

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

3 Wenju Liu^{a*}, Yajun Guo^a, Jiaying Chen^a, Xi Yu^b

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

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

8 **Abstract**

9 The solubility of telmisartan (form A) in nine organic solvents (chloroform,
10 dichloromethane, ethanol, toluene, benzene, 2-propanol, ethyl acetate, methanol and
11 acetone) was determined by laser monitoring technique at different temperatures
12 (from 277.85 to 338.35 K). The solubility of telmisartan (form A) in all the nine
13 solvents increased with temperature and the rates of solubility also increased with
14 temperature except in chloroform and dichloromethane solvent. The molar fraction
15 solubility in chloroform was higher than that in dichloromethane, which were both
16 one order of magnitude higher than that in other seven solvents at the range of
17 experimental temperatures. The solubility data were correlated with the modified
18 Apelblat equation and λh equation, respectively. The results showed that the λh
19 equation was in better agreement with the experimental data than the Apelblat
20 equation. The relative root mean square deviations (σ) of the λh equation were in the
21 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

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

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

8 **1. Introduction**

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

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

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

10 In this work, the solubility of telmisartan (form A) in nine organic solvents including
11 chloroform, dichloromethane, ethanol, toluene, benzene, 2-propanol, ethyl acetate,
12 methanol and acetone was determined with the temperature ranging from 277.85 to
13 338.35 K at atmospheric pressure by a synthetic method of a laser monitoring
14 observation technique. The solubility data of telmisartan in these organic solvents is
15 correlated by the modified Apelblat equation and the λh equation. The
16 thermodynamic properties (e.g. enthalpy, entropy and Gibbs free energy) of
17 dissolution process of telmisartan in these solvents were calculated using regression
18 equations, i.e. Van't Hoff equation and Gibbs equation.

19 **2. Experimental Section**

20 **2.1 Chemicals Used**

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

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

10 **2.2 Apparatus and Procedure.**

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

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

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

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

20

$$21 \quad x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

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

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

14 **3. Results and Discussions**

15 **3.1 The XRD and DSC of telmisartan**

16 Fig. 3a (top) is the X-ray powder diffraction (XRD) data of telmisartan, the pattern is
17 identical with the XRD pattern of telmisartan form A (Fig. 3a, bottom, CCDC
18 reference XUYH0001). Fig. 3b shows the DSC of telmisartan form A. The average
19 melting point and melting enthalpy with uncertainty is $542.42 \pm 0.20 \text{ K}$ and
20 $-105.34 \pm 8.54 \text{ J}\cdot\text{g}^{-1}$, respectively, as shown in Fig. 3b. The melting point result is
21 consistent with the literature reported value $542 \text{ }^\circ\text{C}$ by J.Park [8].

22 **3.2 Solubility**

1 The variation of solubility of telmisartan (form A) in different solvents with
2 temperature is presented in Table 2 and Fig. 4, showing that the solubility of
3 telmisartan (form A) increased with the increasing temperature in all the organic
4 solvents. The solubility values in chloroform and dichloromethane were much higher
5 than those in the other seven solvents. This phenomenon may result from the
6 solute-solvent interaction, which plays an important role in the dissolution process of
7 telmisartan in chloroform and dichloromethane. During the dissolution process, three
8 factors, namely the solute-solute, solute-solvent and solvent-solvent interaction, can
9 affect the solubility. The solubility is generally higher when the solute-solvent
10 interaction plays a main role. The mole fraction solubility of telmisartan (form A)
11 decreased in the following order: chloroform > dichloromethane > benzene >
12 methanol > toluene > acetone > ethanol > ethyl acetate > 2-propanol. For alcoholic
13 solvents, the solubility increased with the increase of the solvent polarity. The
14 dielectric constants of methanol, ethanol and 2-propanol were 33.6, 24.3 and 19.92 at
15 25 °C, respectively. The solubility in chloroform was much higher than that in
16 dichloromethane and the solubility in benzene is higher than that in toluene. The
17 polarity of chloroform and benzene, respectively, is higher than that of
18 dichloromethane and toluene, respectively. For the similar solvents such as alcoholic
19 solvents, the polarity directly correlated with the solubility.

