Measurement and correlation of the solubility of telmisartan (form A) in nine different solvents from (277.85 to 338.35) K

Wenju Liu[a*], Yajun Guo[a], Jiaxing Chen[a], Xi Yu[b]

a: School of Chemistry and Chemical Engineering, Henan University of Technology, Zhengzhou, China

b: European Bioenergy Research Institute (EBRI), School of Engineering & Applied Science, Aston University, Birmingham B4 7ET, UK

Abstract

The solubility of telmisartan (form A) in nine organic solvents (chloroform, dichloromethane, ethanol, toluene, benzene, 2-propanol, ethyl acetate, methanol and acetone) was determined by laser monitoring technique at different temperatures (from 277.85 to 338.35 K). The solubility of telmisartan (form A) in all the nine solvents increased with temperature and the rates of solubility also increased with temperature except in chloroform and dichloromethane solvent. The molar fraction solubility in chloroform was higher than that in dichloromethane, which were both one order of magnitude higher than that in other seven solvents at the range of experimental temperatures. The solubility data were correlated with the modified Apelblat equation and λ h equation, respectively. The results showed that the λ h equation was in better agreement with the experimental data than the Apelblat equation. The relative root mean square deviations (σ) of the λ h equation were in the range from 0.004 % to 0.45%. The uncertainty of the fit parameters also showed that λ

* *Corresponding author. Tel./fax:+86 371 67756718. E-mail Address:wenjuliu@haut.edu.cn

h equation was much better than Apelblat equation. The dissolution enthalpy, entropy and Gibbs free energy of telmisartan (form A) in these solvents were estimated by the Van't Hoff equation and the Gibbs equation. The melting point and the fusion enthalpy of telmisartan (form A) were determined by differential scanning calorimetry (DSC).

Keywords: Telmisartan; Solubility; Apelblat equation; λh Equation; Solution thermodynamic properties

1. Introduction

Telmisartan(2-(4-{[4-Methyl-6-(1-methyl-1*H*-1,3-benzodiazol-2-yl)-2-propyl-1*H*-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid, CAS No.: 144701-48-4, Fig. 1) is a white or off-white crystalline power, which has been used in clinic for the treatment of hypertension as the orally active angiotensin II receptor antagonist (ARB) [1]. An increasing use of telmisartan as the active component in conventional tablets for the treatment of hypertension has been observed because of its efficacious antihypertensive effects and fewer adverse effects [2]. Additionally, telmisartan has also been proved to be effective against cardiovascular diseases and diabetes [3]. Among already reported polymorphic crystalline forms of telmisartan (forms A, B and C) [4], form A is generally employed in the manufacturing of tablets due to its thermodynamic stability at room temperature and the ability of crystallization from various solvents such as ethanol, chloroform and acetic acid solution [5, 6].

The solid-liquid equilibrium data are important in many fields of chemical engineering such as crystallization and extraction. The difference between the

concentrations of a super-saturated solution and the saturated solution is the key influential factor for nucleation, crystal growth and agglomeration during the crystallization process, on which the polymorph, the morphology and the size distribution of the crystals are dependent. In order to control the crystallization process, precise and adequate solubility data is indispensable. Until now, very few experimental data regarding the solubility of telmisartan in alkalized conditions, chloroform, and ethanol has been reported at room temperature [7, 8]. The lack of the data about the solubility of telmisartan (form A) in pure organic solvents at sufficient temperature range has hindered the manufacturing and purifying processes.

In this work, the solubility of telmisartan (form A) in nine organic solvents including chloroform, dichloromethane, ethanol, toluene, benzene, 2-propanol, ethyl acetate, methanol and acetone was determined with the temperature ranging from 277.85 to 338.35 K at atmospheric pressure by a synthetic method of a laser monitoring observation technique. The solubility data of telmisartan in these organic solvents is correlated by the modified Apelblat equation and the λ h equation. The thermodynamic properties (e.g. enthalpy, entropy and Gibbs free energy) of dissolution process of telmisartan in these solvents were calculated using regression equations, i.e. Van't Hoff equation and Gibbs equation.

2. Experimental Section

2.1 Chemicals Used

Telmisartan ($C_{33}H_{30}N_4O_2$, molecular weight 514.62) was purchased from Zhengzhou Chuangyao Technology Co.Ltd., China. The raw material is a white crystalline

powder and the polymorph is form A, measured by XRD. Its purity was 99.3% (determined by HPLC, Model TM 2130, China) after recrystallization, and the telmisartan was put in a desiccator and used without further treatment. The chloroform, dichloromethane, methanol and acetone were purchased from Luoyang Haohua Chemical Reagent Co., China. The ethanol, toluene, benzene, 2-propanol and ethyl acetate were purchased from Tianjin Kewei Chemical Reagent Co., China. All the organic solvents used for the solubility determination were analytical grade reagents with mass purities higher than 99.5 %. The detailed information of the materials used in the experiments is listed in Table 1.

2.2 Apparatus and Procedure.

The solubility measuring apparatus is shown in Figure 2. The solubility was measured using the laser monitoring technique and the synthetic method at a constant temperature [9-14], which have been reported to have similar measuring principle and setup [15].

The laser system (JS2-1009016, Beijing, China) was made up of a laser generator, a digital light-intensity display, and a photoelectric transformer. The solutions were prepared in a 50 mL or 100 mL jacketed glass vessel, and the temperature of the solution inside the glass vessel was controlled by circulating water from a thermostatic water-circulator bath with a digital thermoelectric controller (type HH-601A, China). Temperatures were measured by using a mercury-in-glass thermometer with an accuracy of ±0.1K. The temperatures were only recorded to the nearest ±0.1 °C and then converted to the Kelvin scale by adding 273.15. The solution

was continuously stirred with a magnetic stir bar. A condenser was connected to the vessel to avoid the loss of solvent. Masses of solvents and solute were weighed using an analytical balance (type Mettler Toledo AB204-N, Switzerland) with an accuracy of 0.0001 g.

