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SHORT ARTICLE

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Solubility of Candesartan Cilexetil in Different Solvents at Various Temperatures

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ABSTRACT: The solubility data of candesartan cilexetil of form I in ethanol, 1-propanol, 2-propanol, acetone 2-butanone, and acetonitrile at various temperatures were measured by gravimetrical method under atmospheric pressure, and the solubility data was fitted well with the Apelblat equation. The results show that the solubility of form I in the above solvents increased with an increase of temperature, and at the same temperature, the order of solubility is 2-butanone > acetone > 1-propanol > ethanol > 2-propanol > acetonitrile.

INTRODUCTION

Candesartan cilexetil (1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2-(1*H*-tetrazol-5-yl)[1, 1′-biphenyl]-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate) is an ester prodrug of candesartan, known as a potent angiotensin II receptor antagonist which is useful in the treatment of hypertension.[1,2] The mole mass of candesartan cilexetil is 610.66, and the CAS number is 145040-37-5. The molecular structure of candesartan cilexetil is given in Figure 1. It has been found that candesartan cilexetil has polymorphs, such as form I, form II, amorphous,[3,4] and so forth. The polymorphs were obtained by crystallization in different solvents. Form I is the stable form which is commonly used in pharmacy. The melting point of form I is 442.15 K, measured by a Netzsch DSC 204 differential scanning calorimeter.

The solubility data of drugs are a key thermodynamic parameter used in the pharmaceutical industry for process design and scale-up, especially in the preparation of the targeted polymorph of drugs. Nevertheless, no experimental solubility data of candesartan cilexetil were reported in literature up to date. In this work, the solubility data of candesartan cilexetil of form I in ethanol, 1-propanol, 2-propanol, acetone, 2-butanone, and acetonitrile were measured at various temperatures by a gravimetrical method under atmospheric pressure.

EXPERIMENTAL SECTION

Materials. Candesartan cilexetil of form I with a mass fraction purity higher than 0.995 was supplied by Zhejiang Huahai Pharmaceutical Co. Ltd. of China. The X-ray diffraction (XRD) spectra of samples are shown in Figure 2. Ethanol, 1-propanol, 2-propanol, acetone, 2-butanone, and acetonitrile were purchased from Tianjin Kewei Chemical Co. in China. All of the solvents were analytical reagent grade, and the molar purities were higher than 0.99.

Solubility Measurement. The solubility data were measured by a gravimetric method.[6] In this method, an excess amount of the solid drug was added to the solvent and stirred in the jacketed glass vessel of about 50 cm^3. The temperature was maintained by circulating water through the outer jacket from a thermostatic water-circulator bath (501 A, Shanghai Laboratory Instrument Works Co. Ltd., China) with a stability of 0.05 K. The solution was stirred using a magnetic stirrer for about 4 h to reach the equilibrium. The clear upper portion was filtered with the membrane (0.45 μm) and poured into a weighed Petri dish (m_0). The Petri dish with clear solution was quickly weighted (m_1) and placed in the air mist constant-temperature drybox (101 A, Shanghai Sheng Xin Scientific Instrument Co. Ltd., China) at 323.15 K for 12 h. The Petri dish was reweighed for several times until the weight of Petri dish (m_2) was kept constant. Every experiment was repeated three times. The masses of the solute and Petri dish were measured using an analytical balance (Metler Toledo AB204) with an accuracy of ± 0.0001 g.

The mole fraction of candesartan cilexetil of form I in the sample solution could be calculated by eq 1,

$$x = \frac{(m_2 - m_0)/M_1}{(m_2 - m_0)/M_1 + (m_1 - m_2)/M_2} \quad (1)$$

where M_1 and M_2 are the molar mass of candesartan cilexetil and solvents, respectively. The uncertainty of experimental values is estimated to be less than 1.32 %.

RESULTS AND DISCUSSION

The solubilities of candesartan cilexetil (form I) in ethanol, 1-propanol, 2-propanol, acetone, 2-butanone, and acetonitrile at different temperatures were summarized in Table 1. The experimental data were correlated with the Apelblat equation:[7]

$$\ln(x) = A + \frac{B}{T/\mathrm{K}} + C\ln(T/\mathrm{K}) \quad (2)$$

where x is the mole fraction of candesartan cilexetil of form I; A, B, and C are the parameters of the Apelblat equation.

