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Separation of Tröger's Base Enantiomers Through a Combination of Simulated Moving Bed Chromatography and Crystallization

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Abstract. This paper studies the coupling of simulated moving bed (SMB) chromatography with crystallization for the separation of Tröger's base enantiomers. SMB is used to achieve a certain level of enrichment and then evaporative crystallization of the extract and raffinate streams leads to the final product with the specified purity. The optimization of the combined process is based on thermodynamic data about adsorption isotherms of the two enantiomers in ethanol on microcrystalline cellulose triacetate (CTA) and about solubility of the two enantiomers in ethanol. The results, obtained using a genetic algorithm, prove that there is an optimal value of the purity achieved in the SMB that maximizes the productivity of the combined process.

Keywords: simulated moving bed, crystallization, hybrid process, Tröger's base

1. Introduction

Literature reports indicate that there is a potential gain in productivity when simulated moving bed (SMB) chromatography and crystallization are coupled (see Fig. 1), especially for the separation of enantiomers.

In particular, an improved recovery of enantiomerically pure (−) praziquantel from racemic mixtures by continuous chromatography and crystallization has been reported (Lim et al., 1995). Likewise, a study of the separation of the enantiomers of mandelic acid in aqueous solution indicated an increase of productivity achievable in the combined process (Lorenz et al., 2001). However, beside these examples no thorough analysis of this hybrid process has been reported so far. Such analysis is the objective of this work, where we optimize the hybrid process in the case of the separation of the Tröger's Base (TB) enantiomers (see Fig. 2). This is based on comprehensive thermodynamic data about adsorption isotherms (Pedeferri et al., 1999) and solubility (Worlitschek et al., 2004), and on a proper definition of the objective function. TB is frequently used as a model system in different fields including chiral chromatography (Jacques and Collet, 1981); its derivatives can be used for applications in organic chemistry and bio-chemistry. Our strategy is that of considering a real system, in order to be realistic. At the same time, we intend to draw conclusions that bear general applicability.

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2. Adsorption Isotherms

Adsorption equilibrium of (+)-TB and (−)-TB on microcrystalline cellulose triacetate (CTA) with ethanol as mobile phase at 50°C are well described in a rather broad concentration range by a quadratic and a Langmuir isotherm, respectively (Pedeferri et al., 1999):

$$(+)\text{-TB: } n_A^\circ = \frac{6.986 c_A (0.627 + 0.594 c_A)}{1 + 0.627 c_A + 0.297 c_A^2} \approx \frac{6.45 c_A}{1 + 0.39 c_A} \tag{1}$$

$$(-)\text{-TB: } n_B^0 = \frac{2.18 c_B}{1 + 0.065 c_B} \tag{2}$$

The competitive binary equilibrium can be described properly using Ideal or Real Adsorption Solution

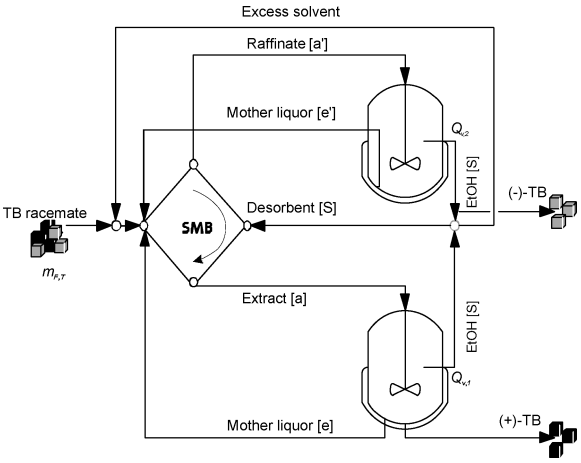

Figure 1. A schematic diagram of the hybrid process. Letters in square brackets refer to the corresponding compositions in Fig. 4. It may be noted that there is no recycle of the mother liquor in the 'base case' where the specified purity is already achieved in the SMB unit.

theory (IAS or RAS) (Migliorini et al., 2000). To speed up the computations, in the following simulations we approximate the quadratic isotherm of (+)-TB with a Langmuir isotherm (see the right hand side of Eq. (1) and Fig. 3), and use the corresponding binary Langmuir isotherm to describe competitive adsorption and to guide the choice of the operating conditions for the SMB.

