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Solubility Models for the Recovery of Rosmarinic Acid from *Orthosiphon Aristatus* Extract Using Solid Phase Extraction

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Abstract: Hildebrand and Hansen solubility parameters, and log *P* value are widely used to determine the solubility of polymers in solvents. The models were used to explain the recovery of phytochemical, rosmarinic acid from *Orthosiphon aristatus* extract in C18 solid phase extraction (SPE) using the eluent consisting of ethyl acetate and chloroform in the decreasing polarity of solvent system. The experimental recovery of rosmarinic acid appeared to be well explained by the Hansen solubility model. The small difference in the Hansen solubility parameters, particularly for dispersion and hydrogen bonding forces, results in a higher polar solvent system for high rosmarinic acid recovery. The results found that the Hansen solubility model fitted well to the recovery of rosmarinic acid from crude extract with high coefficient of determination ($R^2 > 0.8$), low standard error (4.4%), and $p < 0.05$. Hildebrand solubility is likely to be the second fit model, whereas log *P* has poor $R^2 < 0.7$ and higher standard error (7.3%). The Hansen solubility model describes the interaction of solute–solvent in three dimensions (dispersion, polar, and hydrogen bonding forces) which can accurately explain the recovery of rosmarinic acid. Therefore, Hansen solubility can be used to predict the recovery of rosmarinic acid from *O. aristatus* extract using SPE.

Keywords: Hansen solubility parameter; Hildebrand solubility parameter; log *P*; rosmarinic acid; solid phase extraction

1. Introduction

Herbal extract is a very complex mixture of compounds including plant secondary metabolites, which are also known as phytochemicals. The separation of phytochemicals, usually the bioactive marker compound from herbal extract, is a challenge for the herbal processing industry. This marker-enriched plant extract is widely used as a bioactive ingredient for further product formulation, particularly for cosmeceutical and nutraceutical product development.

Several chromatographic techniques and solid phase extraction (SPE) have extensively been applied for the separation of the target compound from the crude extract of plant samples. SPE is a simple and efficient method for the preparation of target compound-enriched plant extract [1]. The performance of SPE is highly dependent on the selection of sorbent and eluent system that lead to the high recovery of the target compound. There is no specific guideline on the selection of sorbent and eluent in relation to the physiochemical property of the target compound.

In the present study, the concept of solubility was used for the prediction of the target compound from a highly complex mixture of plant extract. Solubility is likely to be one of the dominant physiochemical properties to explain the performance of target phytochemical separation. By definition,

solubility is the capacity of a solute to dissolve in a solvent to form a homogeneous solution [2]. Therefore, the solubility of a solute is affected by the properties of both solute and solvent, as well as environmental conditions such as pressure and temperature [2]. In an ideal condition, the solute must be dissolved in solvent with no energy penalty associated with the dissolution process [3]. Nevertheless, the solubility of a solute can be estimated numerically by using solubility parameters such as Hildebrand, Hansen, and log *P* value (partition coefficient of octanol in water).

Previously, the concept of solubility was applied to the solvent selection of bioactive compound extraction using the technique of subcritical fluid extraction [4,5]. The researchers predicted the miscibility of solute-subcritical solvent and the optimal solvent-temperature conditions by comparing the relative energy differences of solute and solvent systems, which was calculated by Hansen solubility parameter. The parameter was also used in solid phase extraction for the selection of the best analyte–sorbent–solvent system by characterizing the interactions between sorbents, eluents, and analytes [6]. A linear equation was constructed using the solubility parameter as a predictor to estimate the recovery of target compound.

According to literature survey, Hildebrand solubility parameter was applied to the selection of mobile phase, and the prediction of retention behavior for high-performance liquid chromatography [7,8]. Schoenmakers et al. [7] reported that the separation of solutes was affected by the difference in polarity between the solutes, as well as the polarity difference between mobile phase and stationary phase. Hildebrand solubility parameter was also successfully applied to the drug design, particularly for the prediction of drug release from hydroxypropyl methylcellulose gels [9]. The Hildebrand-based drug release equation showed a good agreement with the experimental data with high correlation coefficient ($R^2 = 0.94$).