20 In order to quantify the importance of the different interactions to the changes in
21 solubility. We use the linear free energy relationship [16] (Equation(2), based on
22 Abraham model, the subscript-zero indicates that $c = 0$ in \log
23 $P=c+eE+sS+aA+bB+vV$),

1 $\log P = e_0E + s_0S + a_0A + b_0B + v_0V$ (2)

2 where $\log P$ is the solvent/water partition, (e, s, a, b, v) are the solvent coefficients, and
3 (E, S, A, B, V) are the solute descriptors: E is the solute excess molar refractivity, S is
4 the solute dipolarity/polarizability, A and B are the overall or summation hydrogen
5 bond acidity and basicity, and V is the McGowan characteristic volume. The solvent
6 coefficients were from reference 16 and were list in table 3. The solute descriptors
7 were obtained through fit the data at about 298K ($R^2=0.9799$) and the $E=0.71, S=1.35,$
8 $A=-0.16, B=1.33, V=1.27$, respectively. It seems that the hydrogen bond basicity play
9 an important role in the interaction. Also, according to the structure of the solute, there
10 has 5 sites that can act as hydrogen bond acceptors (4 Ns and the COO of the acid
11 group) and one hydrogen bond donating site. When the polarity of the solvents (for
12 similar solvents) is higher, it is much easier to form the strong solute-solvent
13 interaction. Therefore, the solubility will increase. The highest solubility in
14 chloroform maybe attribute to the strong hydrogen bond between telmisartan and
15 chloroform. The electron density around chloroform is higher and also the steric
16 hindrance of the chloroform is smaller, so it is easier to form hydrogen bond than
17 other solvent. The solubility in benzene is higher maybe attribute to the aromatic ring
18 in the structure of temisartan, consistent with the rule of like dissolves like. For the
19 solubility in toluene is lower than in benzene maybe because the steric hindrance of
20 the benzene.

21 **3.3 Correlation of Measured Solubility**

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

25 $\ln x_1 = A + B/T + C \ln(T)$ (3)

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

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

$$7 \quad \sigma = \left[\frac{1}{N} \sum_{i=1}^N \left(\frac{x_{1,i}^{\text{exptl}} - x_{1,i}^{\text{calcd}}}{x_{1,i}^{\text{exptl}}} \right)^2 \right]^{1/2} \quad (4)$$

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

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

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

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

8

$$9 \quad x_1 = \frac{1}{\frac{1}{\lambda} \left\{ \exp \left[\lambda h \left(\frac{1}{T} - \frac{1}{T_m} \right) \right] - 1 \right\} + 1} \quad (5)$$

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

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

3 **3.4 Thermodynamic Functions of Solution**

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

$$7 \quad \ln x_1 = -\frac{\Delta_{\text{sln}} H_m^\circ}{RT} + \frac{\Delta_{\text{sln}} S_m^\circ}{R} \quad (6)$$

8 Equation (6) is Van't Hoff's equation integrated assuming $\Delta_{\text{sln}} H_m^\circ$ is constant within
9 the temperature range investigated, this equivalent to assuming $\Delta_{\text{sln}} C_{p,m}^\circ = 0$. Where x_1
10 is the mole fraction solubility, R is the universal gas constant, T is the absolute
11 temperature, and $\Delta_{\text{sln}} H_m^\circ$ and $\Delta_{\text{sln}} S_m^\circ$ are not the true enthalpy and entropy of
12 solution but are apparent values because activity coefficients are assumed to be unity.
13 Equation (6) shows that the natural logarithm of mole fraction of the solute is a linear
14 function of the reciprocal of the absolute temperature. Thus, the values of enthalpy
15 $\Delta_{\text{sln}} H_m^\circ$ were obtained from the slope of the plot of $\ln x_1$ versus $1/T$, and the values of
16 entropy $\Delta_{\text{sln}} S_m^\circ$ were calculated from the intersection of the regression of $\ln x_1$ versus
17 $1/T$ as shown in Fig. 5. The uncertainty of the $\Delta_{\text{sln}} H_m^\circ$ and $\Delta_{\text{sln}} S_m^\circ$ also were calculated
18 and listed in Table 6. The uncertainties of $\Delta_{\text{sln}} H_m^\circ$ amount to 1.4% (in
19 dichloromethane) to 8.4% (in chloroform) of its values, which were acceptable. But
20 the uncertainties of $\Delta_{\text{sln}} S_m^\circ$ were from 9.5% (in dichloromethane) to 54.7% (in Ethyl
21 acetate) except in the Acetone, which has a much higher uncertainty for $\Delta_{\text{sln}} S_m^\circ$. The