Absolute average relative deviations (AARDs) and root-mean-square deviations (rmsd's) can be calculated by eqs 3 and 4 and

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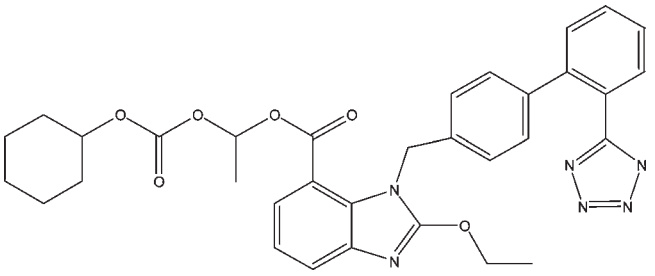

Figure 1. Molecular structure of candesartan cilexetil.

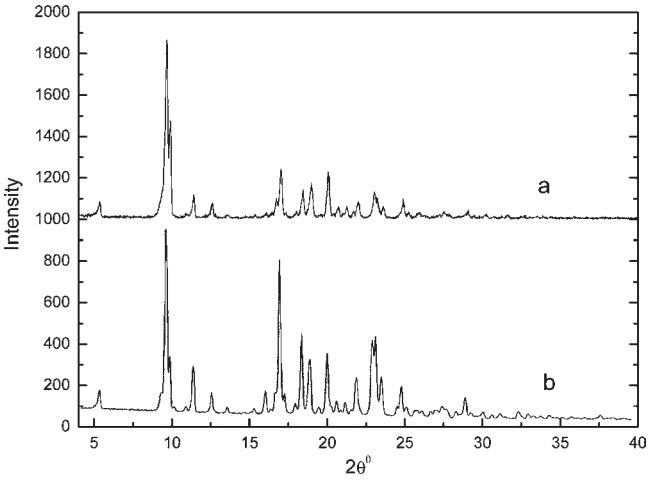

Figure 2. XRD pattern of candesartan cilexetil: a, samples; b, standard XRD pattern.[5]

Table 1. Mole Fraction x Candesartan Cilexetil (Form I) in Different Solvents at Different Temperatures

T/K	$10^3\,x$	$10^3\,x_{cal}$	$100(x - x_{cal})/x$
		Acetone	
278.15	3.83	3.88	−1.22
283.15	4.67	4.66	0.16
288.15	5.66	5.59	1.36
293.15	6.73	6.67	0.79
298.15	7.83	7.95	−1.47
303.15	9.46	9.44	0.26
308.15	11.1	11.17	−0.62
313.15	13.3	13.19	0.73
318.15	15.5	15.53	−0.17
323.15	18.2	18.23	−0.02
		2-Butanone	
278.15	5.75	5.71	0.66
283.15	6.53	6.54	−0.08
288.15	7.49	7.52	−0.40
293.15	8.60	8.69	−1.07
298.15	10.01	10.08	−0.74
303.15	11.8	11.74	0.12
308.15	13.8	13.72	0.21
313.15	16.0	16.08	−0.31
318.15	19.0	18.90	0.53
323.15	22.4	22.28	0.49
328.15	26.4	26.33	0.33
333.15	31.0	31.17	−0.49
		Acetonitrile	
278.15	0.26	0.26	−2.56
283.15	0.33	0.34	−3.20
288.15	0.44	0.44	0.86
293.15	0.58	0.56	3.59
298.15	0.71	0.72	−2.26
303.15	0.91	0.94	−2.57
308.15	1.27	1.21	5.01
313.15	1.59	1.57	1.27
318.15	1.95	2.03	−4.12
323.15	2.63	2.63	−0.23
328.15	3.43	3.41	0.35
333.15	4.42	4.43	−0.12
		1-Propanol	
278.15	0.62	0.61	0.91
283.15	0.79	0.79	0.14
288.15	0.98	1.02	−3.78
293.15	1.32	1.31	0.97
298.15	1.72	1.69	1.86
303.15	2.08	2.17	−4.28
308.15	2.83	2.80	1.37
313.15	3.73	3.59	3.74
318.15	4.52	4.62	−2.08
323.15	5.90	5.93	−0.52
328.15	7.59	7.61	−0.22
333.15	9.77	9.75	0.19
		2-Propanol	
278.15	0.26	0.26	0.84
283.15	0.37	0.36	1.76
288.15	0.52	0.50	3.73
293.15	0.70	0.69	1.83
298.15	0.93	0.93	−0.56
303.15	1.28	1.26	1.32
308.15	1.70	1.69	0.09
313.15	2.21	2.26	−2.39
318.15	2.98	2.99	−0.34
323.15	3.91	3.94	−0.82
328.15	5.26	5.16	1.93
333.15	6.67	6.71	−0.64
		Ethanol	
278.15	0.55	0.55	0.67
283.15	0.66	0.67	−2.07
288.15	0.86	0.83	3.34
293.15	1.03	1.03	−0.17
298.15	1.30	1.30	0.32
303.15	1.63	1.65	−0.90
308.15	2.03	2.10	−3.49
313.15	2.71	2.69	0.42
318.15	3.55	3.48	2.06
323.15	4.58	4.51	1.54
328.15	5.73	5.87	−2.40
333.15	7.72	7.68	0.59

