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Solubility evaluation and thermodynamic modeling of β-lapachone in water and ten organic solvents at different temperatures

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ABSTRACT

Although β-lapachone is a promising drug with pharmacological activity, issues concerning its low aqueous solubility are known. The objective of this study was to measure the solubility of β-lapachone in water and ten organic solvents at temperatures ranging from 298.15 K to 318.15 K under atmospheric pressure. The modified Apelblat model, the Buchowski-Ksiazaczak λh model, and the ideal model were used to correlate experimentally obtained solubility values. Moreover, thermodynamic analysis of β-lapachone dissolution was performed based on experimental solubility data using the van't Hoff equation. The highest mole fraction solubility of β-lapachone at 298.15 K was found in acetone (2.05×10^{-2}), followed by acetonitrile (1.80×10^{-2}), ethyl acetate (8.53×10^{-3}), 1-butanol (7.43×10^{-3}), 1-propanol (6.69×10^{-3}), 2-butanol (5.65×10^{-3}), methanol (5.40×10^{-3}), ethanol (4.99×10^{-3}), 2-propanol (3.76×10^{-3}), propylene glycol (3.06×10^{-3}), and water (2.85×10^{-6}). Correlation results showed that the modified Apelblat model was more accurate than the Buchowski-Ksiazaczak λh model and the ideal model. Thermodynamic analysis indicated that β-lapachone dissolution was endothermic and entropy-driven process in all solvents studied. Data on solubility and thermodynamic properties in various solvents obtained in this study could be helpful in formulation development, purification, and crystallization of β-lapachone.

1. Introduction

β-Lapachone (CAS number: 4707-32-8, Fig. 1), also known as 2,2-dimethyl-3,4-dihydro-2H-benzo[h]chromene-5,6-dione, is a natural naphthoquinone first isolated from the lapacho tree (*Tabebuia avellanedae*). Its molecular formula and molecular weight are $C_{15}H_{14}O_3$ and 242.27 g mol^{-1}, respectively. Due to its promising pharmacological and biological activity against various diseases, β-lapachone has been used as an anti-cancer [1], anti-inflammatory [2,3], anti-fungal, and anti-bacterial [4] agent. Its cytotoxic effect can be enhanced by NAD(P)H:quinone oxidoreductase 1 (NQO1), a flavoprotein overexpressed in various human cancers [5]. Furthermore, recent studies have shown that β-lapachone promoted collagen synthesis in human dermal fibroblasts (HDFs), suggesting its potential applicability as a cosmeceutical ingredient [6,7].

Despite the high potency of β-lapachone, it is practically insoluble in water, limiting formulation development especially in terms of solid and liquid dosage forms. Solubility of β-lapachone in water at a temperature of 298.15 K has been reported as 0.038 mg mL^{-1} [8] and measured to be 0.040 mg mL^{-1} in this experiments. Low aqueous solubility has resulted in poor absorption and low oral bioavailability, indicating the need for strategies to enhance solubility of β-lapachone. Therefore, solubility of poorly water-soluble drugs in aqueous and organic solvents are important to study, because most pharmaceutical techniques for improving drug solubility and dissolution rate such as melt granulation, solid dispersion, micro-emulsion, and self micro-emulsifying drug development systems (SMEDDS) use aqueous or organic solvents.

Solubility data in various solvents are also necessary in the production process. It is well known that crystallization is a crucial step to determine quality and yield of drugs [9]. Thermodynamic solubility data in various solvents can provide the basis for proper solvent selection and design of an optimized crystallization process. However, no studies have reported solubility of β-lapachone in various solvents.

In this study, solubility of β-lapachone in methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, acetonitrile, acetone, ethyl acetate, propylene glycol, and water was obtained at

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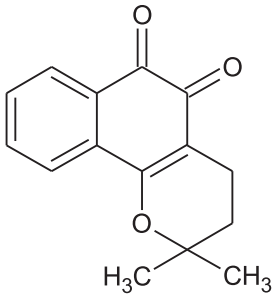

Fig. 1. Chemical structure of β-lapachone.

temperatures ranging from 298.15 K to 318.15 K under atmospheric pressure using the solid-liquid equilibrium method. The modified Apelblat model, the Buchowski-Ksiazaczak λh model, and the ideal model were employed to correlate obtained experimental solubility. In addition, apparent thermodynamic properties during the dissolution of β-lapachone including Gibbs free energy change (ΔG_d°), enthalpy change (ΔH_d°), and entropy change (ΔS_d°) were calculated from the solubility data using van't Hoff analysis.