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

$$2 \quad \Delta_{\text{sln}} G_m^{\circ} = \Delta_{\text{sln}} H_m^{\circ} - T_{\text{hm}} \Delta_{\text{sln}} S_m^{\circ} \quad (7)$$

3 Where T_{hm} is the harmonic mean of the experimental temperature, which can be

4 calculated by $T_{\text{hm}} = n / \sum_{i=1}^n (1/T_i)$, n is the number of experiment. The use of harmonic

5 mean of the temperature was because there are different temperatures when we

6 measured the solubility and the average temperature is needed when the Gibbs free

7 energy was calculated. The T_{hm} values, molar dissolution enthalpy, molar dissolution

8 entropy and the change of Gibbs free energy are shown in Table 6.

9 In order to compare the relative contributions by enthalpy $\Delta_{\text{sln}} H_m^{\circ}$ to that by entropy

10 $\Delta_{\text{sln}} S_m^{\circ}$ toward the solution process, Eq. (8) and (9) were used, respectively [20].

$$11 \quad \% \zeta_H = 100 \times \frac{|\Delta_{\text{sln}} H_m^{\circ}|}{|\Delta_{\text{sln}} H_m^{\circ}| + |T_{\text{hm}} \Delta_{\text{sln}} S_m^{\circ}|} \quad (8)$$

$$12 \quad \% \zeta_{TS} = 100 \times \frac{|T_{\text{hm}} \Delta_{\text{sln}} S_m^{\circ}|}{|\Delta_{\text{sln}} H_m^{\circ}| + |T_{\text{hm}} \Delta_{\text{sln}} S_m^{\circ}|} \quad (9)$$

13 Where $\% \zeta_H$ and $\% \zeta_{TS}$ are the relative contributions to the Gibbs free energy by

14 enthalpy and entropy during the solution process, respectively. The values of

15 $\% \zeta_H$ and $\% \zeta_{TS}$ were given in Table 6. From Table 6, it can be established that 1) the

16 enthalpies of solution $\Delta_{\text{sln}} H_m^{\circ}$ are positive in all solvents, indicating that the

17 dissolution process is always endothermic in these solvents. The entropies of solution

18 $\Delta_{\text{sln}} S_m^{\circ}$ are negative in chloroform and dichloromethane. However, in other solvent

19 the entropies of solution $\Delta_{\text{sln}} S_m^{\circ}$ are positive. The positive entropy variation shows

20 that the entropy of solubilization is unfavorable for solute in solution [24], whereas

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

14 **3.5 Effect of Solvates or Polymorphism on the Telmisartan Solubility Data.**

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

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

5 **4. Conclusion**

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

19 **Acknowledgment**

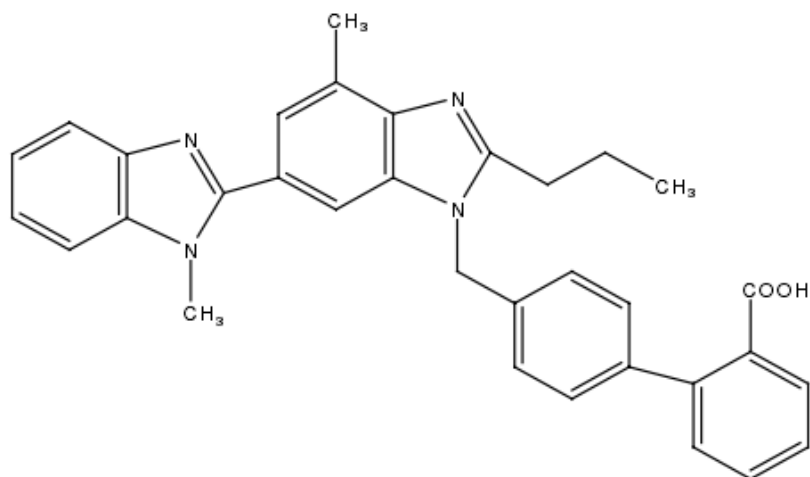
20 The authors would like to thank the National Nature and Science Foundation of China
21 (NSFC, No.21206032), the Science Foundation Henan University of technology (No.
22 2012CXRC08) and the Science Foundation of Henan Province (No.13A530196) for

