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Enantioseparation of racemic aminoglutethimide using asynchronous simulated moving bed chromatography

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ABSTRACT

The separation of aminoglutethimide enantiomers by the continuous multicolumn chromatographic processes were investigated experimentally and theoretically, where the columns were packed with cellulose tris 3,5-dimethylphenyl-carbamate stationary phase (brand name Chiralcel OD) and mobile phase was a mixture of *n*-hexane and ethanol with monoethanolamine additive. The continuous enantioseparation processes included a synchronous shifting process (SMB) and an asynchronous shifting process (VARICOL), which allowed reducing the column number (here from six-column SMB to five-column VARICOL process). Transport-dispersive model with the consideration of both intraparticle mass transfer resistance and axial dispersion was adopted to design and optimize the operation conditions for the separation of aminoglutethimide enantiomers by SMB process and VARICOL process. According to the optimized operation conditions, experiments were carried out on VARICOL-Micro unit using five-column VARICOL process with 1/1.5/1.5/1 configuration and six-column SMB process with 1/2/2/1 configuration. Products of R-aminoglutethimide (R-AG) enantiomer and S-aminoglutethimide (S-AG) enantiomer with more than 99.0% purity were obtained continuously from extract stream and raffinate stream, respectively. Furthermore, the experiemntal data obtained from five-column VARICOL process were compared with that from six-column SMB process, the feasibility and efficiency for the separation of guaifenesin enantiomers by VARICOL processes were evaluated.

1. Introduction

Enantiomers are stereoisomers with nonsuperimposable mirror images, in generally, called by classical notation as D or L, as R or S, or as (+) or (−) enantiomer, respectively. In the pharmaceutical industry, it is clear evidence that often only one enantiomer of a chiral drug provides the desired physiological effect, and the other enantiomer has no effect or is even harmful in many cases. Regulators demand increasingly that chiral drugs are administered in an optically pure form. Therefore, efforts are intensified in industrial and academic research to develop techniques that are capable of producing pure enantiomer with the cheap, reliable, and widely applicable enantioseparation processes. Broader reviews on enantioseparation at the analytical and preparative scales are given in references [1–3].

Aminoglutethimide (AG), 3-(4-aminophenyl)-3-ethyl-2,6-piperidinedio, is used clinically as a drug in the treatment of hormone-dependent metastatic breast cancer, and also in the treatment of adrenocortical tumors and Cushing syndrome. Aminoglutethimide is a typical chiral drug with R-aminoglutethimide (R-AG) enantiomer and S-aminoglutethimide (S-AG) enantiomer, respectively. There is the evidence that R-AG enantiomer has the greater steroidogenesis inhibitory activity (two or three times more potent than racemic AG), while S-AG enantiomer has very little activity. For a safer and more effective drug, it is better to separate aminoglutethimide racemate into single enantiomer before use [4–6].

Many chromatographic methods capable of resolving aminoglutethimide racemate have been reported in literatures [6–11]. Direct liquid chromatographic resolution of aminoglutethimide racemate using Chiralcel OD and Chiralcel OJ columns was carried out [6]. The maximum separation factors with 2-propanol/hexane mobile phase were 8.87 using Chiralcel OD column and 10.34 using Chiralcel OJ column, respectively. Separation of aminoglutethimide racemate on Chiralpak IA column by high performance liquid chro-

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matography (HPLC) was investigated [7]. It was found that the separation factors reached 4.19, 2.27, and 1.88 with the non-conventional mobile phases, such as methyl-*tert*-butyl ether-THF (90:10), pure dichloromethane and pure acetonitrile, respectively. A capillary electrophoretic method for the separation of aminoglutethimide enantiomers using methylated-β-cyclodextrin chiral selector was developed, and the good separation of the racemic AG mixture with separation factor 2.1 was achieved [8]. Enantioseparation of racemic aminoglutethimide was investigated on the capillary Chiralpak ID-3 column with *n*-hexane/2-propanol mobile phase, and separation factor reached 2.25 [9]. Recognitive nano-thin-film composite beads were prepared [10] for the resolution of racemic aminoglutethimide. Furthermore, aminoglutethimide enantiomers were continuously separated by simulated moving bed (SMB), a SMB-Unit Sorbex Prep (UOP, USA) equipped with sixteen 60mm × 16 mm Chiralcel OJ columns, a production of 5.27 g of each enantiomer per day has been obtained with a purity of 99.8% for S-enantiomer (in extract stream) and 99.9% for R-enantiomer (in raffinate stream) [11].

