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Influence of particle size and shell thickness of core–shell packing materials on optimum experimental conditions in preparative chromatography

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ABSTRACT

The applicability of core–shell phases in preparative separations was studied by a modeling approach. The preparative separations were optimized for two compounds having bi-Langmuir isotherms. The differential mass balance equation of chromatography was solved by the Rouchon algorithm. The results show that as the size of the core increases, larger particles can be used in separations, resulting in higher applicable flow rates, shorter cycle times. Due to the decreasing volume of porous layer, the loadability of the column dropped significantly. As a result, the productivity and economy of the separation decreases. It is shown that if it is possible to optimize the size of stationary phase particles for the given separation task, the use of core–shell phases are not beneficial. The use of core–shell phases proved to be advantageous when the goal is to build preparative column for general purposes (e.g. for purification of different products) in small scale separations.

1. Introduction

The growing interest in the pharmaceutical industry for preparative chromatography that permits the purification of significant amounts of drug intermediates, peptides or proteins by eliminating closely related but unwanted compounds and impurities has made the optimization of the experimental conditions in preparative liquid chromatography a topic of serious current concern [1].

Therefore, a number of studies have focused recently on the determination of the optimum experimental conditions and column design parameters in preparative liquid chromatography. The nonlinear nature of preparative chromatography – due to column overload – complicates the separation process so much that the derivation of general conclusions regarding the determination of optimum conditions is a rather difficult – if not impossible – task. The optimization of preparative chromatography is further complicated by the choice of possible objective functions. In industrial applications, the production cost is the major factor to consider. Many components of the production cost, however, are beyond the scope of the separation process itself. Accordingly, a more straightforward approach is chosen and usually simply the production rate is maximized [2–5].

Optimum experimental conditions were also determined considering economic consequences in situations where the cost of the solvent – a major cost factor in certain applications of preparative liquid chromatography – was also taken into account [6–8].

A hybrid objective function was introduced in order to weigh the importance of both the production rate (which should be as high as possible) and the solvent consumption (which should be as low as possible) [6]. Because all the modes of operation considered are usually applied as batch processes, the recovery yield during each run is lower than unity. Some optimization for maximum production rate were carried out with the constraint of a minimum yield [2,3,9].

The simple maximization of the production rate would often lead to scenarios where the yield is unacceptably low and some of the precious feed would remain unpurified. A rather attractive objective function was suggested: the product of the production rate and the recovery yield [10]. It was shown that the production rate only slightly decreased and the recovery yield significantly improved at the optimal experimental conditions found by that

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objective function. This trade-off of a slight decrease in the production rate for a considerable yield improvement would be most economical.

The optimization of the different modes of preparative chromatography allowed the comparison of isocratic or gradient elution and displacement chromatography [9,11,12], revealing the relative advantages of either mode of separation. These studies suggested that elution can offer a larger production rate than displacement chromatography but delivers less concentrated fractions, which may significantly increase the cost of downstream processing.

Core–shell particles have been extremely popular in analytical chromatography [13,14]. The optimization of the core radius fraction in preparative nonlinear liquid chromatography has been recently studied [15] but a holistic optimization has not yet been carried out.

Recently, core–shell columns have been introduced to the market for preparative separations, which also calls for further studies in this area. The aim of this study is to investigate the particle size and core-to-shell ratio of core–shell packing materials for optimum separations in preparative chromatography.

2. Theory

2.1. Characterization of preparative separations

As with any industrial process, preparative chromatography needs to be optimized. For the sake of clarity, it is important to state here the definitions of the main parameters employed to characterize the preparative separations simulated in this work [1].

2.1.1. Loading factor (L_f)

Loading factor is a dimensionless unit that describes the sample size injected. Since adsorbents usually have a finite saturation capacity that corresponds to the formation of a monolayer of adsorbate, a convenient reference to express the sample size in dimensionless units is ratio of amount of sample injected to the amount of sample needed to cover the adsorbent with a monolayer (saturation capacity). The sample size is thus expressed as the loading factor

$$L_f = \frac{V_{inj}\, C_{inj}}{(1-\varepsilon_T)\, S\, L\, q_s} \tag{1}$$

where S is the column cross-sectional area, L the column length, ε_T the total porosity of the bed, q_s the column saturation capacity, C_{inj} the feed concentration, and V_{inj} the sample volume.

