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Solubility of Azilsartan in Methanol, Ethanol, Acetonitrile, *n*-Propanol, Isopropanol, Tetrahydrofuran, and Binary Solvent Mixtures between 293.15 and 333.15 K

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Cite This: *ACS Omega* 2020, 5, 6141−6145

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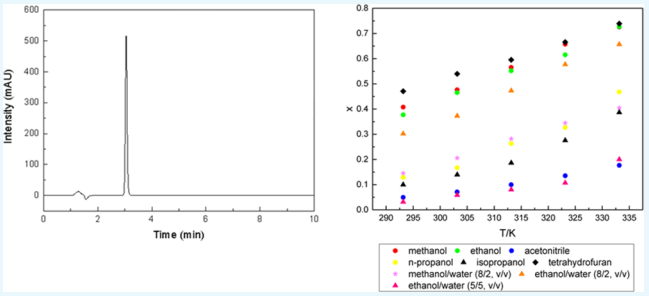
ABSTRACT: A precise determination method of azilsartan solubility between 293.15 and 333.15 K in several ordinary solvents and some of their aqueous mixtures was established by high-performance liquid chromatography. In all tested solvents, its solubility shows exponential growth with the increase in temperature. This trend is especially pronounced in methanol and ethanol. The order of solubility of azilsartan can be expressed as ethanol > tetrahydrofuran > ethanol/water (8/2, v/v) > methanol > methanol/water (8/2, v/v) > *n*-propanol > isopropanol > ethanol/Water (5/5, v/v) > acetonitrile. The solubility data of azilsartan were well correlated by the λh model. Moreover, the thermodynamic data including the dissolving enthalpy, entropy, and Gibbs free energy of azilsartan in each solvent were calculated which is crucial to its preparation technology study.



1. INTRODUCTION

Azilsartan (2-ethoxy-1-([2′-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl)-1*H*-benzimidazole-7-carboxylic acid) (Figure 1), as a hypotensive drug, is a novel angiotensin

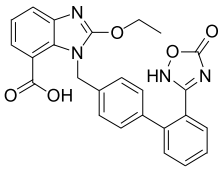


Figure 1. Chemical structure of azilsartan.

II receptor antagonist that competitively blocks the binding of angiotensin to the AT1 receptor.[1,2] It was first synthesized in 1995 by Kohara and approved for sale in Japan in 2012.[3] Because of its high efficiency and less adverse effects such as dry cough compared to the similar products, azilsartan is widely applied clinically[4−7] in recent years. It is reported that there are four kinds of crystalline forms of this chemical,[8−10] and the crystal form, size distribution, and polymorphism could influence its pharmaceutical quality and effectiveness.[11] Despite sufficient studies on its polymorph,[12] the solubility information of this drug has been ignored. Indeed, multiple solvents were applied in its crystallization and recrystallization process such as isopropanol, dimethylformamide, methanol, and acetonitrile. In addition, ethanol was used as the washing solvent in the synthesis process of azilsartan to achieve the desired purity.[13,14]

It is known that the choice of the solvent and its dissolving capacity have a huge impact on the drug manufacturing process efficiency.[15] Technically, the solubility information of drugs is essential in all steps of drug discovery and development processes such as crystallization, separation, liquid extraction, and drug formulation.

In this study, the solubility of azilsartan in methanol, ethanol, acetonitrile, *n*-propanol, isopropanol, tetrahydrofuran, methanol/water (8/2, v/v), ethanol/water (8/2, v/v), and ethanol/water (5/5, v/v) was obtained based on the chromatographic method. The thermodynamic parameters, such as dissolved enthalpy, were calculated according to the van't Hoff equation.

2. RESULTS AND DISCUSSION

2.1. High-Performance Liquid Chromatography. The purity of azilsartan was 99.84% determined by high-performance liquid chromatography (HPLC) with the optimized condition (Figure 2).

