



Systematic and practical solvent system selection strategy based on the nonrandom two-liquid segment activity coefficient model for real-life counter-current chromatography separation



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ABSTRACT

Solvent system selection is the first step toward a successful counter-current chromatography (CCC) separation. This paper introduces a systematic and practical solvent system selection strategy based on the nonrandom two-liquid segment activity coefficient (NRTL-SAC) model, which is efficient in predicting the solute partition coefficient. Firstly, the application of the NRTL-SAC method was extended to the ethyl acetate/*n*-butanol/water and chloroform/methanol/water solvent system families. Moreover, the versatility and predictive capability of the NRTL-SAC method were investigated. The results indicate that the solute molecular parameters identified from hexane/ethyl acetate/methanol/water solvent system family are capable of predicting a large number of partition coefficients in several other different solvent system families. The NRTL-SAC strategy was further validated by successfully separating five components from *Salvia plebeian* R.Br. We therefore propose that NRTL-SAC is a promising high throughput method for rapid solvent system selection and highly adaptable to screen suitable solvent system for real-life CCC separation.

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1. Introduction

Counter-current chromatography (CCC), a support-free chromatographic technique, has been accepted as an efficient technique for isolation and purification of natural compounds [1–4]. Unlike other conventional liquid chromatography such as HPLC, the stationary and mobile phases of CCC are both liquids, which are prepared from a biphasic solvent system [5]. An appropriate biphasic solvent system is the fundamental requirement for a successful CCC separation. However, selection of a proper biphasic liquid system is not an easy task, especially for the inexperienced CCC beginners, which has become a major barrier against the widespread adoption of CCC [3,5–8].

To facilitate the solvent system selection process, several strategies have been proposed. The ‘best solvent’ approach proposed

by Foucault is an intuitive and systematic method for screening biphasic liquid system [9]. The suitable solvent system is chosen by selecting a good solvent (so-called best solvent) for the target compound and two other solvents (generally immiscible) having strongly different polarities. Unfortunately, the ‘best solvent’ approach is rarely used in published works, which is mainly resulted from the fact that several ternary diagrams are not available or the CCC users are not familiar with the application of ternary diagram. Generally, the CCC biphasic solvent systems are composed of three or more solvents. For easing the task of solvent system selection, such multi-solvent systems are always organized in tables with different solvent ratios, so called solvent system families [10]. The polarity of a specific solvent system family is always changed continuously with the varying solvent proportions. Based on the predefined solvent system family, one can screen and modify the solvent system composition by measuring the partition coefficient. The Arizona (heptane/ethyl acetate/methanol/water) family is one of the most frequently used solvent system family [10]. Arizona family covers a wide range of polarity, from the most hydrophilic system A (HepEMWat 0:1:0:1) to the most hydrophobic system Z (HepEMWat 1:0:1:0). With the use of a

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self-designed CCC machine (analytical scale) equipped with three parallel columns, Lu et al. suggested that the optimum AZ composition can be found in half a day using less than 1 L of solvents [11]. Recently, the emergence of predictive method provides novel ideas for rapid solvent system selection [12–15]. By using the predictive method, solvent system selection is performed by predicting the solute partition coefficient in a series of solvent systems.

The partition coefficient (K) is a key index that usually determines which solvent system is suitable for CCC separation. Generally, a suitable solvent system should allow the solute K value to be ranged from 0.4 to 2.5 [16]. In particular, the biphasic system that allows the K value to be close to one is accepted as the best solvent system. In most of previous studies, solvent system selections were performed by experimentally measuring the K value of the targets. Experimental measurements of K values are time-consuming as well as labor intensive, which will reduce the efficiency of the solvent system selection. Hence, if the partition coefficient can be predicted or estimated, the efficiency of the CCC experiment will be significantly enhanced [17]. In fact, many research works have been done to do such predictions. For example, the octanol/water partition coefficient ($P_{O/W}$) has been accurately calculated and predicted [18,19]. However, the prediction of solute partition coefficient in CCC multi-solvent mixture is a more complex operation. Even so, the CCC researchers are still attempting to develop predictive methods for rapidly estimating the K values in CCC solvent systems [12–15]. It is of great importance to predict the partition coefficient for minimizing the experimental effort and cost involved in solvent system selection.

In our previous report [20], the nonrandom two-liquid segment activity coefficient (NRTL-SAC) model was introduced to develop a semi-empirical method. The established method can be successfully used to correlate and predict the solute partition coefficient in two commonly used solvent system families, i.e., hexane/ethyl acetate/methanol/water and heptane/methanol/water [20]. The NRTL-SAC model initially proposed by Chen et al. is a simple thermodynamic method, which employs four predefined conceptual segments to characterize the solvent or solute molecule [21,22]. The four segments including hydrophobic X, repulsive Y⁻, attractive Y⁺, and hydrophilic Z are used to account for the molecular interactions.

