Optimizing preparative separations at high recovery yield

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Abstract

A new objective function is introduced for the optimization of the design and operation conditions in preparative chromatography. Instead of the production rate, we propose to maximize the product of the production rate and the recovery yield. This new objective function leads to optimum experimental conditions under which the production rate is almost as high as it would be if only the production rate were maximized, but the recovery yield is significantly improved. The advantages of the novel objective function are demonstrated by calculations based on both the ideal and the equilibrium-dispersive models of chromatography. The application of this novel objective function is beneficial in isocratic overloaded elution, in overloaded gradient elution and in displacement chromatography.

Keywords: Optimization; Preparative chromatography; Equilibrium–dispersive model; Production rate; Recovery yield

1. Introduction

The optimization of preparative separations has been studied on a theoretical basis by a variety of methods [1–12]. Although the actual aim of the optimization of a process is the achievement of the most economical production possible, many of the factors leading to an economical production are external to the chromatographic process itself and are beyond the control of chromatographers. For this reason, the production rate has been chosen in many publications as the objective function for the optimization of the experimental conditions under which separations are carried out by preparative chromatog-

raphy. The production rate can be calculated under closed analytical form with the ideal model [1]. This result has limited practical usefulness because the ideal model does not account for band broadening and cannot help in optimizing the flow-rate. A simplified band broadening model [2] allows the extension of the results obtained with the ideal model to more realistic situations and the inclusion in the optimization process of experimental parameters such as the mobile phase velocity and the pressure drop which can be taken into account by the ideal model.

The use of the numerical solutions of a more comprehensive model for the optimization of the experimental conditions is the most realistic approach because it makes it possible to take into account any significant contribution to band broadening, whether it originates from axial dispersion or from mass transfer resistances. Several investigations taking into account a different number of the ex-

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perimental parameters that are optimized simultaneously [3–12] have been published. In most cases, the result is obtained by applying a sequential simplex algorithm and by using the production rate as the objective function. This is a reasonable choice because maximizing the production rate is equivalent to minimizing the capital cost of the hardware required to perform a separation. Other objective functions are possible, however, since the production cost has two other important components, the operating costs and the lost feed [7,13,14]. So, minimizing the amount of solvent required to produce the unit amount of purified compound under a given set of experimental conditions allows the minimization of operation costs. Felinger and Guiochon [7] have considered the latter approach. It has been shown that this is, in many cases of practical importance, the major contribution to this cost [13]. Accordingly, we have used solvent consumption as an objective function to be minimized. We have also combined the solvent consumption and the production rate into a new objective function and determined the optimum experimental conditions for hybrid cases when both production rate and solvent saving are important.

However, the maximum production rate is often found at experimental conditions for which the recovery yield is unacceptably small. This happens particularly when the separation factor is rather small. In this case, a constrained optimization with a minimum threshold on the recovery yield (e.g. a yield larger than 90%) has been used so far.

2. Theory

The determination of the optimum experimental conditions can be made by means of either the ideal or the equilibrium–dispersive model. The ideal model has the advantage of supplying the thermodynamic limit, an estimate of the highest production rate and recovery yield allowed. These values could be achieved only with a column of infinite efficiency. In the case of a binary separation, the ideal model allows the calculation in algebraic form of all the attributes of the band profiles, except for the retention time of the shock of the less retained component of the pair. The optimum experimental

conditions have been reported previously for both components [1].

The production rate is the amount of product recovered during the unit time using a column of unit cross-sectional area[2].

$$Pr = \frac{V_p C^0 Y}{\varepsilon St_c} \tag{1}$$

The loading factor is the amount of sample injected compared to the amount of sample which would be needed to saturate the column (i.e., in the case of the Langmuir isotherm, to fill completely the adsorbed monolayer).

