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Experiment and modeling for the separation of guaifenesin enantiomers using simulated moving bed and Varicol units

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ABSTRACT

The separation of guaifenesin enantiomers by both simulated moving bed (SMB) process and Varicol process was investigated experimentally and theoretically, where the columns were packed with cellulose tris 3,5-dimethylphenylcarbamate (Chiralcel OD) stationary phase and a mixture of n-hexane and ethanol was used as mobile phase. The operation conditions were designed based on the separation region with the consideration of mass transfer resistance and axial dispersion, and the experiments to separate guaifenesin enantiomers were carried out on VARICOL-Micro unit using SMB process with the column configuration of 1/2/2/1 and Varicol process with the column configuration of 1/1.5/1.5/1, respectively. Single enantiomer with more than 99.0% purity was obtained in both processes with the productivity of 0.42 $g_{enantiomer}$/d cm^3 CSP for SMB process and 054 $g_{enantiomer}$/d cm^3 CSP for Varicol process. These experimental results obtained from SMB and Varicol processes were compared with those reported from literatures. In addition, according to the numerical simulation, the effects of solid-film mass transfer resistance and axial dispersion on the internal profiles were discussed, and the effect of column configuration on the separation performance of SMB and Varicol processes was analyzed for a few columns system. The feasibility and efficiency for the separation of guaifenesin enantiomers by SMB and Varicol processes were evaluated.

1. Introduction

As a multi-column and continuous chromatographic process, simulated moving bed (SMB) has become one of the powerful technologies for the separation and purification of enantiomers in the field of fine chemicals and pharmaceuticals [1,2]. The significant advantages of SMB over batch chromatography are more effective utilization of the expansive chiral stationary phase, and to achieve a higher productivity with lower solvent consumption et al.

Over the past decades, many modification technologies for the conventional SMB chromatography [3,4] have been proposed to expand the range of application and improve the separation performance, mainly, Varicol process, PowerFeed, ModiCon, Gradient SMB. Moreover, multi-component separation, for example, ternary separation, has also been accomplished by SMB process with three-zone or five-zone [5–7], the cascades of SMB process [8,9], and the JO process (pseudo-SMB) [10–13] et al.

Varicol process was proposed by Novasep Company (France), the principle of this process was based on the asynchronous shifting for the positions of the inlet and outlet lines [14–16]. The number of columns in each zone for Varicol process is different within the switch time, while the number of columns in each zone is kept constant for SMB process with the synchronous shifting. Therefore, the asynchronous shifting makes Varicol process more powerful than conventional SMB process. Varicol process has been proved to be superior to the SMB process in terms of productivity for a given purity of enantiomer by O. Ludemann-Hombourger group [17], where a 5-columns Varicol process permitted the same purities to be reached as a 6-columns SMB process. It was found that the productivity of a 5-columns system could be improved 18.5% over SMB process when Varicol process was performed. R.C.R. Rodrigues et al. [18,19] proposed a single column system to investigate the performance of SMB and Varicol processes. It was shown that the experimental period could be significantly reduced, and Varicol process achieved better performances than classical SMB.

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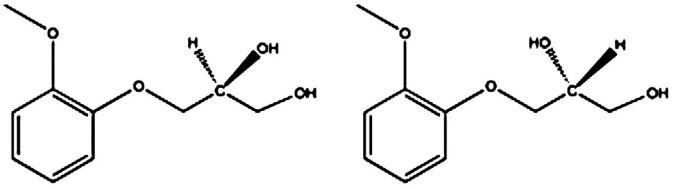

Fig. 1. Chemical structure of guaifenesin enantiomers.

Guaifenesin has been known as an expectorant drug and used widely in the racemic form. However, it has recently been speculated that perhaps one enantiomer may have a better physiological activity or fewer side effects than the other enantiomer [20]. A pair of guaifenesin enantiomers can be expressed as S-(+)-GUA and R-(−)-GUA, as shown in Fig. 1. P.S. Gomes group [21] proposed a procedure to separate racemic mixture of guaifenesin on FlexSMB-LSRE unit with Chiralcel AD chiral stationary phase and n-heptane/ethanol (85/15) mobile phase. Single enantiomer with above 98% purity and 23 $g_{enantiomer}/(dm^3 CSP\ day)$ productivity were obtained. E.R. Francotte group [22] separated the guaifenesin enantiomers by SMB technology with 16 columns using heptane/ethanol (65/35) mobile phase and Chiralcel OD stationary phase. The purity of single enantiomer could reach more than 99.0% and the productivity of each enantiomer was up to 80.6 g/(day·kg CSP).

In this work, guaifenesin enantiomers are separated by Varicol process with the asynchronous control system on VARICOL-Micro unit, and compared with experimental results obtained by the synchronous SMB process, where Chiralcel OD is used as stationary phase and a mixture of n-hexane/ethanol is used as mobile phase. Furthermore, the experimental results are compared with the predicted results by the mathematical model, and the separation performance for guaifenesin enantiomers by SMB and Varicol processes was evaluated.