The octanol/water partition coefficient (log *P*) value is another commonly used solubility parameter. Log *P* describes the relative solubility of a compound in aqueous and organic phase [10]. It is widely applied in the measurement of lipophilicity and prediction of drug diffusivity from the administration site to the active site [10,11]. Log *P* was applied to the prediction of blood–brain barrier penetration using quantitative structure–activity relationship (QSAR) model [12]. The researchers constructed a QSAR model from the polar surface area (PSA) and log *P* value with high correlation coefficient ($R^2 = 0.88$).

It is believed that an accurate estimation of solubility is very important to predict the recovery of the target compound. It is also noteworthy that the solubility highly relies on the physiochemical properties of the target compound in relation to the properties of sorbent and eluent. The objective of this study was to investigate and compare the recovery of rosmarinic acid from the crude extract of *Orthosiphon aristatus* in an SPE system by using different solubility models, namely Hildebrand parameter, Hansen parameter, and log *P* value. Rosmarinic acid is one of the major active compounds in the herb with high potential therapeutic properties [13]. The structural formula of rosmarinic acid is presented in Figure 1. A commonly used reversed-phase C18 cartridge for natural product samples was chosen for SPE. The solvent mixture consisted of ethyl acetate, and chloroform was selected based on the good resolution of rosmarinic acid in thin-layer chromatography (unpublished data).

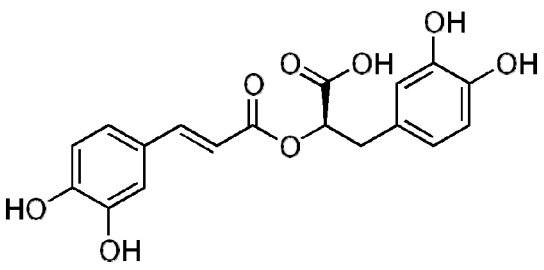

Figure 1. Structural formula of rosmarinic acid.

2. Materials and Methods

2.1. Chemicals

Ethanol (95%) was purchased from Fisher Scientific Co. (Fair Lawn, NJ, USA). HPLC grade methanol (MeOH), acetonitrile (ACN), and formic acid (FA) were purchased from Merck (Darmstadt, Germany). Analytical grade ethyl acetate (EtAc) and chloroform (CHF) were purchased from QRëC (Rawang, Selangor, Malaysia). Further, 18.2 MΩ-cm water was produced from Barnstead NANOpure Diamond water purification system (Thermo, Waltham, MA, USA). The standard chemical of rosmarinic acid (RA) with 96% purity was purchased from Sigma-Aldrich (St. Louis, MO, USA). The plant sample of *Orthosiphon aristatus* (stems and leaves) was purchased from the local supplier (Fidea Resources, Selangor, Malaysia).

2.2. Plant Sample Preparation

The plant sample (10 g) was extracted with 100 mL of 70% *v*/*v* ethanol at 60 °C for 3 h in a reflux setup. The crude extract solution was then filtered and concentrated by drying under vacuum at 60 °C using a rotary evaporator (Heidolph, Laborota 4000, Germany). The concentrated crude extract was kept in an oven at 50 °C until complete dryness. The dried crude extract was stored at −4 °C until further analysis.

2.3. Solid Phase Extraction for Rosmarinic Acid

Solid phase extraction was carried out for the fractionation of rosmarinic acid using Chromabond C18ec cartridges (500 mg, 6 mL, Macherey-Nagel, Düren, Germany). The cartridge was pre-conditioned with methanol (6 mL), and then equilibrated by deionized water (6 mL). The crude extract (0.15 g) was dissolved in 6 mL of methanol, and 1 mL of the crude extract solution was loaded onto the cartridge. The isolation was performed by eluting 3 mL of 0%–100% *v*/*v* ethyl acetate in chloroform. New cartridge was used for each solvent system. The collected fractions were dried by using an IR concentrator coupled with a cold trap system (Micro-Cenvac NB 503CIR, N-BIOTEK Co. Ltd., Gyeonggi-Do, Korea) at 40 °C.