$$L_f = \frac{V_p C^0 b}{\varepsilon SLk'} \tag{2}$$

The recovery yield reported by Golshan-Shirazi and Guiochon [1] for the more retained component is

$$Y_2 = \begin{cases} 1, & \text{if } L_{f,2} \leq \frac{1}{1 + r_1/\alpha} \left[\frac{(\alpha - 1)/\alpha}{1 - x} \right]^2 \\ \frac{1}{L_{f,2}(1 + r_1/\alpha)} \left[\frac{(\alpha - 1)/\alpha}{1 - x} \right]^2, & \text{otherwise} \end{cases} \tag{3}$$

where r_1 is the positive root of the following equation

$$b_2 C_2^0 r^2 - [\alpha - 1 + b_2(C_1^0 - C_2^0)]r - b_2 C_1^0 = 0 \tag{4}$$

x is calculated from the required degree of purity of the more retained component, Pu_2

$$x = \sqrt{\frac{1 - Pu_2}{\alpha r_1 Pu_2}} \tag{5}$$

When the band profiles of the two components overlap, the production rate of the more retained component is

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[2]Note that this definition differs slightly from the definition used in Ref. [1], as the cross-sectional area of the column is not considered in the previous definition of the production rate. Furthermore, in our calculations, identical column saturation capacities were assumed for the two components. Consequently, the equations differ slightly.

$$Pr_2 = \frac{Lk_2'}{(1 + r_1/\alpha)b_2 t_c}\left[\frac{(\alpha - 1)/\alpha}{1 - x}\right]^2 \qquad (6)$$

The production rate in Eq. (6) is derived with a cycle time defined as equal to the corrected analytical retention time of the second component. This definition is somewhat arbitrary but is the most convenient for isocratic overloaded elution [1]. Another option for defining the cycle time is the time elapsed between the emergence of the first component and the disappearance of the second one [4–7]. In displacement and gradient elution chromatography, however, the column requires regeneration and reequilibration after each run. Another definition of the cycle time, taking the time required for these operations into account is needed. For this reason, we must make an estimate of the amount of washing required. Assuming that six column volumes of solvent are needed to regenerate the column, the cycle time will be defined as the analytical retention time of the more retained component plus six times the void time.

$$t_c = t_{R,2} + 6t_0 = t_0(k_2' + 7) \qquad (7)$$

With this definition, the maximum production rate becomes

$$Pr_2 = \frac{u_0 k_2'}{(1 + r_1/\alpha)b_2(k_2' + 7)}\left[\frac{(\alpha - 1)/\alpha}{1 - x}\right]^2 \qquad (8)$$

This maximum production rate is reached when the two bands just touch each other. It remains constant when the loading factor is increased further. The general expression for production rate at any load is thus

$$Pr_2 =$$

$$\begin{cases} \dfrac{u_0 k_2' L_{f,2}}{b_2(k_2' + 7)}, & \text{if } L_{f,2} \leq \dfrac{1}{1 + r_1/\alpha}\left[\dfrac{(\alpha - 1)/\alpha}{1 - x}\right]^2 \\[2mm] \dfrac{u_0 k_2'}{(1 + r_1/\alpha)b_2(k_2' + 7)}\left[\dfrac{(\alpha - 1)/\alpha}{1 - x}\right]^2, & \text{otherwise} \end{cases} \qquad (9)$$

Similar calculations can be carried out for the optimization of the production rate of the less retained component. For the sake of simplicity, we assume that 100% purity of the collected fraction is required (which is possible with the ideal model but is not with other models nor in actual practice). In this case, the recovery yield of the less retained component is [1]:

$$Y_1 =$$

$$\begin{cases} 1, & \text{if } \dfrac{L_{f,2} \leq [(\alpha - 1)/\alpha]^2}{1 - r_1/\alpha} \\[2mm] 1 - \dfrac{\alpha r_1}{L_{f,1}(1 + r_1/\alpha)}\left(\dfrac{\alpha - 1}{\alpha} - \sqrt{1 + r_1/\alpha}\sqrt{L_{f,2}}\right)^2, & \text{otherwise} \end{cases} \qquad (10)$$

With the definition of the cycle time given above, the production rate of this component is

$$Pr_1 = \frac{u_0 L_{f,1} Y_1 k_2'}{b_2(k_2' + 7)} \qquad (11)$$

The optimum conditions for the purification of the less and the more retained component are entirely different. Because of the displacement effect, the intensity of which increases with increasing loading factor for the second component, the maximum production rate of the less retained component cannot be observed except by using values of the loading factor which are so high that the recovery yield becomes unacceptably poor. The production rate of the more retained component reaches a plateau when touching bands takes place, or for a value of the loading factor slightly higher, with little band overlap, depending on the purity requirements.