Since the search for a suitable solvent system largely depends on tedious and time-consuming experimental works which have often discouraged CCC users, a systematic and practical method is an urgent need for facilitating the solvent system selection process. Our previous work has demonstrated the potential of NRTL-SAC method used for correlation and prediction of the solute partition coefficients. The present contribution is focused on a broader application of the NRTL-SAC method to solvent system selection. The ultimate goal is to develop a systematic and practical strategy based on the NRTL-SAC model, which can be easily applied to rapid solvent system selection in CCC.

2. Materials and methods

2.1. Chemicals and reagents

All solvents used for preparation of biphasic solvent system were analytical grade from Shanghai Titan Scientific Co., Ltd (Tianjin, China). Methanol and acetonitrile used for HPLC analysis were HPLC grade from Jiangsu Hanbon Science and Technology Co., Ltd (Huaian, China). Deionized water was obtained with a Milli-Q (18.2 M Ω) system (Millipore Bedford, MA, USA).

Antipyrine, 3,4-dihydrobenzoic acid, coumarin, vanillin, ferulic acid, aspirin and 8-hydroxyquinoline were purchased from TCI, China. Salicin, theophylline, chlorogenic acid, nicotinic acid were

purchased from Sigma, China. Carvone and ionone were obtained from Acros, China.

The dried aerial parts of *Salvia plebeia* R.Br. was purchased from Bozhou, China.

2.2. Instrumentation

Ultimate 3000 Series HPLC systems, equipped with a vacuum degasser, binary pump, auto-sampler, thermostated column compartment and Ultimate 3000 DAD detector, were used for HPLC experiments. A RP Elite C₁₈ (i.d., 5 μ m, 250 mm \times 4.6 mm) column was used for HPLC separation.

The CCC separation was performed on a TBE-300A HSCCC apparatus. The instrument was equipped with three multilayer coil separation columns connected in series (the diameter of tube = 1.6 mm, total volume = 260 mL) and a 20 mL sample loop. The revolution radius R was 5 cm, and the β -value varied from 0.5 (internal layer) to 0.8 (external layer). The revolution speed of the apparatus was regulated with a speed controller in the range between 0 and 1000 rpm. An AKTA prime system (Amersham Pharmacia Biotechnology, Sweden) was used to pump the biphasic liquid system, monitor the UV absorbance, and collect the fraction. A temperature controller HX-1050 (Beijing Boyikang Lab Instrument Co. Ltd., Beijing, China) was utilized to maintain the separation temperature.

2.3. Determination of partition coefficients

The experimental procedure for determining the partition coefficient has been presented in our previous work [15]. In brief, the partition coefficient was measured by HPLC analysis as follows: a suitable amount (3 mg) of the solute was added into a test tube containing 8 mL pre-equilibrated two liquid phases (4 mL upper phase and 4 mL lower phase). The tube was shaken vigorously for 1 min, and the biphasic liquid system was allowed to settle for 1 h at room temperature (25 \pm 2 $^{\circ}$ C). Then 2 mL of each phase was evaporated to dryness. The residues were dissolved with 2 mL methanol and analyzed by HPLC. The K value was calculated through the following expression: $K = A_U/A_L$ (A_U and A_L represent the peak area of the solute in the upper and lower phase, respectively).

2.4. NRTL-SAC solvent system selection method

In previous report, we have shown that the solute partition coefficient is a function of the liquid-liquid equilibrium (LLE) data of the two-phase system and the NRTL-SAC molecular parameters (X, Y⁻, Y⁺, Z) of solvents and solute, of which the relationship is expressed as: $K = f(X, Y^-, Y^+, Z, LLE)$. Since previous report has presented a detailed procedure of the NRTL-SAC solvent system selection method, only a brief introduction to the procedure of the NRTL-SAC method would be described in this work. For applying the NRTL-SAC method to solvent system selection, a process that involves three steps needs to be performed. First, the solute K values in at least three selected solvent systems have to be measured. Second, the measured solute K values are used to fit the NRTL-SAC model, and identify the solute molecular parameters (X, Y⁻, Y⁺ and Z). At last, the solute K values in a large number of solvent systems can be predicted via the NRTL-SAC method. Depending on the calculated K values, one can directly choose the best solvent system for separation.

It should be noted that in the above steps, the measured K values, the solvent molecular parameters (X, Y⁻, Y⁺ and Z), and the liquid-liquid equilibrium (LLE) data of the two-phase system are used as input data. In this work, the molecular parameters of used solvents were taken from the literature (Table S1 in the supplemental material) [22], and the LLE data were calculated by using

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