# Solubility of Artemisinin in Seven Different Pure Solvents from (283.15 to 323.15) K

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The solubility of artemisinin in pure methanol, ethyl acetate, acetone, acetonitrile, cyclohexane, toluene, and chloroform was measured by a synthetic method over the temperature range from (283.15 to 323.15) K at atmospheric pressure. The results show that the solubility of artemisinin increases with increasing temperature in all seven solvents. The experimental data were correlated using the modified Apelblat model, and the agreement with the experimental data was very good.

## Introduction

Artemisinin (CAS no. 63968-64-9, Figure 1) has a peroxide bridge and a $\delta$-lactone ring and is a sesquiterpene lactone substance. It has colorless needles in crystalline form and is bitter in flavor. Artemisinin, whose Chinese name is Qinghaosu, is an important medicinal component of *Artemisia annua* L., which has been used as a traditional Chinese medicine in the treatment of fever and malaria for a long time.[1] Currently, the extraction of artemisinin from *Artemisia annua* leaves occurs mainly by the use of organic solvents.[2,3] The supercritical carbon dioxide extraction with better selectivity and efficiency has a wide application prospect.[4] However, the artemisinin obtained by organic solvent extraction and supercritical carbon dioxide extraction is not pure enough for dosage. A crystallization process is needed to obtain pure artemisinin. To select the proper solvent and to design an optimized separation process, the solubility of artemisinin in different solvents is necessary and very important.[5]

In this work, the solubility data of artemisinin in pure methanol, ethyl acetate, acetone, acetonitrile, cyclohexane, toluene, and chloroform over the temperature range (283.15 to 323.15) K at atmospheric pressure were experimentally determined using a synthetic method and a laser monitoring observation technique.

## Experimental Section

***Materials.*** The artemisinin with a mass fraction purity of 0.99 was supplied by the Shanxi Huisheng Medicament Technology of China. Analytical grade organic solvents with purities of higher than 0.995 in mass fraction were purchased from Tianjin Kewei Chemical Reagent of China.

***Apparatus and Procedures.*** The solubility of artemisinin in seven different solvents was measured with a synthetic method.[6,7] The apparatus for the measurement is shown in Figure 2 and is similar to that described in the literature.[8] A cylindrical double-jacketed glass vessel with a working volume of 100 cm$^3$ was used as the equilibrium cell. A magnetic bar was used for continuous stirring. The temperature, with an uncertainty of ± 0.05 K, was controlled by circulating water through the outer jacket. A condenser was used to prevent solvent evaporation. A laser monitoring system which consisted of a laser generator, a photoelectric convertor and a light intensity display was used to determine the disappearance of the last crystal in the mixtures. An analytical balance (Metler Toledo AB204-N, Switzerland) with an uncertainty of ± 0.1 mg was used for the mass measurements.

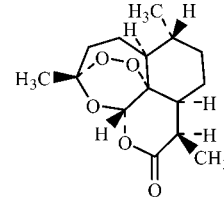

**Figure 1.** Structure of Artemisinin.

At the beginning, a predetermined known mass of artemisinin and solvent were added to the jacketed vessel. The amount of solute was slightly in excess. The contents of the vessel were continuously stirred for 30 min at a fixed temperature. Then, a known mass of additional solvent was introduced to the vessel by an injector. When the last solute just disappeared, the penetrated light intensity reached its maximum value. The mass of the solvent consumed in the experiment would then be recorded. Together with the mass of solute, the solubility would be obtained. The saturated mole fraction of the solute, $x_1$, in different pure solvents can be calculated by the following equation

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

where $m_1$ and $m_2$ represent the mass of solute and solvent and $M_1$ and $M_2$ are the molecular weight of solute and solvent, respectively. All of the experiments were repeated three times. The uncertainty in the solubility values is estimated to be 0.5 %.