Because of this phenomenon, the numerical method of optimization, based on the calculation of solutions of the equilibrium–dispersive model, is cumbersome in many instances. The surface of the objective function is rather flat. Some improvement could be observed by defining a cycle time that depends on the loading factor [4–7]. However, except at very high separation factors, high recovery yield can only be reached by constraining the optimization by introducing a minimum yield, usually set at 90%. Instead of maximizing the production rate with or without a yield constraint, the simultaneous maximization of both the production rate and the recovery yield looks advantageous. A convenient way to achieve this goal is to choose an objective function which is the product of the production rate and the recovery yield. The new objective function can be expressed by the following equations when the ideal model is assumed.

$$Pr_2 \times Y_2 =$$

$$\begin{cases} \dfrac{u_0 k_2' L_{f,2}}{b_2(k_2' + 7)}, & \text{if } L_{f,2} \leq \dfrac{1}{1 + r_1/\alpha}\left[\dfrac{(\alpha - 1)/\alpha}{1 - x}\right]^2 \\ \dfrac{u_0 k_2'}{(1 + r_1/\alpha)^2 b_2(k_2' + 7)}\left[\dfrac{(\alpha - 1)/\alpha}{1 - x}\right]^2, & \text{otherwise} \end{cases}$$

(12)

for the more retained component, and

$$Pr_1 \times Y_1 =$$

$$\begin{cases} \dfrac{u_0 L_{f,1} k_2'}{b_2(k_2' + 7)}, & \text{if } L_{f,2} \leq \dfrac{[(\alpha - 1)/\alpha]^2}{1 + r_1/\alpha} \\ \dfrac{u_0 L_{f,1} k_2'}{b_2 + (k_2' + 7)}\left[1 - \dfrac{\alpha r_1}{L_{f,1}(1 + r_1/\alpha)}\left(\dfrac{\alpha - 1}{\alpha} - \sqrt{1 + r_1/\alpha}\sqrt{L_{f,2}}\right)^2\right]^2, & \text{otherwise} \end{cases}$$

(13)

for the less retained component. Eqs. (12,13) are the solutions of the ideal model. If we use these two objective functions for the optimization of the experimental conditions in preparative chromatography, we will find optimum conditions under which the production rate is somewhat lower than it would be if the production rate itself were the objective function, but the recovery yield will be much higher.

3. Results and discussion

Calculations were carried out by means of both the ideal and the equilibrium–dispersive model of chromatography, in order to determine the optimum conditions, using the functions defined in Eqs. (12,13) as the objective function. When the ideal model was used, the production rates of the more and the less retained components were calculated by Eqs. (9,11), respectively. The recovery yield was calculated by Eqs. (3,10), respectively. Solutions of other models can be calculated numerically. This calculation is easy using algorithms previously discussed [15].

3.1. Optimization with the ideal model

Fig. 1 and Fig. 2 show the results calculated with the ideal model, by the above equations, at a separation factor $\alpha = 1.2$, a retention factor $k_1' = 2$, injected concentrations $C_1^0 = 100$ mg/ml and $C_2^0 = 300$ mg/ml. The values of the b parameters of the Langmuir isotherm were chosen to ensure a $q_s = 260$
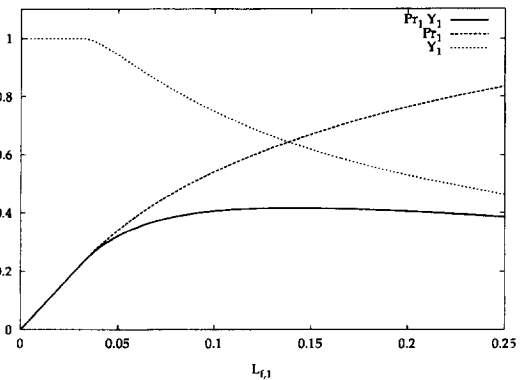

Fig. 1. Plot of the calculated production rate, recovery yield and their product for the less retained component against the loading factor, based on the ideal model. $\alpha = 1.2$; $k_2' = 2$; $C_1^0 = 100$ mg/ml; $C_2^0 = 300$ mg/ml; $q_s = 260$ mg/ml.

