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# ANALYSIS OF THE DESIGN AND OPTIMIZATION OF PREPARATIVE CHROMATOGRAPHY ON THE BASIS OF THE SEPARATION OF A REAL POST-REACTION MIXTURE

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## SUMMARY

The operating conditions for preparative chromatography, as for any industrial process, must be optimized. Such optimization is based on thorough understanding of process variables and economics. Optimization of the operating conditions is the best justification for detailed study of the fundamentals of nonlinear chromatography. It is difficult to optimize a separation without a clear understanding of how the thermodynamics of competitive phase equilibria, the finite rate of mass transfer, and dispersion phenomena combine to affect the individual band profiles of the components to be separated. The operating conditions determine the objectives of the process – yield, productivity, and, ultimately, the cost of the separation.

Because of the severe nonlinearity of the chromatography model, the problem of optimization is difficult to solve, and because of the large number of operating variables and the complexity of the objective functions, the solution found can easily be the result of trapping in a local optimum. It is, therefore, necessary to use an effective mathematical tool for global optimization of nonlinear problems.

In this work a chromatographic process for separation of the *cis* and *trans* isomers of furyl analogues of natural plant terpenes from a real post-synthesis mixture has been optimized. Typical problems during the optimization, which are discussed below, were:

(a) formulation of a model of the process dynamics;
(b) specification of model variables such as isotherm data, system efficiency, and physicochemical properties of the system;
(c) specification of the objectives of the separation process and the process operating variables; and
(d) selection of the optimization procedure.

## INTRODUCTION

The need to optimize chromatography is driven by a continuous demand to minimize production costs, to make the process more competitive, or to conform with environmental protection standards [1,2]. Several scientists have discussed optimization of adsorption and chromatographic processes operated in batch or continuous mode, e.g. the groups of Guiochon [1–5], Morbidelli, Mazzotti, and Ray [6–8], Seidel-Morgenstern [9–12], and Antos and Kaczmarski [9,10,12–14]. Because of the severe nonlinearity of mathematical models of the chromatography process, solution of the optimization problem is very difficult. We cannot be absolutely certain the optimum solution found is the global solution. For optimization of nonlinear unconstrained systems deterministic methods can be used, for example the Marquardt–Levenberg method [15,16] or the Nelder–Mead method [17]. The latter algorithm is a popular method for minimizing unconstrained real functions but is not suitable for solving nonlinear constrained problems or optimization of multimodal functions for which several local optima exist.

Optimization of chromatography process requires solution of a nonlinear constrained problem. Because of the number of variables used as operating conditions, solution of the problem is characterized by the presence of local minima or equivalent global optima. Calculations performed with the original deterministic methods are, therefore, quickly trapped in a poor local minimum. Because of this limitation of the method, the number of operating variables is limited to very few and optimization must be repeated several times starting from different initial conditions [3,4]. For this reason it is necessary to apply an effective tool for global optimization of nonlinear programming (NLP), a problem which remains an object of very intensive investigation. It should be mentioned here that methods for optimization of NLP problems which enable discovery of the global optimum have not yet been discovered. The state of the art of modern techniques for optimization in chemical and process engineering has been summarized elsewhere [18].

It is worth noting that in addition to deterministic methods of optimization stochastic methods are frequently used [15,16,19], because of their advantages of the possibility of finding a global optimum hidden among other poorer local optima, their low sensitivity to the choice of starting point (i.e. initial solution), and, often, the simplicity of the algorithm. Their practical large-scale use has become possible because of the rapidly incre-

asing computation capacity of modern computers. The most recent and most popular stochastic methods are:

(a) *genetic algorithms*, which simulate natural evolution or selection [6–8, 20];
(b) *adaptive random search*, which is based on so-called taboo searching using the sequence of the moves – the output from local optimum is classified as a taboo movement [21]; and
(c) *simulated annealing*, an idea based on the cooling and annealing of metals [12–14,22,23].

Hybrid methods which couple a convergent deterministic algorithm with a stochastic algorithm are extremely effective means of optimization with short computation times. One example of such a hybrid method is the use of a stochastic algorithm to determine an optimum starting point for further optimization with a deterministic method [24,25].

Formulating the target of the optimization process requires the making of a carefully balanced decision about which objective function to use during optimization. Different objective functions and process variables are known to lead to different optimization solutions [1,2]. Optimization of a chromatographic process can be directed toward maximization of profit by maximization of productivity or toward minimization of production costs (e.g. the minimization of consumption of reagents, minimization of capital expenditure, or optimization of the overall dimensions of the apparatus, etc.). It is possible to couple all these optimization problems by correct formulation of the problem – so-called multicriteria optimization. In optimization of a chromatographic process, productivity is typically used as the objective function.

As mentioned above, it is very difficult to optimize a chromatographic process without a good understanding of competitive thermodynamics, the rate of mass transfer, and dispersion phenomena and their effect on the shapes and retention times of the band profiles of each component of the separated mixture. These factors effect the yield and productivity of the process and the cost of the separation.

In the work discussed in this paper, a continuation of work on the problems of scaling-up a chromatographic process [26], a real separation of a binary mixture of isomers was optimized. The efficiency of optimization using different objective functions was examined and the effect of the pressure limit assumed and the choice of the key product on the results of optimization was analyzed. A typical scheme for organization of the optimization procedure is also presented and discussed.

## THEORY

### Organization of the Optimization Procedure

The procedure for optimization of chromatographic process should be organized in the following stages:

1. Acquisition of relevant experimental data and their theoretical interpretation:
   (a) adsorption equilibria in the presence of the multicomponent mobile phase;
   (b) system efficiency;
   (c) physicochemical properties of the system.
2. Choice of chromatography model dynamics accurate enough to simulate the process dynamics. As mentioned above for moderate and high system efficiency simplified pseudo-homogenous models or plate models can be used.
3. Formulation of the optimization problem – objective function, decision variables, process constraints.
4. Choice of optimization method.
5. Optimization and analysis of the results.

This method of organization of the optimization procedure has been illustrated for a real mixture of *cis* and *trans* isomers of furyl analogues of natural plant terpenes. The method used for this particular example, which can be implemented for industrial separation of these components, can be easily transferred to other chromatographic systems.

### Modeling of the Process

Mathematical models used to predict elution profiles in multicomponent nonlinear chromatography can be divided into two main groups:

(a) continuous (dispersion) models [1,2,27,28], based on systems of differential equations that describe the mass balance and the mass transfer and/or adsorption–desorption kinetics of simultaneous parallel and serial partial processes [29]; and
(b) discrete (plate) models, which link a series of equilibration and liquid-phase transport stages occurring in a certain number of plates [11,30–33].

