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Relative importance of column and adsorption parameters on the productivity in preparative liquid chromatography. I: Investigation of a chiral separation system

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ABSTRACT

Starting out from an experimental chiral separation system we have used computer simulations for a systematic investigation on how the maximum productivity depends on changes in column length, packing particle size, column efficiency, back pressure, sample concentration/solubility, selectivity, retention factor of the first eluting component and monolayer saturation capacity. The study was performed by changing these parameters, one at a time, and then calculating the corresponding change in maximum productivity. The three most important parameters for maximum production rate was found to be (i) the selectivity (ii) the retention factor of the first eluting component and (iii) the column length. Surprisingly, the column efficiency and sample concentration/solubility were of minor importance. These findings can be used as rough guidelines for column selection, e.g. a low-efficiency column are more likely perform better, in terms of productivity, than a high-efficiency column that have higher retention factor for the first eluting component.

1. Introduction

Large industrial processes are nearly always optimized using computer simulations [1]. However, prior to optimization experimental scouting is performed to select the separation system [2,3]. Often the initial scouting is focused on the retention of the first component and the selectivity of the potential separation systems. After the initial scouting the solubility of the component(s) is determined [3] and injections, with increasing injection volume, are performed to further investigate the potential separation systems. All this is based on many years of empirical experience.

In a previous theoretical study Felinger and Guiochon [4] investigated the optimal retention factor for the first eluting component, column length and optimal particle size for different values of the selectivity. They found that the optimum retention factor for the first eluting component is always below one and that the productivity increases with selectivity. They also found that for separations with good selectivity (1.8) the optimum is reached using smaller packing (10 μm), shorter columns (around 10–20 cm) and lower efficiency compared to system with lower selectivity.

In this study, we investigate eight parameters: column length, packing particle size, efficiency, back pressure, sample concentration/solubility, selectivity, retention factor of the first eluting component and monolayer saturation capacity of the separation system. That aim of Felinger's and Guiochon's [4] important study was to find optimal values of system parameters and study how that optimal value changed with the other parameters. But the aim of this study is different; here we examine the relative importance of the different system parameters regarding process optimization. This difference is very important to notice in order to understand the purpose and aim of this study. Here we are *not* trying to answer the question: which column length, packing particle size etc. will give the optimal productivity? Instead we are studying how a *change* in one of these parameters, from its initial value, will affect the optimal productivity. From an optimization view point the studied column properties are *not* the decision variables in the process optimization problem (only the injection volume is). For each studied column property we will solve a sequence of process optimization problems, where the column properties are considered to be fixed parameters but where each problem will have a different value of the studied property. The purpose of this is to study how a change in one of the (fixed) column property parameters in the process optimization problem will affect the solution of, i.e., how the optimal productivity that can be achieved changes.

This study should not be considered to be a process optimization strategy; instead it is a fundamental case study of a process optimization problem and we investigate how different column property parameters in the problem affect the optimal productivity. It is important to notice that this study considers a specific

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chiral separation system. The results are therefore only valid for this system, but should be similar for other chiral systems and can be considered as indications of what holds for other separation system. Based on the results here we plan to investigate a more general situation in a follow up study.

To make this study more realistic we have based it on a recently investigate real experimental separation system [5]. This separation system was a Kromasil AmyCoat column used to perform enantiomeric separation of S and R-omeprazole with pure MeOH as eluent and there we studied how packing particle size and back-pressure affected the productivity. To simulate a realistic practical situation we will also limit the process optimization to find the optimal injection volume and we also always use the maximum allowed flow rate.

In addition, the study intends to provide initial, rough guidelines for column selection and design. The conclusions should therefore be of interest for both chromatographers and column manufacturers.

2. Theory

The model of chromatography used in the computer simulations is the Equilibrium-Dispersive model [1] and a finite volume solver is used to numerically estimate the solution [6,7]. The boundary condition to the model is based on previously measured experimental injection profiles [5]. We have previously investigated how the injection profile depends on several system parameters [8] and to model the injection we used a functions developed by us that take into account flow rate as well as injection volumes [9].

From the relationship between experimental flow rate and back pressure, the following function was found to accurately describe how the flow rate, F_V, is related to the back pressure, ΔP, the column length, L, and the packing particle size, d_p,

$$F_V = \frac{d_p \Delta P}{k_{F_V} L}, \tag{1}$$

where k_{F_V} is a constant $\approx 0.190\,\text{bar min/m}^3$. Notice that this function differs from the theory where one should have that $F_V = d_p^2 \Delta P/(k_{F_V} L)$.