2.4. Quantification of Rosmarinic Acid by UPLC-MS/MS

The dried fractions were then reconstituted in methanol for UPLC-MS/MS (ultra-performance liquid chromatography tandem mass spectrometry) analysis. The concentration of rosmarinic acid in the fractions of *O. aristatus* were analyzed by an UPLC (Waters Acquity; Milford, MA, USA) system coupled with a triple quadrupole-linear ion trap tandem mass spectrometer (Applied Biosystems 4000 QTRAP; Life Technologies Corporation, Carlsbad, CA, USA), and a C18 reversed-phase Acquity column (2.1 × 150 mm, 1.7 µm). The negative mode of multiple reaction monitoring method with 3 transition ions, namely m/z 359-179, m/z 359-161, and m/z 359-197 were used for the quantitation.

The mixture of 0.1% formic acid in water (A) and acetonitrile (B) was used as mobile phases. The separation was performed in a gradient profile with the following proportions (*v*/*v*) of solvent A: 0–5 min, 90%; 5–10 min, 90%–10%; 10–14 min, 10%; 14–15 min, 90% at the flow rate of 0.2 mL/min and the injection volume of 5 µL. The standard solutions were prepared by dissolving 5 mg of rosmarinic acid in 5 mL of methanol. The stock standard solution was diluted with different dilution factors to prepare a serial concentration of standard solutions ranging from 0.1 to 1.0 ppm. The samples were filtered by syringe filters (0.22 µm) from Membrane Solutions (Dallas, TX, USA) before injection.

2.5. Hildebrand Solubility Parameter

This concept of solubility was first introduced by Hildebrand [13] who expressed the solubility for non-polar material. The Hildebrand solubility parameter correlates with vaporization and van der Waals force. This is because solubility is similar to the process of vaporization at which the

intermolecular van de Waals forces must be overcome before the dissolution of material. The materials with similar intermolecular attractive force, namely cohesive energy density, is tended to be miscible in each other [8]. Therefore, Hildebrand solubility can be derived from the cohesive energy density (c), which is related to the enthalpy of vaporization (ΔH_v) of the material as presented in Equation (1).

$$\delta_H = \sqrt{c} = \sqrt{\frac{\Delta H_v - RT}{V_m}} \quad (1)$$

where

c: Energy density;
ΔH_v: Enthalpy of vaporization;
R: Gas constant at 8.314 J mol^{-1} K$^{-1;}$
T: Temperature in Kelvin (K);
V_m: Molar volume in cm^3/mol.

2.6. Hansen Solubility Parameter

The Hildebrand solubility parameter was then modified by Hansen who further divides the cohesive energy into three types of forces, namely dispersion (δ_d), polar (δ_p), and hydrogen bond (δ_h) forces (Equation (2)). The total force (δ_t) is the square root of the sum of square for δ_d, δ_p and δ_h [14].

$$\delta_t = \sqrt{{\delta_d}^2 + {\delta_p}^2 + {\delta_h}^2} \quad (2)$$

where

δ_t: Total force,
δ_d: Dispersion,
δ_p: Polar,
δ_h: Hydrogen bond.