When giving a short discussion of the continuous models it should be mentioned that one of the most accurate models is the so-called *general rate model* [1,2,28]. This is a heterogeneous model that consists of two mass-balance equations for the solute in the mobile phase and in the stag-

nant liquid phase within a particle and takes into account axial dispersion, and external and internal (within the pores) mass transport kinetics, which affect band broadening. In practice, several simplified pseudo-homogenous models are used, e.g., the *equilibrium–dispersive model* (ED model) in which dispersion and all resistance to mass transport are combined in an apparent axial dispersion coefficient, or the *transport–dispersive model* (TD model) in which external and internal resistance to mass transport are combined in the overall mass-transport coefficient [1,2,27,28]. These simplified models are sufficiently accurate for moderate and high system efficiency. For low and very low numbers of theoretical plates more accurate heterogeneous models should replace them. In analysis of the model, accuracy criteria developed elsewhere [11,32] can be taken into account. For optimization of chromatography simple discrete models from group (b) are also often used, e.g. the Craig model [30], which is a classical tool used to describe concentration profiles in a chromatographic column [11,33].

In this model the chromatographic column is divided into a series of identical theoretical plates, $N_c$, related to the column efficiency, $N_a$, by the equation:

$$N_c = \frac{\mu_1^2}{\mu_2}\frac{\bar{k}_0'}{1+\bar{k}_0'} = N_a\frac{\bar{k}_0'}{1+\bar{k}_0'} \qquad (1)$$

where $\mu_1$ is the first absolute moment and $\mu_2$ the second central moment (variance) of the band profile of the component, $N_a = \mu_1^2/\mu_2$, is the column efficiency, and $\bar{k}_0'$ is the average value of the retention factor of the sample [34].

The efficiency of a chromatographic column $N_a$ depends on the value of the apparent dispersion coefficient $D_a$ in the ED model, in accordance with the equation:

$$D_a = \frac{wL}{2N_a} = \frac{\bar{H}\bar{E}\bar{T}\bar{P}w}{2} \qquad (2)$$

The number of plates, $N_c$, is calculated here as the average value for all the components of the sample; $\bar{H}\bar{E}\bar{T}\bar{P}$ is the average height of a theoretical plate for both components. This is an important limitation of the Craig model because the retention factor $k_0'$ and *HETP* for each component can be different, because of different resistance to mass transport.

The Craig model is, therefore, not accurate for simulating multicomponent mixtures with components which differ markedly in retention factor. For binary mixtures of analogous components, however (for example isomers, enantiomers, etc.), for which retention is very similar, the inaccuracies of the Craig model can be neglected.

In the first stage of the Craig process at each of the $j$ theoretical plates mass of the sample components is exchanged between phases until equilibrium is reached, as described by an adsorption isotherm. After equilibrium has been reached in the first stage the amount of effluent contained in the last plate is withdrawn and collected, and the mobile phase from each plate is moved to the next. The process is repeated until all sample components are removed from the column.

The mass balance equation in the Craig model for component $i$, plate $j$, and stage $k$ can be expressed as:

$$c_{i,j}^{k+1} - c_{i,j-1}^{k} + F\left(q_{i,j}^{*k+1} - q_{i,j}^{*k}\right) = 0 \text{ , where } F = (1 - \varepsilon_t)/\varepsilon_t \tag{3}$$

for $i = 1 \ldots N$, $j = 1 \ldots N_c$; and $k = 1 \ldots K$.

The time difference between two successive steps of the Craig process, $k$ and $k + 1$, corresponds to the residence time $t_{res}$ of the mobile phase in a theoretical plate. This residence time is related to the column dead time, $t_0$, and the number of plates, $N_c$, as follows:

$$t_{res} = \frac{t_0}{N_c} \tag{4}$$

where

$$t_0 = \frac{V_{col}\varepsilon_t}{V} \tag{5}$$

At the beginning of the Craig process the column is filled with pure mobile phase, i.e.:

$$c_{i,j}^{0} = 0 \text{ and } q_{i,j}^{*0} = 0 \text{ for: } i = 1 \ldots N \text{ and } j = 1 \ldots N_c \tag{6}$$

Sample injection in the $j = 0$ theoretical plate can be described as:

$$c_{i,0}^{k} = \begin{cases} \text{step I } \; c_{i,0} \text{ for } k\Delta t \le t_{inj} \\ \text{step II } \; 0 \text{ for } t_{wash} \ge k\Delta t \ge t_{inj} \end{cases} \quad \text{for: } i = 1 \ldots N \text{ and } k = 1 \ldots K \tag{7}$$

where step I is the injection step and step II is the desorption (washing) step. After accomplishing the washing step the sequence is repeated; $c_{i,0}$ is the concentration of the *i*th component of the sample, and the pulse time $t_{\mathrm{inj}}$ is the sample volume $V_{\mathrm{inj}}$ divided by the volumetric flow $\dot{V}$ :

$$t_{\mathrm{inj}} = \frac{V_{\mathrm{inj}}}{\dot{V}} \tag{8}$$

If the column porosity is $\varepsilon_{\mathrm{t}}$, and the model of the adsorption isotherm and the boundary and initial conditions, values $c_{i,j-1}^{k}$ and $c_{i,j}^{k}$ are known, new equilibrium values $c_{i,j}^{k+1}$ in each theoretical plate $N_{\mathrm{c}}$ can be calculated by use of eq. (3).

**Variables of the Model**

*Column Efficiency*

Efficiency $N_{\mathrm{a}}$ can be calculated as the ratio of the length of the column, $L$, to the height equivalent to a theoretical plate, *HETP*:

$$N_{\mathrm{a}} = \frac{L}{HETP} \tag{9}$$

The height equivalent to a theoretical plate for the chromatographic system depends on velocity of the mobile phase and the size of adsorbent particle. This dependence can be expressed by the Van Deemter equation (eq. 10):

$$HETP_i = a_i d_{\mathrm{p}} + \frac{b_i}{u} + c_i u d_{\mathrm{p}}^2 \tag{10}$$

where the Van Deemter equation terms $a_i$, $b_i$, and $c_i$ are determined empirically [26]. (The physical significance of this equation is discussed in detail elsewhere [1,2].)

