Optimizing Experimental Conditions for Minimum Production Cost in Preparative Chromatography

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Optimum experimental conditions and column design parameters are calculated for most economical separation of binary mixtures by preparative liquid chromatography. The solvent consumption and capital costs are regarded as the two major cost contributions. Calculations were performed by using the numerical solution of the equilibrium-dispersive model of chromatography and a nonlinear simplex algorithm. Solvent consumption depends only on the column efficiency, the retention factor, and the loading factor. The production rate depends on the particle size, the column length, the mobile-phase flow velocity, the retention and the loading factors, and can be optimized with or without recovery yield constraints. A hybrid objective function was constructed to find the tradeoffs between the production rate and the solvent consumption.

Introduction

The optimization of the experimental conditions in preparative liquid chromatography is a topic of serious current concern (Colin, 1993a). This is due to the growing interest of the pharmaceutical industry for this new separation method which permits the purification of significant amounts of drug intermediates, peptides, or proteins by eliminating closely related, but unwanted, compounds. While at the research and development level the actual preparation cost is often a minor fraction of the total cost of the project, in production new perspectives are introduced. This requires that the optimization of the experimental conditions should achieve the lowest possible production cost. This cost includes contributions of capital (such as chromatograph, pumps, tubings and valvings, and building), operating (solvents, stationary phase, raw material lost, and energy), and labor. It is difficult, however, to account for all the cost contributions in the design of a new separation method, especially with a new process like liquid chromatography. Accounting procedures vary widely from company to company, if not within divisions of a large company. For example, overhead may constitute a large fraction of the total costs, and it is calculated following rules specific to each company. For these reasons, general rules cannot be given for the economical optimization of the chromatographic process.

Therefore, we have first searched for the experimental conditions and column design parameters which provide the maximum production rate—the largest possible amount produced during the unit time by a column of unit cross-sectional area—of the compound to be purified (Golshan-Shirazi and Guiochon, 1989a; Felinger and Guiochon, 1992a; Felinger and Guiochon, 1993). However, this approach provides the minimum production cost only if capital amortization is the dominant cost factor. Although there are practical cases where production has to be carried out at the highest possible rate (when demand exceeds the supply), it is obvious that the optimization for maximum production rate does not provide the most economical operation. Recent publications (Colin, 1993a; Colin, 1993b) have shown that the major cost contribution in chromatographic separations which do not use water and simple buffers as the mobile phase is the cost of the solvents used. This single contribution may account for up to 60% of the total separation cost. Thus, it becomes interesting to investigate on a purely technical basis the optimization of experimental conditions for minimum operating cost, by searching for the conditions which minimize the amount of solvent used per unit amount of purified product.

In the first part of this work, we discuss the optimization

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of the experimental conditions for the minimum consumption of solvent in isocratic elution chromatography. Then, we compare the production rate achieved under these conditions to the maximum production rate possible. Finally, we give some guidelines to optimize the experimental conditions when the production cost depends on two factors clearly identified, one proportional to the amount of solvent used, the other a fixed, capital cost.

Theory

Band profile calculations

The band profiles were calculated using the equilibrium-dispersive model of chromatography (Golshan-Shirazi and Guiochon, 1992). In this model, we assume instantaneous equilibrium between the stationary and the mobile phases, and use an apparent dispersion term to account for the smoothing effects of the axial dispersion and the finite rate of the mass transfers. A mass balance equation is written for each component of the sample:

$$\frac{\partial C_i}{\partial t}+F\frac{\partial q_i}{\partial t}+u\frac{\partial C_i}{\partial z}=D_a\frac{\partial^2 C_i}{\partial z^2} \tag{1}$$

where C_i and q_i are the concentrations of component i in the mobile and the stationary phases, respectively; z is the column length, t the time, u the mobile-phase linear velocity, and F the phase ratio, $(1-\epsilon)/\epsilon$, where ϵ is the total porosity of the column. D_a is the apparent dispersion coefficient.

The initial condition is:

$$C_i(z,\,0)=0 \tag{2}$$

indicating that at $t=0$ the column is equilibrated with the mobile phase. We assume further that this phase does not contain an adsorbed additive. The sample is introduced into the column as a rectangular pulse. The concentration of the component i in the sample is C_i^0, and the duration of the sample injection is Δt_s.

The Danckwerts boundary conditions describe the flux at the column inlet and outlet, respectively:

$$uC_i^0=uC_i(z=0,\,t)-D_a\frac{\partial C_i}{\partial z}\,(z=0,\,t) \tag{3a}$$

$$D_a\frac{\partial C_i}{\partial z}\,(z=L,\,t)=0 \tag{3b}$$

Because the chromatographic columns used in actual practice have a high efficiency (Golshan-Shirazi and Guiochon, 1992), the classical Danckwerts boundary conditions can be written simply for each component as:

$$C_i(0,\,t)=C_i^0 \quad 0<t\leq\Delta t_s \tag{3c}$$

For the calculation of the individual profiles of the components of a binary mixture, the system of two partial differential equations is solved using a finite difference scheme written for Eq. 1 with $D_a=0$ (ideal model). The values of the time and length increments of the integration are chosen to provide a numerical dispersion exactly equal to the desired apparent dispersion (Czok and Guiochon, 1990).

Column characteristics

The column efficiency was calculated using the Knox plate height equation (Knox, 1977):

$$h=\frac{2}{\nu}+\nu^{1/3}+\frac{\nu}{10} \tag{4}$$

where $h=H/d_p$ is the reduced plate height, H is the actual height equal to a theoretical plate, d_p is the average particle size, and $\nu=ud_p/D_m$ is the reduced mobile-phase velocity, or particle Peclet number.

The pressure drop between the column inlet and outlet is calculated using the following equation (Martin et al., 1974):

$$\Delta P=\frac{u\eta L}{k_0 d_p^2} \tag{5}$$

where ΔP is the pressure drop, k_0 the specific column permeability (about 1×10^{-3}), and L the column length. A maximum pressure drop of 125 atm was allowed in all calculations.

The total column porosity is $\epsilon=0.8$, the viscosity of the mobile phase is $\eta=1$ cp, and the molecular diffusivity of each component in the mobile phase is $D_m=1\times10^{-5}$ cm^2/s.

Adsorption isotherms

In all the calculations, we assumed that the two components of the sample behave according to the competitive Langmuir isotherm model:

$$q_i=\frac{a_iC_i}{1+b_1C_1+b_2C_2} \quad i=1,\,2 \tag{6}$$

where a_i and b_i are numerical coefficients. They are chosen so that the column saturation capacity, $q_s=a_i/b_i$, is the same for all components, as required for thermodynamic consistency (LeVan and Vermeulen, 1981).

The use of the competitive Langmuir model is a simplification, as in practice most competitive isotherms do not follow it exactly (Jacobson et al., 1991). This model, however, remains a good choice for theoretical studies as it is simple, and deviations from competitive Langmuir isotherm behavior are often small and are properly accounted for by the consequences of the difference in the column saturation capacities for the compounds studied (Golshan-Shirazi et al., 1991).

The choice of the value of the diffusion coefficient and the isotherm model refer to small molecules. For this reason, for protein separations the results of this study are not always valid. For protein separation, another isotherm model and smaller diffusion coefficient should be chosen. Moreover, in the separation of proteins, one cannot assume that the saturation capacity and retention factor are independent of each other.

The numerical parameters in Eq. 6 were chosen as: $a_1=k_1'/0.25$, $a_2=\alpha a_1$, $b_1=k_1'/65$ mL/mg, $b_2=\alpha b_1$. α is the separation factor, and k_1' is the retention factor of the less retained component at infinite dilution. This choice of isotherm parameters implies a saturation capacity of $q_s = 260$ mg/mL for each component.