1 their financial assistance for this project. Thanks for David Kearns for the language
2 revision.

3 **References**

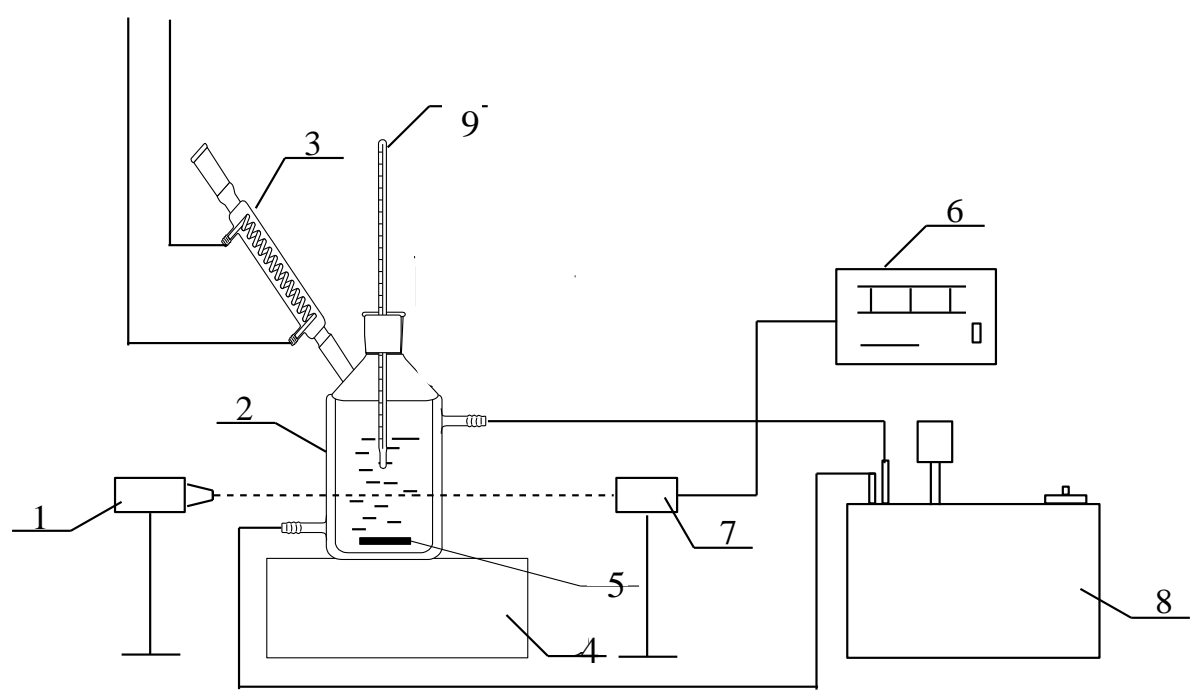
- 4 1. Patel, P.A., Patravale, V.B.: Commercial Telmisartan Tablets: A comparative evaluation with
5 innovator brand micardis. *Int. J. Pharma Sci. Res.* **1**, 282-292 (2010)
- 6 2. Laragh J.: The renin system and the renal regulation of blood pressure. In Seldin DW,
7 Giebisch G,editors. *The kidney: Physiology and Pathophiyology*, 2nd ed. 1411–1453. New
8 York: Raven Press, (1992)
- 9 3. Lepek, P., Sawicki, W., Wlodarski, K., Wojnarowska, Z., Paluch, M., Guzik, L.: Effect of
10 amorphization method on telmisartan solubility and the tableting process. *Eur. J. Biochem.* **83**,
11 114-121 (2013)
- 12 4. Dinnebier, R.E., Sieger, P., Nar, H., Shankland, K., David, W.I.: Structural characterization of
13 three crystalline modifications of telmisartan by single crystal and high-resolution X-ray
14 powder diffraction. *J. Pharm. Sci.* **89**, 1465-1479 (2000)
- 15 5. Adin, I., Iustain, C., Brand, M., Salman, A., Weisman, A.: Processes of preparing highly pure
16 telmisartan form A, suitable for pharmaceutical compositions. US Patent 20060276525,
17 (2006)
- 18 6. Donsbach, K., Hof, I.: Crystalline form of telmisartan sodium. US Patent 6737432, (2004)
- 19 7. Chen, Y., Study on quality control and stability test for telmisartan. Master's thesis, Zhejiang
20 University, (2005)
- 21 8. Park, J., Cho, W., Cha, K., Ahn, J., Han, K., Hwang, S.: Solubilization of the poorly water
22 soluble drug, telmisartan, using supercritical anti-solvent (SAS) process. *Int. J. Pharm.* **441**,
23 50-55 (2013)
- 24 9. Nývlt, J.: Solid-liquid phase equilibria. Academia Pub. House of the Czechoslovak Academy
25 of Sciences. (1977)
- 26 10. Jiang, Q., Gao, G., Yu, Y., Qin, Y.: Solubility of sodium dimethyl isophthalate-5-sulfonate in
27 water and in water + methanol containing sodium sulfate. *J. Chem. Eng. Data* **45**, 292-294
28 (2000)
- 29 11. Liu, B., Sun, H., Wang, J., Yin, Q.: Thermodynamic analysis and correlation of solubility of
30 disodium 5'-guanylate heptahydrate in aqueous ethanol mixtures. *Fluid Phase Equilib.* **370**,
31 58-64 (2014)
- 32 12. Hong, M., Xu, L., Ren, G., Chen, J., Qi, M.: Solubility of Lansoprazole in different solvents.
33 *Fluid Phase Equilib.* **331**, 18-25 (2012)
- 34 13. Wei, Y., Zhang, X., Zhang, J., Dang, L., Wei, H.: Solid–liquid equilibrium of some polycyclic
35 aromatic hydrocarbons in wash oil. *Fluid Phase Equilib.* **319**, 23-29 (2012)
- 36 14. Liu, W., Dang, L., Black, S., Wei, H.: Solubility of carbamazepine (Form III) in different
37 solvents from (275 to 343) K. *J. Chem. Eng. Data* **53**, 2204-2206 (2008)
- 38 15. Zhang, C., Wang, J., Wang, Y.: Solubility of ceftriaxone disodium in acetone, methanol,
39 ethanol, n, n-dimethylformamide, and formamide between 278 and 318 K. *J. Chem. Eng.*
40 *Data* **50**, 1757-1760 (2005)
- 41 16. Bradley, J., Abraham, M.H., Acree, W.E., Lang, A.: Predicting Abraham model solvent
15