Complete miscibility can be achieved if the hydrogen bonding, polar, and non-polar (dispersion) forces are similar between the solute–solvent and solute–solid phase [15]. The degree of miscibility between solute and solvent can be determined by relative energy difference (RED). The smaller value of the square of differences (R_a) indicates better miscibility between the solute and solvent [6].

$$RED = \frac{R_a}{R_0} \quad (3)$$

$$R_a = \sqrt{4(\delta_{d1} - \delta_{d2})^2 + (\delta_{p1} - \delta_{p2})^2 + (\delta_{h1} - \delta_{h2})^2} \quad (4)$$

where

RED: Relative energy difference;
R_a: Miscibility of solute;
R_o: Miscibility of solvent;

where the subscripts of "1" and "2" represent solute and solvent, respectively. The solvent with RED value less than one is considered as a good solvent [14]. Therefore, Hansen solubility is applicable to the polar and hydrogen bond system, particularly polymer–solvent system [14,16].

The solubility components (δ_d, δ_p, and δ_h) can be estimated by group contribution method as suggested by Hansen and Beerbower [17], Hoy [18], van Krevelen and te Nijenhuis [19], Stefanis and Panayitou [20], and Just et al. [21] as presented in Table 1. The components are estimated from

the corresponding functional groups based on the molecular structure of rosmarinic acid [22]. The Hansen solubility parameter can be also predicted computationally using a mathematical software of COSMOquick (COSMO*logic* GmbH & Co. KG, Germany).

Table 1. Solubility variance of rosmarinic acid in different solvent systems.

Ethyl Acetate–Chloroform (%)	Hildebrand	Hansen				ΔLog *P*
	$\Delta\delta_H$	$\Delta\delta_d$	$\Delta\delta_p$	$\Delta\delta_h$	R_a	
100:0	2.98	0.94	10.35	0.45	10.53	0.99
80:20	2.88	0.54	10.79	0.75	10.87	0.507
60:40	2.78	0.14	11.23	1.05	11.28	0.283
40:60	2.68	0.26	11.67	1.35	11.76	0.137
20:80	2.58	0.66	12.11	1.65	12.29	0.027
0:100	2.48	1.06	12.55	1.95	12.88	0.06

2.7. Partition Coefficient of Octanol in Water

The partition coefficient of octanol in water (log *P*) is a simpler model to predict the solubility of a solute. The value is derived according to the partition law, which describes the distribution of a substance in a pair of immiscible solvents [10]. The partition coefficient of a substance is the constant ratio of concentration that partition in the immiscible solvents as described in Equation (5) [23].

$$P = \frac{\text{concentration of substance in nonpolar phase (octanol)}}{\text{concentration of substance in polar phase (water)}} \quad (5)$$

Log *P* value can be predicted by quantitative structure–property relationship (QSPR) algorithms in atomic contribution and group contribution (fragment-based prediction). The fragment-based prediction estimates the log *P* value of a molecule by sum of the fragmentary log *P*, while the atom-based method estimates the log *P* of a compound by sum of its atomic log *P* [24]. The log *P* value of a molecule can be also estimated from the commercial programs such as ACDLogP (Advanced Chemistry Development, Inc, Canada) and Molinspiration (miLogP2.2) [25]. The log *P* value ranges between −1 to 1 is considered as polar compounds, which are more soluble in water. On the other hand, a compound with the log *P* value greater than 4.5 is considered as a nonpolar compound, which will show poor aqueous solubility [10].

2.8. Calculation of Solubility Parameters

The interaction between rosmarinic acid and the above-mentioned solvent systems were estimated by Hildebrand and Hansen models, as well as log *P* value. The solubility parameters of the single-solvent system were obtained from the literature [14]. The solubility and log *P* of the solvent mixture are calculated based on Equations (6) and (7), respectively. The Hildebrand solubility parameter of rosmarinic was calculated by Equation (1). The physical properties such as enthalpy of vaporization and molar volume of rosmarinic acid were obtained from the literature [26]. The solubility parameter of a C18 bonded silica is reported to be 15.345 $MPa^{1/2}$ [27]. The components (δ_d, δ_p, and δ_h) of Hansen solubility parameter were calculated for rosmarinic acid by different group contribution methods as presented in Table 1. The similar components were also predicted using the demonstrative version of COSMOquick software (COSMO*logic* GmbH & Co. KG, Germany) for comparison. The log *P* of rosmarinic acid and solvent were calculated using the ACD ChemSketch freeware (Advanced Chemistry Development, Inc, Canada). The values of the parameters were presented in Table 2.

