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Kinetic and thermodynamic characteristics of fractional precipitation of (+)-dihydromyricetin

Ji-Na Park, Jin-Hyun Kim*

Department of Chemical Engineering, Kongju National University, Cheonan 330-717, South Korea

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ABSTRACT

This study investigated the effect of the precipitation time and temperature on the efficiency of fractional precipitation for the purification of (+)-dihydromyricetin, and analyzed the kinetics and thermodynamics of the fractional precipitation process. The time required to obtain a given yield was the shortest at 277 K in a time-temperature-transformation (TTT) diagram. When the Johnson-Mehl-Avrami-Komolgorov (JMAK) equation was applied to experimental data, simultaneous mechanisms of nucleation and growth were determined at precipitation temperatures of 277, 280, and 283 K, while consecutive mechanisms of nucleation and growth were determined at 263 K and 291 K. A thermodynamic analysis showed that the enthalpy change (ΔH^0) and entropy change (ΔS^0) were both negative, plus the Gibbs free energy change (ΔG^0) was negative and decreased when decreasing the temperature (283, 280, and 277 K). Thus, the precipitation was more feasible when using a lower temperature, and the results indicated that the fractional precipitation process for purifying (+)-dihydromyricetin was exothermic, irreversible, and spontaneous.
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1. Introduction

(+)-Dihydromyricetin [(+)-ampelopsin] (chemical formula: $C_{15}H_{12}O_8$, molecular weight: 320.25) (Fig. 1) is a bioactive compound derived from *Hovenia dulcis* and *Ampelopsis grossedentata*. As a functional substance, it is effective for the treatment of alcohol-related liver diseases and is used as a raw substance in functional foods and pharmaceutical products for relieving hangovers and liver protection [1–5]. Furthermore, in 2002, Du et al. [6] reported an inhibition of hypertension by *Ampelopsis grossedentata*-derived (+)-dihydromyricetin, while Yoshikawa et al. [7] reported an inhibition of muscle relaxation, metabolic stimulation, and liver protection. Plus, anti-allergic effects have also been noted [8].

However, the isolation and purification of (+)-dihydromyricetin for its commercialization as a functional food or pharmaceutical product have not been extensively studied, especially methods of separation and purification that can be used for industrial production. A few limited studies have focused on obtaining low-purity (<10%) (+)-dihydromyricetin by extraction followed of chromatographic resolution with organic solvents, or acquiring a crude extract containing terpenoid, lipid, chlorophyll, and phenol [9,10]. However, such studies have applied an expensive chromatographic method to the pre-purification process for the final purification stage, or a crude extract has been directly used in the final purification by HPLC, which consumes a large amount of organic solvent and reduces the lifetime of the column packing materials and throughput, making this process uneconomical for mass production [6].

In contrast, fractional precipitation that uses the difference in solubility is an easier method for the efficient separation and purification of (+)-dihydromyricetin. The first representative pretreatment process to obtain high-purity and high-yield (+)-dihydromyricetin using fractional precipitation was developed in 2008 [11]. Thereafter, various studies have attempted to reduce the operating time (~32 h) required for fractional precipitation [12]. Notwithstanding, the kinetic and thermodynamic characteristics of the precipitation process have not yet been investigated. The kinetic characteristics can help with understanding or predicting the reaction path, reaction rate, reaction extent, all of which can impact the development of the precipitation process, optimization, and testing [13–15]. Meanwhile, the thermodynamic characteristics can reveal the spontaneity of the reaction, heat of the reaction, and reversibility, representing the pattern of the precipitation process [16–18]. Accordingly, this study investigated the effect of the

* Corresponding author.
E-mail address: jinhyun@kongju.ac.kr (J.-H. Kim).

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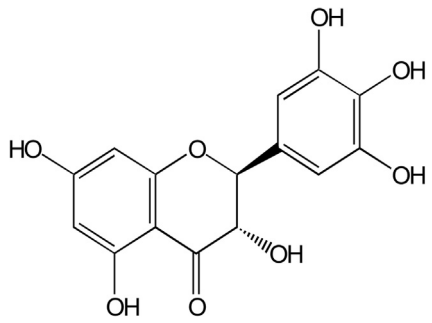

Fig. 1. Chemical structure of (+)-dihydromyricetin.

precipitation time and temperature on the efficiency of the fractional precipitation of (+)-dihydromyricetin, and then analyzed the kinetics and thermodynamics of the fractional precipitation process. The Johnson-Mehl-Avrami-Komolgorov (JMAK) equation was applied to the precipitation process for the kinetic analysis. The activation energy, Gibbs free energy change, enthalpy change, and entropy change were investigated as thermodynamic parameters for a detailed analysis of the reaction pattern for the fractional precipitation of (+)-dihydromyricetin.