3. Solid-Liquid Equilibrium

Many enantiomers crystallize forming a racemic compound, i.e. crystals containing both enantiomers in a 1:1 ratio, and thus exhibiting a eutectic also in the presence of a solvent (Jacques and Collet, 1981). The Tröger's base enantiomers exhibit in fact this behavior, as demonstrated by their solubility diagram in ethanol that has been recently measured at 25, 35, and 50°C and reported (Worlitschek et al., 2004). The equilibrium data have been well described by a proper solution model assuming ideal behavior for the two enantiomers and non-ideal behavior between each enantiomer and ethanol (using NRTL activity coefficients). The experimental data and the calculated solubility curves are illustrated in Fig. 4. In the diagram, the most important piece of information for the analysis that follows is the composition of the eutectic points at 50°C, namely $w_{(+)} = 0.1287$, and $w_{(-)} = 0.0167$ in the case of point e, and $w_{(+)} = 0.0167$, and $w_{(-)} = 0.1287$ in the case of e'. These compositions correspond to a purity of 88.5%.

4. SMB and Hybrid SMB-Crystallization Process

The Simulated Moving Bed (SMB) technology is an established technique for continuous chromatographic separation of enantiomers (Juza et al., 2000). As illustrated in Fig. 5, the SMB technique is based on a simulated countercurrent contact between the mobile phase and the stationary adsorbent phase. Two inlet streams, namely the feed mixture (to be separated), and the eluent, and two outlet streams, namely the extract stream enriched in the more retained species (A, (+)-TB in this case), and the raffinate stream enriched in the less retained compound (B, (−)-TB)), are present in a SMB unit. Often the racemate, and the product enantiomers, which are obtained upon evaporative crystallization of the extract and raffinate streams from the SMB, are in solid form. Usually, the enantiomer purity specifications of the SMB outlets are those of the final product; this is defined as the 'base case' in this study and its performance is used as reference for those achieved in the hybrid process. In the hybrid process of Fig. 1, the SMB extract and raffinate purities are lower than the prescribed value, which is achieved only after crystallization. Thus, having relaxed its purity requirements, the SMB can operate with higher productivity. However, the mother liquors of the crystallizers still contain the valuable enantiomers and have to be recycled. In order to guarantee that the crystallizers yield enantiopure crystals, the composition of their feed streams must be properly controlled (see Fig. 4). The hybrid process can in fact be operated only if the SMB purity is higher than that of the eutectic point in the solubility diagram (at 50°C point e is $w_{(+)} = 0.1287$ or $c_{A,e} = 114.9$ g/l,

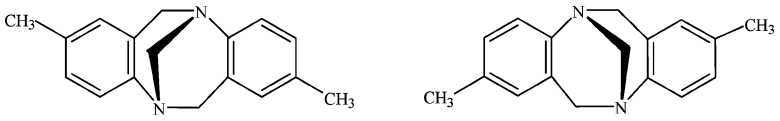

Figure 2. Tröger's Base is chiral with a C_2 axis of symmetry due to the blocked conformation of the two nitrogen atoms of the methano-diazocine bridge.

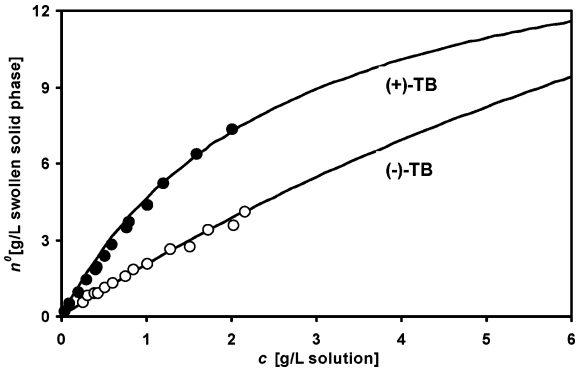

Figure 3. Experimental (symbols) (Pedeferri et al., 1999) and fitted Langmuir isotherms (lines) of TB enantiomers at 50°C.

and $w_{(-)} = 0.0167$ or $c_{B,e} = 14.9$ g/L for an EtOH density of 0.763 g/l, corresponding to 88.5% purity).

The simulations in this work are carried out using a detailed SMB model that properly accounts for the effect of flow rate on column efficiency based on experimental data, thus implying a proper evaluation of the effect of column size on separation performance (Migliorini et al., 2000). This is an important feature of our simulations, since it guarantees that the evaluation of the SMB performance is accurate under all conditions examined. On the contrary, the crystallizers are modeled through simple material balances, assuming equilibrium conditions at 50°C between enantiopure crystals and mother liquor, at the experimental eutectic composition. In practice, the crystallizer performance depends also on kinetic effects that might lead to reduced crystal purity due to inclusions, and the performance of the hybrid process will be worse than that predicted in this study. Inclusion of kinetic effects in the modeling of the crystallizers requires a large amount of information that is not available, and is beyond the scope of this work.