A calibration curve for the concentration of azilsartan was prepared by using a standard solution which was prepared

Received: January 13, 2020
Accepted: February 27, 2020
Published: March 13, 2020

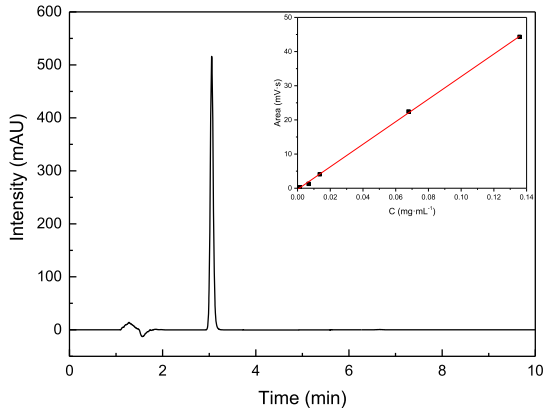


Figure 2. HPLC chromatogram of azilsartan. Inset: linear relationship between the chromatogram peak area (Y) and the concentration (X) of azilsartan in methanol.

from 1.357×10^{-3} to 1.357×10^{-1} mg·mL^{-1} in methanol. All experiments were repeated three times at each temperature. The peak area was considered the average measured by HPLC. The calibration curve was obtained based on the chromatogram (Figure 2).

The linear equation between the mass concentration and the peak area of azilsartan sample solution is $Y = 330.2X - 0.3387$, while correlation coefficient $R^2 = 0.9998$. The linearity range is from 4.1×10^{-4} to 1.4×10^{-1} mg·mL^{-1}.

2.2. Correlation Data of Azilsartan. The melting point of azilsartan was obtained by the differential scanning calorimetry (DSC) study shown in Figure 3. The abscissa and ordinate of

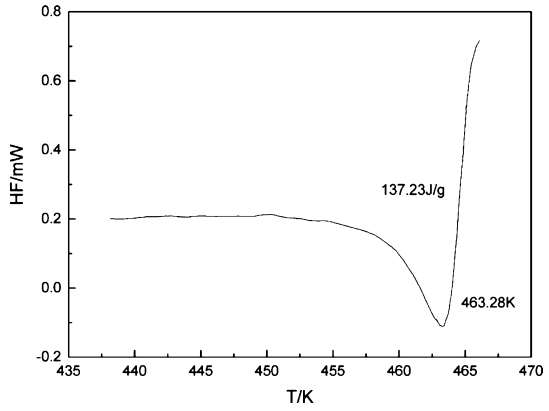


Figure 3. The DSC curve of azilsartan.

the graph is the absolute temperature and the heat flow, respectively. It can be observed that the melting point of this solute is 463.28 K, and the melting enthalpy is 137.23 J/g.

The solubility of azilsartan in the calibration curve is expressed by the mass concentration detected by HPLC. The mole fraction of the solute can be calculated by eq 1.

$$x_A = \frac{m_A/M_A}{m_A/M_A + (m_0 - m_A)/M_B} \quad (1)$$

wherein x_A is the mole fraction of the solute azilsartan; m_0 is the mass of the solution; m_A is the mass of the solute; M_A is the molar mass of the solute azilsartan; and M_B is the molar mass of the solvent. At 95% confidence level, the experimental measurement uncertainty is approximately 5.0%.

The solid−liquid equilibrium was described by the λh model which is one of the thermodynamic models proposed by Buchowski et al.,[16] presented as eq 2.

$$\ln\left[1 + \lambda\frac{(1 - x_A)}{x_A}\right] = \lambda h\left(\frac{1}{T} - \frac{1}{T_m}\right) \quad (2)$$

Here, x is the mole fraction of the solute; T is the experimental temperature corresponding to x; T_m is the melting point of the solute; λ and h are the parameters of the equation.

