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# SCALE-UP AND OPTIMIZATION IN PRODUCTION LIQUID CHROMATO-GRAPHY

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SUMMARY

A strategy is presented for the scale-up and optimization of a separation in liquid chromatography. It requires first a complete representation of the system (a mathematical model), but also an experimental evaluation of its parameters. The model presented takes into account the axial dispersion in the mobile phase and both internal and external resistances to mass transfer in the stationary phase. Small-scale and pilot-plant experiments that yield the equilibrium isotherms, the kinetics of mass transfer and the flow-pattern of the mobile phase are described. These techniques are illustrated with the example of the separation of sugars with an ion-exchange resin.

With the aid of the mathematical model, it becomes possible to approach the optimization of the process. The cost of the separation was found to be a good criterion for production chromatography. The aim of the optimization program was to provide a series of geometric and operating variables minimizing the criterion, taking into account the process purposes: production rate, purity and the characteristics of the apparatus.

INTRODUCTION

This paper describes the modelling and optimization of the separation of the sugars D-xylose and D-mannose using an ion-exchange resin in the lead form with water as eluent. The aim is to show through this example a technique for scaling-up, *i.e.*, how to predict the size and operating variables of a production apparatus from the results of small-scale[1] experiments. This requires a mathematical model of the chromatographic separation, then the experimental determination of the predominant phenomena with the evaluation of their characteristic parameters and finally the definition of the purposes and constraints of the separation in order to find the optimum design parameters.

MATHEMATICAL MODEL

A gas or liquid chromatographic column is usually treated as a packed bed of porous spheres submitted to a pulse of solute[2-7]. The transient mass balance will take into account the following phenomena: dispersed plug flow in the mobile phase;

external resistance to mass transfer around the particles; internal diffusion inside the particles; and adsorption on the solid[3] or exchange and diffusion in another phase[8] (*e.g.*, a liquid grafted on the solid). The basic equations are as follows:

For the mobile phase:

$$\frac{\partial C}{\partial t} = D \cdot \frac{\partial^2 C}{\partial z^2} - u \cdot \frac{\partial C}{\partial z} - 3 \cdot \frac{1-\varepsilon}{\varepsilon R} \cdot \alpha D_i \left(\frac{\partial q}{\partial r}\right)_{r=R} \tag{1}$$

accumulation   dispersion   convection   transfer to stationary phase

The column inlet and outlet conditions are described by Danckwerts'[9] equations for a "closed–closed" system.

For the stationary phase:

$$\frac{\partial q}{\partial t} = D_i \left(\frac{\partial^2 q}{\partial r^2} + \frac{2}{r} \cdot \frac{\partial q}{\partial r}\right) \tag{2}$$

accumulation   internal diffusion

with the boundary conditions

$$D_i \left(\frac{\partial q}{\partial r}\right)_{r=R} = k_L (C - C^*) \tag{3}$$

diffusion          external mass transfer

and

$$\left(\frac{\partial q}{\partial r}\right)_{r=0} = 0 \tag{4}$$

If other interactions are added, eqn. 2 becomes more complex and the number of parameters greater.

In eqns. 1 and 2, dimensionless parameters can be introduced:

Peclet number:

$$Pe = uL/D$$

Number of transfer units:

$$NUT = k_L \, 3(1 - \varepsilon)\alpha\tau/\varepsilon R$$

Time ratio:

$$R_t = D_i\tau/R^2$$

These parameters represent dispersion in the liquid, external mass transfer and diffusion in the particles, respectively.

If the equilibrium isotherm linking the concentrations $C*$ (in the liquid) and $q$ (in the particles) is linear:

$$q = kC* \tag{5}$$

and

$$k' = k\alpha(1 - \varepsilon)/\varepsilon$$

This condition is often satisfied in the case of the separation of sugars on ion-exchange resins[10,11].