Definitions

The loading factor is the ratio of the total amount of the components in the sample to the column saturation capacity:

$$L_f = \frac{V_s b_i (C_1^0 + C_2^0)}{\epsilon S L k_i'} = \frac{V_s (C_1^0 + C_2^0)}{(1-\epsilon) S L q_s} \tag{7}$$

The cycle time—the time lapse between two successive injections—is defined as $\Delta t_c = t_{c,2} - t_{c,1}$, where $t_{c,1}$ is the time when the concentration of the first component increases above 1×10^{-6} mg/mL, and $t_{c,2}$ is the time when the concentration of the more retained component falls below the same threshold. The advantages of this somewhat arbitrary definition were discussed by Felinger and Guiochon (1992a).

The production rate, the most common objective function of optimization in preparative chromatography, is the amount of purified component produced per unit column cross-sectional area, per unit time, in mg·cm^{-2}·s^{-1}:

$$Pr_i = \frac{V_s C_i^0 Y_i}{\epsilon S \Delta t_c} \tag{8}$$

where V_s is the sample volume, and S is the column cross-sectional area. The recovery yield of component i, Y_i is defined as the ratio of the amount of component i recovered in the collected fraction over the amount of the same component in the sample injected.

Specific production

The specific production (SP) is defined as the amount of purified product obtained by using a unit amount of solvent:

$$SP = \frac{\text{amount of pure product}}{\text{amount of solvent}} \tag{9}$$

The above defined specific production is the reciprocal of the solvent consumption. As will be shown, the expressions obtained for the calculation of the specific production are very similar to those of the production rate. For this reason, for computational considerations and because it is easier to discuss and compare the optimum experimental conditions for maximum production with those for maximum specific production rather than for minimum solvent consumption, the characterization of the amount of solvent needed for a particular separation is more conveniently described when using this term. The minimum solvent consumption and the maximum specific production demand identical experimental conditions. Furthermore, the definition of specific production allows consistency in the use of hybrid objective functions consisting of both the production rate and the reciprocal of the solvent consumption.

The amount of solvent pumped through the column during one cycle is proportional to the mobile-phase flow rate and to the cycle time. The amount of purified product made in one cycle is the product of the amount injected and the recovery yield. So the specific production can be written as:

$$SP_i = \frac{V_s C_i^0 Y_i}{\Delta t_c F_v} = \frac{V_s C_i^0 Y_i}{\Delta t_c \epsilon S u} \tag{10}$$

Combining Eqs. 8 and 10 gives:

$$SP_i = \frac{Pr_i}{u} \tag{11}$$

This simple relationship between production rate and specific production shows that to operate chromatographic columns at low levels of solvent consumption, we need to achieve a high production rate at a low mobile-phase linear velocity.

As the feed volume injected is the product of the injection time and the flow rate, Eq. 9 can be rewritten as:

$$SP_i = \frac{\Delta t_s}{\Delta t_c} C_i^0 Y_i \tag{12}$$

It can easily be shown that the specific production depends only on two independent parameters: column efficiency and loading factor. To prove this, we rewrite Eq. 1, using reduced time ($\tau = t/t_0$) and length variables ($x = z/L$). Using these variables and substituting the apparent dispersion coefficient by $D_a = Hu/2 = L^2/(2Nt_0)$, the mass-balance equation (Eq. 1) can be transformed into:

$$\frac{\partial C_i}{\partial \tau} + F \frac{\partial q_i}{\partial \tau} + \frac{\partial C_i}{\partial x} = \frac{1}{2N} \frac{\partial^2 C_i}{\partial x^2} \tag{13}$$

This equation indicates that the reduced band profiles calculated by solving the equation system of the equilibrium model (Eq. 13) do not depend on the column length or the mobile-phase flow velocity, but only on the parameters which appear in Eq. 13 or in the initial and boundary conditions, that is, on the column efficiency (Eq. 13) and the loading factor (Eq. 3). This is true as long as the boundary and initial conditions are kept constant on the reduced scale. This means that, when changing the column length from L_1 to L_2 and the linear velocity from u_1 to u_2 while keeping the column efficiency constant, we have to keep the reduced injection time unchanged to achieve identical band profiles at the column outlet ($z = L$ or $x = 1$) on the reduced time scale:

$$\frac{\Delta t_{s,1}}{t_{0,1}} = \frac{\Delta t_{s,2}}{t_{0,2}} \tag{14}$$

As the dead time is $t_0 = L/u$ and the feed volume injected is $V_s = \Delta t_s u \epsilon S$, Eq. 14 becomes:

$$\frac{V_{s,1}}{L_1} = \frac{V_{s,2}}{L_2} = \frac{L_f (1-\epsilon) S q_s}{C_1^0 + C_2^0} \tag{15}$$

which means that the ratio of the actual volume injected and the column length must be kept constant to obtain identical band profiles on the reduced time scale. This quantity is proportional to the loading factor. Although the above expression contains the value of the injected concentrations too, it has been shown that the shape of the band profile does not depend on the concentration of the sample injected as long as we do not reach a significant volume overload.

That is why the specific production, as well as the recovery yield (Eq. 12), depends only on the loading factor and the column efficiency, no matter how the latter has been achieved. This is not true for the production rate. The latter is given by Eq. 8, which with the dimensionless parameters becomes:

$$Pr_i = \frac{\Delta t_s}{\Delta t_c} C_i^0 Y_i u \tag{16}$$

It depends on the same parameters as SP_i, but also on the mobile-phase velocity.

Parameters to be optimized for maximum production rate

As we have seen, the solvent consumption depends only on the column efficiency and the loading factor. The production rate depends on more parameters. However, Golshan-Shirazi and Guiochon (1989b) have shown that there is no independent optimum value for the column length and the particle diameter, and that only the ratio d_p^2/L can be optimized. This has been confirmed by the results of numerical calculations made using the equilibrium-dispersive model in overloaded elution (Felinger and Guiochon, 1992a) and displacement (Felinger and Guiochon, 1992b) chromatography. As long as the ratio d_p^2/L is unchanged, the production rate remains almost constant. Thus, only one column design parameter has to be optimized.

It has also been shown (Felinger and Guiochon, 1992a) that when all design and operation parameters are optimized together for maximum production rate, the column is always operated at the flow rate corresponding to the maximum inlet pressure allowed, ΔP_M. Rewriting Eq. 5 for the reduced velocity instead of the linear velocity gives:

$$\nu = \frac{\Delta P_M k_0 d_p^3}{D_m \eta L} \tag{17}$$

The reduced plate height at this velocity can be calculated by Eq. 4 and used for the derivation of the column efficiency ($N = L/hd_p$):

$$N = \frac{L}{\dfrac{2D_m \eta L}{\Delta P k_0 d_p^2} + d_p^2 \left(\dfrac{\Delta P k_0}{D_m \eta L} \right)^{1/3} + \dfrac{\Delta P k_0 d_p^4}{D_m \eta L}} \tag{18}$$

We have no practical options to adjust the values of η, D_m and k_0. Thus, Eq. 18 shows that, if the column length is kept constant and the column is operated at the maximum possible inlet pressure, substituting the optimum value of the particle diameter in Eqs. 17 and 18 gives the optimum flow rate and column efficiency for maximum production rate. In this manner, the optimization of the production rate in overloaded elution chromatography can be studied as a function of the same two parameters as that of the specific production. This approach is valid as long as the maximum inlet pressure is constant and the Knox plate height equation (Eq. 4) remains unchanged. This observation makes easier the comparison of the optimum conditions required for minimum solvent consumption and for maximum production rate.

Computational procedures

Band profiles were calculated using the equilibrium-dispersive model of chromatography (Golshan-Shirazi and Guiochon, 1992). Then, the cutting points were determined according to a 99% purity requirement, and the amount produced during the cycle, the recovery yield, the specific production, and the production rate were calculated. Experimental conditions were changed to maximize the objective function. As a maximum search algorithm, the so-called *supermodified simplex* algorithm was applied (Morgan et al., 1990). The computation was carried on until the standard deviation of the vertex coordinates dropped below 0.1%.