2. Experimental

2.1. Materials

β-lapachone with mass fraction purity >99.9% was purchased from Sigma-Aldrich (St. Louis, MO, USA). Methanol, ethanol, and acetonitrile were purchased from Avantor Performance Materials (Center Valley, PA, USA). 1-Propanol, 2-propanol, 2-butanol, and acetone were purchased from Daejung Chemical & Metals Co., Ltd. (Siheung, Korea). 1-Butanol, ethyl acetate, and propylene glycol were purchased from Junsei Chemical Co., Ltd. (Tokyo, Japan). Detailed information about β-lapachone and solvents used is shown in Table 1.

2.2. Thermal analysis

Melting temperature and enthalpy of fusion for β-lapachone were determined using differential scanning calorimetry (DSC) (Q-2000, TA Instruments, New Castle, DE, USA). Accurately weighed samples (3 mg) of β-lapachone were sealed in an aluminum DSC pan. A blank pan was employed as a reference. In order to ensure isothermal starting conditions, the pans were kept at 273.15 K for 5 min before initiating analysis. DSC measurements were carried out at a scan rate of 10 K min^{-1} from 273.15 K to 523.15 K under nitrogen flow of 50 mL min^{-1}.

2.3. Solubility measurement

Equilibrium solubility of β-lapachone in water and ten organic solvents (methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, acetonitrile, acetone, ethyl acetate, and propylene glycol) was measured at temperatures ranging from 298.15 K to 318.15 K using a solid-liquid equilibrium method [10]. Five milliliters of each solvent were added to separate glass vials, and then an excess amount of β-lapachone was added to each vial. The solute-solvent mixtures were vortexed for 10 min, followed by shaking in a water bath (BS-21, Jeiotech Co., Ltd., Daejeon, Korea) at 100 rpm for 24 h. The temperature uncertainty of water bath was 0.1 K. Preliminary studies were performed with shaking times of 6 h, 12 h, 24 h, and 48 h to optimize saturation time. Results indicated that 24 h was optimal to establish solid-liquid equilibrium in the glass vial. After 24 h of shaking, the mixtures were kept static for 2 h at the same temperature to allow undissolved particles to settle. Subsequently, supernatants were filtered using 0.45 μm syringe filters, transferred to volumetric flasks, and weighed. After dilution with methanol, the concentration of β-lapachone was analyzed using a UV spectrophotometer (OPTIZEN POP, Mecasys Co., Ltd., Daejeon, Korea) at 256 nm. The standard calibration curve of β-lapachone was found to be linear in the concentration range of 0.5 μg mL^{-1} to 8 μg mL^{-1} (correlation coefficient = 0.9999). All measurements were performed three times.

Mole fraction solubility (x_e) of β-lapachone was calculated using the following equation:

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

where m_1 and m_2 represent mass of β-lapachone and solvent, respectively. M_1 and M_2 represent molar mass of β-lapachone and solvent, respectively.

3. Results and discussion

3.1. Thermal analysis

DSC thermogram of β-lapachone is shown in Fig. 2. An endothermic peak at 428.99 K was evident, indicating melting temperature (T_m). Intensity and sharpness of the peak indicated the crystalline nature of the drug. The T_m value determined in this experiment was slightly lower than the value reported in the literature (430.45 K) [11], although it was within the range of experimental limits. This might have been due to differences in sample purity, equipment, or experimental conditions. In addition,

Table 1
Properties and sources of materials used in the study.[a]

Solvent	Source	Molar mass (g·mol^{-1})	Mass fraction purity (%)	Analysis method
β-Lapachone	Sigma-Aldrich	242.27	99.9	HPLC[b]
Methanol	Avantor Performance Materials	32.04	99.9	GC[c]
Ethanol	Avantor Performance Materials	46.07	99.9	GC
1-Propanol	Daejung Chemical & Metals Co., Ltd.	60.10	99.5	GC
2-Propanol	Daejung Chemical & Metals Co., Ltd.	60.10	99.7	GC
1-Butanol	Junsei Chemical Co., Ltd.	74.12	99.5	GC
2-Butanol	Daejung Chemical & Metals Co., Ltd.	74.12	99.5	GC
Acetonitrile	Avantor Performance Materials	41.05	99.9	GC
Acetone	Daejung Chemical & Metals Co., Ltd.	58.08	99.8	GC
Ethyl acetate	Junsei Chemical Co., Ltd.	46.07	99.5	GC
Propylene glycol	Junsei Chemical Co., Ltd.	76.09	99.0	GC
Water	Lab made	18.01	Double distilled	

[a] Standard uncertainty for mass fraction u is u (c) = ± 0.005.
[b] High performance liquid chromatography.
[c] Gas chromatography.