2.1.2. Cycle time (Δt_c)

The cycle time is the time difference between two successive injections. Δt_c can be defined in different ways. In this work, Δt_c is defined as the sum of elution time and the time required for column regeneration and stabilization.

2.1.3. Recovery yield (Y)

The recovery yield is the ratio between the amount of the desired component in the purified fraction, n_{pur}, and the amount injected in the column with the feed.

$$Y = \frac{n_{pur}}{V_{inj}\, C_{inj}} \tag{2}$$

Y is a function of the purity at which the products must be prepared.

2.1.4. Production rate (Pr)

The production rate is the amount of desired compound produced per unit time. It can be calculated as the product of the feed volume, the concentration of the corresponding component in the feed, and the recovery yield, divided by the cycle time.

$$Pr = \frac{V_{inj}\, C_{inj}\, Y}{\Delta t_c} = \frac{n_{pur}}{\Delta t_c} \tag{3}$$

2.1.5. Specific production (SP)

The amount of solvent consumed per unit amount of purified product prepared is an important contribution to the total cost of production in many cases. The amount of solvent used during a cycle is the product of the cycle time and the flow rate. SP is the amount of purified component produced per unit volume of solvent used, and it can be calculated as

$$SP = \frac{n_{pur}}{\Delta t_c\, F} = \frac{Pr}{F} \tag{4}$$

where F is the flow rate of the mobile phase.

2.1.6. Cut points

The correct determination of the beginning and end of fraction collection is critical to the purity of products in preparative separations. Cut points represent the start and end of fraction collection. Cut points should be determined considering the purity requirement of the given products.

2.2. Equilibrium-dispersive model

Several mathematical models were developed to describe the chromatographic processes [1]. One of the most important models is the equilibrium-dispersive (ED) model which assumes that the mobile and the stationary phases are constantly in equilibrium. In this model, the contributions of different processes that cause band dispersion (e.g., mass transfer resistances, finite kinetics of adsorption-desorption). are lumped together in an apparent dispersion coefficient. Accordingly, the differential mass balance equation of the solute is given by

$$\frac{\partial c(z,t)}{\partial t} + \varphi \frac{\partial q(z,t)}{\partial t} + u_0 \frac{\partial c(z,t)}{\partial z} = D_a \frac{\partial^2 c(z,t)}{\partial z^2} \tag{5}$$

where q and c are the stationary and the mobile phase concentrations of the compound, respectively, t is the time, z the distance along the column, u_0 the linear velocity, and $\varphi = (1-\varepsilon_T)/\varepsilon_T$ is the phase ratio with ε_T the total porosity of the column.

$$u_0 = \frac{F}{S\varepsilon_T} = \frac{L}{t_0} \tag{6}$$

where F is the flow rate of the mobile phase, t_0 the column hold-up time, and $S = d_c^2\pi/4$ the cross-sectional area of the column with the d_c column diameter.

The total porosity can be calculated as

$$\varepsilon_T = \varepsilon_e + (1-\varepsilon_e)\varepsilon_p(1-\rho^3) \tag{7}$$

where ε_e is external porosity of the column (fractional volume of the cavities in the bed that are around the particles), ε_p the porosity of particles (or internal porosity), ρ the ratio of core radius to that of the particle ($\rho = r_{core}/r_p$).

According to Eqs. (6) and (7), both the column hold-up time and phase ratio depends on the size of non-porous core.

In Eq. (5), q is related to c through the isotherm equation, $q = f(c)$.

3. Experimental

All the calculations were carried out by a software written in house in C++ language using the GNU Scientific Library (GSL) [16]. The source code of the program was compiled by g++ shipped by GNU Compiler Collection ver. 4.5.3. O1 optimization level was set during the compilation since it turns on the most common forms