The optimum conditions were calculated successively for the less and the more retained components of binary mixtures with relative concentrations 1:3 and 3:1, respectively, for separation factors $\alpha = 1.2$, 1.5, and 1.8; and for values of the retention factor between 0.2 and 6. In some calculations, the retention factor was optimized as an operating parameter as well, even if in many practical separations it may be difficult to adjust.

Results and Discussion

Optimization for maximum specific production

Since the specific production depends on two parameters, the column efficiency and the loading factor, a grid search can easily be performed to visualize its dependence on the two parameters. The results of this search in Figure 1 show the contour plots in the cases of a 3:1 and a 1:3 mixtures, at a separation factor $\alpha = 1.5$, and a retention factor $k_1' = 6$. Figures 1a and 1b show that at each column efficiency there is an optimum loading factor which gives a maximum specific production. This is true for both the less and the more retained component. However, the higher the column efficiency, the higher the specific production. Due to the decreasing apparent band dispersion, the optimum loading factor increases with increasing column efficiency, and so does the recovery yield at a given loading factor. Figures 2a and 2b show the contour plots of the recovery yield in an N, L_f grid. The increasing distances between the contour lines indicate that the increase of the specific production becomes insignificant above a certain column efficiency. This phenomenon is shown in Figures 3a and 4a, where the specific production of the first and second component of the two binary mixtures are plotted against the column efficiency for the optimum value of the loading factor at $N = 2{,}500$ and $k_1' = 6$.

Figures 3a and 4a show that after a steep increase at low column efficiency, a plateau is reached where there is not much improvement in the specific production. Comparison of Figures 3a and 4a shows that the higher the separation factor, the lower the column efficiency for which this plateau is reached. As indicated by Eq. 12, there is a strong correlation between the specific consumption and the recovery yield. This is illustrated in Figures 3a and 3b for $\alpha = 1.2$ and in Figures 4a and 4b for $\alpha = 1.5$.

Calculations were also carried out to optimize the retention factor together with other parameters. Earlier results (Felinger

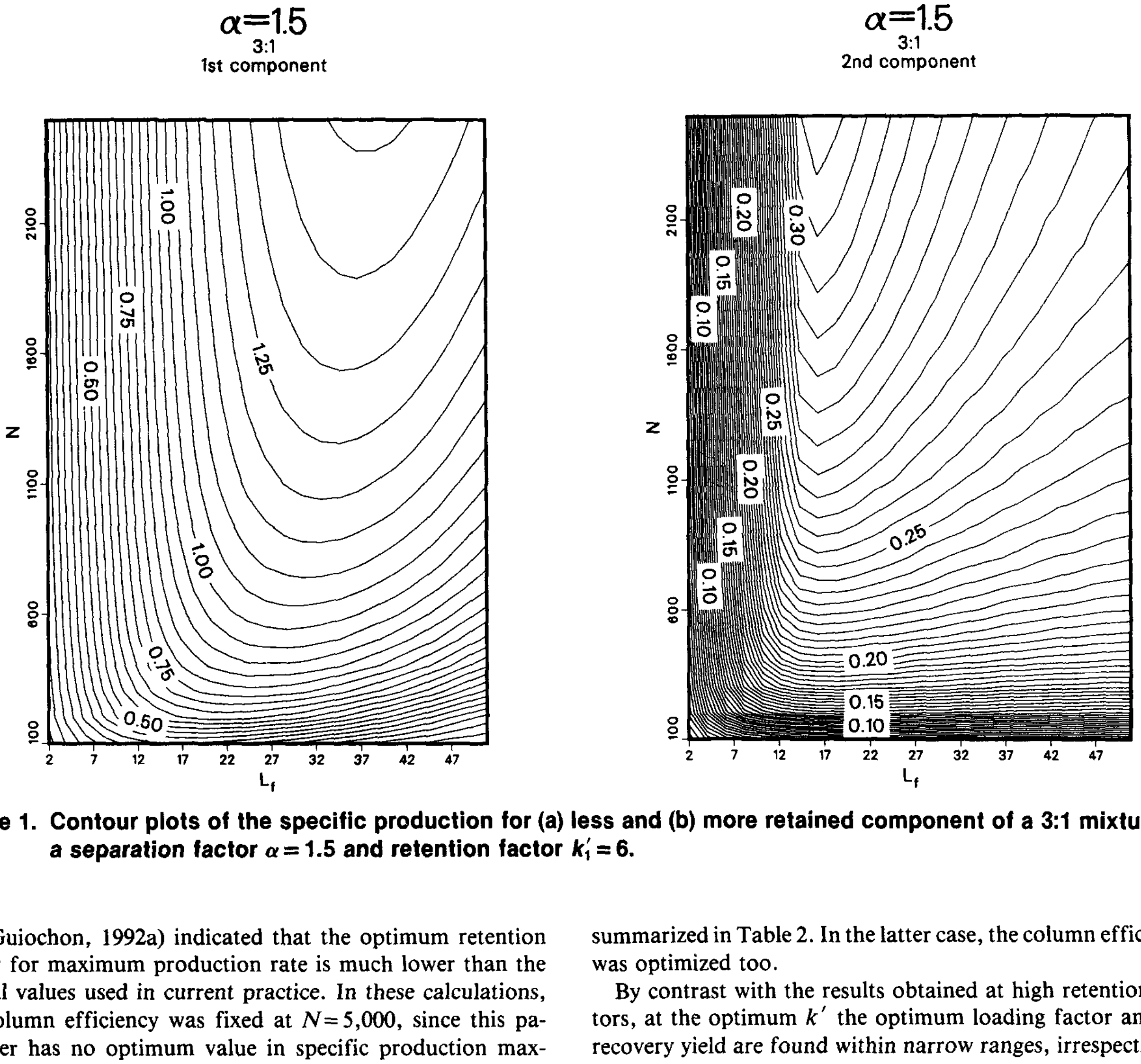

Figure 1. Contour plots of the specific production for (a) less and (b) more retained component of a 3:1 mixture at a separation factor $\alpha = 1.5$ and retention factor $k_1' = 6$.

and Guiochon, 1992a) indicated that the optimum retention factor for maximum production rate is much lower than the typical values used in current practice. In these calculations, the column efficiency was fixed at $N = 5{,}000$, since this parameter has no optimum value in specific production maximization. The results are summarized in Table 1. The optimum retention factor is very much the same for both minimum solvent consumption and maximum production rate and in all cases, k_1' is smaller than 1. For comparison, the optimum experimental conditions for maximum production rate are summarized in Table 2. In the latter case, the column efficiency was optimized too.

By contrast with the results obtained at high retention factors, at the optimum k' the optimum loading factor and the recovery yield are found within narrow ranges, irrespective of the separation factor. The optimum retention factor also varies little with the separation factor, while the data in Table 1 show a stronger dependence in the case of optimization for maximum specific production. This, however, is largely due to the fact that the results shown in Table 1 were calculated for $N = 5{,}000$,

Table 1. Optimum Parameters Leading to Minimum Solvent Consumption at $N = 5{,}000$

α	C_1^0/C_2^0	Comp. No.	k_1'	L_f %	SP_i mg/mL	(Pr_i) mg/cm²·s	Y_i %
1.2	3:1	1	0.43	9.3	4.760	1.648	45.4
1.2	3:1	2	0.53	3.6	0.728	0.245	51.8
1.2	1:3	1	0.69	7.9	1.290	0.447	58.6
1.2	1:3	2	0.44	3.6	3.254	1.126	68.1
1.5	3:1	1	0.21	27.6	20.30	7.011	57.7
1.5	3:1	2	0.23	13.3	3.995	1.379	69.2
1.5	1:3	1	0.29	20.3	5.285	1.829	72.2
1.5	1:3	2	0.21	12.6	14.39	4.979	80.9
1.8	3:1	1	0.17	45.7	35.02	12.13	66.5
1.8	3:1	2	0.18	23.4	7.569	2.626	78.6
1.8	1:3	1	0.19	30.0	8.743	3.026	76.2
1.8	1:3	2	0.16	21.5	24.26	8.397	83.5