mg/ml saturation capacity for both components. When the purification of the more retained component (Fig. 2) is optimized, the recovery yield is 100% until the bands of the two components touch each other. The production rate increases linearly with increasing value of the loading factor. When the two bands begin to overlap, the recovery yield begins to decrease with increasing value of $L_{f,2}$, while the production rate remains constant. Choosing the product of these two quantities as a new objective function, we observe a sharp maximum at the loading factor where overlap begins. The yield achieved is 100% and the production rate is maximum, an ideal situation.
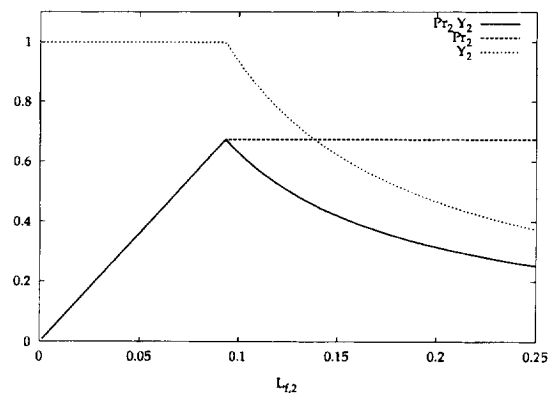

Fig. 2. Same as Fig. 1, except calculations were made for the more retained component.

On the other hand, when we optimize the separation of the less retained component (Fig. 1), the ideal model fails to identify an optimum value of the loading factor for maximum production rate. The production rate increases monotonously with increasing loading factor, while the recovery yield decreases with increasing value of $L_{f,1}$ beyond the value at which touching bands is reached. With the new objective function we are able to find an optimum value of the loading factor, although the maximum is very flat in most instances. With the current values of the parameters (see Fig. 1), the optimum loading factor is at $L_{f,1} = 14\%$, where the recovery yield of this component is 64%.

Fig. 3 shows plots of the new objective function for the first component versus its loading factor at $\alpha = 1.5$ (instead of 1.2 in Figs. 1 and 2) and at different values of the retention factor of between one and six. When the separation factor is not small, the ideal model predicts the existence of a relatively sharp maximum of the new objective function for the less retained component at tolerable experimental conditions. The recovery yield at the optimum is smaller than it is for the more retained component, but it is still approximately 75% in the whole range of retention factors studied. Note that it has been shown in a previous publication that the optimum conditions for the maximum production rate were at low values of the retention factor [5,6]. Fig. 3 shows that this is also true for the new objective function.

3.2. Optimization with the equilibrium–dispersive model

Further calculations were carried out using band profiles obtained by numerical integration of the equilibrium–dispersive model. Previous results suggested that the optimum conditions are determined essentially by the values of the loading factor and the column efficiency [7]. Accordingly, the optimization was carried out by finding, with a sequential simplex routine, the optimum value of these two experimental parameters maximizing the new objective function.

3.2.1. Overloaded isocratic elution

The optimization of the experimental conditions for the purification of a 1:1 mixture ($C_1^0 = C_2^0 = 100$ mg/ml) was studied at a separation factor $\alpha = 1.2$, in overloaded isocratic elution. The left-hand chromatograms in Fig. 4 and Fig. 5 show the band profiles obtained under the optimum conditions for the maximum production rate of the less retained (Fig. 4) and the more retained (Fig. 5) component. In both cases, there is a considerable degree of overlap of the two bands, the mixed zone is very important and the recovery yield is rather poor. This is especially true for the more retained component because of the important tag-along effect. The displacement effect
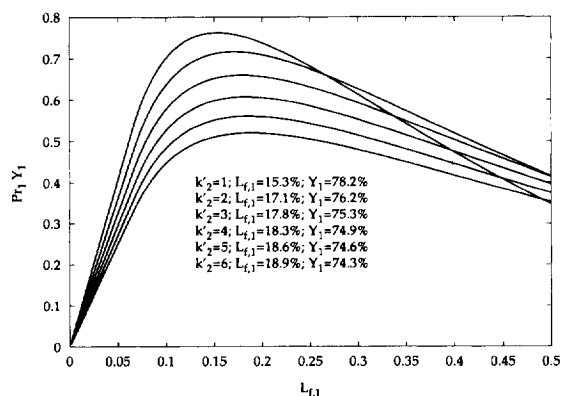