Initially, the pure solvent (about 50 g, or about 100g at lower temperature) was prepared in the jacketed vessel until the temperature varied within 0.05 K. Then predetermined known mass of telmisartan (form A) was added into the stirred solution. The amount of solvents was of a little excess. An additional solute of known mass (about 10 mg) was added into the stirred solution after being agitated at a fixed temperature for 1 h. This procedure was repeated until the last portion of the solute cannot be dissolved completely within the interval of addition of 30 min. The solute mass consumed during the solubility determination was recorded (included the last portion).The dissolution of the solute was monitored by a laser beam. When the solute dissolved completely, the solution was clear, and the laser intensity penetrated through the solution reached its maximum. When the laser intensity did not exceed 90% of the maximum, the solute was believed not to be dissolved completely. The amount of solute leading to the laser intensity decrease 10% from the maximum is less than 1.0 mg. The saturated mole fraction solubility of telmisartan form A (x_1) in each solvent was calculated using the following equation (Eq. 1):

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \qquad (1)$$

where *M* and *m* represent mole mass and mass, respectively, and subscripts 1 and 2 represent solute telmisartan (form A) and solvents, respectively. The same solubility measurement was conducted twice. The uncertainty of the experimental solubility values was due to the weighing procedure, temperature measurements, and temperature variation of the water bath.

The melting point and the molar enthalpy of fusion of telmisartan form A were determined in triplicate by the differential scanning calorimetry (Metter Toledo DSC 822. Thermal curves were recorded with a heating rate of 10.0 K•min^{-1} with the temperature ranging from 298 to 623 K under a dry nitrogen purge (80 ml•min^{-1}). The masses of the telmisartan form A sample used in the different runs performed were taken practically identical (~ 4.0 mg). The peak temperature was taken as the melting point. The melting point and the molar enthalpy of fusion of telmisartan form A were measured by DSC and repeated three times.

3. Results and Discussions

3.1 The XRD and DSC of telmisartan

Fig. 3a (top) is the X-ray powder diffraction (XRD) data of telmisartan, the pattern is identical with the XRD pattern of telmisartan form A (Fig. 3a, bottom, CCDC reference XUYH0001). Fig. 3b shows the DSC of telmisartan form A. The average melting point and melting enthalpy with uncertainty is 542.42 ±0.20 K and -105.34±8.54 J•g-1, respectively, as shown in Fig. 3b.The melting point result is consistent with the literature reported value 542 ^{o}C by J.Park [8].

3.2 Solubility

The variation of solubility of telmisartan (form A) in different solvents with temperature is presented in Table 2 and Fig. 4, showing that the solubility of telmisartan (form A) increased with the increasing temperature in all the organic solvents. The solubility values in chloroform and dichloromethane were much higher than those in the other seven solvents. This phenomenon may result from the solute-solvent interaction, which plays an important role in the dissolution process of telmisartan in chloroform and dichloromethane. During the dissolution process, three factors, namely the solute-solute, solute-solvent and solvent-solvent interaction, can affect the solubility. The solubility is generally higher when the solute-solvent interaction plays a main role. The mole fraction solubility of telmisartan (form A) decreased in the following order: chloroform > dichloromethane > benzene> methanol > toluene > acetone > ethanol > ethyl acetate > 2-propanol. For alcoholic solvents, the solubility increased with the increase of the solvent polarity. The dielectric constants of methanol, ethanol and 2-propanol were 33.6, 24.3 and 19.92 at 25 ^{o}C, respectively. The solubility in chloroform was much higher than that in dichloromethane and the solubility in benzene is higher than that in toluene. The polarity of chloroform and benzene, respectively, is higher than that of dichloromethane and toluene, respectively. For the similar solvents such as alcoholic solvents, the polarity directly correlated with the solubility.

In order to quantify the importance of the different interactions to the changes in solubility. We use the linear free energy relationship [16] (Equation(2), based on Abraham model, the subscript-zero indicates that c = 0 in *log* $P=c+eE+sS+aA+bB+vV$),

$$log\ P = e_0E+s_0S+a_0A+b_0B + v_0V \qquad (2)$$

where log*P* is the solvent/water partition, (e, s, a, b, *v*) are the solvent coefficients, and (E, S, A, B, V) are the solute descriptors: E is the solute excess molar refractivity, S is the solute dipolarity/polarizability, A and B are the overall or summation hydrogen bond acidity and basicity, and V is the McGowan characteristic volume. The solvent coefficients were from reference 16 and were list in table 3.The solute descriptors were obtained through fit the data at about 298K(R^2=0.9799) and the E=0.71, S=1.35, A=-0.16, B=1.33,V=1.27, respectively. It seems that the hydrogen bond basicity play an important role in the interaction. Also, according to the structure of the solute, there has 5sites that can act as hydrogen bond acceptors (4 Ns and the COO of the acid group) and one hydrogen bond donating site. When the polarity of the solvents (for similar solvents) is higher, it is much easier to form the strong solute-solvent interaction. Therefore, the solubility will increase. The highest solubility in chloroform maybe attribute to the strong hydrogen bond between telmisartan and chloroform. The electron density around chloroform is higher and also the steric hindrance of the chloroform is smaller, so it is easier to form hydrogen bond than other solvent. The solubility in benzene is higher maybe attribute to the aromatic ring in the structure of temisartan, consistent with the rule of like dissolves like. For the solubility in toluene is lower than in benzene maybe because the steric hindrance of the benzene.