*Adsorption Isotherm Model*

The most important information required to solve the mass-balance equation (eq. 3) is the relationship between the concentrations of the component in the mobile and solid phases, $q_i^* = f(\mathbf{c})$, i.e. the adsorption isotherm [1,2,35], where **c** is a vector of a local concentration in the mobile

phase of the mixture components. The correctness of the model of the adsorption isotherm usually determines the accuracy of prediction of the process dynamics. In this work the *i*th component of the competitive Langmuir isotherm model has been used [1,2,26]:

$$q_i^* = \frac{q_i^\infty K_i c_{\text{mod}} c_i}{1 + \sum_{j=1}^{NC} K_j c_{\text{mod}} c_j} \tag{11}$$

where $c_i$ is the concentration of the component in the mobile phase, $q_i^*$ is the amount adsorbed at the equilibrium, $q_i^\infty$ is the loading capacity, $K_i$ is equilibrium constant, and $c_{\text{mod}}$ is the concentration of the mobile phase modifier in the mobile phase. The effect of the concentration of modifier, $c_{\text{mod}}$, in the isotherm (eq. 11) on the equilibrium constant $K_i$ is expressed by a power-law type of equation with a theoretical basis [36,37]:

$$K_i = p1\left(c_{\text{mod}}\right)^{-p2} \tag{12}$$

## Optimization of the Preparative Chromatography

*Method of Optimization*

For local optimization a derivative-free method based on the Nelder–Mead algorithm [9,10,24,25] was used. The original Nelder–Mead algorithm serves as a local optimizer which can be used to solve non-linear unconstrained optimization problems. As already mentioned, however, optimization of chromatography is a nonlinear constrained problem. For this reason a few modifications have been included in the original algorithm, which increased the probability of finding a global optimum [9,10]. The method also enables equality and inequality constraints to be taken into consideration.

*Objective Functions of the Optimization*

Different objective functions (OF) can be considered depending on the specificity of chromatographic separations. The most typical objective function in optimization of chromatography is the productivity *Pr* of the process. The productivity $Pr_i$ is defined as the amount of component *i* recovered from injections during a cycle time $\Delta t_c$ [1,2]:

$$Pr_i = \frac{m_i}{\varepsilon_t F_{col} \Delta t_c} \tag{13}$$

where $\Delta t_c$ is defined as the duration of two successive cycles $\Delta t_c = t_N^{end} - t_1^{start}$ (Fig. 1)

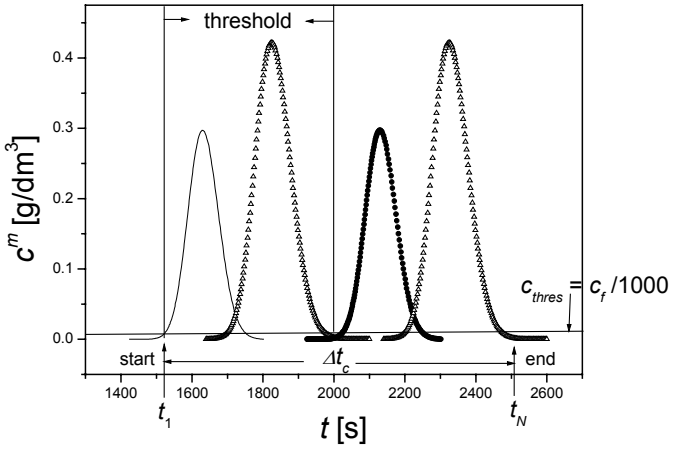


**Fig. 1**

Schematic representation of an elution profile for a binary chromatographic mixture. Indicated are the start and end of the cycle and the cycle time $\Delta t_c$, which depends on these times

Alternatively, the product of productivity and yield, *Y*, called the productivity factor *Pf* [11], can be used as the objective function:

$$Pf = Pr_i \, Y_i \tag{14}$$

where $Y_i$ is defined as the ratio of mass of the *i*th component collected to the mass of this component introduced in the feed [1,2]:

$$Y_i = \frac{m_i}{V_{inj} c_{i,F}} 100\% \tag{15}$$

An advantage of optimization of *Pf* is that its optimum value is only slightly lower than the optimum value of *Pr*, whereas the yield, *Y*, is markedly improved compared with when *Pr* alone is optimized.

*Constraints and Decision Variables*

After the performance index has been established as the objective function, OF, the results of optimization also become dependent on constraints

and on *continuous* or *discrete decision variables*, $\overline{x}$, where OF = $f(\overline{x})$. Here the optimization was performed subject to the following typical *constraints*:

(a) The purity of the target component should be higher than a stipulated minimum:

$$Pu \geq Pu_{\min} \tag{16}$$

$Pu_i$, is defined as:

$$Pu_i = \frac{\overline{c}_i}{\overline{c}_1 + \overline{c}_2} \tag{16a}$$

where $\overline{c}_i$ is the average concentration of the $i$th component in the fraction collected.

(b) The pressure drop in the system is constrained:

$$\Delta p < p_{\max} \tag{17}$$

where the pressure drop can be calculated by the use of the equation [1,2]:

$$\Delta p = \frac{u \eta_{\mathrm{m}} c_{\mathrm{mod}} L}{k_0 d_{\mathrm{p}}^2} \tag{17a}$$

where $\eta_{\mathrm{m}}\, c_{\mathrm{mod}}$ is the viscosity of the mobile phase as a mixture, which depends on the concentration of the mobile phase modifier, and $k_0$ is the specific permeability, which depends on the diameter and shape of an adsorbent particle [1,2]. For spherical particles $k_0 = 1.2 \times 10^{-3}$.

Note that manipulation of the composition of the mobile phase results in changes in the pressure drop, because of variation of the viscosity of the mobile phase. This effect is typically neglected in the optimization of chromatographic processes, which can lead to incorrect interpretation of the results obtained. *Here this problem has been taken into account*.

*Continuous decision variables* typically used for optimization of chromatography processes include:

(a) mobile phase composition, i.e. the concentration of the mobile phase modifier $c_{\mathrm{mod}}$;

(b) volumetric flow $\dot{V}$, which is limited by the capacity of the pump and the limit of the pressure drop (eq. 17);

(c) the mass loading of the column, which can be defined by the loading factor $L_{\mathrm{f},i}$ [1,2], a dimensionless quantity expressed as the ratio of the mass of component $i$ injected in the feed to the value of the loading capacity $q_i^{\infty}$ of the adsorbent for the component under consideration:

$$L_{\mathrm{f},i} = \frac{V_{\mathrm{inj}} c_{i,\mathrm{F}}}{\left(1-\varepsilon_{\mathrm{t}}\right) V_{\mathrm{col}} q_i^{\infty}} \tag{18}$$

where $c_{i,\mathrm{F}}$ is the feed concentration and $V_{\mathrm{inj}}$ is the injection (feed) volume. The total loading factor $L_{\mathrm{f,tot}}$ is a sum of the loading factors of all the components of the feed stream:

$$L_{\mathrm{f,tot}} = \sum_{i=1}^{N} L_{\mathrm{f},i} \tag{18a}$$

(d) the washing time of the column $t_{\mathrm{wash}}$, which determines the time between successive chromatographic cycles. During this time pure mobile phase is introduced at the column inlet (eq. 7).

*Discrete Decision Variables*

Decision variables optimized discretely were the length of the column $L$ and the particle diameter of the adsorbent $d_{\mathrm{p}}$. It is most convenient to express both these variables as a single decision variable, i.e. $d_{\mathrm{p}}^2 / L$ ($\mu\mathrm{m}^2\ \mathrm{cm}^{-1}$) [7–11]. This representation is a consequence of eq. (17a), which indicates that $\Delta p$ depends on $d_{\mathrm{p}}^2 / L$ [1,2].

