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PREDICTION OF BAND PROFILES IN DISPLACEMENT CHROMATOGRAPHY BY NUMERICAL INTEGRATION OF A SEMI-IDEAL MODEL

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SUMMARY

A numerical solution for the semi-ideal model of chromatography, incorporating dispersion in the numerical integration scheme, has been developed for the prediction of intermediate and isotachic peak profiles of a multi-component mixture in displacement chromatography. The model was used here to study the effect of various operating parameters on the band shapes, production and yield for a binary mixture.

The effect of the displacer concentration and the column length on the yield and the production was investigated. Optimal concentrations can be found that maximize the yield or the production. Very low displacer concentrations lead to peak shapes identical with those in overloaded elution chromatography and extremely large displacer concentrations result in the lack of a separation. The band profiles obtained prior to the formation of the isotachic train are in agreement with profiles taken from the literature.

INTRODUCTION

The differences between elution and displacement chromatography were recognized by Tswett in the early 1900s[1]; however, it was in 1942 that Tiselius[2] clearly defined and discussed the various possible modes of chromatography (elution, frontal and displacement). During the last 40 years the enormous growth of linear elution chromatography for analytical separations has overshadowed the use of displacement chromatography, in spite of the development of several important industrial applications that took place during this period. In the 1940s, the isolation of various rare earth oxides was accomplished in the displacement mode[3], which proved to be more productive than elution chromatography[4]. Later, displacement chromatography was employed at the American Petroleum Institute[5] to fractionate petroleum distillates in 52.4 ft. × 3/4 in. I.D. columns. In the 1960s, Sorbex and several other

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similar processes were developed at UOP, using various novel technologies to achieve what is essentially displacement chromatography on a moving bed column, without physically moving the column packing[6].

For the last four decades, however, displacement chromatography has basically been ignored by analysts and separation chemists alike and no fundamental research was carried out in this area until in the late 1970s when Horváth and co-workers reintroduced the technique. They were able to capitalize on the various technological advances developed for elution chromatography, *e.g.*, microparticulate stationary phases, high-efficiency columns and fast high-performance liquid chromatography (HPLC) analyses to follow the band profiles at the column exit. They developed methods for separating small organic molecules[7], polymyxin antibiotics[8], steroids[9], amino acids[10], short peptides[11–13], nucleotides[14] and, more recently, proteins[15]. The utility of this method has been confirmed by other results for the separation of insulins[16] and oligomycins[17]. Carrier displacement chromatography has been employed for the displacement of proteins using carboxymethyldextrans as spacers as well as a displacer[18–20]. Other workers have investigated the separation of lithium isotopes[21–24] for either the enrichment or the isolation of pure isotopes by ion-exchange displacement chromatography. These studies demonstrated experimentally the utility of this technique for the separation of various mixtures and its capacity to achieve high yields and high purities.

On the theoretical front, various models have been proposed to describe the displacement process. Gluckauf[25] provided an analysis of displacement development and discussed the importance of the solute and displacer concentrations on the band development. The equations corresponding to ideal chromatography have been solved by Helfferich and Klein[26], employing the H-transform, and in a similar approach by Rhee and Amundson[27]. Experimental studies showed good agreement between theory and experiment[28]. More recently, Basmadjian and Coroyannakis[29] proposed a model neglecting accumulation in the fluid phase and axial dispersion, and assuming infinitely fast mass transfer. They discussed the importance of the displacer adsorption strength and its concentration on the profiles of a two-component system (one solute and one displacer). However, in real systems one does not have an infinite column efficiency and one does not have vertical boundaries between the isotachic bands[30]. Guiochon and co-workers[31,32] developed a numerical solution of the system of partial differential equations accounting for the behavior of chromatographic systems under non-linear, non-ideal conditions. These results were used for the simulation of the separation of multi-component samples in overloaded elution chromatography[33–36]. We report here on the application of these theoretical results to the prediction of isotachic and non-isotachic band profiles in displacement chromatography. The model was extended to three components (two solutes in a binary mixture and the displacer) and the initial conditions were adjusted accordingly.