In order to verify the uncertainty of the data, the relative deviation (δ) was introduced according to eq 3. Moreover, the deviation between x_A^{calc} and x_A was estimated by mean deviation (MD), measuring the correlation degree of the mathematical model.

$$\delta = \frac{x_A - x_A^{calc}}{x_A} \quad (3)$$

where x_A is the mole fraction of solute azilsartan; x_A^{calc} can be calculated from eq 2.

$$MD = 100\frac{\sum \frac{|x_A - x_A^{calc}|}{x_A}}{N} \quad (4)$$

here N is the number of experimental data; x_A and x_A^{calc} are the experimental and calculated values of solubility, respectively.

The solubility data of azilsartan in methanol, ethanol, acetonitrile, *n*-propanol, isopropanol, tetrahydrofuran, and mixed solvents in the temperature range from 293.15 to 333.15 K are listed in Table 1 and graphically presented in Figure 4.

The data of molar fraction (x_A) of the solubility are close to the theoretical molar fraction x_A^{calc}, indicating that the solubility experimental data have good reliability and particularly instructive.

The equation parameters, the determination coefficient R^2, and the MD values obtained by fitting with the λh model are listed in Table 2.

This shows that the λh model fitted the data well because the value of determination coefficient R^2 was between 0.9524 and 0.9998, while the value of MD was between 1.218 and 10.98. Besides the λh model, polynomial empirical equation, Apelblat model, and Wilson model were also used to correlate the solubility of azilsartan. However, when the polynomial empirical equation was used for fitting, the calculated solubility was significantly different from the experimental value. Moreover, when the Apelblat model and the Wilson model were used for fitting, the determination coefficient R^2 is negative, which means the fitting cannot converge.

The solid phase of azilsartan in equilibrium with the saturated solutions was also characterized by X-ray powder diffraction analysis, and significant differences were observed among the diffraction patterns. According to the characteristic diffraction peak, three kinds of crystalline forms were definitely distinguished. Six strong diffraction peaks between 9.183°−23.808° were observed in the X-ray powder diffractograms obtained in methanol, ethanol, acetonitrile, *n*-propanol, methanol/water (8/2, v/v), ethanol/water (8/2, v/v), and ethanol/water (5/5, v/v), which was defined as crystalline form I, while 10 strong diffraction peaks together with the characteristic diffraction peak at $2\theta = 7.834°$ in isopropanol as crystalline form II and seven strong diffraction peaks together with the characteristic diffraction peak at $2\theta = 22.420°$ in

https://dx.doi.org/10.1021/acsomega.0c00156
ACS Omega 2020, 5, 6141−6145

Table 1. Solubility of Azilsartan as a Function of Temperature in Different Solvents under 0.1 MPa[a]

solvent	T/K	x_A	x_A^{calc}	100δ
methanol	293.15	0.4074	0.3963	2.73
	303.15	0.4761	0.4871	−2.32
	313.15	0.5655	0.5739	−1.48
	323.15	0.6575	0.6523	0.79
	333.15	0.7251	0.7203	0.66
ethanol	293.15	0.3771	0.3721	1.34
	303.15	0.465	0.4644	0.12
	313.15	0.552	0.5540	−0.37
	323.15	0.6153	0.6360	−3.37
	333.15	0.7268	0.7076	2.65
acetonitrile	293.15	0.0493	0.05345	−8.43
	303.15	0.0709	0.0760	−7.21
	313.15	0.0997	0.1050	−5.34
	323.15	0.135	0.1412	−4.59
	333.15	0.1764	0.1849	−4.81
n-propanol	293.15	0.1285	0.1135	11.67
	303.15	0.167	0.1757	−5.21
	313.15	0.2629	0.2559	2.64
	323.15	0.3268	0.3506	−7.30
	333.15	0.4683	0.4527	3.32
isopropanol	293.15	0.0998	0.0858	13.99
	303.15	0.1394	0.1351	3.10
	313.15	0.1862	0.2011	−8.03
	323.15	0.2755	0.2831	−2.77
	333.15	0.3868	0.3768	2.58
tetrahydrofuran	293.15	0.4706	0.4644	1.32
	303.15	0.5395	0.5390	0.10
	313.15	0.5956	0.6084	−2.15
	323.15	0.6658	0.6711	−0.79
	333.15	0.7390	0.7262	1.73
methanol/water (8/2, v/v)	293.15	0.1454	0.1537	−5.69
	303.15	0.2056	0.2075	−0.93
	313.15	0.2819	0.2701	4.18
	323.15	0.3444	0.3395	1.41
	333.15	0.4047	0.4130	−2.06
ethanol/water (8/2, v/v)	293.15	0.3022	0.2912	3.62
	303.15	0.3729	0.3836	−2.88
	313.15	0.4728	0.4793	−1.38
	323.15	0.5772	0.5714	1.01
	333.15	0.6568	0.6547	0.32
ethanol/water (5/5, v/v)	293.15	0.0315	0.0273	13.28
	303.15	0.0586	0.0478	18.37
	313.15	0.0801	0.0797	0.43
	323.15	0.1072	0.1264	−17.94
	333.15	0.1999	0.1902	4.86