Table 2. Optimum Parameters Leading to Maximum Production Rate

α	C_1^0/C_2^0	Comp. No.	k_1'	N	d_p μm	L_f %	Pr_i mg/cm²·s	(SP_i) mg/mL	Y_i %
1.2	3:1	1	0.35	6,844	7.4	9.7	1.649	5.947	44.3
1.2	3:1	2	0.37	8,335	6.9	3.6	0.245	1.020	51.2
1.2	1:3	1	0.55	6,986	7.4	8.0	0.464	1.697	59.9
1.2	1:3	2	0.39	6,035	7.8	3.4	1.127	3.714	76.9
1.5	3:1	1	0.25	3,392	9.5	25.6	7.111	15.86	58.7
1.5	3:1	2	0.32	2,809	10.1	15.2	1.434	2.831	60.5
1.5	1:3	1	0.34	3,854	9.1	19.9	1.833	4.445	73.4
1.5	1:3	2	0.28	2,657	10.2	13.7	5.193	9.897	71.6
1.8	3:1	1	0.21	2,189	10.9	42.0	13.34	22.51	62.6
1.8	3:1	2	0.28	1,733	11.7	26.6	2.955	4.433	67.6
1.8	1:3	1	0.24	3,226	9.6	29.5	3.210	6.733	75.0
1.8	1:3	2	0.26	1,460	12.3	24.1	9.258	12.20	69.2

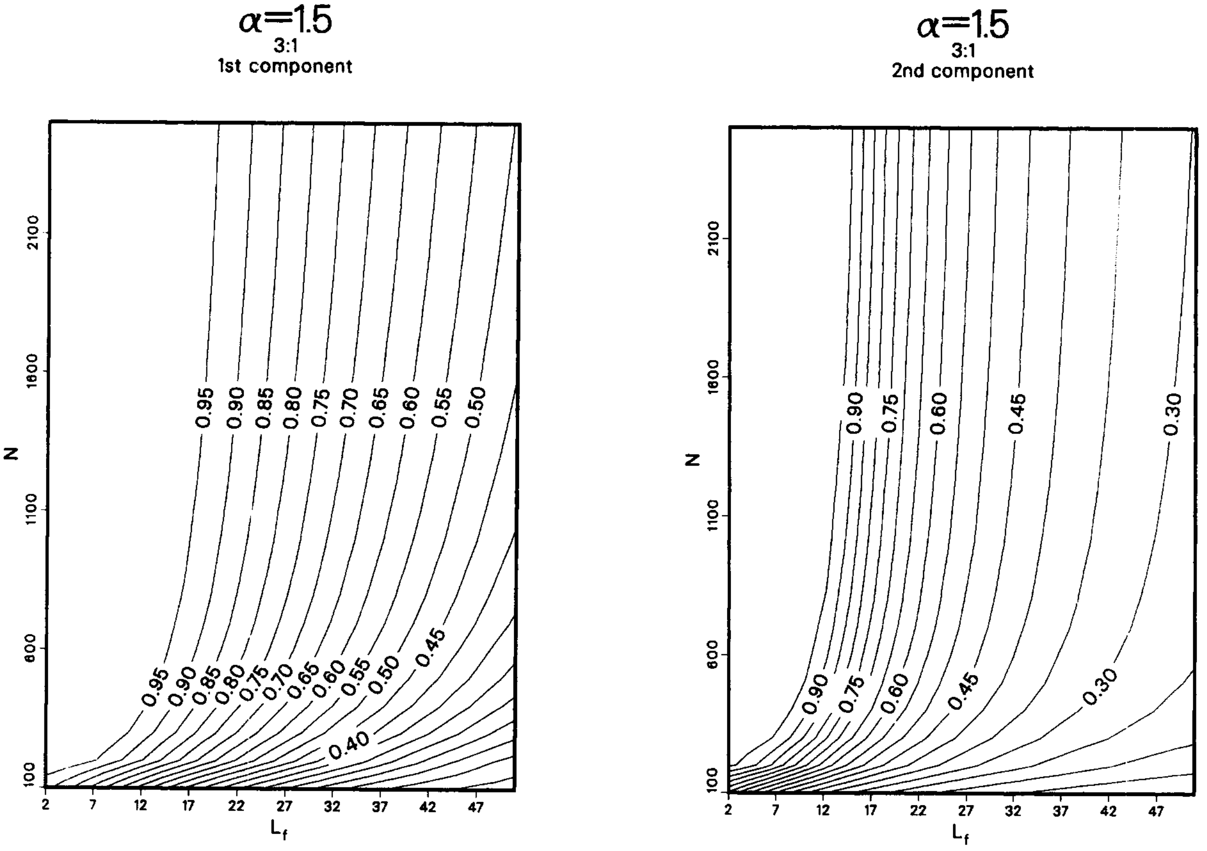

Figure 2. Contour plots of the recovery yield for (a) less and (b) more retained component of a 3:1 mixture at a separation factor $\alpha = 1.5$ and retention factor $k_1' = 6$.

an efficiency which is not sufficient to permit the separation of the binary mixture at low values of the separation factor. As Table 2 shows, at $\alpha = 1.2$, the optimum efficiency for maximum production rate is between 6,000 and 8,000 theoretical plates. Note that, to achieve a resolution unity between two peaks with $k' = 0.4$ and $\alpha = 1.2$, one needs 7,000 theoretical plates in linear chromatography.

Table 3. Comparison of Optimum Conditions for Maximum Production Rate and for Maximum Specific Production: $\alpha = 1.2$

C_1^0/C_2^0	Comp. No.	k_1'	N	d_p μm	L_f %	Pr_i mg/cm²·s	SP_i mg/mL	Y_i %
3:1	1	2	1,396	12.6	10.0	0.973	1.231	47.9
3:1	1	2	5,000	8.32	14.8	0.706	2.042	51.9
3:1	2	2	1,966	11.3	3.3	0.153	0.241	65.6
3:1	2	2	5,000	8.32	3.1	0.123	0.354	87.0
1:3	1	2	2,550	10.4	9.3	0.300	0.556	61.4
1:3	1	2	5,000	8.32	15.5	0.260	0.753	53.8
1:3	2	2	1,238	12.9	3.3	0.672	0.803	76.7
1:3	2	2	5,000	8.32	3.7	0.495	1.430	96.6
3:1	1	6	859	14.4	10.7	0.440	0.424	46.4
3:1	1	6	5,000	8.32	17.0	0.263	0.760	52.1
3:1	2	6	1,117	13.3	3.5	0.078	0.069	59.4
3:1	2	6	5,000	8.32	3.3	0.046	0.134	90.0
1:3	1	6	1,628	11.9	10.0	0.137	0.193	59.5
1:3	1	6	5,000	8.32	19.7	0.098	0.284	49.7
1:3	2	6	605	15.9	4.0	0.295	0.234	58.5
1:3	2	6	5,000	8.32	3.8	0.183	0.529	98.3

Table 3 contains the optimum experimental conditions for both production rate and specific production at retention factors higher than optimum ($k_1' = 2$ and 6), for $\alpha = 1.2$. In these cases, since the higher the retention factor the smaller the optimum column efficiency, the optimum experimental conditions differ markedly for maximum production rate and for maximum specific production. For the production of the less retained component, the high efficiency permits the use of a higher loading factor and the resulting yield is not changed. For the second component, the loading factor is the same at low and high efficiencies, but the recovery yield improves, exceeding 90% at $N = 5{,}000$. This conforms to the predictions made on the basis of the ideal model (Golshan-Shirazi and Guiochon, 1989a), which indicates that for the more retained component the maximum production rate is achieved at the touching band status. For both components, the loss of production rate when operating at minimum solvent consumption increases from 20% (at $k_1' = 2$) to 40% (at $k_1' = 6$), whereas the specific production decreases from 40% (at $k_1' = 2$) to 50% (at $k_1' = 6$) when operating at maximum production rate.