- 1 coefficients. Chem. Cent. J. **9**, 1-10 (2015)
- 2 17. Apelblat, A., Manzurola, E.: Solubility of oxalic, malonic, succinic, adipic, maleic, malic,
3 citric, and tartaric acids in water from 278.15 to 338.15 K. J. Chem. Thermodyn. **19**, 317-320
4 (1987)
- 5 18. Buchowski, H., Ksiazczak, A., Pietrzyk, S.: Solvent activity along a saturation line and
6 solubility of hydrogen-bonding solids. J. Phys. Chem. **84**, 975-979 (1980)
- 7 19. Mo, Y., Dang, L., Wei, H.: Solubility of α -form and β -form of l-glutamic acid in different
8 aqueous solvent mixtures. Fluid Phase Equilib. **300**, 105-109 (2011)
- 9 20. Kai, W., Hu, Y., Yang, W., Song, G., Ying, S.: Measurement and correlation of the solubility
10 of 2,3,4,5-tetrabromothiophene in different solvents. J. Chem. Thermodyn. **55**, 50-55 (2012)
- 11 21. Hefter, G.T., Tomkins, R.P.T.: Chapter 1.1. Thermodynamics of Solubility. John Wiley &
12 Sons, Ltd. (2004)
- 13 22. Ness, H.C.V.: Chemical Thermodynamics, Vol. 2: by M.L. McGlashan (Senior Reporter), The
14 Chemical Society, London, 1978. Fluid Phase Equilib. **2**, 312 (1979)
- 15 23. Rodríguez, G.A., Delgado, D.R., Martínez, F., Jouyban, A., Acree, W.E.: Solubility of
16 naproxen in ethyl acetate+ethanol mixtures at several temperatures and correlation with the
17 Jouyban–Acree model. Fluid Phase Equilib. **320**, 49-55 (2012)
- 18 24. Panteli, E.K., Voutsas, E.K.: Solubilities of cinnamic acid esters in ionic liquids. J. Chem.
19 Eng. Data **54**, 812-818 (2009)
- 20 25. El-Bindary, A.A., El-Sonbati, A.Z., Ahmed, E.M.A.M., El-Bindary, A.A., El-Sonbati, A.Z.:
21 Potentiometric and thermodynamic studies of azosulfonamide drugs. X. Chem. Pap. **57**,
22 255-258 (2003)
- 23 26. Kapil B, Shipra B, Measurement and correlation for solubility of some pyrimidine derivatives
24 in different solvents. J. Appl. Chem. **2014**, 1-7(2014)