3.3 Correlation of Measured Solubility

Fig. 4 shows the trend of the solubility of telmisartan (form A) in these organic solvents at the temperature from 277.85 to 338.35 K. The mole fraction solubility data was correlated by the Apelblat's empirical equation [17]:

$$\ln x_1 = A + B/T + C\ln(T) \qquad (3)$$

where x_1 is the mole fraction solubility of telmisartan, *A*, *B*, and *C* are all empirical constants determined by least square analysis, and *T* is the absolute solution

temperature. Equation (3) of this revised version will be obtained by integration of van't Hoff's equation when $\Delta_{sln}C^{o}_{p,\,m}=0$ is assumed and the solutions are ideal. Correlation parameters (*A*, *B*, and *C*) of Eq. 3 for telmisartan (form A) in different solvents are listed in Table 4 as well as the relative root-mean square deviation (σ), which shows the derivation between the estimated solubility value by equation 3 with the experimental solubility result at each temperature:

$$\sigma = \left[\frac{1}{N} \sum_{i=1}^{N} \left(\frac{x_{1,i}^{expt1} - x_{1,i}^{calcd}}{x_{1,i}^{expt1}} \right)^2 \right]^{1/2} \qquad (4)$$

where N is the number of experimental solubility data, $x_{1,i}^{calc}$ is the solubility estimated by Eq 3, and $x_{1,i}^{exp}$ is the experimental solubility. Fig. 4 shows that the calculated solubility is consistent with the experimental results in all the solvents. Also, according to the values of relative root-mean square deviation (σ) in Table 4, the Apelblat model (Eq.3) is well fitted to the measured solubility data of telmisartan (form A) in the selected solvents, with the relative root mean square deviation σ changed from 1.19 % to 7.61%.

To evaluate fitting equation, the random errors (uncertainties) of the fit parameters also were calculated. The uncertainties value is the standard error (got from the integration of the equation) divided by the parameter value. The uncertainties values for the 3 parameters (A, B and C) were showed in table 4. It can be seen that many of the uncertainty of the 3 parameters exceed the values, such as the case of telmisartan in methanol the uncertainties of the A, B and C amount to 1.779, 2.828 and 1.583 of their values, respectively. Also, the uncertainty of some parameters in other 4 solvents

exceed the parameters values. Thus the Apelblat equation is not well fitted to the measured solubility data of telmisartan (form A) regardless of the higher relative root mean square deviation. The Apelblat eqution contributes only very uncertain values to the thermodynamic basis of these systems, and its use as fitting equation is questionable.

The solubility data can also be described by the λ h equation (Eq.5) with two parameters λ and h [18]:

$$x_1 = \frac{1}{\frac{1}{\lambda}\left\{\exp\left[\lambda h\left(\frac{1}{T} - \frac{1}{T_m}\right)\right] - 1\right\} + 1} \qquad (5)$$

Where T represents the system absolute temperature, T_m is the melting temperature of telmisartan (form A) in Kelvin, x_1 is the mole fraction solubility of telmisartan, λ and h are model parameters determined by correlating the experimental data. These correlations can also be evaluated with relative root-mean square deviation (σ, Eq.4). The correlation results of λh equation are presented in Table 5. The value of the relative root-mean square deviation σ (with the range from 0.004 % to 0.45%) in the λh equation is better than those in the modified Apelblat equation for this system. Also the uncertainties of the 2 parameters were calculated and listed in Table 5. It can be seen that the uncertainties of the λ amount to from 6.2% to 30.8% of its values. And for the h, the values were from 3.7% to 25.3%. Compare with the uncertainties of the Apelblat equation. The λh equation is much better than the modified Apelblat equation for this system. The parameter λ is a measure of non-ideality of the saturated solution.

The values of λ are much smaller than 1 (the λ is 1 when the solution is ideal) in this study, so these solution all deviated from the ideal solution.

3.4 Thermodynamic Functions of Solution

For the dilute or ideal solutions, the modified Van't Hoff equation relates the logarithm of mole fraction of the solute as a linear function of the reciprocal to the absolute temperature by the following equation (Eq. 6) [19, 20, 21, 22]:

$$\ln x_1 = -\frac{\Delta_{\mathrm{sln}} H_{\mathrm{m}}^{\mathrm{o}}}{RT} + \frac{\Delta_{\mathrm{sln}} S_{\mathrm{m}}^{\mathrm{o}}}{R} \qquad (6)$$

Equation (6) is Van't Hoff's equation integrated assuming $\Delta_{\mathrm{sln}} H_{\mathrm{m}}^{\mathrm{o}}$ is constant within the temperature range investigated, this equivalent to assuming $\Delta_{\mathrm{sln}} C_{p,\mathrm{m}}^{\mathrm{o}}$=0. Where x_1 is the mole fraction solubility, R is the universal gas constant, T is the absolute temperature, and $\Delta_{\mathrm{sln}} H_{\mathrm{m}}^{\mathrm{o}}$ and $\Delta_{\mathrm{sln}} S_{\mathrm{m}}^{\mathrm{o}}$ are not the true enthalpy and entropy of solution but are apparent values because activity coefficients are assumed to be unity. Equation (6) shows that the natural logarithm of mole fraction of the solute is a linear function of the reciprocal of the absolute temperature. Thus, the values of enthalpy $\Delta_{\mathrm{sln}} H_{\mathrm{m}}^{\mathrm{o}}$ were obtained from the slope of the plot of lnx_1 versus 1/T, and the values of entropy $\Delta_{\mathrm{sln}} S_{\mathrm{m}}^{\mathrm{o}}$ were calculated from the intersection of the regression of lnx_1 versus 1/T as shown in Fig. 5. The uncertainty of the $\Delta_{\mathrm{sln}} H_{\mathrm{m}}^{\mathrm{o}}$ and $\Delta_{\mathrm{sln}} S_{\mathrm{m}}^{\mathrm{o}}$ also were calculated and listed in Table 6. The uncertainties of $\Delta_{\mathrm{sln}} H_{\mathrm{m}}^{\mathrm{o}}$ amount to 1.4% (in dichloromethane) to 8.4% (in chloroform) of its values, which were acceptable. But the uncertainties of $\Delta_{\mathrm{sln}} S_{\mathrm{m}}^{\mathrm{o}}$ were from 9.5% (in dichloromethane) to 54.7% (in Ethyl acetate) except in the Acetone, which has a much higher uncertainty for $\Delta_{\mathrm{sln}} S_{\mathrm{m}}^{\mathrm{o}}$. The