Fig. 3. Plot of the novel objective function against the loading factor. Calculations for the less retained component on the basis of the ideal model. $\alpha = 1.5$; $C_1^0 = 100$ mg/ml; $C_2^0 = 100$ mg/ml; $q_s = 260$ mg/ml.
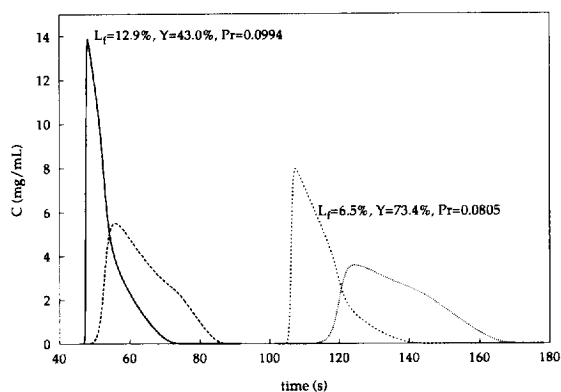

Fig. 4. Optimum separations calculated by the equilibrium–dispersive model for isocratic overloaded elution for the purification of the less retained component. The production rate (left) and the product of the production rate and the recovery yield (right) were maximized, respectively. $\alpha = 1.2$; $k_1' = 2$; $C_1^0 = 100$ mg/ml; $C_2^0 = 100$ mg/ml.
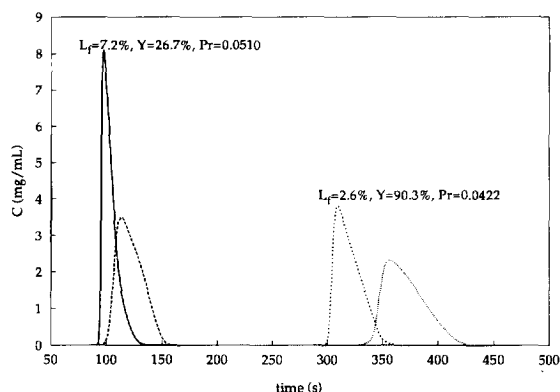
Fig. 5. Same as Fig. 4, except calculations were made for the more retained component.

Fig. 6. Plot of the production rate of the less retained component against the loading factor and plate number. $\alpha = 1.2$; $k_1' = 2$; $C_1^0 = 100$ mg/ml; $C_2^0 = 100$ mg/ml.

allows a higher loading factor for the purification of the first component and leads to a higher recovery yield. The chromatograms on the right-hand side of Figs. 4 and 5 were obtained for the optimum separation when the product of the production rate and recovery yield is maximized instead of the production rate. Obviously, since this objective function is weighed equally by production rate and recovery yield, the optimum loading factor is smaller for both components than in the previous case and the recovery yield is significantly higher. The improvement is particularly spectacular in the case of the more retained component, where the loading factor is almost three times lower, and the yield, at 90.3%, is more than three times higher than it had been previously. A recovery yield above 90% is usually considered as satisfactory. The considerable improvement in the recovery yield is achieved at the cost of a 20% reduction of the production rate. Depending on the economics of the process, one of the two options may be chosen or an intermediate set of conditions may be preferred.

It has been shown previously that the columns should be operated at the highest possible flow-rate in order to achieve maximum production rate [5–7]. This is a serious inconvenience since high flow-rates mean high pressure drop and, to a large extent, significant dilution. When the novel objective function is used, the required column efficiency is slightly higher than when it is the production rate. This demands for the use of smaller particles at constant column length. Consequently, the linear
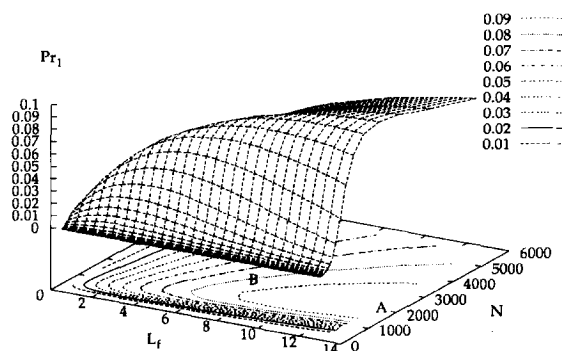
velocity of the mobile phase will be smaller at the same pressure drop. For this reason, the cycle times are longer when the novel objective function is used. This leads to smaller values of the production rate. However, the decrease of the production rate remains modest due to the improvement of the recovery yield.