Eqns. 1 and 2 can then be integrated by means of the Laplace transform. The Laplace transform of the exit concentration is:

$$\overline{C}_s = \overline{C}_e Pe \cdot \frac{V - W}{V^2 \exp(-W) - W^2 \exp(-V)}$$

$$V = \frac{Pe}{2}\left\{1 + \sqrt{1 + \frac{4}{Pe}[s - G(s)]}\right\}$$

$$W = Pe - V \tag{6}$$

where the function $G(s)$ represents the phenomena occurring in the stationary phase:

$$G(s) = \frac{-F(s)}{1 + \dfrac{F(s)}{NUT}}; \quad F(s) = 3R_t\left(\sqrt{\frac{s}{R_t}}\coth\sqrt{\frac{s}{R_t}} - 1\right) \tag{7}$$

By derivation of the Laplace transform, $\overline{C}_s$, it is also possible to calculate the first two moments of the exit curve:

$$m_1 = \tau(1 + k') \tag{8}$$

$$m_2 = \tau^2\left[\frac{2}{Pe}(1 + k')^2 + \frac{2}{NUT} \cdot k'^2 + \frac{2}{15} \cdot \frac{k'}{R_t}\right] \tag{9}$$

It can be seen from eqn. 9 that the width of a peak (related to $m_2$) depends on three factors, flow pattern and external and internal mass transfer, and that these phenomena act independently and in a similar manner. Hence it is impossible to identify simultaneously, from a concentration peak, the parameters corresponding to these phenomena.

As the separation mechanism of our system is based on the difference between the strengths of sugar–ion complexes[12,13], adsorption can be neglected. In order to reduce the number of parameters in our model, we tried to determine with small-scale experiments which phenomenon is predominant.

EXPERIMENTAL

*Materials*

The separation of D-xylose and D-mannose[14] was achieved on an ion-exchange resin Duolite C-204/2078 (Rohm & Haas). The resin had a cross-linkage of 6.4% of divinylbenzene and was in the lead form; the particle diameters ranged between 0.15 and 0.30 mm. A temperature of 50°C was chosen. The sugar concentrations in the feed ranged between 100 and 500 kg/m$^3$.

*Equilibrium isotherms*

Equilibrium isotherms were plotted by contacting 90 cm$^3$ of sugar solutions of different concentrations $C_0$ with 10 cm$^3$ of wet resin in a well stirred reactor at constant temperature. Samples of sugar solution were withdrawn and the concentration $C_{eq}$ was evaluated by refractometry when equilibrium had been reached. The concentration $q_{eq}$ inside the resin was deduced from a mass balance on sugar. The isotherm at 50°C was plotted (Fig. 1). For both sugars, the isotherms are linear in the working range with values of the slopes of $k_{xylose} = 0.33$ and $k_{mannose} = 0.42$. This linearity was a necessary condition for a simple integration of the differential eqns. 1 and 2.

*Internal diffusion*

The kinetics of internal diffusion were studied in a stirred reactor, where dispersion and external mass transfer could be neglected. The experimental apparatus and conditions were the same as above, but the time dependence of the sugar concentration in the liquid phase was studied.

For both sugars, equilibrium was reached by the first withdrawal (30 s); it was therefore impossible to evaluate the diffusion coefficient, $D_i$. However, we could conclude that the diffusion inside the particles was very fast and consequently that this phenomenon could be neglected, and that the concentration could be assumed to be uniform in a particle.
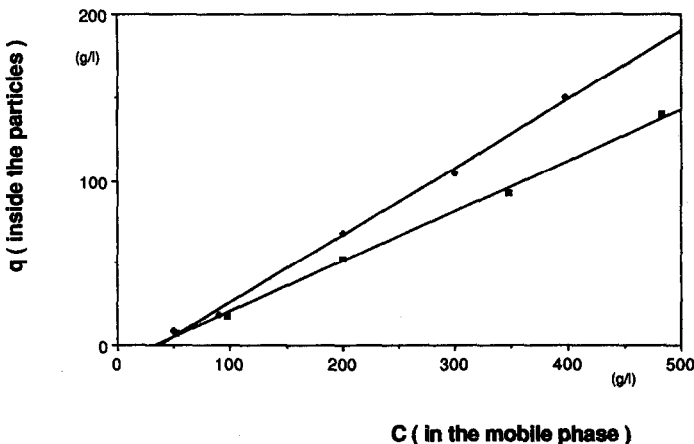


Fig. 1. Equilibrium isotherms of (□) D-xylose and (◆) D-mannose at 50°C.