## Results and Discussion

The solubility data of artemisinin in pure methanol, ethyl acetate, acetone, acetonitrile, cyclohexane, toluene, and chlo-

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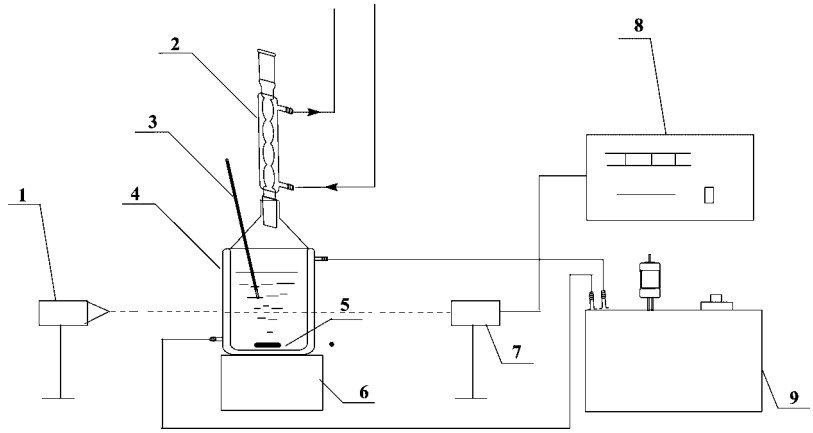


**Figure 2.** Schematic setup for the solubility determination. 1, laser generator; 2, condenser; 3, thermometer; 4, equilibrium vessel; 5, stir bar; 6, magnetic stirrer; 7, photoelectric convertor; 8, digital display; 9, thermostat.

**Table 1. Solubility of Artemisinin in Methanol, Ethyl Acetate, Acetone, Acetonitrile, Cyclohexane, Toluene, and Chloroform from (283.15 to 323.15) K**

| $T$/K | $10^4(x_1^{exptl})$ | $[(x_1^{exptl} - x_1^{calcd})/x_1^{exptl}]\cdot 10^2$ | $T$/K | $10^4(x_1^{exptl})$ | $[(x_1^{exptl} - x_1^{calcd})/x_1^{exptl}]\cdot 10^2$ |
|---|---|---|---|---|---|
| | Methanol | | | Ethyl Acetate | |
| 283.15 | 5.5871 | 0.4534 | 283.15 | 52.5294 | − 7.1989 |
| 288.15 | 7.7347 | −0.8320 | 288.15 | 78.6100 | −0.9871 |
| 293.15 | 11.0950 | 2.5249 | 293.15 | 116.8526 | 5.3173 |
| 298.15 | 14.5088 | − 2.2707 | 298.15 | 152.8011 | 0.1813 |
| 303.15 | 19.4804 | − 3.4565 | 303.15 | 204.6851 | − 1.6667 |
| 308.15 | 26.6922 | −1.5704 | 308.15 | 282.0574 | 0.3292 |
| 313.15 | 37.5218 | 3.6871 | 313.15 | 376.7422 | 0.1335 |
| 318.15 | 47.7480 | − 0.0082 | 318.15 | 498.8313 | − 0.0411 |
| 323.15 | 62.2157 | − 0.5757 | 323.15 | 656.6532 | 0.0570 |
| | Acetone | | | Acetonitrile | |
| 283.15 | 38.8060 | − 2.9224 | 283.15 | 1.9782 | − 0.5952 |
| 288.15 | 50.9541 | − 2.8580 | 288.15 | 2.5700 | − 6.9237 |
| 293.15 | 67.2883 | −1.2874 | 293.15 | 3.5637 | −6.6565 |
| 298.15 | 86.3055 | − 1.8122 | 298.15 | 5.1757 | − 1.7149 |
| 303.15 | 114.0663 | 1.4916 | 303.15 | 7.2319 | − 0.9299 |
| 308.15 | 145.2396 | 1.8345 | 308.15 | 10.2887 | 1.5563 |
| 313.15 | 180.6762 | 0.6113 | 313.15 | 14.3215 | 1.8023 |
| 318.15 | 223.4925 | − 0.4849 | 318.15 | 19.6368 | 0.5215 |
| 323.15 | 278.2854 | − 0.2470 | 323.15 | 26.9605 | − 0.6650 |
| | Cyclohexane | | | Toluene | |
| 283.15 | 4.4012 | −3.0546 | 283.15 | 374.5060 | −0.2095 |
| 288.15 | 5.8504 | − 2.4620 | 288.15 | 435.4345 | − 1.5725 |
| 293.15 | 7.4502 | − 5.4106 | 293.15 | 519.5632 | 0.1915 |
| 298.15 | 10.5903 | 3.6576 | 298.15 | 602.8861 | − 0.3603 |
| 303.15 | 13.6961 | 3.9809 | 303.15 | 710.5086 | 1.0980 |
| 308.15 | 17.0979 | 1.6089 | 308.15 | 815.3558 | 0.3482 |
| 313.15 | 20.9175 | − 2.1411 | 313.15 | 936.9766 | 0.1540 |
| 318.15 | 26.4545 | − 1.8668 | 318.15 | 1069.5903 | − 0.3050 |
| 323.15 | 34.1159 | 1.0213 | 323.15 | 1224.2806 | − 0.1084 |
| | | | | Chloroform | |
| 283.15 | 486.8483 | − 0.9191 | 308.15 | 1569.6479 | 0.5472 |
| 288.15 | 612.5478 | − 2.6930 | 313.15 | 1926.2803 | 0.0967 |
| 293.15 | 794.6997 | − 0.4994 | 318.15 | 2359.3246 | 0.1006 |
| 298.15 | 1013.1789 | 0.7065 | 323.15 | 2865.2702 | − 0.1242 |
| 303.15 | 1268.8714 | 0.8817 | | | |