*Quantities Monitored During the Optimization Procedure*

The quantities monitored are the yield $Y_i$, defined by eq. (15) (if *Pr* or *Pf* is optimized), and mobile phase consumption, *EC*, measured as the mass or volume of mobile phase which is consumed to obtain unit mass of the key product:

$$EC = \frac{V_{\mathrm{elu}}}{V_{\mathrm{inj}} Y c_{i,\mathrm{F}}} \tag{19}$$

## RESULTS AND DISCUSSION

### Terms of the Model

*System Efficiency – the van Deemter Equation*

The empirical terms of the van Deemter curve, represented by eq. (10), have been determined by investigating column efficiency as a function of particle diameter and mobile phase flow rate [26]. The values of *a*,

*b*, and *c* are shown in Table I for both isomers. The values of $N_c$ for each isomer did not differ by more than 3–4% and changed in the range 900–1100 theoretical plates, which is indicative of moderate system efficiency. The Craig model was therefore selected as sufficiently accurate for simulating the process [1,2,11,33]. To solve the Craig model (eq. 3) the average value of the height equivalent to a theoretical plate, $\overline{HETP}$ , for the *cis* and *trans* isomers was used.

**Table I**

Values of *a*, *b*, and *c* of eq. (10) for the *cis* and *trans* isomers

| $HETP_i = a_i d_p + \frac{b_i}{u} + c_i u d_p^2$ (10) | |
|---|---|
| *cis* isomer | *trans* isomer |
| $a = 8.2 \times 10^{-5}$<br>$b = 0.02528$<br>$c = 6.4 \times 10^{-6}$ | $a = 1.56 \times 10^{-4}$<br>$b = 0.02510$<br>$c = 7.2 \times 10^{-6}$ |

Note that both *u* and $d_p$ in eq. (10) simultaneously affect column efficiency and the pressure drop. The effects conflict with each other – increasing the particle size leads to a decrease of the column efficiency, which has an unfavorable effect on separation performance, but markedly reduces the pressure drop, which in contrast, favors process performance because higher flow rates can be used. Increasing the flow rate results in reduction of separation time of the process but reduces efficiency (van Deemter equation, eq. 10). It is, therefore, evident that to find the best operating conditions optimization of the process is indispensable.

*Mobile Phase Viscosity*

The dependence of mobile phase viscosity on modifier concentration $c_{mod}$ can be expressed as a quadratic polynomial equation:

$$\eta_m = -2.36857 \times 10^{-11}\, c_{mod}^2 + 1.594 \times 10^{-7}\, c_{mod} + 3.553 \times 10^{-4} \quad (20)$$

*Model of the Adsorption Isotherm*

The coefficients of the adsorption isotherm were determined elsewhere [26] and are presented in Table II. The functional dependences of the equilibrium constants $K_i$ on modifier concentration (eq. 11) for the *cis* and *trans* isomers, i.e. $K_i = f(c_{mod})$ are given in Table III.

## Table II

Terms of the Langmuir competitive isotherm model (eq. 11) for the *cis* and *trans* isomers

| $q^*$ = const. (g dm$^{-3}$) | $K$ (dm$^3$ g$^{-1}$) | |
|---|---|---|
| | *cis* isomer | *trans* isomer |
| 2934 ± 117.4 | 0.01490 ± 0.00045 | 0.01760 ± 0.0009 |

## Table III

Effect of mobile phase modifier concentration $c_{mod}$ on the equilibrium constant from the Langmuir competitive isotherm model (eq. 12)

| $K = p1(c_{mod})^{-p2}$ | | | |
|---|---|---|---|
| *cis* isomer | | *trans* isomer | |
| $p1$ | $p2$ | $p1$ | $p2$ |
| $1.816 \pm 1.344 \times 10^{-1}$ | $1.353 \pm 2.458 \times 10^{-2}$ | $1.926 \pm 1.361 \times 10^{-1}$ | $1.333 \pm 2.330 \times 10^{-2}$ |

## Formulation of the Optimization Problem

*Choice of Optimization Method*

As mentioned in the Introduction, several optimization methods, both deterministic or stochastic, are available. Because of the complexity of the problem, however, we do not recommend any deterministic method. All typical deterministic methods failed to locate the optimum – the calculations were trapped in poor local optima. The method of choice is a stochastic method, i.e. random search, genetic algorithms for which have already been examined in the literature [6–14,21–25]. Promising results were also achieved by use of a hybrid method involving both deterministic and stochastic algorithms.

*Objective Function*

Optimization was performed for objective functions, i.e. productivity $Pr$ (eq. 13) and productivity factor $Pf = Pr \times Y$ (eq. 14) and the efficiency of optimization for each function was compared. The optimization problem $max(Pr \text{ or } Pf) = f(L_f, c_{mod}, \dot{V}, t_{wash}, d_p^2/L)$ was solved subject to $Pu > Pu_{min}$. The performance functions yield, $Y$, and mobile phase consumption, $EC$, were also monitored.

*Constant Optimization Terms*

The diameter, $\Phi$, of the preparative column (10 mm) and total column porosity, $\varepsilon_t = 0.75$ (model term in eq. 3), were assumed to be constant (see details in Ref. [26]).

The model mixture was a real post-reaction mixture of the *cis* and *trans* isomers of the furyl analogues of natural, plant terpenes [26,38]. The feed concentration $c_{iF}$ was limited by solubility in the mobile phase. It is known in chromatography that concentration overloading is superior to volume overloading [1,2]. In this work concentration overloading was used during optimization. Hence, the maximum feasible sample concentration $c_{Fmax}$ soluble in the mobile phase [26] was assumed. The mixture contained *cis* and *trans* isomers in the approximate ratio 40:60 (% *m*/*m*), i.e. for the assumed $c_{Fmax} = 93$ (g dm$^{-3}$), $c_{Fcis} = 37.2$ (g dm$^{-3}$) and $c_{Ftrans} = 55.8$ (g dm$^{-3}$).

*Optimization Constraints*

The stipulated purity of the collected fractions was $Pu_{min} \geq 98\%$ and the threshold concentration for fractionation was $-c^{m}_{thresh} = 0.001 c_F$ (Fig. 1). To investigate the effect of limiting the pressure drop two different values of $p_{max}$ were assumed, 30 or 10 MPa. The first value is typical of modern, preparative chromatography pumps with an isocratic volumetric flow in the range 1–200 (cm$^3$ min$^{-1}$) whereas the second is typical of industrial chromatography pumps for columns with diameters, $d_{col}$, ≥50 mm.

*Continuous Variables of the Optimization*

For mobile phase composition, i.e. modifier concentration $c_{mod}$, the same solvent mixture as in Ref. [26] was assumed – ethyl acetate as mobile phase modifier and *n*-hexane as the inert component of the mobile phase. The search range in the optimization routine was $c_{mod} = 2$–$100\%$ (*v*/*v*) ($c_{mod} = 18$–$881$ g dm$^{-3}$). The lower bound resulted from the stability of the mobile phase – for mobile phases rich in *n*-hexane problems with cavitations occurred. This is a typical problem in normal-phase chromatography.