Gibbs free energy solution can be obtained from the following equation (Eq. 7) [23]:

$$\Delta_{\mathrm{sln}}G_{\mathrm{m}}^{\mathrm{o}} = \Delta_{\mathrm{sln}}H_{\mathrm{m}}^{\mathrm{o}} - T_{\mathrm{hm}}\Delta_{\mathrm{sln}}S_{\mathrm{m}}^{0} \quad (7)$$

Where T_{hm} is the harmonic mean of the experimental temperature, which can be calculated by $T_{\mathrm{hm}} = n/\sum_{i=1}^{n}(1/T_i)$, n is the number of experiment. The use of harmonic mean of the temperature was because there are different temperatures when we measured the solubility and the average temperature is needed when the Gibbs free energy was calculated. The T_{hm} values, molar dissolution enthalpy, molar dissolution entropy and the change of Gibbs free energy are shown in Table 6.

In order to compare the relative contributions by enthalpy $\Delta_{\mathrm{sln}}H_{\mathrm{m}}^{\mathrm{o}}$ to that by entropy $\Delta_{\mathrm{sln}}S_{\mathrm{m}}^{\mathrm{o}}$ toward the solution process, Eq. (8) and (9) were used, respectively [20].

$$\%\zeta_H = 100 \times \frac{\left|\Delta_{\mathrm{sln}}H_{\mathrm{m}}^{\mathrm{o}}\right|}{\left|\Delta_{\mathrm{sln}}H_{\mathrm{m}}^{\mathrm{o}}\right| + \left|T_{\mathrm{hm}}\Delta S_{\mathrm{m}}^{\mathrm{o}}\right|} \quad (8)$$

$$\%\zeta_{TS} = 100 \times \frac{\left|T_{\mathrm{hm}}\Delta_{\mathrm{sln}}S_{\mathrm{m}}^{\mathrm{o}}\right|}{\left|\Delta_{\mathrm{sln}}H_{\mathrm{m}}^{\mathrm{o}}\right| + \left|T_{\mathrm{hm}}\Delta S_{\mathrm{m}}^{\mathrm{o}}\right|} \quad (9)$$

Where $\%\zeta_H$ and $\%\zeta_{TS}$ are the relative contributions to the Gibbs free energy by enthalpy and entropy during the solution process, respectively. The values of $\%\zeta_H$ and $\%\zeta_{TS}$ were given in Table 6. From Table 6, it can be established that 1) the enthalpies of solution $\Delta_{\mathrm{sln}}H_{\mathrm{m}}^{\mathrm{o}}$ are positive in all solvents, indicating that the dissolution process is always endothermic in these solvents. The entropies of solution $\Delta_{\mathrm{sln}}S_{\mathrm{m}}^{\mathrm{o}}$ are negative in chloroform and dichloromethane. However, in other solvent the entropies of solution $\Delta_{\mathrm{sln}}S_{\mathrm{m}}^{\mathrm{o}}$ are positive. The positive entropy variation shows that the entropy of solubilization is unfavorable for solute in solution [24], whereas

the negative entropy is owing to more ordered structure in solutions [25]. The order depends on the solvent as well as on the functional groups present in the solute. The negative entropy change in chloroform and dichloromethane (the chlorine atoms make the carbon atom easier to attract electrons) may be attributed to the interactions such as H-bonds between solute and solvent molecules which may display more ordered structure in solution, that is, the solute-solvent interaction is stronger than the solvent-solvent interaction in these two solvents. Another reason may be that the molecular structures of chloroform and dichloromethane are hard to be disrupted [26]. 2) the molar Gibbs free energy of dissolution are positive in all cases, which indicates that the dissolution process of telmisartan in all these organic solvents is not spontaneous; 3) all the values of $\%\zeta_H$ are higher than 69.69%, which indicates that the change of the enthalpy contributes more to the Gibbs free energy of dissolution of telmisartan in the these nine organic solvents than the change of the entropy.

3.5 Effect of Solvates or Polymorphism on the Telmisartan Solubility Data.

One possible source of systematic error in this kind of experiment is the transformation of the solid to a solvate or another polymorph during the experiment. During the solubility measurement, the temperature was always below 65 ^{o}C, the telmisartan form A was stable. The solubility data can be fitted well by the both the λh equation and modified Apelblat equation without any inflection points. It is reported that polymorph of telmisartan was always the form A by cooling crystallization in some systems [4]. In this study solid telmisartan form A, kept in saturated solution with these solvents for several hours, consisted still of long, needle-like crystals,

which as determined by XRD maintained form A. Therefore, the consistent increase of the solubility value and the determination of solid in slurry by power XRD both demonstrate that no solvates or the other polymorph appeared during the measurements.