Figure 5 reflects the optimization at constant column efficiency but varying retention factor (see Table 1). Both the specific production and the production rate show identical behavior. This result was expected, since in this case (constant efficiency) the linear mobile-phase velocity is constant. However, when the production rate is maximized at changing retention factor, as illustrated in Figure 6, the smaller the retention factor, the larger the specific production, because now the

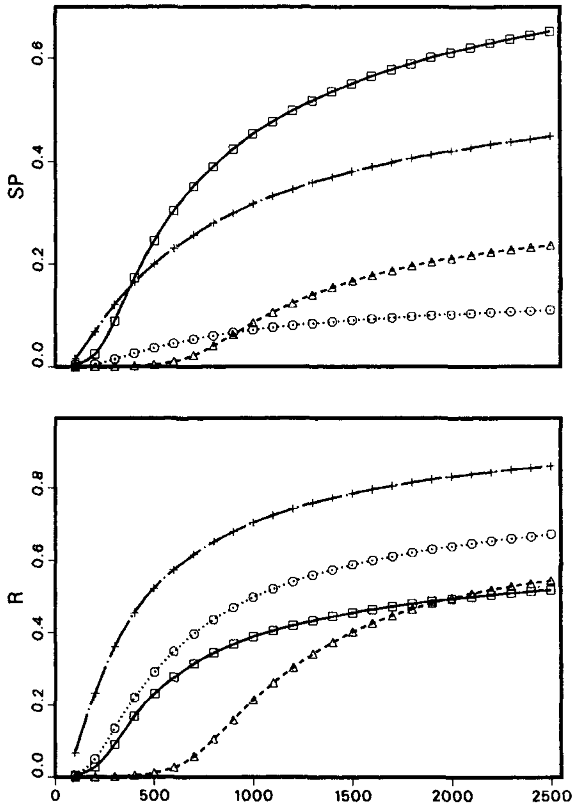

Figure 3. (a) Specific production and (b) recovery yield against the column efficiency at $\alpha = 1.2$ and $k_1' = 6$.

Less (□) and more (○) retained components of a 3:1 mixture; less (△) and more (+) retained components of a 1:3 mixture.

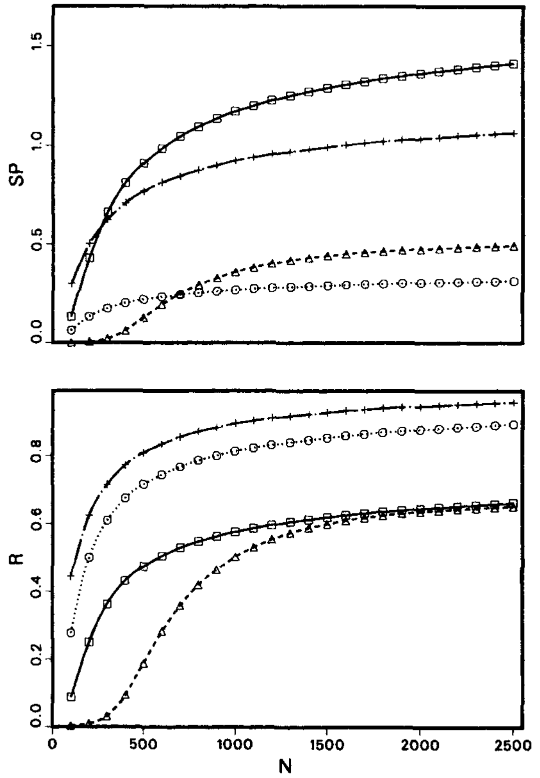

Figure 4. Same as Figure 3, except $\alpha = 1.5$.

column efficiency is one of the parameters to be optimized. The optimum conditions at lower retention factors correspond to a higher column efficiency which, in turn, results in a lower solvent consumption, because of a lower dilution of the feed during the separation. Figure 6 corresponds to the results shown in Table 2.

Weighted optimization

As we have seen, the optimum conditions for minimum solvent consumption and for maximum production rate are very different. The high efficiency required for small solvent consumption is optimal for maximum production rate only in few cases, when both the separation factor and the retention factor are small.

Separations are usually carried out at high values of the retention factor, not only for practical reasons but because few users realize the potential savings afforded by making the separations at low retention factors. This situation requires the use of less efficient columns to achieve the same separation. For this reason, the production rate becomes rather low at minimum solvent consumption. As a tradeoff between these two factors, a hybrid objective function can be constructed that considers the importance of the solvent consumption and of the production rate with a given weight.

The hybrid objective function is based on the optimization of the unit cost of the purification, which is the ratio of the costs of the purification and the production rate. The two major factors of the purification costs are the fixed (F_c) and the operating cost, while the cost of the wasted feed is usually negligible at high recovery yield. As the operating cost is essentially proportional to the amount of solvent used, this factor is expressed by the cost of solvent (S_u), the solvent consumption (the reciprocal of specific production), and the production rate, which is, hence, Pr_iS_u/SP_i. The unit cost of the purification can be written as:

$$\frac{P_c}{Pr_i} = \frac{F_c}{Pr_i} + \frac{S_u}{SP_i} \tag{19}$$

In this manner, the hybrid objective function can be transformed into:

$$\frac{1}{Pr_i^*} = \frac{(1-w)}{Pr_i} + \frac{w}{SP_i} \tag{20}$$

Combining Eqs. 11 and 20 gives:

$$Pr_i^* = \frac{Pr_i}{1-w+wu} \tag{21}$$

where parameter $w (0 \leq w \leq 1)$ reflects the significance of the production rate or solvent consumption. If $w = 0$, the production rate is maximized regardless of the solvent consumption. If $w = 1$, the objective function is simply the specific production, used in the previous section. Intermediate values

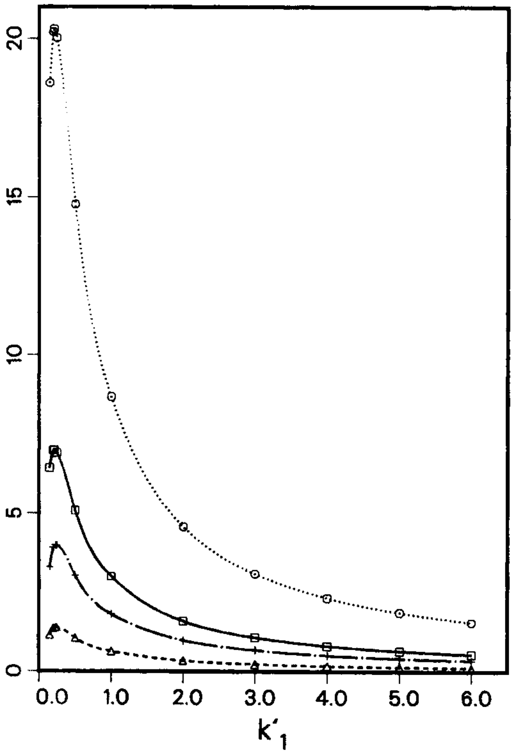

Figure 5. Optimization at constant column efficiency ($N = 5{,}000$) and varying retention factor: $\alpha = 1.5$, mixture composition 3:1.

Specific production for the less (o) and the more (+) retained component; production rate of the less (□) and more (△) retained component.