roform at the different temperatures are listed in Table 1 and shown in Figures 3 and 4.

From Table 1 and Figures 3 and 4, it can be seen that within the temperature range of the measurements, the solubility of artemisinin in chloroform, toluene, ethyl acetate, acetone, methanol, cyclohexane, and acetonitrile increased with an increase in temperature.

On the basis of the experimental results, the polarity of the solvents has some influence on the solubility of artemisinin. From Table 1 and Figure 3, it can be seen that the medium polarity solvents such as chloroform, toluene, ethyl acetate, and acetone have good dissolving ability for artemisinin. Figure 4 shows that the artemisinin is sparingly soluble in the strong polar solvents methanol and acetonitrile and the nonpolar solvent cyclohexane.

The process of dissolution is determined by a combination of enthalpy and entropy factors. The principle of "like dissolves like" could, to a certain extent, explain the solvency difference of different solvents. If the interactions in the solute and solvent are similar, then the dissolution of the solute is easy. If the solute and solvent molecules greatly differ in polarity, then dissolution does not easily happen. From the structure of artemisinin in Figure 1, artemisinin has a peroxide bridge and a $\delta$-lactone ring; therefore, it has

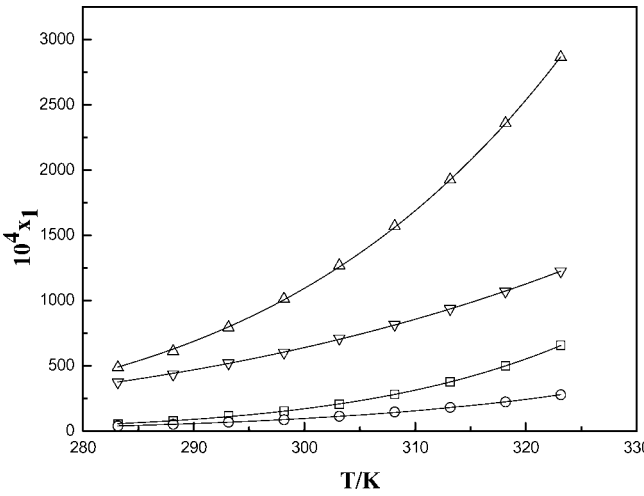


**Figure 3.** Experimental and calculated mole fraction solubility of artemisinin in four different pure solvents. △, chloroform; ▽, toluene; □, ethyl acetate; ○, acetone.