2. Materials and methods

2.1. (+)-Dihydromyricetin materials

The crude extracts of *Ampelopsis grossedentata* for the fractional precipitation were purchased from Guilin Natural Ingredient, Inc. (Guilin, China). (+)-Dihydromyricetin was the major component of the extracts and constituted approximately 50.0% of the total sample based on weight. Authentic (+)-dihydromyricetin (purity: 98%) was also purchased from Guilin Natural Ingredient, Inc. (Guilin, China) and used as the standard for the analysis of (+)-dihydromyricetin [11].

2.2. Analysis of (+)-dihydromyricetin

The (+)-dihydromyricetin content was analyzed using a HPLC system (SCL-10 AVP, Shimadzu, Japan) equipped with a Capcell Pak C18 column (250 × 4.6 mm, 5 μm, Shiseido, Japan). The elution was performed based on a gradient using a distilled water-acetonitrile mixture varying from 90:10 to 30:70 within 60 min (flow rate = 1.0 mL/min). The injection volume was 20 μL and the effluent was monitored at 254 nm using a UV detector. The retention time of (+)-dihydromyricetin was 15 min. Each sample was analyzed in triplicate.

2.3. Fractional precipitation

After dissolving the (+)-dihydromyricetin sample (purity: 80.0%) in acetone (0.1 g/mL), distilled water (distilled water/acetone solution ratio = 5/1, v/v) at pH 9.0 was dropped during stirring (350 rpm) to induce the precipitation of (+)-dihydromyricetin using the solubility difference. The reactor volume was 20 mL and the working volume was 6 mL. The solution for fractional precipitation was then placed in a thermo-hygrostat (KCL-2000W, EYELA, Japan) at −10 °C (263 K) for different times (4, 8, 12, 16, 20, 24, 28, 32 h) for the precipitation of (+)-dihydromyricetin. The same method was used at temperatures of 4 °C (277 K), 7 °C (280 K), 10 °C (283 K), and 18 °C (291 K). A schematic diagram of the fractional precipitation of (+)-dihydromyricetin is shown in Fig. 2. After the fractional precipitation, the precipitate was filtered (Whatman Grade 4, 20–25 μm particle retention, 150 mm diameter), dried in a vacuum oven (UP-2000, EYELA, Japan) at 40 °C for 24 h, and analyzed by HPLC.

2.4. Analysis of (+)-dihydromyricetin precipitate

The shape and size of the (+)-dihydromyricetin precipitate in the fractional precipitation were measured using an SV-35 Video Microscope System (Some Tech, Korea) at a high magnification (×100) [19]. The measurements were also verified in dynamic images using IT-Plus software (Some Tech). The particle size measured by microscopy was expressed as an average value.

2.5. Kinetic analysis

The JMAK equation is generally applied to crystallization or precipitation as it is effective in the case of a random particle distribution or independent particle growth, plus it can copy the phase transition behavior in an isothermal process [20–22]. The JMAK equation is expressed as Eq. (1) and is rearranged as a linear equation in Eq. (2).

$$X(t) = 1 - \exp\left[-kt^n\right] \tag{1}$$

$$\log\left(ln\left(\frac{1}{1-X(t)}\right)\right) = logk + n \quad \log\ t \tag{2}$$

$X(t)$ is the yield of precipitated (+)-dihydromyricetin over time. In Eq. (2), the JMAK exponent, n, and constant, k, can be calculated using the slope and y-intercept, respectively.

2.6. Validity of kinetic model

The applicability of a kinetic model can be identified using the coefficient of determination (r^2) and root mean square deviation (RMSD). The RMSD can be expressed as Eq. (3):

$$RMSD = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(experimental - calculated)^2} \tag{3}$$

where n is the number of experimental runs.

2.7. Thermodynamic analysis

The activation energy (E_a, kJ/mol) is the minimum energy required for a reaction and can be calculated using the Arrhenius equation shown in Eq. (4).

$$lnk = lnA - \frac{E_a}{RT} \tag{4}$$

The thermodynamic parameters were used as follows: the standard enthalpy change (ΔH°, kJ/mol) was used to determine the reaction heat that was absorbed or emitted, the standard entropy change (ΔS°, J/mol) was used an indicator of entropy to determine reversibility, and the standard Gibbs free energy change (ΔG°, kJ/mol) was used to determine the spontaneity of the reaction. ΔG° was calculated using the equilibrium constant (K_e) as shown in Eq. (5), where K_e is the concentration ratio of precipitated (+)-dihydromyricetin to (+)-dihydromyricetin remaining in the supernatant. As shown in Eq. (6), ΔS° and ΔH° can be calculated using the Van't Hoff equation that shows the relation between $\ln K_e$ and T.

$$\Delta G^\circ = -RTlnK_e \tag{5}$$

$$lnK_e = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R} \tag{6}$$

The equilibrium state between an activated complex and a reactant is called the transition state. When an activated complex passes

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