*External resistance to mass transfer*

External resistance to mass transfer depends on the hydrodynamic conditions around the particles, so it has to be studied in a packed bed; we chose a thin bed where dispersion could be neglected. The reactor used is shown in Fig. 2; it was adapted from the differential reactor described by Ford *et al.*[15]. A thin packed bed (2.5 cm in diameter, 1.5 cm high) of particles was prepared between two stainless-steel grids. A section of glass beads (1 mm in diameter) placed at the reactor entrance allowed a good distribution of liquid over the whole section of the reactor. A peristaltic pump (Masterflex) ensured the recirculation of the liquid between the reactor and the reservoir. The flow-rates ranged between 0.6 and 7 cm$^3$/min in order to have the same velocities as in the column. The reactor and tubing were immersed in a constant-temperature water-bath.

The reservoir was initially charged with a sugar solution of concentration $C_0$ and samples of concentration $C_L$ were withdrawn from the resevoir and analysed by refractometry.

If the bed of resin is thin enough, we may assume that the amount of sugar fixed in the reactor is very small and the concentration, $C$, in the reactor is uniform, and it is possible to derive an expression for $C_L$ from the following mass balance:

in the reservoir:

$$V_R \cdot \frac{dC_L}{dt} = Q(C - C_L)$$

in the reactor:

$$V_L \cdot \frac{dC}{dt} = k_L A(C^* - C) = V_s \cdot \frac{dq}{dt} \tag{10}$$

$$C_L = \frac{C_0}{1 + \beta} + \frac{\beta C_0}{1 + \beta} \exp\left(-\frac{k_L A}{V_L} \cdot \frac{1 + \beta}{\beta} \cdot t\right) \tag{11}$$

where $\beta = k(V_s/V_L)$ and $q = kC^*$.

The experimental concentration $C_L/C_0$ is plotted in Fig. 3 for D-xylose and the mass transfer coefficient $k_L$ was obtained from eqn. 11. The values obtained for different conditions of flow-rate and initial concentration are given on Table I,
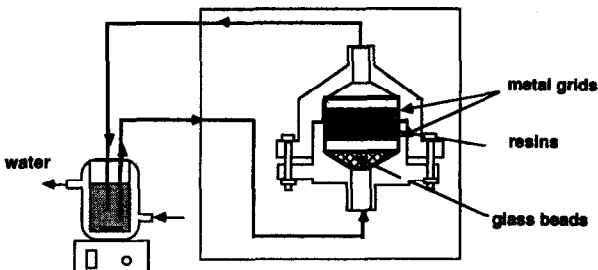


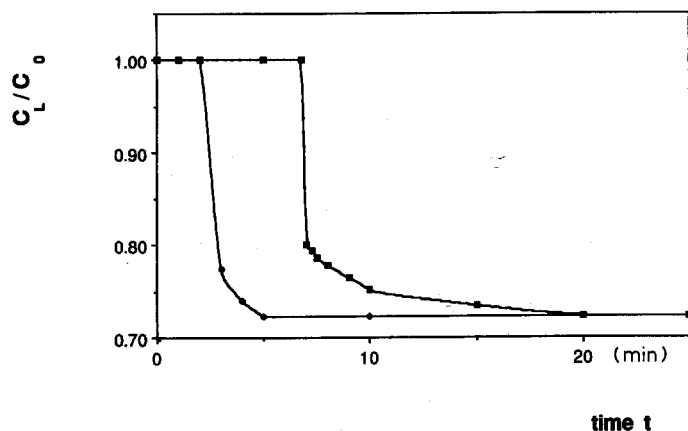Fig. 2. Schematic diagram of differential reactor.

Fig. 3. Time dependence of xylose concentration in the reservoir of the recirculation system. Experimental conditions: $C_0 = 10$ g/l; $T = 50°C$. Flow-rate: $\square$ = 1.6; $\blacklozenge$ = 7 ml/min.

together with the corresponding values calculated using the correlation of Dwivedi and Upadhyay[16]. It can be seen from Table I that our experimental $k_L$ values are consistent with those calculated using the correlation and yield high values for *NUT*. The Peclet numbers that would produce the same contribution to $m_2$ range between 30 000 and 100 000; it seems improbable that our Peclet numbers reached such values. Consequently, dispersion in the mobile phase can be considered as the limiting step in the column.