27
28 **Figure 1.** Molecular structure of telmisartan
29
30

1
2
3
4
5
6
7
8
9
10
11
12



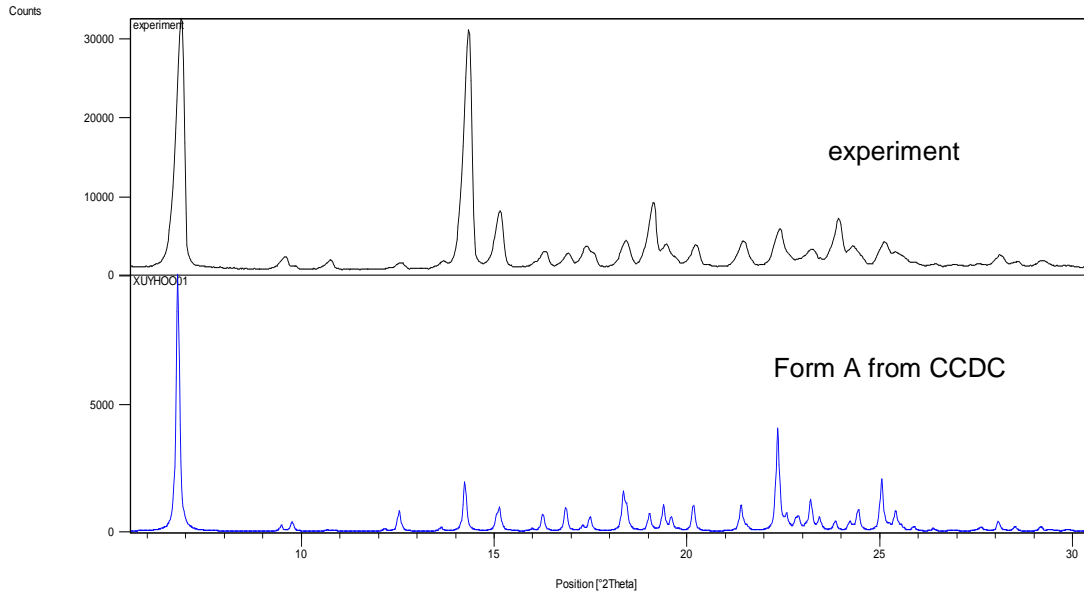
13
14
15
16
17
18
19

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

1

2

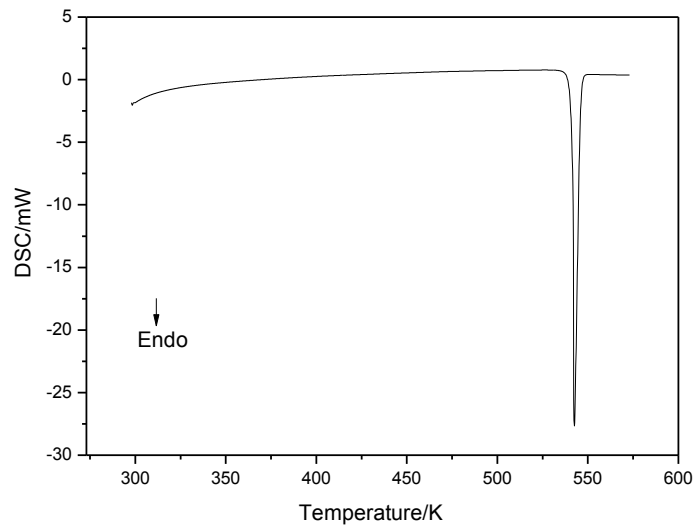