THEORETICAL

Neglecting axial dispersion and assuming infinitely fast kinetics of radial mass transfer, we can write the following mass balance for each component involved in the process:

$$(1 + k_i') \frac{\partial C_i}{\partial t} + u \cdot \frac{\partial C_i}{\partial z} = 0 \tag{1}$$

where t is time, z the column length, C_i the concentration of each species in the mobile phase, u the linear velocity of the mobile phase and

$$k_i' = \varphi \cdot \frac{\partial q_i}{\partial C_i} \tag{2}$$

where q_i is the concentration of each species in the stationary phase at equilibrium and φ is the stationary phase to mobile phase ratio[31,32]. This is the classical model of ideal chromatography[26,27,31].

Competitive Langmuir isotherms were employed for each component in the solution and for the displacer. They have the form

$$q_i = a_i C_i / (1 + \sum b_i C_i) \tag{3}$$

Eqn. 3 corresponds to the simplest model of competitive adsorption behavior and its representativeness will be discussed later.

A mass balance equation (eqn. 1) and an isotherm equation (eqn. 3) must be written for each component of the sample and for the displacer. The carrier is inert in classical displacement chromatography, and therefore no mass balance was written for it. The system is solved numerically using a finite difference method[31]. It has been shown that a stable numerical solution is obtained if the space and time increments used for the calculations are chosen appropriately to meet the Courant–Friedrichs–Lewy condition[37]. The finite column efficiency can be accounted for by relating the space increment to the Courant number and the HETP of the chromatographic column used[32]. We have chosen a Courant number of 2 and the values of the respective space and time increments are given by

$$\delta z = H \tag{4}$$

$$\delta t = 2H/uz \tag{5}$$

where uz is the average velocity of the concentration profiles at infinite dilution. Comparison between experimental and theoretical results for the elution of large concentration bands of a pure compound showed excellent agreement between the recorded and predicted profiles[38].

In displacement chromatography, the column is first equilibrated with a carrier stream, a mobile phase which elutes the solutes considered with large retention factors. Then the feed (the solute mixture, usually dissolved in the mobile phase) is injected or pumped into the column. Lastly, the displacer, a solution containing a species which is more strongly adsorbed than any of the feed components, is pumped continuously through the column until all the components of the feed have left the column. A typical batch process involves a final step of regenerating the column on completion of the displacement process and re-equilibration with a carrier stream. Then the column is ready for the next run. The regeneration process has not been modeled in this study.

The initial and boundary conditions for displacement chromatography (the displacer is component n) are

$$t \leqslant 0: 0 < z < \mathrm{L}, C_i = 0, i = 1, n \tag{6}$$

$$0 < t < R\delta t: z = 0, C_i = C_i^0, i = 1, n - 1, C_n = 0 \tag{7}$$

$$R\delta t < t < t_a: z = 0, C_i = 0, i = 1, n - 1, C_n = D_0 \tag{8}$$

where C_i^0 is the concentration of component i in the stream entering the column, D_0 is the displacer concentration, t_a is the analysis time and $R\delta t$ is the time it takes for the sample to enter the column. In practice, the sample volume can be significant compared with the column volume and then the sample concentration is relatively dilute. However, the components are retained strongly by the packing material in the carrier. Moreover, it is practical to express the sample size as a fraction of the column saturation capacity[39].

RESULTS AND DISCUSSION

In displacement chromatography, the displacer plays an essential role in the separation process. It can be shown that provided the concentration of the displacer is large enough and the column is long enough, an isotachic train forms[7,25]. The profile of each zone is stable and its width depends on the amount of each solute in the sample. The concentration of the isotachic zone depends on the concentration of the displacer, D_0, and its isotherm, *i.e.*, on the characteristic speed of its front[40]. The concentrations of the individual solute species under isotachic conditions are given by the intersection of solute isotherms with the operating line. The operating line (Fig. 1) is the chord extending from the origin to the displacer isotherm and which has a slope q_1/D_1, where q_1 is the equilibrium concentration of the displacer in the stationary phase corresponding to D_1.

Investigations of the role of the displacer in displacement development and the effect of its concentration on the height and the width of rectangular isotachic displacement bands have been carried out employing the ideal model of chromatography[26]. We used here a more realistic semi-ideal model which provides exact predictions of zone profiles as long as the kinetics of mass transfer between mobile and stationary phase are fast. This model provides an opportunity to view isotachic and non-isotachic peak profiles under non-ideal conditions and to investigate the effects of the experimental conditions on the yield, production and product purity. The effects of the displacer concentration and of the column length will be discussed in some detail here to demonstrate the utility of the model and to illustrate the importance of these two parameters in the optimization of the displacement process for a two-component separation problem.