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Table 2. Parameters of the Apelblat Equation for Candesartan Cilexetil (Form I) in Different Solvents

solvent	*A*	*B*	*C*	10^5 rmsd	10^2 AARD
ethanol	−341.77	11699.12	53.14	5.86	−0.01
acetonitrile	−219.21	5871.95	34.96	3.38	−0.33
2-butanone	−198.83	6678.19	31.37	8.24	−0.06
1-propanol	−179.16	4181.40	29.07	6.18	−0.14
acetone	−54.53	−99.13	9.99	6.64	−0.02
2-propanol	−52.93	−2253.87	10.60	3.93	0.56

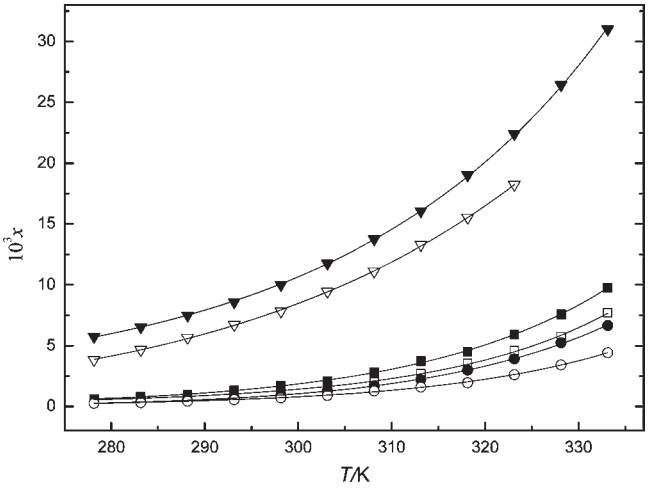

Figure 3. Experimental mole fraction of candesartan cilexetil (form I) in different solvents at different temperatures: ▼, 2-butanone; ▽, acetone; ■, 1-propanol; □, ethanol; ●, 2-propanol; ○, acetonitrile. The solid lines represent the calculated values.

are listed in Table 2.

$$\text{AARD} = \frac{1}{N}\sum_{i}^{N}\frac{x - x_{\text{cal}}}{x} \tag{3}$$

$$\text{rmsd} = \left[\sum_{i=1}^{N}\frac{(x - x_{\text{cal}})^2}{N-1}\right]^{1/2} \tag{4}$$

where x_{cal} is the calculated value by the Apelblat equation; N is the number of experiment points.

The curve of the temperature versus the solubilities of form I candesartan cilexetil in the different solvents was shown in Figure 3. It indicates that the solubilities of form I in six pure solvents (ethanol, 1-propanol, 2-propanol, acetone, 2-butanone, and acetonitrile) increased with an increase of temperature as in Table 1 and Figure 3. At the same temperature, the solubility trend is 2-butanone > acetone > 1-propanol > ethanol > 2-propanol > acetonitrile. Moreover, form I candesartan cilexetil dissolves much more in 2-butanone and acetone, which may result from two carbonyl groups existing in a candesartan cilexetil molecule. The calculated solubility data by the modified Apelblat model are in good agreement with the experimental data.

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