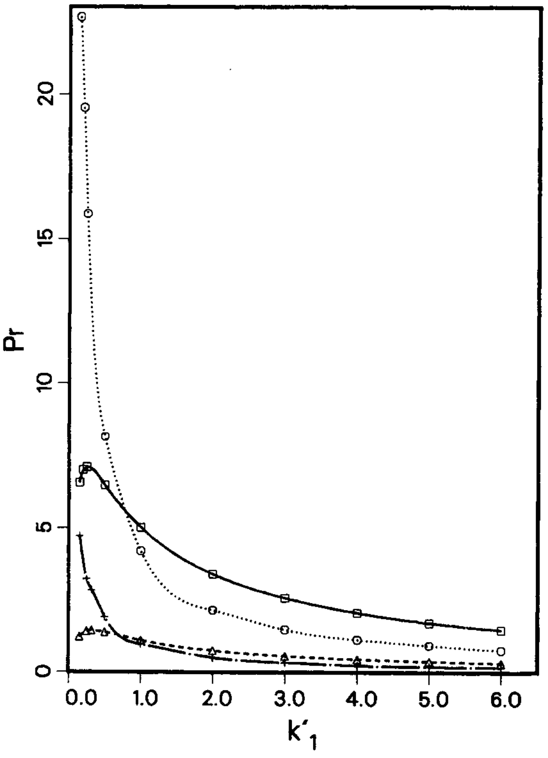

Figure 6. Optimization of the production rate at varying retention factor: $\alpha = 1.5$, mixture composition 3:1.

Specific production for the less (o) and the more (+) retained component; production rate of the less (□) and more (△) retained component.

of w involve both factors and result in a tradeoff between production rate and solvent consumption. By choosing a weight, w, inversely proportional to the ratio of the capital costs (fixed) and the operating (solvent) costs, we can use this objective function to reflect approximately the total production cost.

To permit an easier comparison between the values of the optimum parameters for minimum solvent consumption and for maximum production rate, we used the method described earlier, which permits the elimination of all parameters, except the column efficiency and the loading factor. All the calculations were done assuming a column length of $L = 25$ cm. The particle size was chosen accordingly to achieve the desired efficiency at the maximum possible flow rate.

Figures 7a and 7b show the contour plot of the production rate for the same separation for which the specific production is shown in Figures 1a and 1b, respectively. A rapid comparison of Figures 1 and 7 shows how far the optima of the two objective functions (for $w = 0$ and $w = 1$) are located. For maximum production rate, an efficiency of about 300 theoretical plates is optimum. (Note that the optimum efficiency at the optimum retention factor is ten times larger, Table 1.) At this low efficiency, the solvent consumption is very high.

Figures 8 and 9 show two series of surfaces that illustrate the transition of the hybrid objective function from the maximization of the production rate to that of the specific production. The first surfaces in both Figures 8 and 9 ($w = 0$) are the 3-D representations of the contour plots in Figures 7a and 7b, respectively, while the last surfaces in Figures 8 and 9 ($w = 1$) are those of the contour plots in Figures 1a and 1b. The other surfaces correspond to intermediate values, $w = 0.2$, 0.4, 0.6, and 0.8, respectively. The experimental conditions at the optima for this series of calculations are summarized in Table 4.

The transition of the location of the optimum on these surfaces is gradual. In the case of the optimization of the production of the less retained component (Figure 8), when w increases from 0 to 0.5, the optimum loading factor increases by nearly 30%, and the optimum column efficiency is threefold, but the production rate at $w = 0.5$ is still 84% of that at $w = 0$. However, the maximum has nearly vanished for $w = 0.4$, and we can observe only an inconspicuous mound which has seemingly disappeared at $w = 0.6$. At this stage, the dependence of the production rate on N becomes completely flat, and any column that has more than 500 theoretical plates will give nearly identical results, but a very flat optimum can always be identified.

Similar results are observed when the purification of the more retained component is optimized (Figure 9). The optimum column efficiency and maximum production rate change in nearly the same proportion as for the optimization of the production of the first component. The only noticeable differences are the steady improvement of the recovery yield and the decrease of the optimum loading factor.

For both components, the specific production is about twice

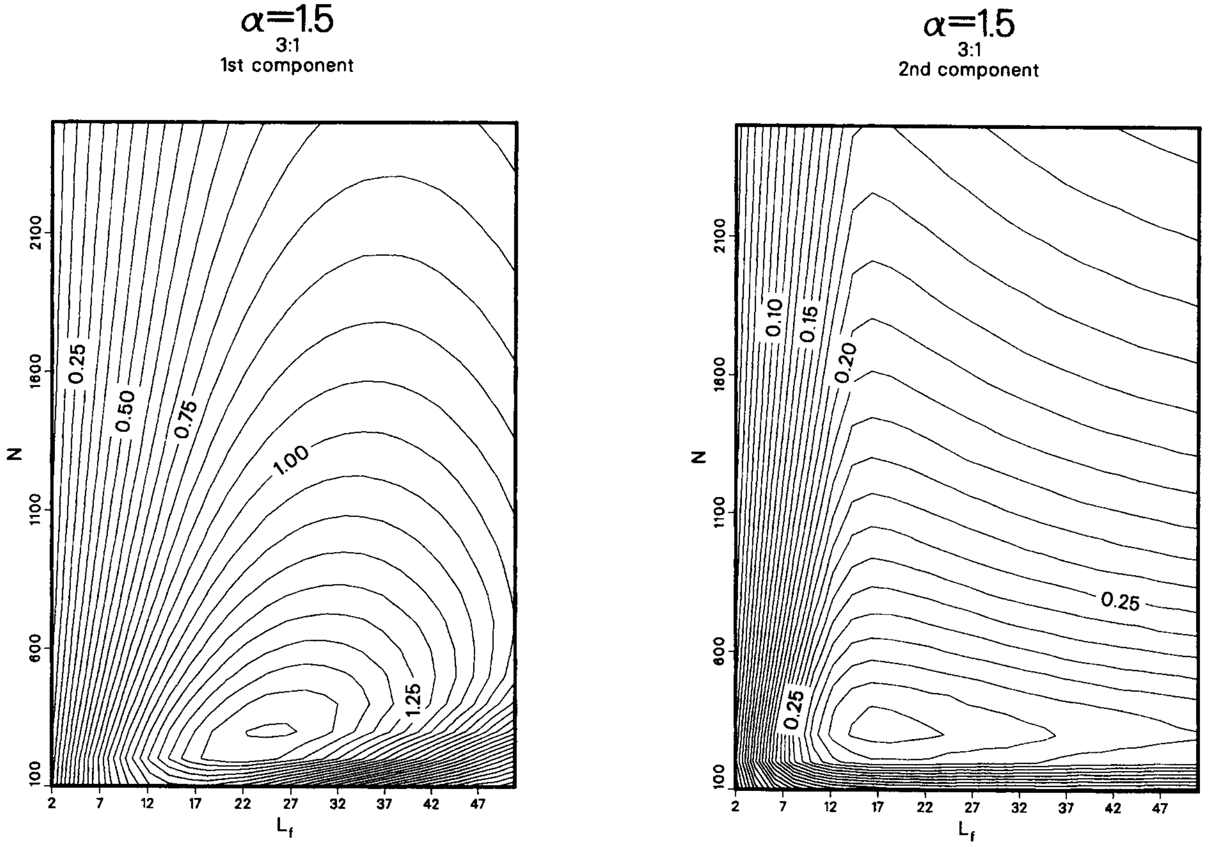

Figure 7. Contour plots of the production rate for (a) less and (b) more retained component of a 3:1 mixture at a separation factor $\alpha = 1.5$ and retention factor $k_1' = 6$.

smaller at the maximum production rate ($w = 0$) as at $N = 5{,}000$. On the other hand, at the high efficiency where the solvent consumption is minimum, the production rate is reduced to nearly a third (exactly 36%) of its maximum. When a compromise is made ($w = 0.5$), the production rate loss is only 15%, while around 30–40% more solvent is needed at $N = 5{,}000$.