The search range of volumetric flow, $\dot{V}$, was 0–100 (cm$^3$ min$^{-1}$). The value of $\dot{V}$ was limited by the maximum pressure drop in the system (eq. 17a).

Because the feed concentration was set according to solubility, which is also typical of chromatography separations, the value of the loading factor, $L_f$, depended on the injection volume $V_{inj}$, which was used as a decision variable in this work. The search range was $V_{inj} = 5$–$20$ (cm$^3$).

*Discrete Variables of the Optimization*

To improve efficiency of the optimization procedure process variables such as column length and particle diameter were optimized discretely. The values examined were:

(a) column length, $L$, = 25, 50, 75, and 100 cm, equivalent to series connection of different a number ($n$ = 1–4) of columns of typical length 25 cm;

(b) particle diameter of the adsorbent $d_p$, = 5, 10, 12, 15, and 25 μm, i.e. the different sizes of adsorbent particles of LiChrospher Si 60 silica (pore diameter 60 Å) available commercially, examined in previous work [26]; as mentioned above, the column diameter $L$ and particle diameter $d_p$ were coupled in a single term $d_p^2/L$ (μm$^2$ cm$^{-1}$); the values of this term investigated were, therefore:

- for $L$ = 25 cm: $d_p^2/L$ = 1, 4, 5.76, 9, and 25;
- for $L$ = 50 cm: $d_p^2/L$ = 0.5, 2, 2.67, 4.505, and 12.5;
- for $L$ = 75 cm: $d_p^2/L$ = 0.333, 1.333, 1.969, 3, and 8.333;
- for $L$ = 100 cm: $d_p^2/L$ = 1, 1.44, 2.25, and 6.25 (for the longest column results for $d_p$ = 5 μm were not measured).

(c) for the sample component selected as key product, three options were considered (i) both the isomers are key products; (ii) the less retained (i.e. first eluted) component was regarded as the key product; and (iii) the more retained isomer was regarded as the key product.

Analysis of the results of the calculations enabled selection of the optimum values of these terms.

## RESULTS OF CALCULATIONS

### Effect of Changing the Length and Particle Diameter

The effects of column length and particle diameter on process performance were examined for $p_{max}$ = 30 MPa and with both isomers regarded as key products. The values of productivity and yield as a function of $d_p^2/L$ are depicted in Figs 2a and 2b and the optimum conditions are reported in Table IV (rows 1, 1′, 2, and 2′). Figure 2a depicts the results of optimization of productivity $Pr_{tot}$ as the objective function, OF, whereas Fig. 2b depicts the results of optimization of productivity factor $Pf_{tot}$ = $Pr_{tot} \times Y_{tot}$ as the objective function.

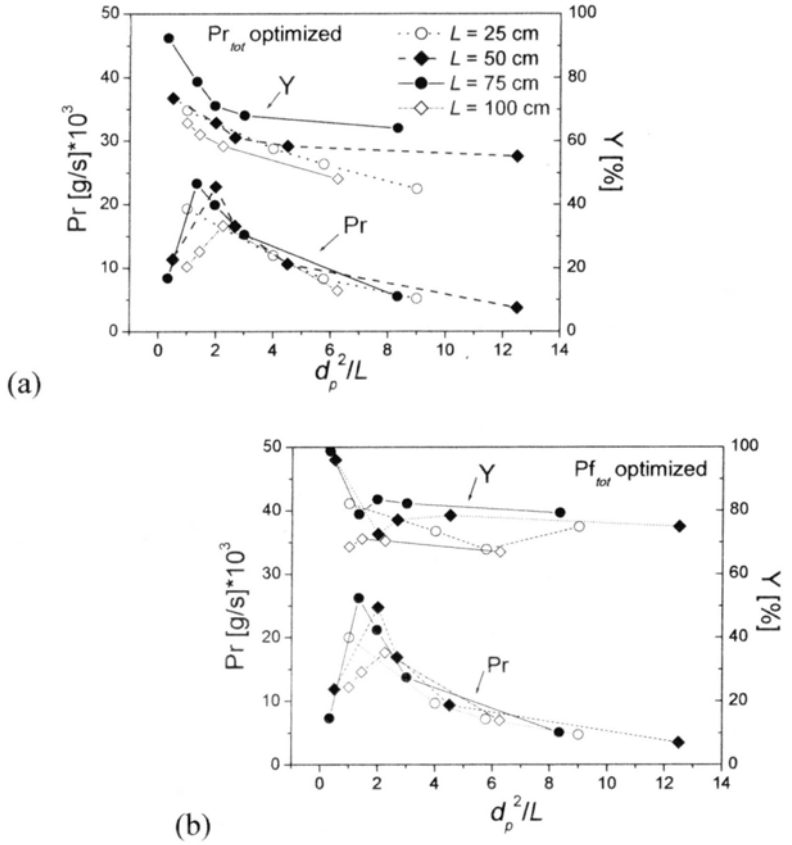


**Fig. 2**

Dependence of $Pr_{tot}$ and $Y_{tot}$ on $d_p^2/L$ for $p_{max}$ = 30 MPa. In (a) the OF is $Pr_{tot}$ and in (b) the OF is $Pf_{tot}$. The symbols in (b) have the same meaning as in (a)

It is evident from Table IV that maximum productivity $Pr_{tot}$ can be obtained for column length $L$ = 75 cm and particle diameter $d_p$ = 10 μm ($d_p^2/L$ = 1.33). This optimum is independent of the choice of objective function. The optimum value of $d_p$ also results in similar values of productivity $Pr_{tot}$ for $L$ = 50 cm ($d_p^2/L$ = 2.0) and $L$ = 75 cm ($d_p^2/L$ = 1.33). Further increasing the column length (or the number of columns in series, e.g. $L$ = 100 cm) results in worsening of productivity – because of the increased length the volumetric flow must be reduced, because of the pressure drop limitation. To compensate for this effect the particle diameter must be increased which, in turn, results in marked worsening of system efficiency,

