 3.66
308.6	150.40 ± 3.14	308.6	178.00 ± 1.17
314.1	170.74 ± 3.62	314.1	193.00 ± 4.31
318.8	179.82 ± 1.75	318.8	207.00 ± 5.91
322.2	188.28 ± 3.78	322.2	218.00 ± 2.52
325.6	202.64 ± 2.36	325.6	230.00 ± 2.07
331.2	223.75 ± 2.37	331.2	250.00 ± 2.50
333.8	233.63 ± 2.07	333.8	255.00 ± 1.56

^{a} Standard deviations (SD) are based on at least three measurements at each condition.

where n is the number of experimental points; x_i^{cal} represents the mole fraction solubility calculated from equation of 1; and x_i^{exp} represents the experimental mole fraction solubility. As shown in Figures 1 and 2, the experimental solubility data correlate very well with the calculated solubility data. Therefore, the experimental solubility data and the proposed model can be used in the purification process of quercetin.

Conclusions

The solubilities of quercetin in water + methanol and water + ethanol mixtures were measured at temperatures from (292.8 to 333.8) K. Raising the temperature increased the solubility of quercetin; on the other hand, at constant temperature, the solubilities of quercetin increased with increasing mole fractions of alcohols. On the basis of the above results, the solubilities
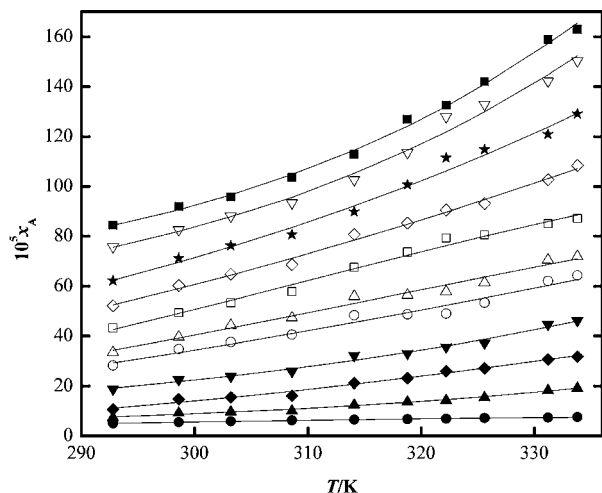
Figure 1. Mole fraction solubility (x_A) of quercetin (A) in water (B) + methanol (C) as a function of temperature: ●, $x_C^o = 0.0000$; ▲, $x_C^o = 0.1031$; ♦, $x_C^o = 0.2024$; ▼, $x_C^o = 0.3054$; ○, $x_C^o = 0.4039$; △, $x_C^o = 0.5024$; □, $x_C^o = 0.6010$; ◇, $x_C^o = 0.7022$; ★, $x_C^o = 0.8080$; ▽, $x_C^o = 0.9330$; ■, $x_C^o = 1.0000$; −, correlated data with eq 1.
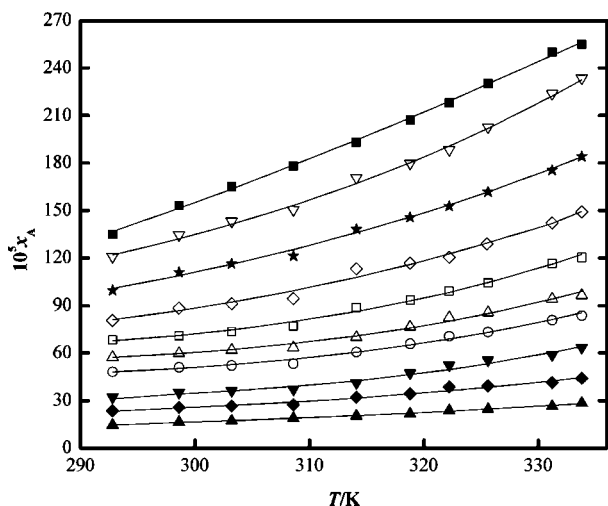

Figure 2. Mole fraction solubility (x_A) of quercetin (A) in water (B) + ethanol (D) as a function of temperature: ▲, $x_D^o = 0.1031$; ♦, $x_D^o = 0.2024$; ▼, $x_D^o = 0.3054$; ○, $x_D^o = 0.4039$; △, $x_D^o = 0.5024$; □, $x_D^o = 0.6010$; ◇, $x_D^o = 0.7022$; ★, $x_D^o = 0.8080$; ▽, $x_D^o = 0.9330$; ■, $x_D^o = 1.0000$; −, correlated data with eq 1.

Table 2. Parameters of Equation 1 for Quercetin in Water + Methanol and Water + Ethanol Mixtures in the Temperature Range from (292.8 to 333.8) K

	A	B	C	10^5 rmsd[a]
		Water (B) + Methanol (C)		
x_C^o				
0.0000	99.859	−5863.675	−15.798	0.092
0.1031	−130.148	4279.260	20.700	0.359
0.2024	116.874	−7431.274	−15.685	0.789
0.3054	−69.230	1578.282	11.760	0.971
0.4039	73.761	−4785.440	−9.515	1.841
0.5024	121.883	−6938.925	−16.665	1.672
0.6010	162.530	−8820.732	−22.652	1.521
0.7022	32.958	−2772.955	−3.438	1.351
0.8080	−28.906	68.883	5.776	2.398
0.9330	−165.559	6458.600	26.028	2.676
1.000	−213.121	8187.599	31.355	1.500
		Water (B) + Ethanol (D)		
x_D^o				
0.1031	−55.104	1382.116	9.344	0.278
0.2024	−160.698	6292.976	25.065	1.082
0.3054	−313.089	13274.459	47.755	1.469
0.4039	−268.539	11455.705	41.075	1.263
0.5024	−273.462	11751.257	41.795	1.409
0.6010	−251.417	10646.731	38.607	1.461
0.7022	−153.308	6072.787	24.115	0.496
0.8080	−92.483	3287.099	15.119	1.727
0.9330	−19.111	4441.287	19.147	2.067
1.000	18.339	−2418.491	−2.936	1.400

[a] rmsd = the root-mean-square deviation.

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of quercetin in different solvent mixtures are in the following order: $x_{water+ethanol} > x_{water+methanol}$. The temperature dependence of solubilities of quercetin in different solvent mixtures can be well-correlated by the modified Apelblat equation, and the calculated solubilities show good agreement with the experimental solubility data.