*Dispersion phenomenon*

The column[14] was a glass tube (200 cm × 1.7 cm I.D.) packed by sedimentation of the resin particles. The temperature was kept constant (50°C) with water circulated through a jacket around the column. Deionized water, used as the eluent, was fed downwards by a peristaltic pump at a flow-rate of 0.6 cm³/min. The sugar solution was applied at the top of the column; generally the sample volume was 1.5 cm³, and the sugar concentration ranged between 100 and 500 kg/m³. The sugar solutions were synthetic, prepared with D-xylose (Prolabo) and D-mannose (Sigma or Extrasynthese) in equal proportions.

TABLE I

EXPERIMENTAL VALUES OF $k_L$ AND *NUT* OBTAINED WITH DIFFERENT INITIAL CONCENTRATIONS AND FLOW-RATES, COMPARED WITH $k_L$ VALUES ISSUED FROM CORRELATIONS

| Superficial velocity (cm/min) | Initial concentration (g/l) | $k_L$ (experimental) ($10^{-3}$ cm/s) | | $k_L$ (correlation) ($10^{-3}$ cm/s) | NUT | $\dfrac{2k'}{NUT}$ |
|---|---|---|---|---|---|---|
| | | Xylose | Mannose | | | |
| 0.35 | 10 | 5.2 | | 4.2 | 20 000 | $6 \cdot 10^{-5}$ |
| | 20 | 4.8 | 5.0 | | | |
| 1.54 | 10 | 7 | | 5.8 | 5000 | $2 \cdot 10^{-4}$ |
| | 20 | 8.1 | 8.7 | | | |

Fractions of 1–10 cm$^3$ were collected automatically at the exit of the column with a fraction collector (Gilson). Sugars were then assayed by refractometry (Milton-Roy) after a separation by high-performance liquid chromatography using a Milton-Roy system equipped with an Aminex HPX 87P column (Bio-Rad Labs.).

The void fraction of the packed bed was estimated as

$$\varepsilon = \frac{\text{volume of interstitial liquid}}{\text{volume of packed bed}}$$

The interstitial liquid was collected by opening the outlet and stopping the feed; $\varepsilon$ was found to be 0.40.

The dispersion in the mobile phase may be assumed to be the unique source of peak broadening. It therefore becomes possible to obtain $Pe$ and $k'$ from the response curve of the column from the injection of one sugar.

If $X$ is the dimensionless injection volume, the Laplace transform of the exit concentration is given by eqn. 6, where

$$G(s) = -k'_s; \qquad \overline{C}_e(s) = [1 - \exp(-Xs)]/Xs \tag{12}$$

The identification technique involves the following steps: calculation of the Fourier transform (using an FFT algorithm[17]) of the experimental concentration $C_{exp}(t)$; calculation by means of eqns. 6 and 12 of the theoretical response curve, $\overline{C}_{theo}\,(j2\pi f)$ as a function of $Pe$ and $k'$; and minimization of a criterion of the form

$$E = \sum_{i=0}^{N-1} \left[ \overline{C}_{theo}(j2\pi f_i) - \overline{C}_{exp}(j2\pi f_i) \right]^2 \tag{13}$$

by a Gauss–Newton method.

As can be seen from Fig. 4, we obtained good agreement between the experimental and theoretical curves, indicating that the model accurately describes the behaviour of the column. The magnitude of the Peclet numbers (less than 4000) (Table II) confirms the assumption that the term accounted for mass transfer in eqn. 9, is much smaller than the hydrodynamic term.

OPTIMIZATION

We shall consider here that the column is fed with the sugar solution during time intervals $\Delta t$ separated by a period $T$.