Fig. 6 illustrates the shift of the position of the optimum experimental conditions for the first component when the production rate is replaced by the new objective function for the optimization. The maximum production rate is at point A, while the product of the production rate and the recovery yield reaches its maximum at point B. The contour lines clearly show that, while the optimum experimental conditions are markedly shifted, the production rate is hardly lower at the new optimum. On the other hand, Fig. 7 demonstrates how considerably the
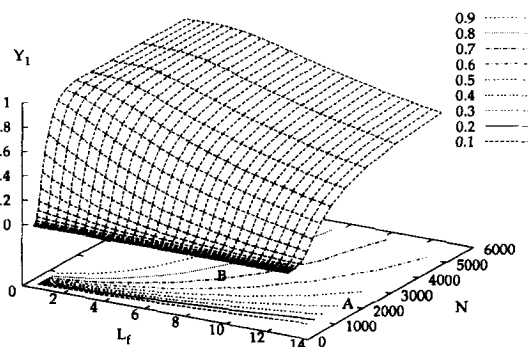

Fig. 7. Same as Fig. 6, except that the recovery yield is plotted.
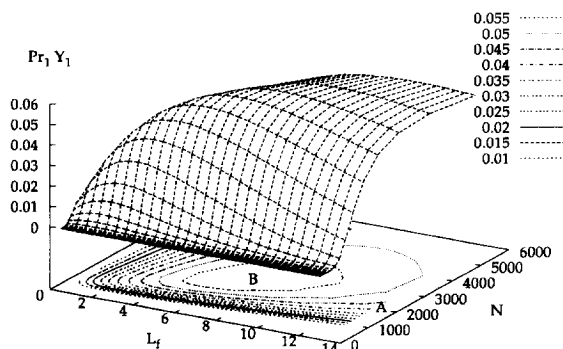
Fig. 8. Same as Fig. 6, except that the product of the production rate and the recovery yield is plotted.

Fig. 10. Same as Fig. 7, except that calculations were made for the more retained component.

recovery yield is improved when the experimental conditions are shifted from point A to point B. Finally, Fig. 8 shows that the surface determined by the novel objective function exhibits a well defined maximum, which makes the numerical optimization stable. By contrast, Fig. 6 shows that there is no maximum, or a very poorly defined one, for the production rate.

This property of the two surfaces and the corresponding functions, Pr and PrY, is still more important for the optimization of the production of the more retained component. Fig. 9 shows that the production rate of the second component reaches a flat plateau at high loading factors, as forecasted by the ideal model. This feature of the surface makes the numerical optimization very problematic. It causes the optimization program to locate the optimum conditions at values of the loading factor which are too high, under conditions for which the
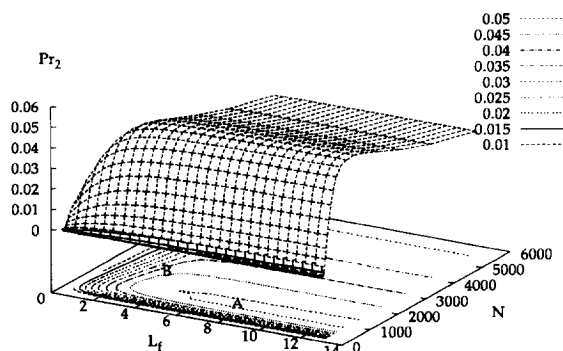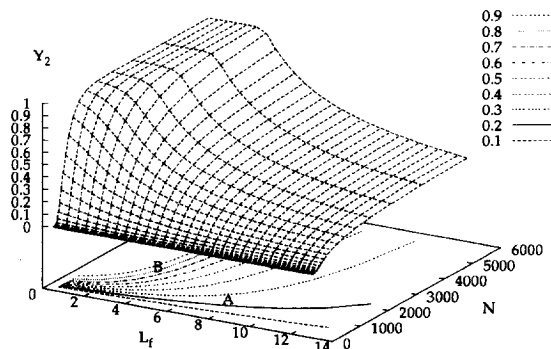
recovery yield is unsatisfactory and the result of the optimization somewhat meaningless. In the case of the second component as in that of the first one, the optimum is being significantly shifted with the introduction of the novel objective function, from point A to point B (Fig. 9). The drop in the production rate is still smaller than in the case of the less retained component. Fig. 10 illustrates the significant improvement in the recovery yield. The sharp maximum of the new objective function is shown in Fig. 11.

