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Competitive adsorption equilibrium model with continuous temperature dependent parameters for naringenin enantiomers on Chiralpak AD column

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ABSTRACT

Determination of competitive adsorption equilibrium model with continuous temperature dependent parameters is important for the design and optimization of a chromatographic separation process operated under non-isothermal conditions. In this study, linear pulse experiments were first carried to determine the parameters of transport-dispersive model and their temperature dependences in the range of 283–313 K. Overloaded band profiles of naringenin enantiomers on a Chiralpak AD column were acquired under various temperatures. Three of them were first separately fitted using Langmuir, linear-Langmuir and bi-Langmuir isotherm models substituted into the transport-dispersive column model. The comparison showed that bi-Langmuir model captures more details of the experimental results. This model was then extended with three extra parameters accounting for adsorption heat effects and used to simultaneously fit the band profiles at three temperatures.

1. Introduction

Thanks to the recent development of versatile chiral stationary phase (CSP) materials, high pressure liquid chromatographic (HPLC) processes, especially, the simulated moving bed (SMB) technology, have become a promising alternative for efficient chiral separation of enantiomers [1], which has become a top-class topic in both academic community and pharmaceutical industry due to the U.S. FDA regulations on newly developed stereoisomeric drugs [2] and process analytical technology (PAT) [3]. In the past two decades, several operation modes, such as VariCol [4,5], PowerFeed [6] and ModiCon [7], have been proven to facilitate higher SMB productivity with reduced solvent consumption. More recently, the feasibility of further improving SMB performance by introducing adsorption strength gradients has been investigated. Adsorption strength can be adjusted by varying mobile phase composition [8,9] and temperature [10,11]. Temperature has significant effects on almost all factors, namely, adsorption equilibrium, solubility, viscosity and diffusivity, which directly determine the efficiency of chromatographic separations. The implantation of temperature gradients has been studied for batch chromatography [12], binary SMB separation (TG–SMB) [10,11] as well as reactive SMB processes [13].

Computer-based simulation and optimization are necessary for successful design and operation of SMB processes [14]. Reliable determination of competitive adsorption equilibrium is required by SMB modeling. Inverse method (IM) is a numerical scheme that derives adsorption isotherm by fitting overloaded band profiles [15–17]. Compared with conventional methods such as frontal analysis (FA) and perturbation method (PM), IM has the advantages of less solvent consumption and reduced experimental time. In the case of chiral compound studies, IM is particularly attractive since its application allows for the use of only racemic samples. It has been successfully used for various enantiomers on analytical columns [18–24]. We showed in a previous study that satisfactory results can be obtained for preparative columns with relatively low efficiencies (few hundred number of theoretical plates) by incorporating IM with transport-dispersive (TD) model [25].

Temperature effects on adsorption isotherm parameters have been investigated by Kim et al. [26] and Ahmad et al. [22] using IM. In both studies, isotherm parameters were separately acquired at different temperatures. However, temporal and spatial temperature distribution is continuous in a non-isothermal SMB system. Therefore, modeling non-isothermal SMB processes requires an equilibrium model that is valid in the entire temperature range.

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The current study is aimed at acquiring a competitive adsorption equilibrium model with continuous temperature dependent parameters. For this purpose, naringenin enantiomers with different pharmaceutical activities [27] were used as the model system. The stationary phase is a Chiralpak AD preparative column and the mobile phase is methanol.

2. Theories

2.1. TD chromatography column model and parameters

The use of IM involves simulating the chromatography behaviors. In the case of preparative column, the efficiency is relatively low and TD model is required to describe component mass balance [25]. For a binary system, TD model has the following form:

$$\frac{\partial c_i}{\partial t} + \varphi\frac{\partial q_i}{\partial t} + u\frac{\partial c_i}{\partial z} - D_{L,i}\frac{\partial^2 c_i}{\partial z^2} = 0 \quad (1)$$

$$\frac{\partial q_i}{\partial t} = k_{m,i}(q_i^* - q_i) \quad (2)$$

$$q_i^* = f_i(c_A, c_B) \quad (3)$$

where c_i and q_i are concentrations of component i in the mobile and stationary phases, t is time, z is axial coordinate, φ is phase ratio related to total column voidage ε_t by $\varphi = (1-\varepsilon_t)/\varepsilon_t$, u is the interstitial velocity of mobile phase, D_L is axial dispersion coefficient, k_m is mass transfer coefficient, f defines the adsorption equilibrium, and A denotes the stronger adsorbate. Eq. (1) is a partial differential equation, the initial and boundary conditions are given as:

$$c_i(z)\big|_{t=0} = 0 \quad (4)$$

$$\left.\frac{\partial c_i}{\partial z}\right|_{z=0} = \frac{u}{D_L}(c_i|_{z=0} - c_{i,F}) \quad (5)$$