The first step is then to determine the purposes of the separation, the requirements with respect to yield and purity, the technical limitations and the different variables of the system. A number of workers[18–21] chose to maximize the throughput $P_0$ (amount of product isolated per unit time), but this criterion seems better suited to an occasional preparative separation (on an apparatus that already exists). We preferred an economical criterion[22] to evaluate the performances of a production set, and adopted the total separation cost per unit mass of product. Our constraints are the purity of the product, the throughput ($P_0$) and a technical limitation, the maximum pressure drop over the column.
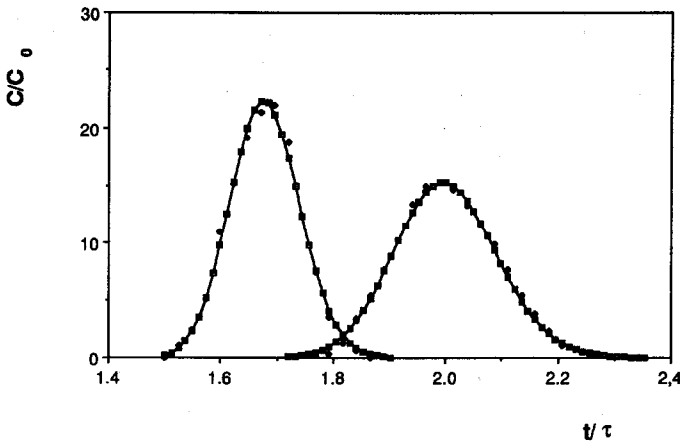
Fig. 4. Separation of xylose and mannose at 30°C (experimental and calculated elution curves). Experimental conditions: $C_0$ = 500 g/l (50:50 xylose–mannose); $Q$ = 0.63 cm$^3$/min; $V_i$ = 1.5 cm$^3$. $\square$ = Xylose (theoretical); $\blacklozenge$ = xylose (experimental); $\blacksquare$ = mannose (theoretical); $\lozenge$ = mannose (experimental).

*Derivation of optimization equations*

*Purity.* We specified that the separation had to be complete between solutes A and B for one injection and for two following injections:

$$t_{2A} \leqslant t_{1B} \tag{14}$$

$$(t_{2B})_n \leqslant (t_{1A})_{n+1} \tag{15}$$

with[23]

$$t_{1i} = t_n + t_{Ri} - 2\sigma_i$$

$$t_{2i} = t_n + \Delta t + t_{Ri} + 3\sigma_i$$

TABLE II

*Pe* AND *k'* VALUES IDENTIFIED FROM EXPERIMENTS REALIZED WITH DIFFERENT SUGAR FEED CONCENTRATIONS AND DIFFERENT COLUMN TEMPERATURES

| Tempera-ture (°C) | Injection concentration (g/l) | | | Injection concentration (g/l) | | |
|---|---|---|---|---|---|---|
| | 100 | 300 | 500 | 100 | 300 | 500 |
| 30 | $Pe_X^a$ = 1430 $Pe_M$ = 1085 | | $Pe_X$ = 1442 $Pe_M$ = 955 | $k'_X$ = 0.66 $k'_M$ = 0.96 | | $k'_X$ = 0.66 $k'_M$ = 0.98 |
| 50 | | $Pe_X$ = 2684 $Pe_M$ = 2310 | | | $k'_X$ = 0.65 $k'_M$ = 0.95 | |
| 70 | $Pe_X$ = 4145 $Pe_M$ = 3634 | | $Pe_X$ = 2502 $Pe_M$ = 2108 | $k'_X$ = 0.61 $k'_M$ = 0.77 | | $k'_X$ = 0.57 $k'_M$ = 0.76 |

$^a$ X = Xylose; M = mannose.

These conditions lead to the following equalities at the optimum:

$$\Delta t_{opt} = t_{RB} - t_{RA} - (2\sigma_B + 3\sigma_A) \tag{16}$$

$$T_{opt} = t_{RB} - t_{RA} + \Delta t_{opt} + (3\sigma_B + 2\sigma_A) \tag{17}$$

This condition with respect to purity may seem too drastic, and can be replaced by a maximum percentage superposition of the peaks.

*Throughput:* The throughput, $P_o$, can be expressed as

$$P_O = QC_0\Delta t/T = \varepsilon SuC_0\Delta t/T \tag{18}$$

*Variables.* Two types of variables are involved, geometric ($S$, $L$) and operating ($u$, $T$, $\Delta t$) variables. The particle diameter ($d_p$) cannot be considered as a continuous variable, and each value will be considered separately. The initial concentration $C_0$ will be the maximum concentration of the linear domain of the isotherms.