As illustrated in the previous figures, there are major differences between the behavior of the two components. One of the most noteworthy is in the nature of the shift of the experimental conditions from one objective function to the other (i.e., from point A to point B). In the case of the less retained component, the column efficiency is just about 9%

Fig. 9. Same as Fig. 6, except that calculations were made for the more retained component.
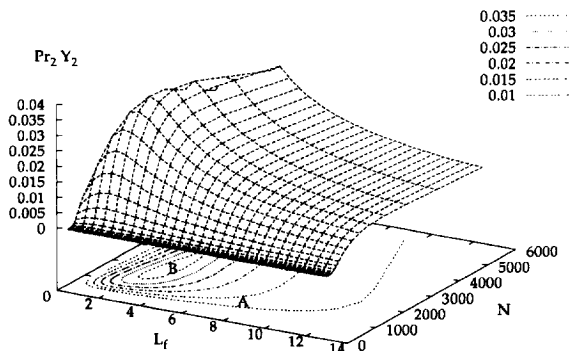

Fig. 11. Same as Fig. 8, except that calculations were made for the more retained component.

higher at point B than at point A. The improved yield is only due to the reduced value of the loading factor. On the contrary, the purification of the more retained component requires a markedly more efficient column (almost twice as efficient in the case in point) and the loading factor is considerably reduced.

3.2.2. Overloaded gradient elution

The novel objective function was successfully applied to the optimization of overloaded gradient elution chromatography. Fig. 12 compares the chromatograms obtained under the optimum conditions given by the two objective functions (Pr and PrY) for the purification of the more retained component of a binary mixture of relative concentration 1:3. The separation factor was $\alpha = 1.2$, the retention factor at the initial mobile phase composition was $k_0' = 10$, the gradient steepness was $G = 0.5$. The chromatogram on the left-hand side (LHS) of the figure corresponds to maximum production rate, the one on the right-hand side (RHS) to the maximum product of the recovery yield and the production rate.

In spite of the strong gradient steepness, both objective functions give values of the optimum loading factor and of the recovery yield achieved under optimum conditions which are very similar in isocratic and in gradient elution. At the maximum production rate, the recovery yield is only 31.7%. With the novel objective function, the optimum

loading factor is 57% smaller but the recovery yield is almost 90%. The optimum experimental conditions found by the two methods are quite different, but the production rate is only 15% smaller with the new objective function. The amount of pure fraction collected during each run is much higher with the novel objective function due to the improved yield. The production rate is smaller because the new optimum is achieved at a higher column efficiency, i.e. for a smaller linear velocity, which increases the cycle time.

3.2.3. Displacement chromatography

The novel objective function was also tested in displacement chromatography. Fig. 13 compares the chromatograms obtained under the optimum conditions given by the two methods, maximum production rate (LHS) and maximum product of production rate and recovery yield (RHS), for the separation of a 1:3 binary mixture at a separation factor $\alpha = 1.2$. The retention factor of the less retained component was $k_1' = 2$ (close to the optimum value for maximum production rate). These chromatograms correspond to an optimized purification of the more retained component. The shift of the optimum conditions is quite similar to those that we have observed earlier in both isocratic and gradient overloaded elution. At the maximum production rate (see the chromatogram on the left side in Fig. 13),
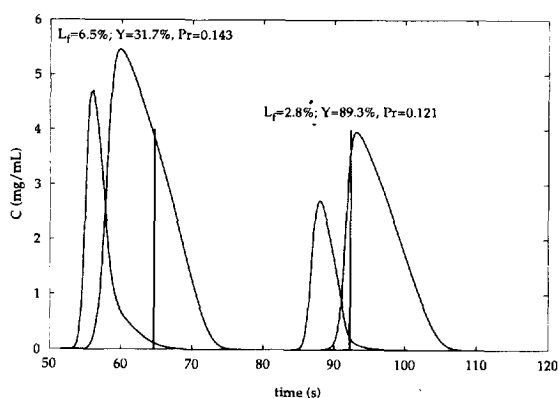