5. Optimization

As in many cases, the problem we are dealing with is more easily formulated in terms of a multiobjective optimization problem. In the case of the SMB-crystallization hybrid, the process performance are measured in terms of throughput per unit volume of the SMB unit (assuming that the expensive part of the investment cost is associated with the chromatographic columns and the stationary phase), i.e. in terms

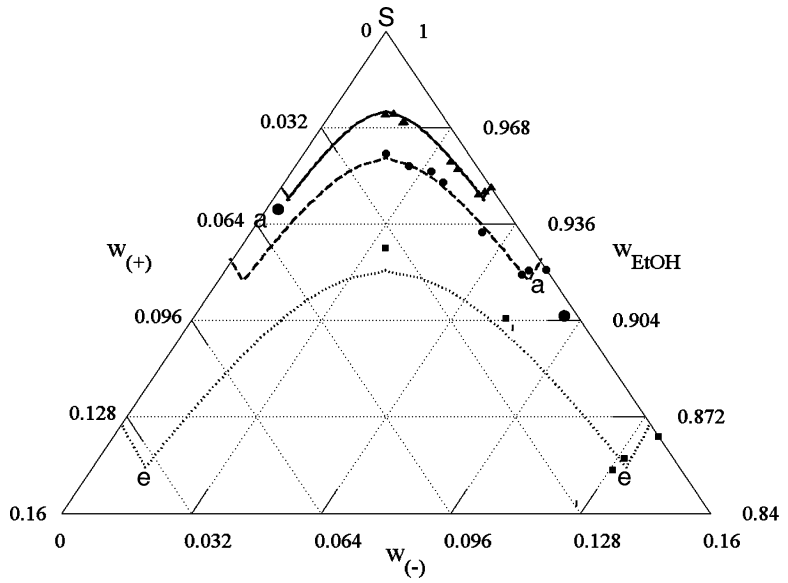

Figure 4. Ternary solubility diagram in terms of mass fractions, $w_{(-)}$, $w_{(+)}$, and w_{EtOH}; experimental data at 25°C (triangles), 35°C (circles), and 50°C (boxes). Lines correspond to calculated liquidus lines (Worlitschek et al., 2004). Four points are highlighted in this diagram that correspond to the compositions of specific streams in Fig. 1. These are points a and a′, corresponding to the extract and raffinate streams, respectively, and points e and e', corresponding to the mother liquors that are recycled from the extract and raffinate crystallizer, respectively. The eutectic points at 50°C have compositions: $w_{(+)} = 0.1287$, and $w_{(-)} = 0.0167$ in the case of point e; $w_{(+)} = 0.0167$, and $w_{(-)} = 0.1287$ in the case of point e'.

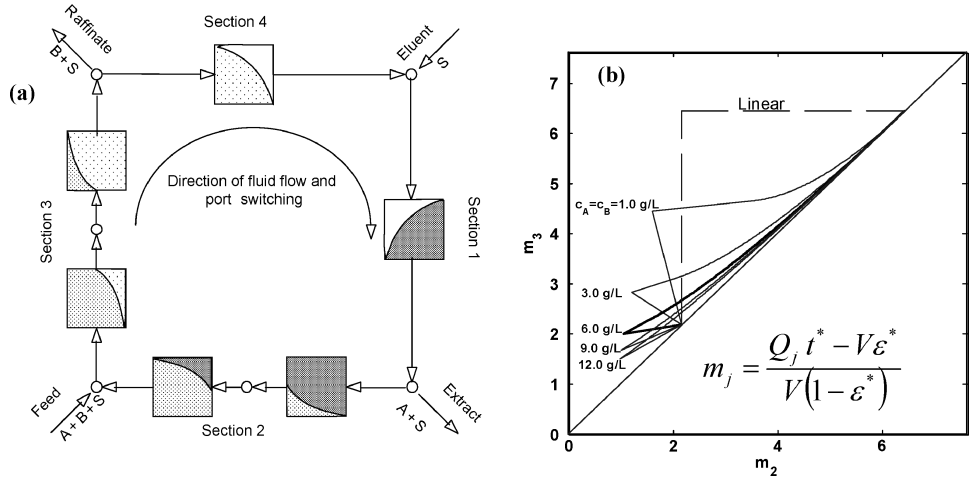

Figure 5. (a) Scheme of an SMB unit with six columns and configuration 1-2-2-1. (b) Regions of complete separation in the operating parameter plane for an SMB with different feed concentrations. In the equation for m_j there are: Q_j, flow rate in section j; t^*, switch time; V, column volume; ε^*, overall bed void fraction.

of productivity, and of energy costs associated to the evaporation of the solvents in the crystallizers. We are implicitly assuming that in all cases, the starting material is in solid form, and that the final products must be delivered also as powders at a specified purity. This corresponds to aiming at the maximization of the specific productivity, Pr, i.e.

$$\mathrm{Pr} = \frac{m_{F,T}}{AL} \tag{3}$$

and at the minimization of the specific solvent evaporation rate, Q_v, i.e.

$$Q_v = \frac{Q_{v,1} + Q_{v,2}}{m_{F,T}} \tag{4}$$

where $m_{F,T}$ is the total mass of feed (see Fig. 1), A and L are the column cross-sectional area and length, respectively, $Q_{v,1}$ and $Q_{v,2}$ are the flow rates of solvent evaporated from each crystallizer.