*Criterion.* The total separation cost involves[24] the costs of depreciation, operating labour, maintenance, utilities and packing renewals. For simplification, we consider here only the cost of the packing, $G$.

$$\text{crit} = G = SLg(d_p) \tag{19}$$

where $g$ is the cost of packing per unit volume. Substituting eqns. 16, 17 and 18 into eqn. 19 yields

$$G = P_oTLg(d_p)/\varepsilon C_0u\Delta t \tag{20}$$

Without the constant term, it gives the following criterion:
$$\text{crit} = LT/u\Delta t \tag{21}$$

The optimization problem then consists in minimizing eqn. 21, together with eqns. 16 and 17, with respect to $L$ and $u$, and with the constraint of maximum pressure drop:

$$\Delta P < \Delta P_{lim}$$

$\Delta P$ may be developed with the Blake–Kozeny equation[25]:

$$\Delta P = \eta Lu/K_0$$

The expressions for $t_{Ri}$ and $\sigma_i$ involved in eqns. 16 and 17 are given by eqns. 8 and 9, where $Pe$ and $NUT$ are written as functions of the variables $u$ and $L$ using the correlations of Chung and Wen[26] for Peclet numbers and Dwivedi and Upadhyay[16] for $k_L$.

*Results*

The first result is that the optimum conditions yield for $\Delta P$ the limit value, $\Delta P_{lim}$, and that the optimum velocity is proportional to $\Delta P_{lim}$ (see Fig. 5). It can also be seen
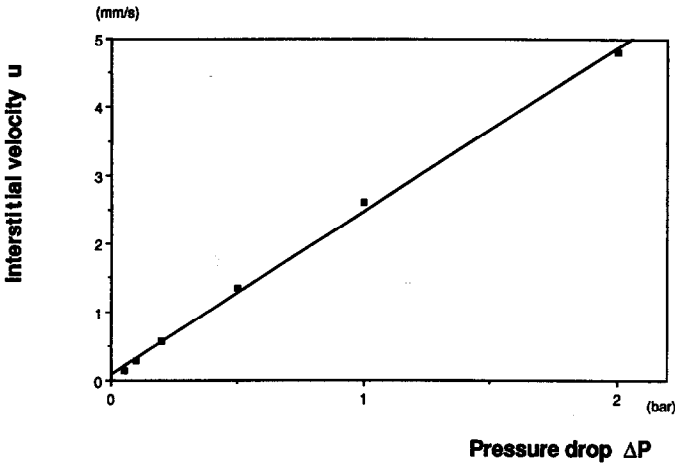
Fig. 5. Plot of interstitial velocity against pressure drop for optimum conditions.

from Fig. 6 that a higher $\Delta P_{lim}$ or a higher velocity will lead to a smaller criterion. It is then interesting to work with high liquid velocities.

From Fig. 7 it can be concluded that the column length does not vary greatly in this range of velocities; this is not the case for the column diameter, which is reduced by a higher velocity.

As can be seen in Table III, the values of the optimum variables (the values but not the trends) are very dependent of the value of the Peclet number, *i.e.*, the efficiency of the column. Hence it would be interesting to establish experimentally, on pilot plants, more precise correlations for Peclet numbers.
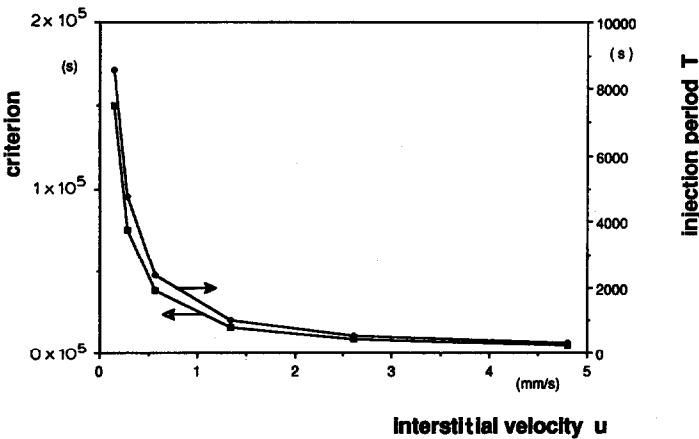