[a]Standard uncertainties u are $u(T)$ = 0.1 K, $u(p)$ = 0.05 MPa, and related standard uncertainty $u_r(x)$ = 0.05 (0.95 level of confidence).

tetrahydrofuran as crystalline form III (Supporting Information).

2.3. Thermodynamic Properties for Azilsartan Dissolution. In order to have an insight into the azilsartan dissolve process in each solvents, the Gibbs energy ($\Delta_{sol}G^\circ$), the dissolving enthalpy ($\Delta_{sol}H^\circ$), and the dissolving entropy ($\Delta_{sol}S^\circ$) were further studied.

The chemical potential of the solute azilsartan in the solid and liquid phases is equivalent when the dissolution equilibrium is achieved.[17] It can be expressed as eq 5.

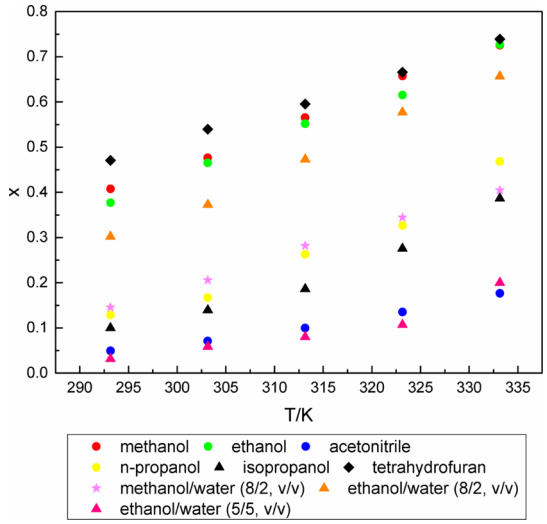


Figure 4. Temperature dependence of mole fraction of azilsartan in several solvents.

Table 2. Parameters of λh Model in Different Solvents

solvent	λ	h	R^2	MD
methanol	36.07	89.05	0.9927	1.596
ethanol	37.35	88.90	0.9848	1.568
acetonitrile	3.365	991.2	0.9998	6.077
n-propanol	36.22	124.5	0.9789	6.029
isopropanol	26.27	171.3	0.9850	6.094
tetrahydrofuran	19.68	128.4	0.9881	1.218
methanol/water (8/2, v/v)	9.574	332.2	0.9906	2.856
ethanol/water (8/2, v/v)	39.00	93.40	0.9950	1.843
ethanol/water (5/5, v/v)	17.93	287.6	0.9524	10.98

$$\mu_A^\circ(s, T) = \mu_A(1, T, \alpha_A) = \mu_A^\circ(1, T) + RT \ln \gamma_A x_A \quad (5)$$

here, μ_A° is the chemical potential of solute azilsartan when the atmospheric pressure is 0.1 MPa; α_A is the activity of the real solution, which is defined as $\alpha_A = \gamma_A x_A$; γ_A is the activity coefficient of the solute; and x_A is the mole fraction of solute azilsartan.