4. Conclusion

In this work, the solubility of telmisartan (form A) in chloroform, dichloromethane, ethanol, toluene, benzene, 2-propanol, ethyl acetate, methanol and acetone were determined by laser monitoring techniques. There is no polymorphic transformation during the measurement from 277.85 to 338.35 K in these nine organic solvents. The solubility of telmisartan in chloroform and dichloromethane is much higher than that in the other seven solvents at the temperature ranging from 277.85 to 338.35 K. The solubility in these nine organic solvents increased with the increase of temperature, but the temperature increments were different for different solvents. Based on the values of the relative root mean square deviation σ and the uncertainties of the parameters, the solubility of telmisartan in the solvents can be fitted much better with λh equation than with the modified Apelblat equation. It also indicates that the correlated equation in this work could provide essential data for purifying and manufacturing processes of telmisartan in industry.

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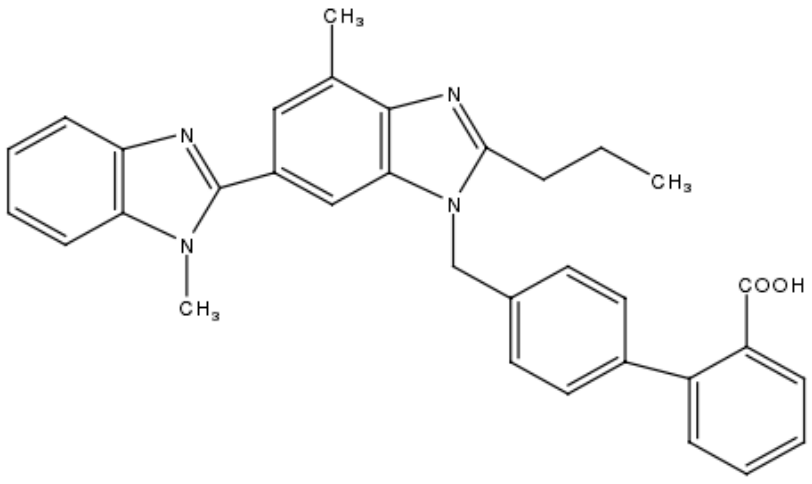


Figure 1. Molecular structure of telmisartan

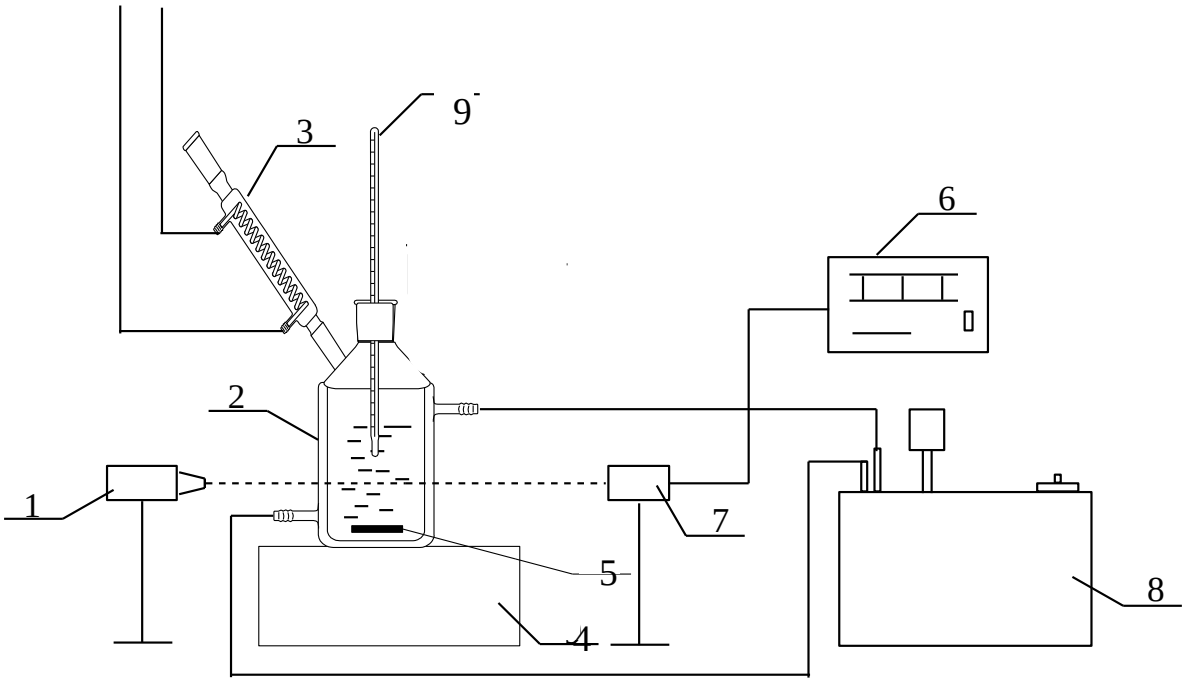
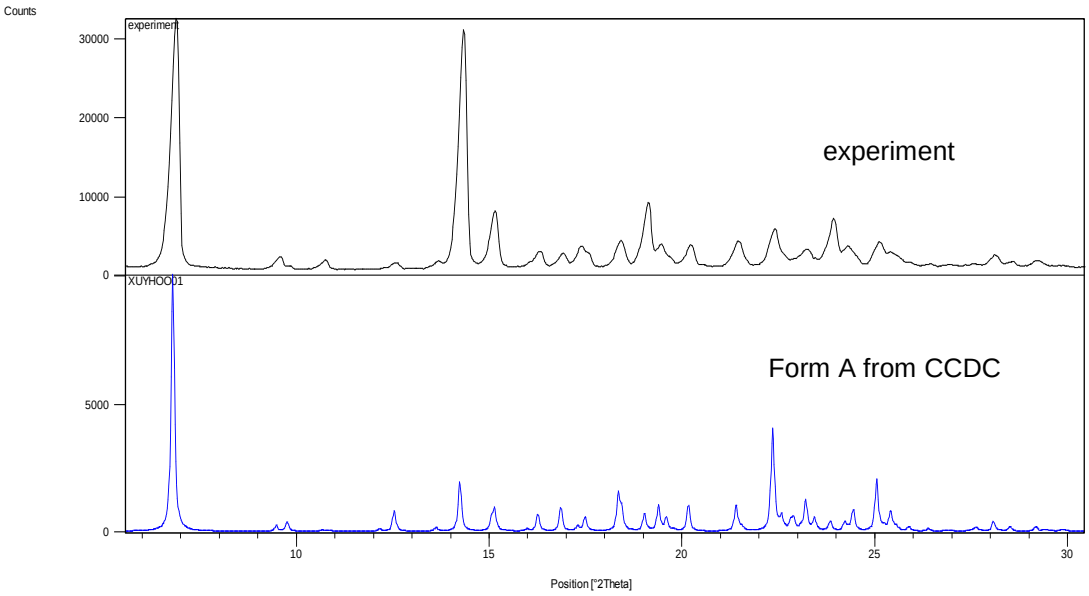