$$\delta_{mixture} = \frac{\sum x_i \delta_i}{\sum x_i} \quad (6)$$

$$\log P_{mixture} = \log\left[\frac{\sum x_i P_i}{\sum x_i}\right] \quad (7)$$

Table 2. Hansen solubility parameters for rosmarinic acid calculated by different group contribution methods.

Group Contribution Method	Hansen Solubility Parameters ($MPa^{1/2}$)			
	δ_d	δ_p	δ_h	δ_t
Hansen and Beerbower (1971)	21.45	7.8	18.85	29.62
Hoy (1967)	16.74	15.65	7.65	24.16
van Krevelen and te Nijenhuis (2009)	18.61	4.42	18.91	26.89
Stefanis and Panayitou (2008)	21.51	14.06	39.76	47.34
Just et al. (2013)	18.55	23.67	13.83	33.10
COSMOquick software	16.44	9.84	12.94	23.12

2.9. Solubility Models for Recovery Prediction

According to Hennion [28], recovery is defined as the ratio between the extracted amount and the loaded amount. The recovery for an analyte from SPE column is dependent on the breakthrough volume (V_b), which is the maximum sample volume that gives an ideal 100% recovery. The breakthrough volume can be estimated from the retention factor (k_s) of the analyte eluted by the mobile phase (Equation (8)). Hence, the recovery can also be predicted from the retention factor of the analyte.

$$V_b = (1 + k_s)(1 - 2.3/\sqrt{N})V_m \quad (8)$$

where

V_b: Breakthrough volume;
k_s: Retention factor;
N: Theoretical number of plates of SPE cartridge;
V_m: Void volume of the cartridge.

The retention mechanism is related to the hydrophobic interaction between the analyte, mobile phase, and solid phase, which can also be described by the log P values of the analyte [29]. In other words, the retention factor can be defined as the ratio of the solute concentration in non-polar phase (solid phase) to polar phase (mobile phase). The linear relationship of retention factor and log P value is expressed in (Equation (9)) [30].

$$\log k_s = a \log P + b \quad (9)$$

where a and b are constants related to the properties of column and mobile phase composition.

Alternatively, the retention factor can be expressed in terms of solubility parameters based on the Flory–Huggins model (Equation (10)) [31]. Therefore, the recovery of rosmarinic acid can be predicted from the log P value and the solubility parameters using multiple linear regression analysis.

$$\ln k_s = \frac{\upsilon_i}{RT}[(\delta_i - \delta_m)^2 - (\delta_i - \delta_s)^2] \quad (10)$$

where

k_s: Retention factor;
υ_i: Molar volume of analyte;
δ_i: Solubility parameter of rosmarinic acid;
δ_m: Solubility parameter of mobile phase;
δ_s: Solubility parameter of solid phase;

R: Gas constant at 8.314 J·mol^{-1}·K$^{-1;}$

T: Temperature in Kelvin (K).

3. Results and Discussion

In the present study, the performance of SPE to recover rosmarinic acid is highly dependent on the eluent system. The performance was evaluated by using the solubility models including Hildebrand and Hansen solubility, as well as log P. The solvent, which has a strong interaction with rosmarinic acid, is better in miscibility and elution power, and therefore rosmarinic acid is easily eluted out from the packed column. The magnitude of the interaction between rosmarinic acid and solvent can be estimated from the solubility parameters. Based on the theoretical estimation, the solvent system with a higher percentage of ethyl acetate will have a stronger interaction with rosmarinic acid and a smaller difference in the solubility. Table 3 clearly shows that only the difference in Hansen solubility is increasing with the decrease of solvent polarity. The correlation coefficient of rosmarinic acid and R_a is ~0.8. Of the three components in Hansen solubility, the results in Table 3 explains that dispersion and hydrogen bonding forces have a smaller difference than the polar bonding force of rosmarinic acid and solvent system. This is expected because rosmarinic acid consists of two molecules of caffeic acids and has five hydroxyl groups per molecule. These hydroxyl groups promote the hydrogen interaction with the solvent system for better miscibility. However, the concept of small difference for better miscibility of solute in solvent seems not in line with Hildebrand and log P models. The Hansen solubility model contributes a small difference in solubility in a more polar solvent system, which also recovered higher rosmarinic acid concentration.