Therefore, the relationship between the mole fraction of solute azilsartan x_A and the Gibbs free energy change in the dissolution process was established when the two phases reached equilibrium at any certain temperature (T) as eq 6.

$$\ln \gamma_A x_A = \frac{\mu_A^\circ(s, T) - \mu_A^\circ(1, T)}{RT} = -\frac{\Delta_{sol}G_A^\circ(T)}{RT} \quad (6)$$

where $\Delta_{sol}G_A^\circ(T)$ is the Gibbs energy of dissolution of the solute azilsartan at temperature T.

Generally, the Gibbs energy of dissolution at temperature T is given by eq 7.

$$\Delta_{sol}G_A^\circ(T) = \Delta_{sol}H_A^\circ - T\Delta_{sol}S_A^\circ \quad (7)$$

Therefore, the mole fraction of solute azilsartan x_A can be associated with the changes of entropy and enthalpy in the dissolution process as eq 8.

$$\ln \gamma_A x_A = -\frac{\Delta_{sol}H_A^\circ}{RT} + \frac{\Delta_{sol}S_A^\circ}{R} \quad (8)$$

The activity coefficient (γ_A) goes to 1 when the mole fraction of the solute (x_A) goes to zero in an ideal dilute solution. Equation 8 was simplified as eq 9. Moreover, the

https://dx.doi.org/10.1021/acsomega.0c00156
ACS Omega 2020, 5, 6141−6145

Table 3. Dissolving Thermodynamic Data of Azilsartan in Different Solvents

solvent	$\Delta_{sol}H^\circ$ (kJ·mol^{-1})	$\Delta_{sol}S^\circ$ (J·K^{-1}·mol^{-1})	$\Delta_{sol}G^\circ$ (kJ·mol^{-1})	% ζ_H	% ζ_{TS}
methanol	12.5957	35.297	1.565	53.312	46.688
ethanol	12.9615	36.254	1.632	53.359	46.641
acetonitrile	26.3828	64.913	6.097	56.532	43.468
n-propanol	26.4377	72.866	3.666	53.725	46.275
isopropanol	27.4736	74.287	4.258	54.200	45.800
tetrahydrofuran	8.6881	23.489	1.348	54.204	45.796
methanol/water (8/2, v/v)	20.913	55.701	3.506	54.574	45.426
ethanol/water (8/2, v/v)	16.194	45.329	2.028	53.340	46.660
ethanol/water (5/5, v/v)	34.8772	90.548	6.580	55.208	44.792

relative contributions of enthalpy % ζ_H and entropy % ζ_{TS} in the dissolution process were introduced to measure the contribution of enthalpy and entropy to the change of the Gibbs free energy during the dissolution process, as eq 10 and 11.

$$\ln x_A = -\frac{\Delta_{sol}H_A^\circ}{RT} + \frac{\Delta_{sol}S_A^\circ}{R} \quad (9)$$

$$\%\ \zeta_H = \frac{|\Delta_{sol}H^\circ|}{|\Delta_{sol}H^\circ| + |T\Delta_{sol}S^\circ|} \times 100 \quad (10)$$

$$\%\ \zeta_{TS} = \frac{|T\Delta_{sol}S^\circ|}{|\Delta_{sol}H^\circ| + |T\Delta_{sol}S^\circ|} \times 100 \quad (11)$$

The dissolving thermodynamic data of azilsartan obtained are shown in Table 3.

The dissolution of azilsartan in the selected solvents was an endothermic and entropic increase process. In the aqueous solution, the heat absorption and entropy increased with the increase in the water ratio during the dissolution process.