Figure 2. Sketch of the apparatus for measurement of the solubility

1-laser generator；2-dissolver；3-condenser；4-magnetic stirrer；5- magnetic stir bar；6-light intensity recorder；7-photoelectric transformer；8-thermostatic water bath；9-thermometer


Counts
experiment
30000
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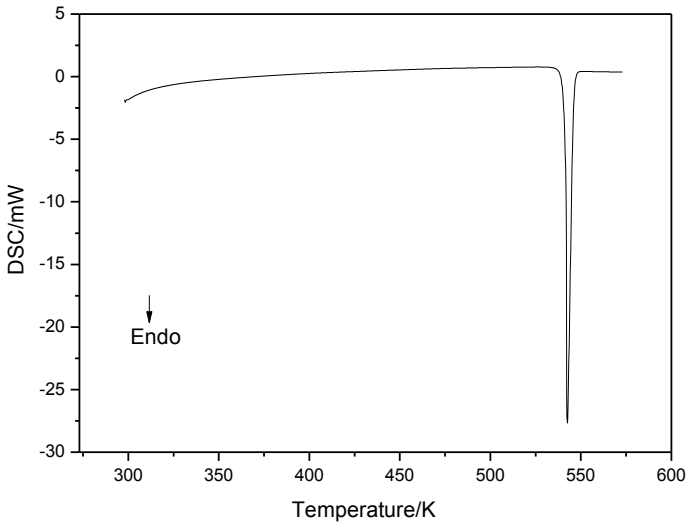
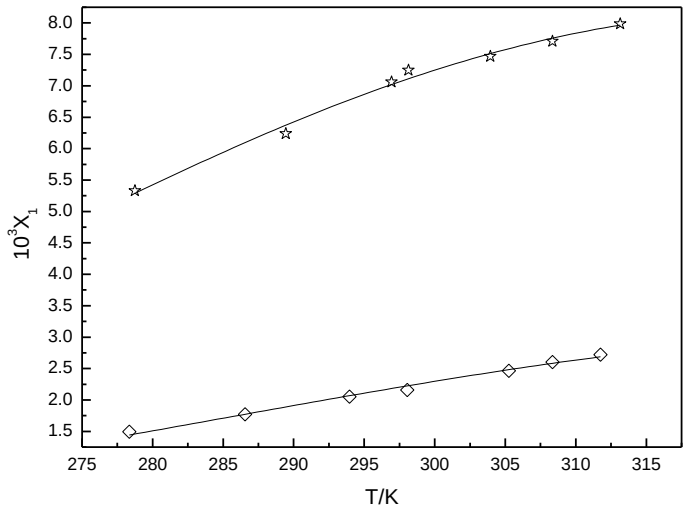
Position [°2Theta]

(a)

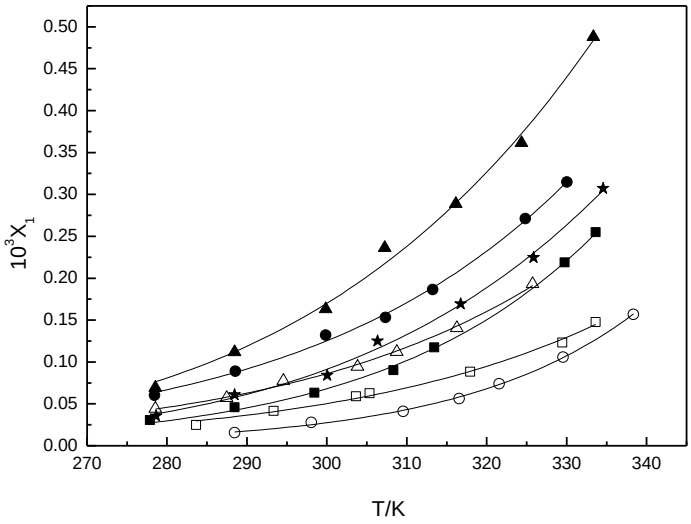

5
0
-5
-10
-15
-20
-25
-30
DSC/mW
Endo
300
350
400
450
500
550
600
Temperature/K

(b)

Figure 3. Powder XRD (a) and DSC (b) curve of telmisartan (form A)



(a)



(b)

Figure 4. Mole fraction solubility of telmisartan, x_1, in different solvents:

(a)☆,chloroform ;◇,dichloromethane ; (b)▲,benzene; ●,methanol ; ★, toluene; △,

acetone; ■, ethanol;□, ethyl acetate ; ○,2-propanol. Curves are data fits using Eq 2 and the parameters in Table 3.