**Table IV**

Set of optimum conditions

| No. | OF* | KP** | $d_p$ (μm) | $d_p^2/L$ (μm$^2$ cm$^{-1}$) | $c_{mod}$ (g dm$^{-3}$) | $\dot{V}$ (cm$^3$ min$^{-1}$) | $V_{inj}$ (cm$^3$) | $t_{wash}$ (s) | $Pr$ (g s$^{-1}$) × 10$^3$ | $Y$ (%) | $EC$ (dm$^3$ g$^{-1}$) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $L$ = 50 cm | | | | | | | | | | | |
| 1 | *Pr* | 1 and 2 | 10 | 2.00 | 134 | 89 | 12.5 | 25.0 | 22.8 | 65.7 | 0.065 |
| 1′ | *Pf* | 1 and 2 | 10 | 2.00 | 130 | 75 | 10.3 | 31.7 | 24.7 | 67.6 | 0.077 |
| $L$ = 75 cm | | | | | | | | | | | |
| 2 | *Pr* | 1 and 2 | 10 | 1.33 | 200 | 57 | 13.0 | 23.8 | 23.3 | 78.7 | 0.041 |
| 2′ | *Pf* | 1 and 2 | 10 | 1.33 | 206 | 55 | 11.4 | 30.0 | 26.2 | 72.8 | 0.054 |
| $p_{max}$ = 30 MPa | | | | | | | | | | | |
| 3 (2′) | *Pf* | 1 and 2 | 10 | 1.33 | 206 | 55 | 11.4 | 30.0 | 26.2 | 92.2 | 0.054 |
| 4 | *Pf* | 1 | 10 | 1.33 | 168 | 58 | 13.7 | 39.9 | 8.6 | 91.4 | 0.114 |
| 5 | *Pf* | 2 | 10 | 1.33 | 159 | 59 | 13.8 | 34.2 | 14.2 | 89.9 | 0.069 |
| $p_{max}$ = 10 MPa | | | | | | | | | | | |
| 6 | *Pf* | 1 and 2 | 15 | 3.00 | 136 | 33 | 15.6 | 95.1 | 10.6 | 90.6 | 0.052 |
| 7 | *Pf* | 1 | 15 | 3.00 | 161 | 33 | 15.7 | 76.9 | 4.6 | 86.7 | 0.118 |
| 8 | *Pf* | 2 | 15 | 3.00 | 155 | 33 | 13.5 | 69.7 | 7.1 | 89.4 | 0.077 |

*Objective function
**Key product

in accordance with the van Deemter equation (eq. 10). For shorter columns, e.g. $L = 25$ cm ($d_p^2/L = 1$) optimum productivity is also evidently lower, because of deterioration of the separation. Hence, the optimum length is in the range $L = 50$–75 cm. The advantage of longer columns is the value of the yield, $Y$, which is always higher for a longer column. It is also apparent from Table IV that use of a longer column enables reduction of mobile phase consumption.

The discussion above shows that optimization of $d_p^2/L$ alone is not sufficient – the column length should also be optimized. This is a general conclusion valid for optimization of all chromatographic processes.

Comparison of the optimization achieved by use of two different objective functions revealed that *Pf* is more effective because it enables higher values of both performance indexes – productivity and yield – to be achieved compared with the results obtained by independent optimization of *Pr*. This conclusion also can be regarded as general for typical chromatographic separations. For this reason *Pf* was used as the sole objective function in further analysis.

**Effect of Mobile Phase Velocity**

The effect of mobile phase velocity on process performance was analyzed with both isomers regarded as key products. The mobile phase velocity, measured as the ratio of the volume flow rate to the column cross-section, affects the pressure drop. High velocity usually results in improvement of productivity, because of shortening of process time (i.e. cycle time, eq. 13) and the pressure drop determines the upper velocity (eq. 16). Increasing the velocity leads to worsening of column efficiency, however, (van Deemter equation, eq. 10) and both these effects conflict in the optimization procedure. The choice of maximum acceptable pressure drop in the system, $p_{max}$, significantly affects the results from optimization. It was found that for $p_{max}$ = 30 MPa the maximum value of productivity *Pr* for the column of $L$ = 75 cm and optimum particle diameter $d_p$ = 10 μm ($d_p^2/L$ = 1.33) was *Pr* = 26.2. For $p_{max}$ = 10 MPa the *Pr* value evidently decreases, i.e. *Pr* = 10.6 (Fig. 3a and Table IV, rows 3 and 6). This is not surprising, because velocity must be reduced in accordance with the new limit of the pressure drop. The other process conditions can, however, be adjusted to compensate for this restriction on $p_{max}$, i.e. to reduce the pressure drop, and the maximum value of *Pr* is obtained by use of a larger particle diameter, $d_p$ = 15 μm ($d_p^2/L$ = 3.0).

Because of the lower feasible velocity, which results in improvement of column efficiency (eq. 10), the value of yield, *Y*, for $p_{max}$ = 10 MPa is higher than for $p_{max}$ = 30 MPa (Fig. 3b).

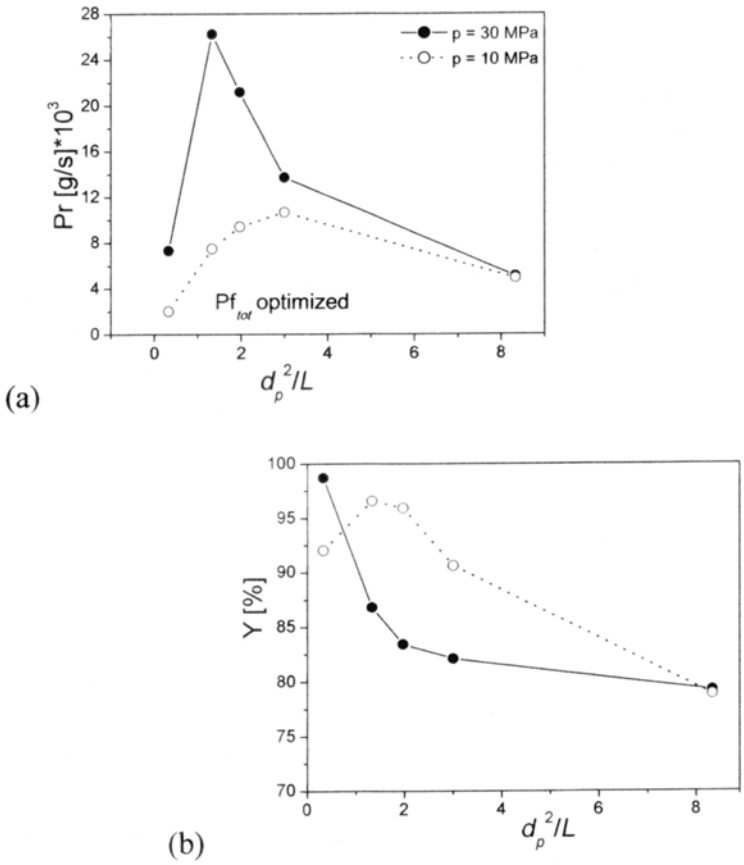


**Fig. 3**

Dependence of (a) $Pr_{\text{tot}}$ and (b) $Y_{\text{tot}}$ on $d_{\text{p}}^2/L$ for $p_{\max}$ = 10 and 30 MPa, column length, $L$, = 75 cm, and $Pf_{\text{tot}}$ as OF. The symbols in (b) have the same meaning as in (a)

## Effect of Mobile Phase Composition

Mobile phase composition has a substantial effect on process performance:

(a) It affects adsorption selectivity, $S_{\text{R}ij}$, defined as:

$$S_{\text{R}ij} = \frac{k'_{0_i}}{k'_{0_j}} = \frac{H_{\text{r}i}}{H_{\text{r}j}} \tag{21}$$

Because easy separations are characterized by high $S_{\text{R}ij}$ values, higher $S_{\text{R}ij}$ values are preferable for the separation process. Typically, separation

selectivity decreases with the concentration of the strongly adsorbed solvent-modifier. This situation was also observed for the system investigated in this work. The dependence of $S_{Rij}$ on mobile phase modifier content is illustrated in Fig. 4 [26].