Fig. 12. Optimum separations calculated by the equilibrium–dispersive model for gradient overloaded elution for the purification of the more retained component. The production rate (left) and the product of the production rate and the recovery yield (right) were maximized, respectively. $\alpha = 1.2$; $k_{0.1}' = 10$; $G = 0.5$; $C_1^0 = 100$ mg/ml; $C_2^0 = 300$ mg/ml.
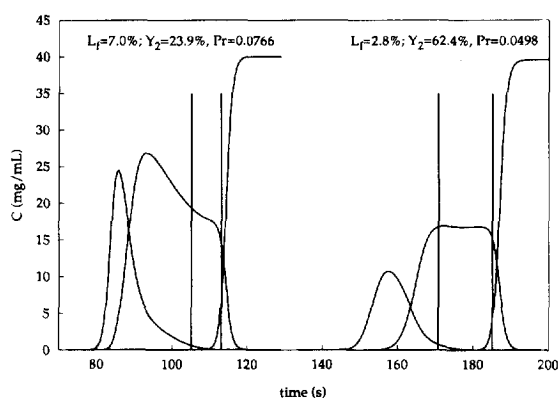

Fig. 13. Optimum separations calculated by the equilibrium–dispersive model for displacement chromatography for the purification of the more retained component. The production rate (left) and the product of the production rate and the recovery yield (right) were maximized, respectively. $\alpha = 1.2$; $k_1' = 2$; $C_1^0 = 100$ mg/ml; $C_2^0 = 300$ mg/ml.

the recovery yield is rather poor, only about 24%. When the product of the production rate and the recovery yield is maximized instead (see chromatogram on the right-hand side), the optimum loading factor is 2.5 times smaller, but the recovery yield is 2.6 times higher. Although the production rate is decreased by 35% when switching to the new objective function, the amount of pure product obtained during one run is higher, as seen in Fig. 13 from the area between the two vertical lines indicating the cut points.

4. Conclusions

The optimization of the experimental conditions can be solved successfully by using the product of the production rate and the recovery yield as an objective function to be maximized. Calculations made with the ideal model show that for the purification of the more retained component, the optimum loading factor is reached when the two bands just touch each other, at 100% recovery yield. The optimum conditions cannot be determined for the purification of the less retained component by means of the ideal model when the production rate is maximized. When the new objective function is used, however, the optimum loading factor can be determined both for the more and the less retained component. The recovery yield is around 70–80% at the optimum loading factor, depending on the other parameters of the separation. Such experimental conditions are usually acceptable.

These results are confirmed by calculations based on the use of the equilibrium–dispersive model, in isocratic and gradient elution, as well as in displacement chromatography. This model and the ideal model give a similar value of the recovery yield under optimum experimental conditions for the extraction of the first component. The recovery yield of the more retained component is usually around 90%, in both isocratic and gradient elution. In the displacement mode the yield is somewhat smaller, but it is still much higher than the one achieved without considering the value of the recovery yield in the objective function. When the yield is taken into account in the objective function, the optimum experimental conditions shift towards much smaller

values of the loading factor and higher column efficiency (particularly in the case of the more retained component), but the loss of production rate is minor compared to the gain in recovery yield.

The loss of production rate is important only at very small separation factors. Eq. (12) indicates that the maximum of the new objective functions is approximately proportional to the fourth power of $(\alpha - 1)/\alpha$, while the maximum production rate is proportional to the second power of that expression. This, however, is the price to pay to achieve high values of the recovery yield at small separation factors. Preliminary calculations based on the equilibrium–dispersive model in gradient elution chromatography confirm this finding [8]. Although no systematic calculations have been carried out, we note that the production loss is about twice as large in displacement chromatography as it is in elution or gradient elution (cf. Figs. 4 and 5,12 and 13).

5. Glossary of symbols

b	coefficient of the Langmuir isotherm, cm^3/mg
C^0	mobile phase concentration of the solute injected, mg/cm^3
k'	retention factor at infinite dilution
L	column length, cm
L_f	loading factor
Pr	production rate, $mg/cm^2/s$
Pu	purity of the collected fraction
r	variable in Eq. (4)
S	column cross-sectional area, cm^2
t_0	void time of the column, s
t_c	cycle time, s
t_R	retention time
u_0	linear velocity of the mobile phase, cm/s
V_p	volume injected
x	auxiliary parameter (Eq. (5))
Y	recovery yield
α	separation factor
ε	porosity of the column packing

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