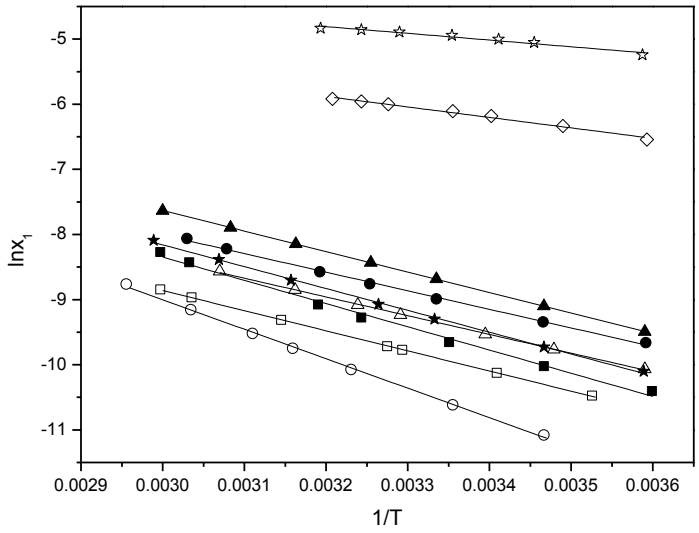


Figure 5. The Van't Hoff plots of ln $x_1$verse 1/T for telmisartan form A in different solvents ☆,chloroform ;◇,dichloromethane ; ▲,benzene; ●,methanol ; ★, toluene; △, acetone; ■, ethanol;□, ethyl acetate ; ○,2-propanol

Table 1 The Source and Mass Fraction Purity of Chemicals[a]

Materials	Source	Initial Purity (mass fraction)
Chloroform	Haohua Chemical Reagents Co. China	99.5%
Dichloromethane	Haohua Chemical Reagents Co.China	99.5%
Benzene	Tianjin Kewei Chemical Reagent Co., China	99.5%
Methanol	Haohua Chemical Reagents Co. China	99.5%
Toluene	Tianjin Kewei Chemical Reagent Co., China	99.5%
Acetone	Haohua Chemical Reagents Co.China	99.5%
Ethanol	Tianjin Kewei Chemical Reagent Co., China	99.7%
Ethyl acetate	Tianjin Kewei Chemical Reagent Co., China	99.5%
2-Propanol	Tianjin Kewei Chemical Reagent Co., China	99.7%
Telmisartan[b]	Zhengzhou Chuangyao Technology Co. China	99.0%

a: All of the solvents were used without further purification.

b: Telmisartan, purified by recrystallization and the purity was 99.3% (determined by HPLC)

Table 2 Mole Fraction Solubilities of Telmisartan (form A), x_1, in Chloroform , Dichloromethane, Benzene, Methanol, Toluene, Acetone, Ethanol, Ethyl acetate, and 2-Propanol.[a](Experimental pressure is 101.3 KPa)

T/K	10^3 x_1^{exptl}	$10^5(x_1^{exptl} - x_1^{calcd})$	*T*/K	$10^3 x_1^{exptl}$	$10^5(x_1^{exptl} - x_1^{calcd})$
		Chloroform			
278.75	5.33	4	303.95	7.47	-4
289.45	6.24	-14	308.35	7.71	-5
296.95	7.01	4	313.15	7.99	2
298.15	7.25	13			
		Dichloromethane			
278.35	1.50	5	305.25	2.46	-2
286.55	1.77	0	308.35	2.61	2
293.95	2.05	-2	311.75	2.72	3
298.05	2.16	-7			
		Benzene			
278.55	0.0695	-0.59	316.15	0.289	-0.2
288.45	0.111	0	324.35	0.361	-1.2
299.85	0.163	-0.6	333.35	0.488	0.5
307.25	0.236	1.8			
		Methanol			
278.45	0.0603	-0.34	313.25	0.186	-0.2
288.55	0.0890	0.15	324.85	0.271	0.2
299.85	0.132	0.7	330.05	0.315	0
307.35	0.153	-0.4			
		Toluene			
278.65	0.0355	-0.56	316.75	0.169	0.3
288.45	0.0608	0.12	325.85	0.225	-0.4
300.05	0.0840	-0.75	334.55	0.307	0

306.35	0.125	1.0				
			Acetone			
278.55	0.0442	0.16		308.75	0.112	-0.2
287.45	0.0571	-0.04		316.25	0.141	-0.3
294.55	0.0776	0.50		325.75	0.193	0.3
303.85	0.0945	-0.33				
			Ethanol			
277.85	0.0306	0.03		313.45	0.117	0.3
288.45	0.0457	0.14		329.75	0.219	0.1
298.45	0.0633	-0.09		333.65	0.255	-0.1
308.35	0.0900	-0.37				
			Ethyl acetate			
283.65	0.0247	-0.35		317.95	0.0883	-0.19
293.35	0.0417	0.16		329.45	0.123	-0.40
303.65	0.0590	0.20		333.65	0.148	0.3
305.35	0.0626	0.23				
			2-Propanol			
288.45	0.0155	0		321.55	0.0741	0.06
298.05	0.0277	0.32		329.55	0.106	0
309.55	0.0410	-0.11		338.35	0.157	0
316.55	0.0562	-0.22				

a:the temperature accuracy is 0.1 K, analytical balance accuracy is 0.0001 mg

Table 3 Solvent Coefficients in Equation 2 for Different Solvents

Solvent	e_0	s_0	a_0	b_0	v_0
chloroform	0.089	-0.358	-3.051	-3.538	4.493
dichloromethane	0.076	-0.112	-2.957	-4.13	4.488
benzene	0.452	-0.554	-2.964	-4.643	4.564
methanol	0.312	-0.649	0.33	-3.355	3.691
toluene	0.412	-0.615	-2.962	-4.764	4.589
acetone	0.287	-0.047	-0.509	-4.792	4.103
ethanol	0.453	-0.983	0.396	-3.623	3.971
ethyl acetate	0.195	-0.068	-0.924	-4.571	4.152
2-propanol	0.355	-1.026	0.438	-3.839	4.048