3

4

5

(a)



6

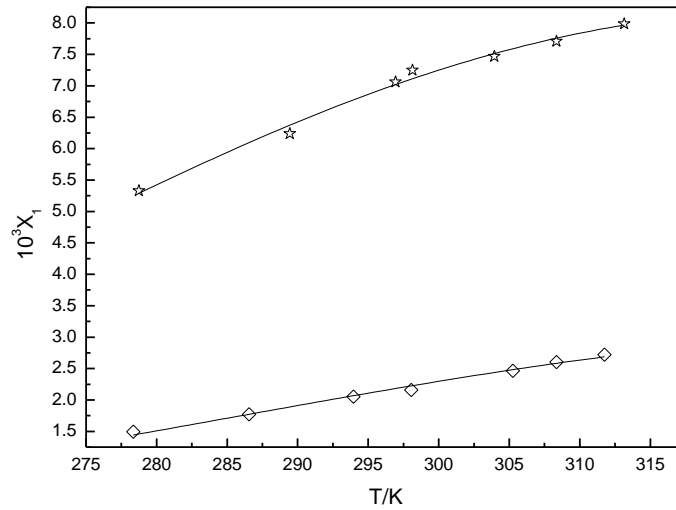
7

8

(b)

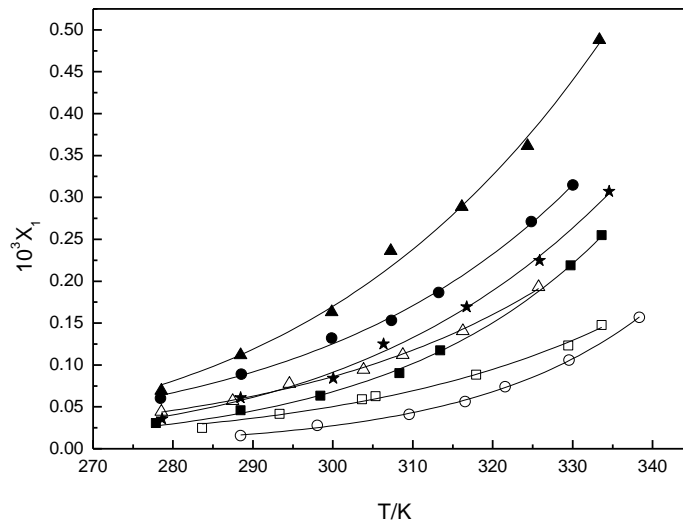
1
2
3
4
5

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



6
7

(a)



8
9

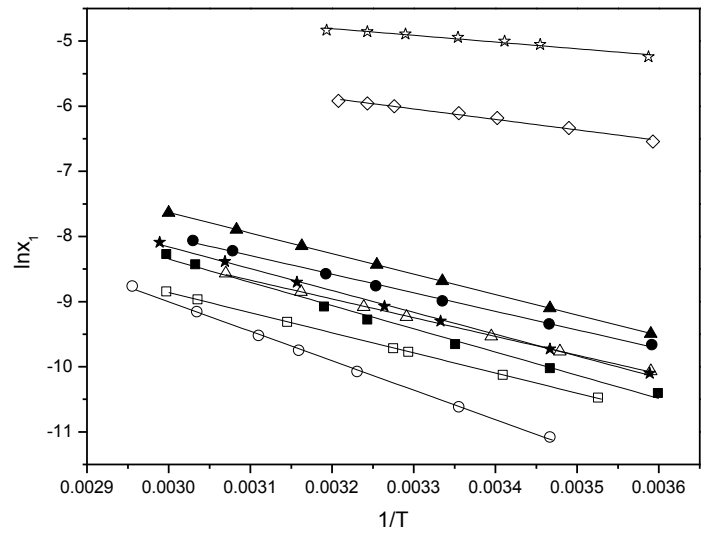
(b)