From the relationship between experimental flow rate and number of theoretical plates, the following six parameter function was found to accurately describe how the efficiency varies with the packing particle size and the mobile phase linear velocity, u,

$$H = a_0 d_p + \sum_{i=1}^{2} a_i d_p^i u + b_0 u + \sum_{i=1}^{2} \frac{b_i}{u^i}, \tag{2}$$

where H is the plate height and a, b are some constants. The number of theoretical plates, N_x, for a column is L/H. The mobile phase linear velocity is related to the flow rate according to,

$$u = \frac{F_V}{\varepsilon D^2 \pi/4}, \tag{3}$$

where ε is the column porosity and the D is the column diameter.

The adsorption behaves according to a two site competitive bi-Langmuir adsorption isotherm, i.e., we have that for component i (1 or 2),

$$q_i = \frac{a_{\text{I},i} C_i}{1 + \sum_{j=1}^{2} b_{\text{I},j} C_j} + \frac{a_{\text{II},i} C_i}{1 + \sum_{j=1}^{2} b_{\text{II},j} C_j} = q_{i,\,\text{I}} + q_{i,\,\text{II}}, \tag{4}$$

where q_i is the total stationary phase concentration; $q_{i,\text{I}}$, $q_{i,\text{II}}$ is the stationary phase concentration on site I or II; C is the mobile phase concentration and a, b are the adsorption isotherm parameters for site I and II, see Table 2. The monolayer saturation capacity on site k, $q_{s,k,i}$, for a component i is defined to be,

$$q_{s,k,i} = \lim_{C_{j \neq i}=0,\; C_i \to \infty} q_{i,k} = \frac{a_{k,i}}{b_{k,i}}, \tag{5}$$

and the total monolayer saturation capacity for component i is defined to be,

$$q_{s,i} = \lim_{C_{j \neq i}=0,\quad C_i \to \infty} q_i = q_{s\text{I},\,i} + q_{s\text{II},\,i} = \frac{a_{\text{I},i} b_{\text{II},\,i} + a_{\text{II},\,i} b_{\text{I},\,i}}{b_{\text{I},\,i} b_{\text{II},\,i}}. \tag{6}$$

The retention factor k_i for component i is defined to be,

$$k_i = \frac{1-\varepsilon}{\varepsilon} \left. \frac{\partial q_i}{\partial C_i} \right|_{C_*=0} = \frac{1-\varepsilon}{\varepsilon} (a_{\text{I},i} + a_{\text{II},i}), \tag{7}$$

and the selectivity α between component 1 and 2, is defined to be,

$$\alpha = \frac{k_2}{k_1} = \frac{a_{\text{I},2} + a_{\text{II},2}}{a_{\text{I},1} + a_{\text{II},1}}. \tag{8}$$

The process optimization was performed using the maximum allowed flow rate, see Eq. (1), and the injection volume that maximizes the productivity was determined. Here the productivity, P_R, is normalized with respect to the stationary phase weight, m_{csp}, i.e., for component i we have that,

$$P_{R,i} = \frac{n_{coll,i}}{t_c m_{csp}} \quad \text{where} \quad n_{coll,i} = F_V \int_{t_{start,i}}^{t_{stop,i}} C_i(t)dt, \quad m_{csp} = \rho \frac{\pi D L}{4}, \tag{9}$$

where ρ is the stationary phase density (≈ 0.56 kg/L), n_{coll} is the amount collected between the fractional cut point times t_{start} and t_{stop}, t_c is the cycle time, i.e., the time elapsed between when the first injected component begins to elute and when the last component is completely eluted. Here the cycle is assumed to begin when then concentration sum of the eluted components first is greater than 1/100 of the maximum concentration sum achieved and ends the last time it is less than 1/100 of it. The yield, Y, of component i is defined to be,

$$Y_i = \frac{n_{coll,i}}{n_{inj,i}}, \tag{10}$$

where $n_{inj,i}$ is the injected amount the component, i.e., the yield gives how much of the injected amount is collected. The purity, PU, for component i is defined to be,

$$PU_i = \frac{n_{coll,i}}{F_V \sum_j \int_{t_{start,i}}^{t_{stop,i}} C_j(t)dt}, \tag{11}$$

i.e., the fraction collected of component i of the total collected amount of all components between the fractional cut point times t_{start} and t_{stop}.

3. Calculations

To investigate how the system parameters affect the productivity each parameter was changed, one at the time, from 50% to 200% of their initial value, see Table 1. Notice that a change in back pressure, the packing particle size or column length will lead to a change in maximum allowed flow rate, see Eq. (1), and any change in the flow rate will affect the efficiency of the system, see Eqs. (2) and (3).

When one of the system parameters total monolayer saturation capacity, selectivity or retention factor for the first component is changed the other two must remain constant, see Eqs. (6)–(8). This is achieved by replacing the adsorption isotherm parameters a and b in Eq. (4), with $\tilde{a}$ and $\tilde{b}$ according to below, δ is a variation