Table 4 Parameters of Apelblat Equation, Eq. 3, for Telmisartan (Form A) in Different Solvents

Solvent	A^a	δ_A[1]	B	δ_B[2]	C	δ_C[3]	$10^2\sigma^b$
Chloroform	223.48	0.293	-10665.53	0.251	-32.60	0.279	1.19
Dichloromethane	222.23	1.11	-11129.61	0.478	-32.31	0.928	1.89
Benzene	17.92	0.667	-3565.35	0.447	-1.37	0.756	4.75
Methanol	-101.30	1.78	2054.61	2.82	16.19	1.58	3.26
Toluene	-88.12	1.87	1042.74	0.898	14.42	2.61	7.61
Acetone	-57.93	0.689	41.26	1.47	9.70	0.69	3.30
Ethanol	-208.88	0.185	6329.04	0.257	32.45	0.174	2.26
Ethyl acetate	-19.38	0.593	-1866.93	0.429	3.97	0.611	6.18
2-Propanol	-128.81	0.894	1960.85	1.76	20.80	0.74	4.78

a *A*, *B* and *C* are parameters of Eq. 3

b Calculated by Eq. 4

1 random error (uncertainty) of A, δ_A=standard error/ $|A|$

2 random error (uncertainty) of B, δ_B=standard error/$|B|$

3 random error(uncertainty) of C, δ_C=standard error/ $|C|$

Table 5 Parameters of λh Equation, Eq. 5, for Telmisartan (Form A) in Different Solvents

Solvent	λ[a]	δ_{λ}^{*}	h	$\delta_{h}^{\#}$	10^3σ[b]
Chloroform	0.00874	29.3 %	61187	12.0 %	0.71
Dichloromethane	0.01468	6.2 %	92300	3.7 %	1.70
Benzene	0.01663	18.3 %	185505	15.1 %	1.38
Methanol	0.00965	11.3 %	302690	8.93 %	0.04
Toluene	0.01569	28.6 %	220573	23.9 %	1.45
Acetone	0.00633	15.7 %	456333	12.1 %	0.09
Ethanol	0.02184	19.1 %	177642	15.5 %	4.53
Ethyl acetate	0.00474	30.8 %	644998	25.3 %	0.52
2-Propanol	0.03052	28.4 %	155832	24.2 %	3.19

a λ and h are parameters of Eq. 5

b Calculated by Eq. 4

∗ random error(uncertainty) of λ, δ_{λ}=standard error/ $|\lambda|$

random error(uncertainty) of h, δ_{h}=standard error/$|h|$

Table 6 Apparent Thermodynamic Functions Relative to Solution Process of Telmisartan (Form A) in Nine Solvents

Solvent	T_{hm}^{*} (K)	$\Delta_{sln}H_{m}^{o}$☆ (kJ·mol^{-1})	δ_1[a] (%)	$\Delta_{sln}S_{m}^{o}$△ (J·mol^{-1}·K^{-1})	δ_2[b](%)	$\Delta_{sln}G_{m}^{o}$★(kJ·mol)	$\%\zeta_H$☆	$\%\zeta_{TS}$#
Chloroform	298.00	8.6	8.4	-12.5	19.8	12.31	69.69	30.31
Dichloromethane	297.04	13.4	1.6	-6.2	9.5	15.19	87.95	12.05
Benzene	305.78	26.2	3.1	15.1	15.6	21.57	85.02	14.98

Methanol	305.06	23.7	2.4	4.6	33.5	22.32	94.41	5.59
Toluene	306.10	27.9	3.4	15.8	15.8	23.04	85.20	14.80
Acetone	301.38	23.9	3.4	2.0		23.30	97.48	2.52
Ethanol	305.94	29.67	4.0	19.5	20.4	23.67	83.22	16.78
Ethyl acetate	308.64	25.7	4.0	3.4	54.7	24.64	96.10	3.90
2-Propanol	313.75	37.6	3.4	38.0	11.2	25.70	75.94	24.06

$^{*}T_{hm}$ The harmonic mean of the experimental temperatures

$^{☆}\Delta_{sIn}H_m^o$ The dissolution enthalpy of telmisartan (form A)

$^{△}\Delta_{sIn}S_m^o$ The dissolution entropy of telmisartan (form A)

$^{★}\Delta_{sIn}G_m^o$ The Gibbs free energy of the telmisartan (form A)

$^{☆}\%\zeta_H$ The relative contributions by enthalpy toward the solution process

$^{\#}\%\zeta_{TS}$ The relative contributions by entropy toward the solution process

a random error(uncertainty) of $\Delta_{sIn}H_m^o$ δ_1=standard error/ $|\Delta_{sIn}H_m^o|$

b random error(uncertainty) of $\Delta_{sIn}S_m^o$, δ_2=standard error/ $|\Delta_{sIn}S_m^o|$