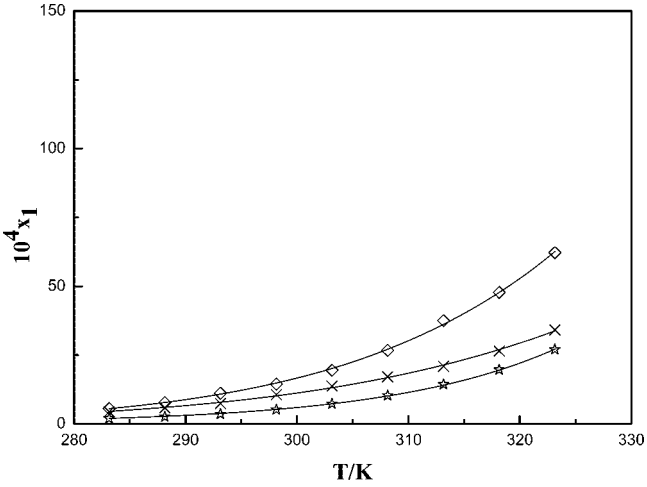


**Figure 4.** Experimental and calculated mole fraction solubility of artemisinin in three different pure solvents. ◇, methanol; ×, cyclohexane; ☆; acetonitrile.

weak polarity. So the solubility of artemisinin in the medium polarity solvents is relatively large. But the polar difference of solvents is only one of the factors affecting the dissolution behavior. Further analysis of the dissolution process in an organic solvent is complicated and beyond the scope of this article.

The temperature dependence of the solubility of artemisinin was correlated by the following semiempirical equation.[9−11]

$$\ln(10^4 x_1) = A + \frac{B}{T/\mathrm{K}} + C\ln(T/\mathrm{K}) \qquad (2)$$

where $T$ is the absolute temperature and $A$, $B$, and $C$ are empirical constants. The correlated values of $A$, $B$, and $C$ of the seven different solvents are listed in Table 2.

**Table 2. Parameters of Equation *2* for Artemisinin in Different Solvents**

| solvents | *A* | *B* | *C* | ($10^4$)rmsd |
|---|---|---|---|---|
| methanol | 13.3084 | − 5178.1 | 1.1866 | 0.5640 |
| ethyl acetate | 18.5010 | − 5375.7 | 0.7997 | 2.7187 |
| acetone | 14.4142 | − 4222.2 | 0.7412 | 1.4706 |
| acetonitrile | − 264.8578 | 6929.4 | 42.6982 | 0.1617 |
| cyclohexane | 0.8660 | − 3832.9 | 2.5120 | 0.3786 |
| toluene | 4.5587 | − 2215.1 | 1.6281 | 3.8960 |
| chloroform | 18.7247 | − 3958.6 | 0.2574 | 8.0264 |

The root-mean-square deviation (rmsd) is defined as follows

$$\mathrm{rmsd} = \sqrt{\frac{\sum_{i=1}^{N}\left(x_1^{\mathrm{exptl}} - x_1^{\mathrm{calcd}}\right)^2}{N}} \qquad (3)$$

where $N$ is the number of experimental points and $x_1^{\mathrm{exptl}}$ and $x_1^{\mathrm{calcd}}$ represent the experimental and calculated values of the solubility, respectively. The rmsd of the seven different solvents is also listed in Table 2.

## Conclusions

(1) The solubility of artemisinin in pure methanol, ethyl acetate, acetone, acetonitrile, cyclohexane, toluene, and chloroform increased with an increase in temperature. (2) Ethyl acetate and acetone are low price and low toxicity solvents, and their dissolving ability for artemisinin obviously varies with temperature; therefore, they can be used as purification solvents. (3) The calculated solubility data by the semiempirical equation are in good agreement with the experimental values.

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