In none of the above calculations was a specified minimum required recovery yield assumed, as the aim of this study is to show the very different optimum experimental conditions that depend on the nature of the objective function and on the component of the sample to be purified. However, when a minimum acceptable recovery yield is specified by the technology, instead of the 2-D optimization, the maximum search must be performed along one of the paths of the contour lines in Figures 2a and 2b. The higher the minimum recovery yield, the smaller the optimum loading factor; either the minimum solvent consumption or the maximum production rate is our aim. Moreover, the optimum column efficiency is slightly increased when the production rate is maximized. The trade-off is, however, smaller production rate and larger solvent consumption when a minimum recovery yield is considered.

The effect of a constraint on recovery yield is demonstrated in Figure 10, where the contour plots of the production rate (solid lines) and those of the recovery yield (dotted lines) are superposed when producing the second component at $\alpha = 1.5$, from a 3:1 mixture. When setting a 95% bound on minimum recovery, the position of the optimum is shifted from $L_f = 21.6\%$ and $N = 321$ to $L_f = 10\%$ and $N = 515$, but the production rate is only 17% smaller than it was at the global optimum.

Conclusion

The solvent consumption depends only on the loading factor and the column efficiency. The maximum production rate, on the other hand, depends also on the ratio d_p^2/L. Furthermore, the more efficient the column, the smaller the solvent consumption, while the optimum column efficiency for maximum production rate is not the maximum possible efficiency, but a lower value achieved at a high flow velocity. Thus, a compromise between high production rate and low solvent consumption is needed. This compromise will be dictated by the relative importance of fixed and proportional costs.

Although the influence of the retention factor on the production cost has been ignored so far, it should be emphasized that our results demonstrate that the solvent consumption is minimum, and the production rate maximum for rather low values of the retention factor of the first component of importance, often lower than 0.5. This first component may be the last impurity eluted before the component to purify, or one of the main components to extract from a mixture. Operating with low retention factors lead to a marked reduction of the cycle time and may cause maintenance problems by requiring higher frequency of valve switching and control problems by requiring lower fluctuations of the flow rate. It also requires a more efficient column, that is, a larger amount of

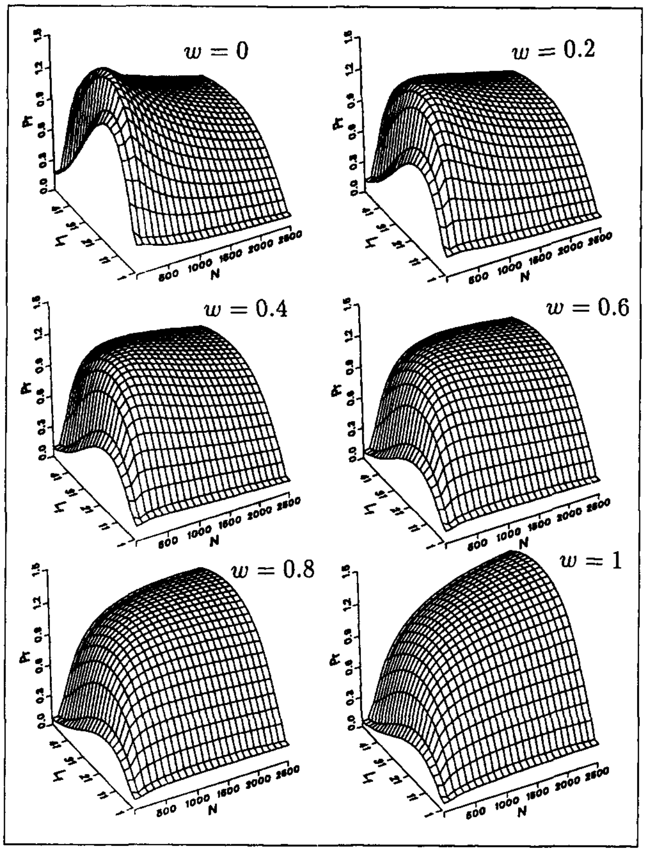

Figure 8. 3-D plot of the hybrid objective function (defined in Eq. 15) for less retained component of a 3:1 mixture at a separation factor $\alpha = 1.5$ and retention factor $k_1' = 6$.

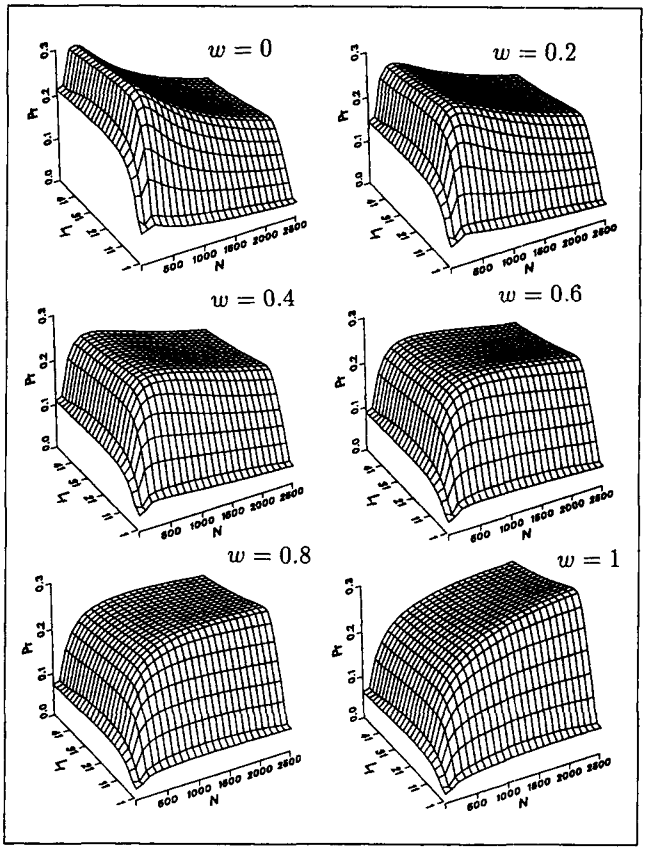

Figure 9. Same as Figure 8, but more retained component is optimized.

finer particle, hence more expensive stationary phase. This may result in an increased cost. Nevertheless, the development of new preparative separations should be done with the knowledge that considerable savings could be achieved by reducing the retention factor below the 3 to 6 range which seems to be the most popular at present.

In addition, the maximum production rate and the minimum solvent consumption require quite different operational parameters at high retention factors, whereas, when the retention factor is also optimized, all the values of the optimum parameters for maximum production rate or minimum solvent consumption are closer.

As a first approximation, we can separate the production costs into two contributions: a fixed cost contribution and a solvent cost contribution. The former include all capital costs and labor, because the manpower requirements are determined more by regulations and the need for a minimum size crew, and will be the same whether the plant operation is conducted under conditions of maximum production rate or minimum solvent consumption. The latter cost contribution includes solvent and energy costs. Because most of the energy is needed to evaporate the solvent, concentrate the purified product from the collected fractions, and purify the recycled solvent by distillation, this contribution is proportional to the volume of the solvent used. When a given relative importance is attributed to these two costs, a weighted objective function can be con-

Table 4. Optimum Experimental Conditions at the Maximum of Weighted Objective Function: Mixture Composition 3:1, $\alpha = 1.5$, $k_1' = 6$

w	N	d_p μm	L_f %	Pr_i mg/cm²·s	SP_i mg/mL	Y_i %
First Component						
0.0	257	20.1	23.5	1.479	0.730	63.2
0.1	293	19.4	24.5	1.469	0.790	64.5
0.2	420	17.6	27.0	1.416	0.913	66.0
0.3	477	17.0	28.1	1.387	0.960	65.8
0.4	596	16.0	29.0	1.321	1.036	67.8
0.5	754	14.9	30.2	1.238	1.109	67.9
0.6	852	14.4	31.5	1.191	1.145	67.8
0.7	1,230	13.0	33.5	1.045	1.245	68.2
0.8	1,930	11.3	36.3	0.868	1.356	67.6
0.9	3,452	9.4	39.3	0.655	1.478	67.3
1.0	5,000	8.3	42.3	0.536	1.550	65.6
Second Component						
0.0	321	19.0	21.6	0.324	0.180	48.9
0.1	348	18.6	17.5	0.324	0.188	60.5
0.2	454	17.2	17.0	0.314	0.212	67.2
0.3	622	15.8	16.6	0.294	0.236	73.6
0.4	656	15.5	17.3	0.289	0.239	71.9
0.5	767	14.9	16.6	0.277	0.251	76.7
0.6	972	13.9	15.9	0.257	0.266	82.6
0.7	1,258	12.9	16.1	0.234	0.282	84.6
0.8	1,793	11.7	16.7	0.203	0.298	84.9
0.9	2,956	9.9	16.1	0.157	0.321	90.9
1.0	5,000	8.32	15.7	0.117	0.339	96.0