Table 3. Solubility parameters of rosmarinic acid and solvent systems.

Ethyl Acetate—Chloroform (%)	Hildebrand Solubility Parameter (MPa$^{1/2}$)	Hansen Solubility Parameters (MPa$^{1/2}$)				Log P
	δ_H	δ_d	δ_p	δ_h	δ_t	
Rosmarinic acid	21.18	16.74	15.65	7.65	24.16	1.70
100:0	18.2	15.8	5.3	7.2	18.15	0.71
80:20	18.3	16.2	4.86	6.9	18.27	1.19
60:40	18.4	16.6	4.42	6.6	18.40	1.42
40:60	18.5	17.0	3.98	6.3	18.56	1.56
20:80	18.6	17.4	3.54	6.0	18.74	1.67
0:100	18.7	17.8	3.1	5.7	18.95	1.76

The components (δ_d, δ_p, and δ_h) in the Hansen solubility parameter were calculated for rosmarinic acid using different group contribution methods as presented in Table 1. The results found that the Hansen solubility parameters calculated by the Hoy group contribution method was closer to the predicted value from COSMOquick software, as well as the Hildebrand solubility parameter (Tables 1 and 2). According to Burke [32], the total force of Hansen solubility parameter is equal to the Hildebrand solubility parameter. Therefore, the Hansen solubility parameter calculated by the Hoy method was chosen in order to develop the solubility model for the prediction of rosmarinic acid recovery.

The Hildebrand and Hansen solubility models predict the recovery of rosmarinic acid based on the solute–solvent interaction, as well as the solute–sorbent interaction. Nevertheless, the Hildebrand solubility model was less accurate than the Hansen solubility model because the assumption of the Hildebrand solubility parameter, where the solubility behavior is similar to vaporization behavior, and the interaction force to vaporize a liquid is almost similar to dissolution. This kind of assumption is not applicable in the real-world scenario [33]. Furthermore, the Hildebrand solubility parameter is only applicable for nonpolar and non-hydrogen bonding solvents [14].

Log *P* model was less accurate in the prediction of solubility as its application is only limited for neutral or un-ionizable compounds. The log *P* value of ionizable compound varies with pH [34]. Besides that, the log *P* value estimated by the commercial software is not consistent and less accurate due to the difference in the assumptions for the estimation of log *P* value.

The experimental recovery of rosmarinic acid and the calculated retention factor (k_s) for the fractions from SPE are listed in Table 4. It was found that the retention factor of Hansen solubility is increased as the polarity of solvent system is decreased. In other words, a polar compound will preferably be retained in the non-polar cartridge rather than be eluted in the less polar solvent system. In this case, rosmarinic acid is a polar compound, which tends to be eluted from the C18 nonpolar cartridge by a polar solvent. This also explains that higher concentration of rosmarinic acid could be obtained at higher polarity of solvent system (higher percentage of ethyl acetate). However, the experimental recovery of rosmarinic acid was not in line with the retention factor of the Hildebrand solubility model, as well as not in good agreement with the difference in log *P* of rosmarinic acid and the solvent system. The difference in log *P* was found to be greater in the higher polarity of the solvent system. Supposedly, the smaller difference would be preferable for higher recovery of rosmarinic acid. Therefore, the recovery of rosmarinic acid from SPE cannot be well explained by the Hildebrand solubility model and log *P*.