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

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

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

3



4

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

8

9

10

11

12

13

14

15

16

17

18

19

1 **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%

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

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

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

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

T/K	$10^3 x_1^{\text{exptl}}$	$10^5(x_1^{\text{exptl}} - x_1^{\text{calcd}})$	T/K	$10^3 x_1^{\text{exptl}}$	$10^5(x_1^{\text{exptl}} - x_1^{\text{calcd}})$
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			

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

2

3

4

5

6

7

8

1

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

2

3

4

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

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

6 b Calculated by Eq. 4

7 1 random error (uncertainty) of A , δ_A =standard error/ $|A|$ 8 2 random error (uncertainty) of B , δ_B =standard error/ $|B|$ 9 3 random error(uncertainty) of C , δ_C =standard error/ $|C|$

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

Solvent	λ^a	δ_λ^*	h	$\delta_h^\#$	$10^3\sigma^b$
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

2 *a* λ and h are parameters of Eq. 5

3 *b* Calculated by Eq. 4

4 * random error(uncertainty) of λ , $\delta_\lambda = \text{standard error} / |\lambda|$

5 # random error(uncertainty) of h , $\delta_h = \text{standard error} / |h|$

6

7

8

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

10 Nine Solvents

Solvent	T_{hm}^* (K)	$\Delta_{sln} H_m^{\circ \star}$ (kJ·mol ⁻¹)	δ_l^a (%)	$\Delta_{sln} S_m^{\circ}$ (J·mol ⁻¹ ·K ⁻¹)	δ_2^b (%)	$\Delta_{sln} G_m^{\circ \star}$ (kJ·mol ⁻¹)	% ζ_H *	% ζ_{TS} #
Chloroform	298.0 0	8.6	8.4	-12.5	19.8	12.31	69.69	30.31
Dichloromethane	297.0 4	13.4	1.6	-6.2	9.5	15.19	87.95	12.05
Benzene	305.7 8	26.2	3.1	15.1	15.6	21.57	85.02	14.98

Methanol	305.0 6	23.7	2.4	4.6	33.5	22.32	94.41	5.59
Toluene	306.1 0	27.9	3.4	15.8	15.8	23.04	85.20	14.80
Acetone	301.3 8	23.9	3.4	2.0		23.30	97.48	2.52
Ethanol	305.9 4	29.67	4.0	19.5	20.4	23.67	83.22	16.78
Ethyl acetate	308.6 4	25.7	4.0	3.4	54.7	24.64	96.10	3.90
2-Propanol	313.7 5	37.6	3.4	38.0	11.2	25.70	75.94	24.06

-
- 1 $*T_{hm}$ The harmonic mean of the experimental temperatures
- 2 $^*\Delta_{sIn}H_m^O$ The dissolution enthalpy of telmisartan (form A)
- 3 $^{\Delta}\Delta_{sIn}S_m^O$ The dissolution entropy of telmisartan (form A)
- 4 $^*\Delta_{sIn}G_m^O$ The Gibbs free energy of the telmisartan (form A)
- 5 $^*\% \zeta_H$ The relative contributions by enthalpy toward the solution process
- 6 $^{\#}\% \zeta_{TS}$ The relative contributions by entropy toward the solution process
- 7 a random error(uncertainty) of $\Delta_{sIn}H_m^O$ $\delta_1 = \text{standard error} / |\Delta_{sIn}H_m^O|$
- 8 b random error(uncertainty) of $\Delta_{sIn}S_m^O$, $\delta_2 = \text{standard error} / |\Delta_{sIn}S_m^O|$
- 9
- 10
- 11
- 12
- 13
- 14
- 15