3. CONCLUSIONS

In this study, the liquid chromatographic method was introduced to measure the solubility of azilsartan in methanol, ethanol, acetonitrile, *n*-propanol, isopropanol, tetrahydrofuran, methanol/water (8/2, v/v), ethanol/water (8/2, v/v), and ethanol/water (5/5, v/v). In the single organic solvents, the molar fraction of azilsartan in methanol, ethanol, and tetrahydrofuran is much greater than it in acetonitrile, *n*-propanol, and isopropanol. In the mixed solvents, azilsartan has the highest solubility in ethanol/water (8/2, v/v) aqueous solutions. Moreover, its solubility decreased when the proportion of water in the mixed solvents increased. The solubility of azilsartan in nine solvents definitely increases with the increasing temperature, and the largest solubility change happened in methanol and ethanol, which could provide the theoretical basis in its recrystallization process.

4. EXPERIMENTAL SECTION

4.1. Materials. Azilsartan used in this work was provided by Shandong Xinhua Pharmaceutical Co., Ltd. Methanol, ethanol, acetonitrile, and tetrahydrofuran (chromatographic grade) were purchased from the Beijing Bellingway Technology Co., Ltd. without further purification. *n*-Propanol and isopropanol were obtained from Beijing Guangtong Fine Chemical Company without further processing. Deionized water (18.25 MΩ·cm^{-1}) was obtained from a Millipore Mili-Q Plus water system. All solution was filtered through 0.22 μm membranes before use.

4.2. Liquid Chromatographic Conditions. The purity and content analysis of azilsartan were performed on an UltiMate 3000 HPLC and UHPLC system (America). The stationary and mobile phase were TechMate C18 ST-II (4.6 × 150 mm, 5 μm, 100 Å) and acetonitrile/water (57/43, v/v, 1 wt % glacial acetic acid), respectively. The detection wavelength was 251 nm; the flow rate was 1.0 mL·min^{-1}; and the injection volume was 10 μL.

4.3. Measurement of Azilsartan Solubility. An excess of azilsartan was taken in a glass vial and mixed with 10 mL of methanol, ethanol, acetonitrile, *n*-propanol, isopropanol, tetrahydrofuran, methanol/water (8/2, v/v), ethanol/water (8/2, v/v), and ethanol/water (5/5, v/v) to get a supersaturated solutions, respectively. Sequentially, the vial was incubated in temperature thermostatic water bath stirring at 293.15, 303.15, 313.15, 323.15, and 333.15 K for 12 h until the dissolution equilibrium was obtained, respectively. The temperature was determined by a pure solvent bottle with a thermometer inside. The uncertainty of the temperature was ±0.1 K. After another 12 h standing at the corresponding temperature,[18,19] aliquots of 1.0 mL of supernatant of each vial was withdrawn by a syringe with a 0.22 μm membrane. The solution was transferred to a dried, weighed double dish, and the dish was weighed quickly to determine the mass of the solution (m_0) with an uncertainty of ±0.1 mg. After the solution was completely dried under nitrogen, the residue was dissolved in methanol and exactly diluted to 10 mL. Then 10 μL of the reconstituted samples was taken for HPLC analysis. All of the experiments were carried out three times simultaneously and analyzed by HPLC.

Meanwhile, the solid phase in the equilibrium with the saturated solutions was characterized by the X-ray powder diffraction at 296(2) K under Moka ray (λ = 0.71073 Å) and ω-scanning method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c00156.

X-ray powder diffractogram of azilsartan in methanol, ethanol, acetonitrile, *n*-propanol, isopropanol, tetrahydrofuran, methanol/water (8/2, v/v), ethanol/water (8/2, v/v), and ethanol/water (5/5, v/v) (PDF)

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https://dx.doi.org/10.1021/acsomega.0c00156
ACS Omega 2020, 5, 6141−6145

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We express our profound thanks to the instrumental analysis center of Beijing Institute of Technology for their kind help.

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