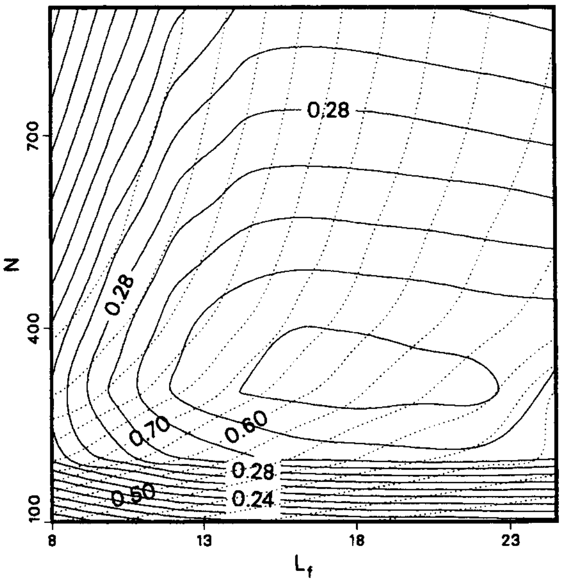

Figure 10. Superposed contour plots of the production rate (—) and recovery yield (. . . .).

More retained component is purified at $\alpha = 1.5$ from a 3:1 mixture.

structed to find a compromise between the requirements of minimum solvent consumption and maximum production rate. In this case, we found that there are two regions. When the capital costs are larger than the solvent costs, the optimum column efficiency remains close to the value that is optimal for maximum production rate, though it gradually increases. When the solvent costs are larger than the fixed costs, the optimum column efficiency is large, as for minimum solvent consumption. In the intermediate cases, when both costs contributions are similar, the optimization problem is ill-posed, and the optimum conditions depend hardly on the column efficiency in a wide range of this parameter.

Finally, in some infrequent cases, a most expensive stationary phase may be needed, and we may need to minimize this capital cost. In all the calculations discussed in this work, a constant column length ($L = 25$ cm) was assumed. The reduced mobile-phase velocity, the particle diameter, and the maximum inlet pressure determined the column efficiency. For this reason, the contribution of the stationary phase cost is the same in each and every case. A different approach would permit a simple solution. Choosing the smallest particles available and calculating the column length required to reach the desired efficiency would give the minimum amount of the stationary phase needed to produce a unit amount of purified product.

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Notation

a = first coefficient of the Langmuir isotherm
b = second coefficient of the Langmuir isotherm, $\mathrm{cm^3 \cdot mg^{-1}}$
C = mobile-phase concentration of the solute, $\mathrm{mg \cdot cm^{-3}}$
d_p = average particle diameter of the stationary phase, cm
D_a = apparent dispersion coefficient, $\mathrm{cm^2 \cdot s^{-1}}$
D_m = solute diffusion coefficient, $\mathrm{cm^2 \cdot s^{-1}}$
F = phase ratio
F_v = flow rate of the mobile phase, $\mathrm{cm^3 \cdot s^{-1}}$
h = reduced plate height
H = height equal to a theoretical plate, cm
k' = retention factor at infinite dilution
k_0 = specific column permeability
L = column length, cm
L_f = loading factor
N = number of theoretical plates
Pr = production rate, $\mathrm{mg \cdot cm^{-2} \cdot s^{-1}}$
Pr^* = hybrid objective function
q = equilibrium stationary-phase concentration of the solute, $\mathrm{mg \cdot cm^{-3}}$
q_s = saturation capacity, $\mathrm{mg \cdot cm^{-3}}$
S = column cross-sectional area, $\mathrm{cm^2}$
SP = specific production, $\mathrm{mg \cdot cm^{-3}}$
t = time, s
t_0 = dead time of the column, s
u = linear velocity of the mobile phase, $\mathrm{cm \cdot s^{-1}}$
V_s = volume of the sample injected, $\mathrm{cm^3}$
w = weighing factor
x = reduced length
Y = recovery yield
z = length, cm

Greek letters

α = separation factor
ϵ = porosity of the column packing
η = mobile-phase viscosity, cp
ν = reduced velocity of the mobile phase
τ = reduced time
ΔP = inlet pressure, bar
Δt_c = cycle time, s
Δt_s = injection time, s

Subscript

MP = maximum production rate
sm = minimum solvent consumption

Literature Cited

Colin, H., "Large-Scale High-Performance Preparative Chromatography," *Preparative and Production Scale Chromatography*, G. Ganetsos and P. E. Barker, eds., Marcel Dekker, p. 11 (1993a).

Colin, H., and G. Cox, "Some Considerations about the Optimization Costs in Preparative Liquid Chromatography," private communication (1993b).

Czok, M., and G. Guiochon, "Comparison of the Results Obtained with Different Models of the Simulation of Preparative Chromatography," *Comput. Chem. Eng.*, **14**, 1435 (1990).

Felinger, A., and G. Guiochon, "Optimization of the Experimental Conditions and the Column Design Parameters in Overload Elution Chromatography," *J. Chromatogr.*, **591**, 31 (1992a).

Felinger, A., and G. Guiochon, "Optimization of the Experimental Conditions and the Column Design Parameters in Displacement Chromatography," *J. Chromatogr.*, **609**, 35 (1992b).

Felinger, A., and G. Guiochon, "Comparison of Maximum Production Rates and Optimum Operating/Design Parameters in Overloaded Elution and Displacement Chromatography," *Biotechnol. Bioeng.*, **41**, 134 (1993).

Golshan-Shirazi, S., and G. Guiochon, "Theory of Optimization of the Experimental Conditions of Preparative Elution Using the Ideal Model of Liquid Chromatography," *Anal. Chem.*, **61**, 1276 (1989a).

Golshan-Shirazi, S., and G. Guiochon, "Theory of Optimization of the Experimental Conditions of Preparative Chromatography: Optimization of the Column Efficiency," *Anal. Chem.*, **61**, 1368 (1989b).

Golshan-Shirazi, S., and G. Guiochon, "The Equilibrium-Dispersive Model of Chromatography," *Theoretical Advancement in Chromatography and Related Separation Techniques*, F. Dondi and G. Guiochon, eds., Kluwer (1992).

Golshan-Shirazi, S., J. X. Huang, and G. Guiochon, "Comparison of an Experimental Competitive Isotherm and the LeVan-Vermeulen Model and Prediction of Band Profiles in a Case of Selectivity Reversal," *Anal. Chem.*, **63**, 1147 (1991).

Jacobson, S. C., S. Golshan-Shirazi, and G. Guiochon, "Isotherm Selection for Band Profile Simulation in Preparative Chromatography," *AIChE J.*, **37**, 836 (1991).

Knox, J. H., "Practical Aspects of LC Theory," *J. Chromatogr. Sci.*, **15**, 352 (1977).

LeVan, M. D., and T. Vermeulen, "Binary Langmuir and Freundlich Isotherms for Ideal Adsorbed Solutions," *J. Phys. Chem.*, **85**, 3247 (1981).

Morgan, E., K. W. Burton, and N. Graham, "Optimization Using the Super-Modified Simplex Method," *Chemometr. Intell. Lab. Syst.*, **8**, 97 (1990).

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