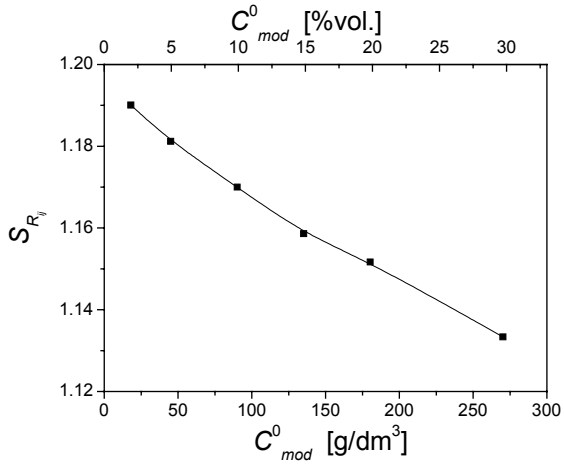


**Fig. 4**
Dependence of adsorption selectivity $S_{Rij}$ on the concentration of modifier $c^0_{\mathrm{mod}}$ in the mobile phase [26]

(b) Mobile phase composition also affects the retention of the components to be separated. The presence of the modifier alters the adsorption equilibria of the components. Increasing its concentration leads to reduced retention, thus shortening the duration of the process and, hence, improving process productivity.
(c) Finally, mobile phase composition also affects the pressure drop in the column. Increasing the amount of polar solvent in the mobile phase leads to a change in the viscosity of the mobile phase. For the solvents investigated in this work, i.e. *n*-hexane and ethyl acetate, increasing the modifier concentration results in increased mobile phase viscosity and a greater pressure drop in the system.

It is evident that mobile phase composition affects chromatographic performance in different, conflicting ways. The effect of mobile phase composition (modifier concentration $c_{\mathrm{mod}}$) on separation selectivity $S_{Rij}$ is shown indirectly in Table IV rows 1, 1′, 2, and 2′. For the longer column the separating power is higher (greater number of theoretical plates $N_a$), which can partly compensate for worsening of the separation on this column caused

by increasing the modifier concentration. Hence, for longer columns higher $c_{mod}$ can be used, which improves process productivity *Pr* (effect b, above) – compare rows 1, 1′, 2, and 2′ of Table IV.

For the other examples (Table IV, rows 3–8), the optimum modifier concentration results from all the conflicting effects (a) to (c), given above.

**Effect of Selection of Key Product**

The effect of the choice of the key product on the optimization results is depicted in Fig. 5a for $p_{max}$ = 30 MPa and in Fig. 6a for $p_{max}$ = 10 MPa.

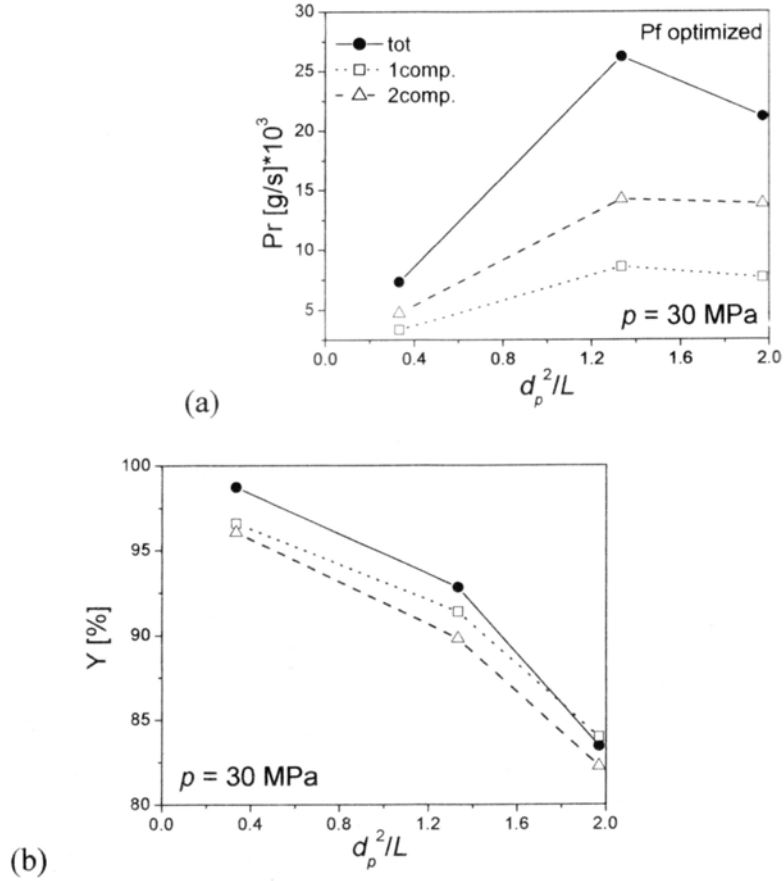


**Fig. 5**

Dependence of (a) *Pr* and (b) *Y* on $d_p^2/L$ for both components as key products and for the first or second component as key product. The symbols in (b) have the same meaning as in (a). The pressure drop, $p_{max}$, was 30 MPa, the column length, *L*, was 75 cm, and the OF was *Pf*