The optimization problem is mathematically formulated as follows:

$$\text{Max} \quad J_1 = \mathrm{Pr}(m_1, m_2, m_3, m_4, L, t^*), \tag{5}$$

$$\text{Min} \quad J_2 = Q_v(m_1, m_2, m_3, m_4, L, t^*), \tag{6}$$

where m_1, m_2, m_3, m_4 are the flow rate ratios in the four sections of the SMB (see Fig. 5(b) for the definition). The two functions above have to be optimized subject to a number of constraints, which define the separation specifications (purities of extract, P_E, and raffinate, P_R) and express the technical constraints on the plant (maximum pressure drop, $\Delta p_{\max}$, and minimum switch time, $t^*_{\min}$):

- overall feed concentration to the SMB = 12 g/l (as shown in Fig. 5(b), to guarantee robust operating conditions; material balances show that the feed concentration remains the same for the hybrid process);
- $P_E = P_R = x \pm 0.002$ (with $x = 0.900$; 0.950; 0.970; 0.999, where the last value corresponds to the base case, and it is assumed that the crystallizers deliver a product with the specified purity);
- $\Delta p_{\max} = 40$ bar;
- $t^*_{\min} = 30$ s;
- SMB configuration: 1:2:2:1.

The pressure drop in the columns is computed using Darcy's law:

$$\frac{\Delta p}{L} = \phi Q, \tag{7}$$

and the following parameter values are used in the simulations (Migliorini et al., 2000): dispersion coefficients, $D_{L,A} = D_{L,B} = 5.00 \times 10^{-4}$ cm^2/s (at $u =$ 0.05 cm/s); mass transfer coefficients, $k_A = 0.09$ 1/s; $k_B = 0.15$ 1/s; overall bed void fraction $\varepsilon^* = 0.59$; $\phi = 2.34 \times 10^6$ g/(s^2 cm^2); $T = 50^\circ$C. As indicated in Eqs. (5) and (6), six decision variables are considered in this study. The switch time t^* corresponds always

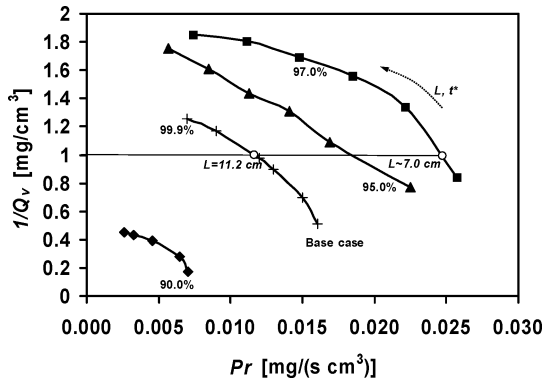

Figure 6. Pareto optimal solutions of the 'base case' and of the hybrid process for different purity values reached in the SMB.

to the maximum pressure drop, thus maximizing productivity. A non-sorting genetic algorithm (NSGA) is used as an optimization algorithm (Zhang et al., 2003).

6. Results, Discussion and Conclusions

The solution of the two-objective optimization problem can be represented in the plane, whose coordinates are the two objective functions of Eqs. (5) and (6), as a Pareto set, i.e. a set of non-dominant points (see Fig. 6). Moving away from any point in the Pareto set, only one objective function can be improved but not both. It can be readily observed in Fig. 6, that the Pareto set for 90.0% purity in the SMB lies below the 'base case' of 99.9% purity. On the contrary for 95.0% and 97.0% purity in the SMB, the Pareto curves are above that of the 'base case', thus indicating that better performance can indeed be achieved by adopting the hybrid process. It is worth noting that the length of the column varies along a Pareto curve, and that for a given fixed evaporation flow rate the hybrid process allows saving stationary phase, besides productivity gain.

The results presented here prove that the hybrid process outperforms the 'base case' SMB provided that the purity reached in the SMB crystallization is large enough. There is in fact an optimum SMB purity value (about 97% in this case), whose occurrence is due to the detrimental effect of the recycle of the mother liquor that increases while the purity specified for the SMB step decreases.

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