Fig. 6. Behaviour of the criterion and injection period with the velocity for optimum conditions.
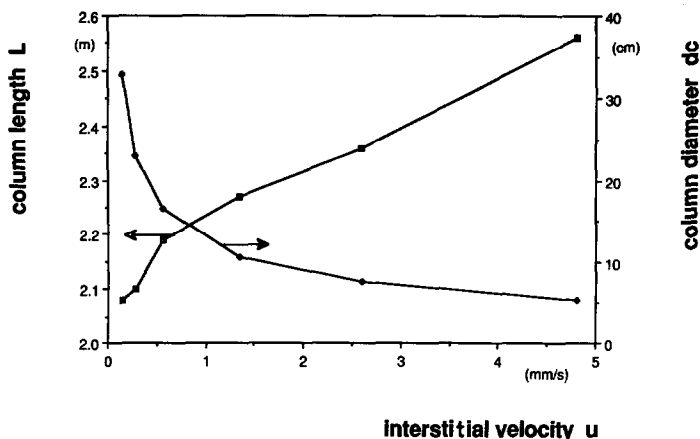
Fig. 7. Behaviour of column length and diameter with the velocity for optimum conditions.

TABLE III

INFLUENCE OF *Peg* NUMBER ON THE OPTIMIZATION RESULTS

| Peg | L (m) | u (mm/s) | Crit (s) |
|------|-------|----------|----------|
| 0.11 | 2.56 | 4.8 | 4844 |
| 0.20 | 1.79 | 6.8 | 2260 |
| 0.40 | 1.37 | 8.9 | 1223 |

CONCLUSION

This work must be considered as a development of a strategy for scaling-up. It requires three steps: modelling of the column, experimental determination of the parameters and derivation of optimization equations. Each step has been simplified here, but the method is still valid for more complex systems. The model can be complicated if more phenomena are added (adsorption, etc.), but it will then require the corresponding experiments to evaluate the new parameters. The model may also be non-linear, and will then need a numerical integration. The optimization may also involve less restrictive conditions on purity, or a more detailed cost function. However, none of these factors will alter the principles of the method.

SYMBOLS

$A$    Total area of particles in the reactor (m$^2$)
$C$    solute concentration in the mobile phase (kg/m$^3$)
$C^*$    concentration in the liquid in equilibrium with the solid phase
$\overline{C}(s)$    Laplace transform of $C(t)$
$d_c$    column diameter (m)
$d_p$    particle diameter (m)
$D$    dispersion coefficient (m$^2$/s)

$D_i$    internal diffusion coefficient (m$^2$/s)

$f_i$    frequency (s$^{-1}$)

$g$    cost of packing (US\$/m$^3$)

$G$    separation cost (US\$)

$j$    complex number, $j^2 = -1$

$k$    distribution coefficient

$k_L$    mass transfer coefficient (cm/s)

$k'$    capacity factor

$K_0$    permeability constant of the column

$L$    column length (m)

$\Delta P$    pressure drop (Pa)

$Pe$    Peclet number, $uL/D$

$Peg$    Peclet number, $udp/D$

$P_o$    throughput (kg/s)

$Q$    flow-rate (cm$^3$/min)

$q$    concentration inside the particles (kg/m$^3$)

$r$    distance from the centre of the particle (m)

$R$    particle radius (m)

$s$    dimensionless Laplace variable

$S$    column cross-section (m$^2$)

$t$    time (s)

$t_R$    retention time (s)

$\Delta t$    injection time (s)

$T$    injection period (s)

$u$    interstitial velocity (m/s)

$V$    volume (m$^3$)

$X$    dimensionless injection volume

$z$    distance in the column (m)

$\alpha$    internal particle porosity

$\varepsilon$    external voidage of the packed-bed

$\tau$    $(= L/u)$ mean residence time of the solute in the mobile phase

$\sigma^2$    variance (s$^2$)

$\eta$    viscosity of the mobile phase

*Subscripts*

L    in the liquid phase

R    in the reservoir

S    in the solid phase

0    at time zero

1    beginning of a peak

2    end of a peak

$n$    $n$th period

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