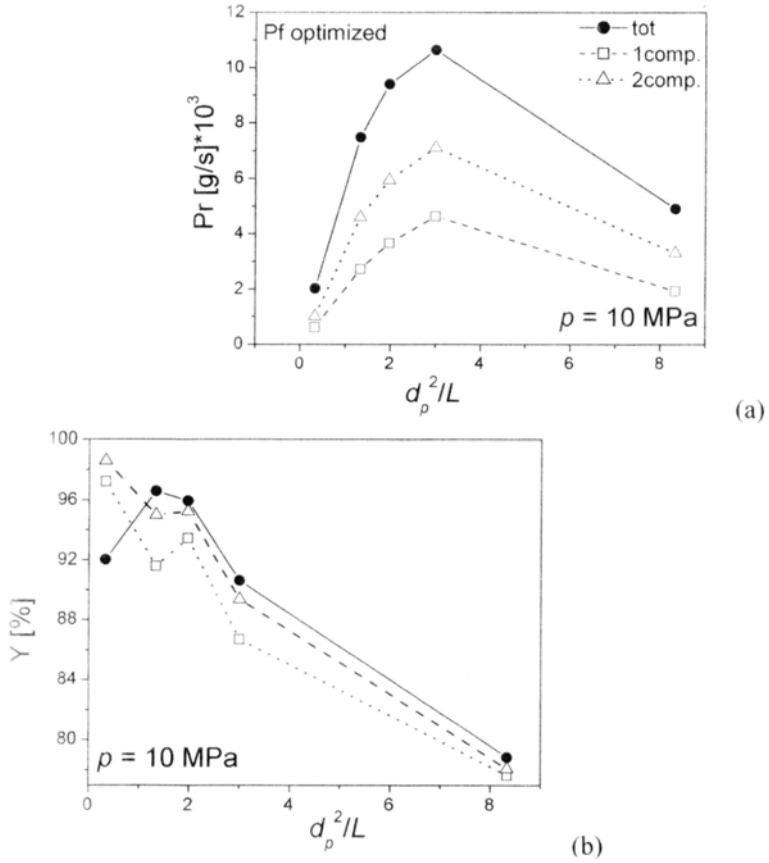


**Fig. 6**

Dependence of (a) *Pr* and (b) *Y* on $d_p^2/L$ for both components as key products and for the first or second component as key product. The symbols in (b) have the same meaning as in (a). The pressure drop, $p_{max}$, was 10 MPa, the column length, *L*, was 75 cm, and the OF was *Pf*

For $p_{max}$ = 30 MPa the maximum productivity *Pr* corresponds to a column of $L$ = 75 cm and $d_p^2/L$ = 1.33, and for $p_{max}$ = 10 MPa the maximum value of *Pr* corresponds to $d_p^2/L$ = 3.0, irrespective of the choice of the key product (Table IV, rows 3 and 6). For both the pressure limits, $p_{max}$, tested the *Pr* value is always higher for the more retained second component as key product than for the first component.

The value of yield *Y* obtained from optimization is similar and high, ca 90%, for all conditions (Table IV, rows 3–8). For $p_{max}$ = 30 MPa *Y* is highest when both isomers are target products (Fig. 5b). For $p_{max}$ = 10 MPa

yield, *Y*, is similar when both isomers are the key products or when the second component is the key product (Fig. 6b). When the first component is the key product yield, *Y*, decreases to 86%. Mobile phase consumption is highest when the first component is the target product. This results from the displacement effect typical of the chromatographic process – the second component of the mixture displaces the first, leading to narrowing of the band profile of the former and worsening of the separation conditions.

The optimum conditions for all the decision variables are shown in Table IV.

## CONCLUSIONS

Optimization of a preparative chromatographic separation has been discussed. The stages of organization of the optimization procedure were:

1. acquisition of experimental data relating to (i) adsorption equilibria in the presence of the multicomponent mobile phase, (ii) system efficiency, and (iii) the physicochemical properties of the system;
2. choice of appropriate model dynamics;
3. choice of the objectives and decision variables of the process;
4. choice of the optimization method; and
5. optimization of the process.

These stages were analyzed by use of an example of a real separation process.

The results from the optimization have been discussed. Apart from specific conclusions relating exclusively to the pair of isomers separated, general conclusions have also been drawn:

1. Use of the productivity factor *Pf* as the objective function in optimization of the chromatography gives better results than use of productivity *Pr*.
2. The column length, *L*, and the ratio $d_p^2/L$ should be optimized simultaneously – optimization of $d_p^2/L$ alone is not sufficient.
3. The results of the optimization are highly dependent on the limit of the pressure drop of the system. The effect of this limit can be partly compensated by changing other operating variables;
4. The results of optimization depend on the choice of key product, i.e. the target of the separation process.
5. The concentration of the mobile phase components affects both the selectivity of the separation and the pressure drop, because of variations of the viscosity of the mobile phase. This effect should be taken into account.

## SYMBOLS

| | | |
|---|---|---|
| $c$ | Concentration in the mobile phase | (g dm$^{-3}$) |
| $c^{\mathrm{m}}_{\mathrm{thresh}}$ | Threshold concentration | (g dm$^{-3}$) |
| $D_{\mathrm{a}}$ | Apparent dispersion coefficient | (m$^2$ s$^{-1}$) |
| $F = (1 - \varepsilon_{\mathrm{t}})/\varepsilon_{\mathrm{t}}$ | Phase ratio | |
| $H = Kq^{\infty}$ | Henry's constant | (dm$^3$/dm$^3$ of packing) |
| $HETP$ | Height equivalent to a theoretical plate | (cm) |
| $k_0'$ | Retention coefficient | - |
| $K$ | Equilibrium constant | (dm$^3$ g$^{-1}$) |
| $L$ | Column length | (cm) |
| $N_{\mathrm{a}}$ | Column efficiency | |
| $N_{\mathrm{c}}$ | Theoretical plate number in the Craig model | |
| $p$ | Pressure | (MPa) |
| $q$ | Concentration in the adsorbed phase | (g dm$^{-3}$ packing) |
| $q^{\infty}$ | Loading capacity | (g dm$^{-3}$ packing) |
| $T$ | Time coordinate | (s; min) |
| $t_{\mathrm{r}}$ | Retention time | (min) |
| $t_{\mathrm{res}}$ | Residence time | |
| $t_0$ | Dead time | (min) |
| $u$ | Superficial mobile phase velocity | (cm min$^{-1}$) |
| $w = u/\varepsilon_{\mathrm{t}}$ | Real velocity of the mobile phase | (cm min$^{-1}$) |
| $V$ | Column or sample volume | (dm$^3$) |
| $\dot{V}$ | Volumetric flow | (dm$^3$ min$^{-1}$) |
| $V_{\mathrm{inj}}$ | Injection volume | (cm$^3$) |
| $z$ | Space coordinate | (cm) |
| $EC$ | Mobile phase consumption | (dm$^3$ g$^{-1}$) |
| OF | Objective function | |
| $L_{\mathrm{f}}$ | Loading factor | |
| $Pf = Pr \times Y$ | Productivity factor | (g s$^{-1}$) |
| $Pr$ | Productivity | (g s$^{-1}$) |
| $Pu$ | Purity of key product | (%) |
| $Y$ | Yield | (%) |

**Greek letters**

| | | |
|---|---|---|
| $\varepsilon_{\mathrm{t}}$ | Total porosity of the column | |
| $\eta$ | Mobile phase viscosity | (Pa s) |

**Subscripts and superscripts**

| | |
|---|---|
| *i* | Denotes component index |
| *j* | Denotes theoretical plate |
| *k* | Denotes cycle |
| F | Denotes feed |
| inj | Denotes injection |
| mod | Denotes eluent modifier |
| * | Denotes equilibrium conditions |
| M | Denotes mixture |
| P | Denotes adsorbent particle |
| tot | Indicates that both components are key products |
| 0 | Denotes initial conditions |

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