In this work, we intend to investigate enantioseparation of aminoglutethimide racemate using VARICOL process, an improved simulated moving bed (SMB) process. As known, SMB process has become one of the powerful technologies for the separation and purification of enantiomers [12–15]. The significant advantage of SMB process over batch chromatography is more effective utilization of the expansive chiral stationary phase to achieve a higher productivity with lower solvent consumption. There is a tendency to construct the multicolumn SMB unit with a small number of columns in order to reduce the packed amount of expensive chiral stationary phases. For the small number of columns, VARICOL process is proved to be superior to the conventional SMB process in terms of productivity and solvent consumption for a given purity of enantiomer [16–25]. The principle of VARICOL process is based on the asynchronous shifting for the positions of the inlet and outlet lines. The number of columns in each zone for VARICOL process is different within the switch time interval, while the number of columns in each zone is kept constant for SMB process with the synchronous shifting. According to our previous research [24], it was found that 5-columns VARICOL process (1/1.5/1.5/1) had a better performance than 6-columns SMB process (1/2/2/1) for resolution of guaifenesin racemate, the productivity was increased by 17.0% due to the reduction of one packed column in VARICOL process.

In this work, aminoglutethimide racemate is separated using VARICOL process, where columns are packed with cellulose tris 3,5-dimethylphenylcarbamate (brand name Chiralcel OD) stationary phase and a mixture of *n*-hexane and ethanol with monoethanolamine additive is used as mobile phase. The mathematical model is set up to design and optimize the operation conditions, and experiments are run on VARICOL-Micro unit for the separation of aminoglutethimide racemate using VARICOL process with the column configuration of 1/1.5/1.5/1 and SMB process with the column configuration of 1/2/2/1, respectively. Up to now, this work provides the first enantioseparation data of aminoglutethimide racemate using VARICOL process in the literature, the feasibility and effectiveness of this process is evaluated.

2. Theoretical

2.1. Transport-dispersive model for VARICOL process and SMB process

Transport-dispersive model [26–29], with the consideration of both the mass transfer resistance inside chiral stationary phase and axial dispersion in the packed columns, is described as following, where the solid-film linear driving force model is used to calculate the intraparticle mass transfer rate.

Mass balance in the packed column k is:

$$\frac{\partial c_{i,k}}{\partial t} + \frac{u_k}{\varepsilon}\frac{\partial c_{i,k}}{\partial x} + \frac{(1\text{-}\varepsilon)}{\varepsilon}\frac{\partial q_{i,k}}{\partial t} = D_{L,i}\frac{\partial^2 c_{i,k}}{\partial x^2} \tag{1}$$

Mass tansfer rate for chiral stationary phase is:

$$\frac{\partial q_{i,k}}{\partial t} = k_{L,i}(q^*_{i,k} - q_{i,k}) \tag{2}$$

where $i = R, S$ are enantiomers in racemate mixture, $c_{i,k}$(mg/ml) is i enantiomer concentration of mobile phase in k column, $q_{i,k}$(mg/ml) is the average adsorbed concentration of the chiral stationary phase, $q^*_{i,k}$ (mg/ml) is the adsorbed concentration of the chiral stationary phase in equilibrium with the mobile phase concentration, ε is bed porosity in the packed column, u_k(cm/s) is superficial velocity, x(cm) is axial distance along the packed column, t(s) is time, $D_{L,i}$(cm^2/s) is axial dispersion coefficient of enantiomer i in the packed column, $k_{L,i}$(cm/s) is the overall mass transfer coefficient of enantiomer i in the packed column.

The competitive adsorption isotherms of aminoglutethimide racemate on the specified chiral stationary phase should be determined by the individual experiments. In general, Henry-Langmuir isotherm model [30] is used to describe the competitive adsorption between two enantiomers. The general equation is described as:

$$q^*_{i,k} = H_i c_{i,k} + \frac{q_s b_i c_{i,k}}{1 + \sum_{i=1}^{2} b_i c_{i,k}} \tag{3}$$

Where H_i is the equilibrium constant of enantiomer i on nonselective sites, q_s is the saturation capacity on enantioselective sites. b_i(ml/mg) is equilibrium constant of enantiomer i on enantioselective sites.

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

$$t = 0, c_{i,k} = 0 \tag{4}$$

$$x = 0 : D_{L,i}\frac{\partial c_{i,k}}{\partial x} = \frac{u_k}{\varepsilon}(c_{i,k} - c^{in}_{i,k}) \tag{5a}$$

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

where L_k(cm) is the length of a column k, $c^{in}_{i,k}$(mg/ml) is inlet concentration of enantiomer i in the packed column k.

To reduce the consumption of mobile phase, a close loop is adoped for the recylce utilization of mobile phase. Mass balance at each node is expressed as:

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

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

$$\text{At feed node, } c^{in}_{i,k+1} = \frac{Q_F C^F_i + Q_2 C_{i,k}(t, x = L_k)}{Q_3} \tag{6c}$$

$$\text{At raffinate node, } c^{in}_{i,k+1} = c_{i,j}(t, x = L_k) \tag{6d}$$

$$\text{At node between the other coloumn, } c^{in}_{i,k+1} = c_{i,k}(t, x = L_k) \tag{6e}$$

Global balances are:

$$Q_1 = Q_D + Q_4 \tag{7a}$$

$$Q_2 = Q_1 - Q_{Ex} \tag{7b}$$

$$Q_3 = Q_2 + Q_F \tag{7c}$$