Table 4. Experimental recovery of rosmarinic acid and calculated retention factor (k_s) for the fractions.

Ethyl Acetate—Chloroform (%)	Experimental Recovery (%)	Log $k_{s\cdot(Hildebrand)}$	Log $k_{s\cdot(Hansen)}$	Log k_s (log*P*)
100:0	23.73	−1.217	1.476	0.99
80:20	34.47	−1.246	1.914	0.51
60:40	41.12	−1.273	2.396	0.28
40:60	16.11	−1.300	2.921	0.14
20:80	10.942	−1.325	3.488	0.03
0:100	0.255	−1.349	4.098	0.06

The relationship between the recovery of rosmarinic acid and its retention factor was also evaluated statistically by using multiple linear regression (MLR) analysis. The linear equations of the relationship are expressed in terms of Hildebrand, Hansen, and log *P* solubility models in Equations (11)–(13), respectively.

$$\text{Recovery } (\%) = 278.78 + 207.45 \log k_{s.Hildebrand} \quad (11)$$

$$\text{Recovery } (\%) = 40.61 - 10.46 \log k_{s.Hansen} \quad (12)$$

$$\text{Recovery } (\%) = 4.11 + 24.16 \log k_{s(\log P)} \quad (13)$$

The linear equations were used to predict the recovery of rosmarinic acid from the plant crude extract (Table 5). The results revealed that all the three models could predict the recovery of rosmarinic acid. It is noted that Hansen solubility model is being the best solubility model to explain the recovery of rosmarinic acid from plant crude extract. This is because Hansen solubility gave the smallest error in recovery. However, log *P* contributes to the largest error in recovery if the data were compared to the experimental recovery. Previously, the same group of researchers published the use of SPE to recover rosmarinic acid up to 27% from the crude extract of the plant using water and acetonitrile as the solvent system [35].

The MLR results of the solubility models are presented in Table 6. The goodness of the fit was evaluated by the coefficient of determination (R^2), adjusted R^2, standard error, and *p*-value. Both the Hildebrand and Hansen solubility models show good fit results with R^2 and adjusted R^2 values larger than 0.80. Both models are also significant for rosmarinic acid recovery with the *p*-value less than 0.05, lower standard errors, and higher F values. The Hansen solubility model is likely to be the best fit

model for the recovery of rosmarinic acid from SPE. On the other hand, log *P* is the least fit model because of lower R^2 and higher standard error (Table 4).

Table 5. Experimental and predicted recovery of rosmarinic acid using different solubility models.

Ethyl Acetate: Chloroform	Experimental Recovery (%)	Model Predicted Recovery (%)		
		Hildebrand	Hansen	Log *P*
100:0	23.73	26.232	25.16959	28.02638
80:20	34.47	20.352	20.58031	16.42862
60:40	41.12	14.672	15.54211	10.87136
40:60	16.11	9.193	10.05498	7.48868
20:80	10.942	3.915	4.118914	4.83086
0:100	0.255	−1.163	−2.26608	5.55572

Table 6. The results of multiple linear regression for solubility models.

Solubility Model	R^2	Adjusted R^2	Standard Error (%)	*p*-Value
Hildebrand	0.866	0.832	4.512	0.007
Hansen	0.871	0.839	4.426	0.007
Log *P*	0.644	0.555	7.355	0.055

4. Conclusions

In this study, the interaction between rosmarinic acid and SPE eluents was described by three solubility models. The prediction of rosmarinic acid recovery was performed by MLR. The Hansen solubility model could explain the rosmarinic acid–solvent and rosmarinic acid–sorbent interactions better than the other models with higher R^2 and lower standard error. Most probably, the Hansen solubility model considers the three-dimensional energy composed of dispersion, polar, and hydrogen bonding forces. These forces are critical for polar compound, namely rosmarinic acid in this study.

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