2. Theoretical

2.1. Modeling equations

In this work, mathematical model is used to predict the separation performance of guaifenesin enantiomers by SMB and Varicol processes [23–26], where axial dispersion and mass transfer resistances in the columns and chiral stationary phases are taken into account. The solid-film linear driving force model is used to describe the intraparticle mass transfer rate.

Mass balance over a volume element of the packed column k is:

$$\frac{\partial c_{i,k}}{\partial t} + \frac{u_k}{\varepsilon_T}\frac{\partial c_{i,k}}{\partial x} + \frac{(1-\varepsilon_T)}{\varepsilon_T}\frac{\partial q_{i,k}}{\partial t} = D_{ax,i,k}\frac{\partial^2 c_{i,k}}{\partial x^2} \quad (1)$$

Mass balance in the chiral stationary phase is:

$$\frac{\partial q_{i,k}}{\partial t} = k_{L,i,k}\frac{3}{r_p}(q_{eq,i,k} - q_{i,k}) \quad (2)$$

where $i = A, B$ are the species in the mixture, $c_{i,k}$ (mg/ml) is the concentration of species i in the column k in the fluid phase, $q_{i,k}$ (mg/ml) is the average adsorbed phase concentration in adsorbent, $q_{eq,i,k}$ (mg/ml) is the adsorbed phase concentration in equilibrium with the fluid phase concentration, ε_T is the total porosity in the column, u_k (cm/s) is the superficial velocity, x (cm) is the axial distance from the column entrance, t (s) is the time, $D_{ax,i,k}$ (cm^2/s) is the axial dispersion coefficient of species i in the column k, $k_{L,i,k}$ (cm/s) the mass transfer coefficient of species i in the column k.

The competitive adsorption isotherms of guaifenesin enantiomers on the specified chiral stationary phase are determined by the individual experiments, the general equation can be described as:

$$q_{eq,A,k} = f_A(c_{Ak}, c_{Bk}) \quad (3a)$$

$$q_{eq,B,k} = f_B(c_{Ak}, c_{Bk}) \quad (3b)$$

The initial and boundary conditions in each packed column k are:

$$t = 0, \qquad c_{i,k} = 0 \quad (4)$$

$$x = 0 : D_{axi,k}\frac{\partial c_{i,k}}{\partial x} = u_k(c_{i,k} - c_{i,k}^{in}) \quad (5a)$$

$$x = L_k : \frac{\partial c_{i,k}(t, x = L_k)}{\partial x} = 0 \quad (5b)$$

where L_k (cm) is the length of the column k, $c_{i,k}^{in}$ (cm^2/s) is the inlet concentration of species i in the column k.

Mass balance at each node is:

$$\text{At eluent node,} \quad c_{i,k+1}^{in} = \frac{Q_4 c_{i,k}(t, x = L_k)}{Q_1} \quad (6a)$$

$$\text{At extract node,} \quad c_{i,k+1}^{in} = c_{i,k}(t, x = L_k) \quad (6b)$$

$$\text{At feed node,} \quad c_{i,k+1}^{in} = \frac{Q_F C_i^F + Q_2 C_{i,k}(t, x = L_k)}{Q_3} \quad (6c)$$

(6d)At raffinate node, $c_{i,k+1}^{in} = c_{i,j}(t, x = L_k)$(6e)At the node between the other columns, $c_{i,k+1}^{in} = c_{i,k}(t, x = L_k)$

Global balances are:

$$Q_1 = Q_D + Q_4 \quad (7a)$$

$$Q_2 = Q_1 - Q_{Ex} \quad (7b)$$

$$Q_3 = Q_2 + Q_F \quad (7c)$$

$$Q_4 = Q_3 - Q_{Ra} \quad (7d)$$

where Q_1 (ml/min), Q_2 (ml/min), Q_3 (ml/min), Q_4 (ml/min) are the flow rates of section 1, 2, 3 and 4 in SMB and Varicol processes. Q_{Ra} (ml/min), Q_{Ex} (ml/min), Q_F (ml/min), Q_D (ml/min) is raffinate flow rate, extract flow rate, feed flow rate and desorbent flow rate, respectively. C_i^F (mg/ml) is the concentration of component i in feed solution.

2.2. Numerical solution

Eqs. (1)–(7) include partial differential and algebraic equations. The partial differential equations are transferred into a set of ordinary differential-algebraic equations through the discretization of the axial domain, where the discretization method of orthogonal collocation on finite element method (OCFEM) over a uniform grid of 30 intervals is used. Then, the set of ordinary differential-algebraic equations are integrated by the DASOLV solver with the absolute and relative tolerances of 10^{-5}. The simulation is carried out using the software of gPROMS 3.2 purchased from Process System Enterprise (London).

For the simulation of SMB process, each column plays different function during one cycle because of the periodic switch of the inlet and outlet lines. So, the boundary conditions for each column change at the end of each switch time interval. The same opinion is also suitable for the simulation of Varicol process. A Varicol 1/1.5/1.5/1 configuration can be considered as the combination of SMB with column configuration of 1/2/1/1 and SMB with column configuration of 1/1/2/1.