$$\left.\frac{\partial c_i}{\partial z}\right|_{z=L} = 0 \quad (6)$$

where L is the column length, and F denotes the feed solution. Eq. (2) is a local deferential equation and the initial condition is:

$$q_i(z)\big|_{t=0} = 0 \quad (7)$$

During the application of IM, the two parameters of TD model, namely, D_L and k_m, can be pre-determined by linear pulse experiments [25]. It may be proven that, in the linear range, mass transfer effects can be lumped into the axial dispersion, and TD model reduces to the simpler equilibrium-dispersive (ED) model that has only one model parameter N for each component. N is the number of equivalent theoretical plates and is correlated to u, D_L and k_m in the following form [28,29]:

$$\frac{1}{N_i} = \frac{2D_{L,i}}{uL} + \frac{2u}{\varphi L H_i k_{m,i}}\left(\frac{\varphi H_i}{1+\varphi H_i}\right)^2 = \frac{1}{N_{L,i}} + \frac{1}{k_{m,i}}u\lambda_i \quad (8)$$

where H is Henry's constant and $\lambda_i = (2/\varphi L H_i)((\varphi H_i)/(1+\varphi H_i))^2$ is defined as a function of φ, L and H for conciseness in the following discussions. In the linear range, H and N can be calculated using peak statistical moments

$$H_i = \frac{q_i^*}{c_i} = \frac{1}{\varphi}\left(\frac{\tau_i u}{L} - 1\right) \quad (9)$$

$$N_i = \frac{\tau_i^2}{\sigma_i^2} \quad (10)$$

where τ and σ^2 are the 1st and 2nd moments, respectively. Alternatively, if the column efficiency is high and the elution profile is symmetric, H and N can be estimated by

$$H_i = \frac{1}{\varphi}\left(\frac{t_{R,i}u}{L} - 1\right) \quad (11)$$

$$N_i = \alpha\left(\frac{t_{R,i}}{W_{h/2,i}}\right)^2 \quad (12)$$

where t_R is retention time, $W_{h/2}$ is width at half-height, $\alpha \approx 5.54$.

2.2. Competitive isotherm model

The use of IM requires that an isotherm model be proposed in advance. In the literature, Langmuir model is most commonly used to describe multi-component adsorption equilibrium. For a binary system, it has three parameters.

$$q_i^* = \frac{q_s b_i c_i}{1 + \sum(b_i c_i)} \quad i = A, B \quad (13)$$

Among various modifications to Langmuir model that have been used for the study of enantiomers, linear-Langmuir model is the simplest [30]. It introduces an additional parameter describing a non-selective portion of sites on which both enantiomers are linearly and equivalently adsorbed.

$$q_i^* = H_{ns}c_i + \frac{q_s b_i c_i}{1 + \sum(b_i c_i)} \quad (14)$$

where the footnote of "*ns*" denotes the non-selective sites. It should be mentioned that linear adsorption on non-selective sites at elevated concentrations is not a physically sound assumption. However, linear-Langmuir model has been widely used in chiral SMB studies [30]. For completeness, it is also considered in the current work.

Another normally used isotherm model is bi-Langmuir model, which assumes Langmuir adsorption on the non-selective sites and has five parameters for a binary system [25,29]:

$$q_i^* = \frac{q_{ns} b_{ns} c_i}{1 + b_{ns}\sum(c_i)} + \frac{q_s b_i c_i}{1 + \sum(b_i c_i)} \quad (15)$$

All of the above three isotherm models were evaluated in this work and will be involved in the following discussions.

2.3. Numerical scheme

The TD model was first discretized along axial direction by Martin–Synge method, which replaces the 2nd derivative ($\partial^2/\partial z^2$ term) in Eq. (1) with truncation error brought in by the 1st order backward approximation of $\partial/\partial z$ (numerical dispersion) [31]. As such, Eq. (1) becomes

$$\frac{dc_{i,M}}{dt} + \varphi\frac{dq_{i,M}}{dt} + u\frac{c_{i,M} - c_{i,M-1}}{\Delta z} = O(\Delta z^2) \quad (16)$$

where $\Delta z = 2D_L/u = L/N_L$ is the equally spaced stepsize, M denotes the mesh points ($M = 0$ for the inlet and $M = N_L$ for the outlet). Noted is that, due to the elimination of 2nd order derivatives, only inlet boundary condition is retained:

$$c_{i,M=0} = c_{i,F} \quad (17)$$

The discretized TD model (Eqs. (16) and (2)) forms an initial value problem (IVP) system, which was then integrated by the LSODE package [32].

IM acquires isotherm model parameters by fitting overloaded band profiles. The objective function in this study was defined as

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