In presenting the results of a computer simulation, the parameters of the model must have specific values. The results presented here consider the separation of a binary mixture (concentration ratio 1:3) with retention factors (k') for component 1, component 2 and the displacer of 5.75, 6.25 and 7.5, respectively. These values are reasonable and typical. We note that the relative retention of the displacer with respect

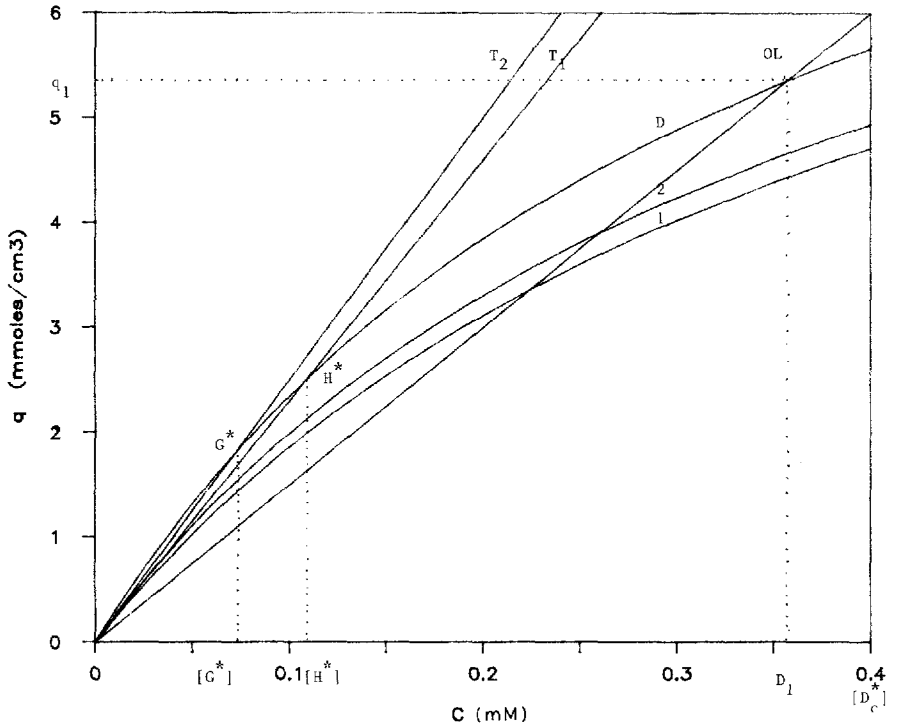

Fig. 1. Single-component adsorption isotherms for each component and the displacer. OL = operating line; T_1 = tangent to component 1 isotherm; T_2 = tangent to component 2 isotherm.

to component 2 is 1.2 and that it need not be too large. The column void fraction was assumed to be 0.8. The parameters of the ternary isotherm, b_1, b_2, b_3, are 2.38, 2.56 and 2.8 mmol^{-1}, respectively. These three isotherms are slowly divergent (Fig. 1). The column HETP was 48 μm, which corresponds to a well packed column with 15–20 μm particles, a grade frequently used at present in preparative applications. Much lower values of H could be achieved with real columns. Such columns would take a longer CPU time to simulate than the columns used here.

The column lengths were varied from 5 to 50 cm and the displacer concentrations from 0.02 to >6 mM. The individual zone profiles and the total profiles presented can be considered to be the response of a specific detector and non-specific detector, respectively. In these simulations, unless stated otherwise, the injection simulates a Dirac injection pulse as a narrow rectangular band of width δt. The sample size is 0.2 mmol, which is 1.3% of the column saturation capacity.

Effect of displacer concentration

The effect of the displacer concentration on the shape of the band profiles on a 25-cm column with the parameters specified above is illustrated in Figs. 2 and 3. Fig. 2a shows that at low displacer concentrations the band shape corresponds to that obtained in overloaded elution chromatography. The velocity of the solute band is greater than that of the displacer and no interference occurs between the zones of the

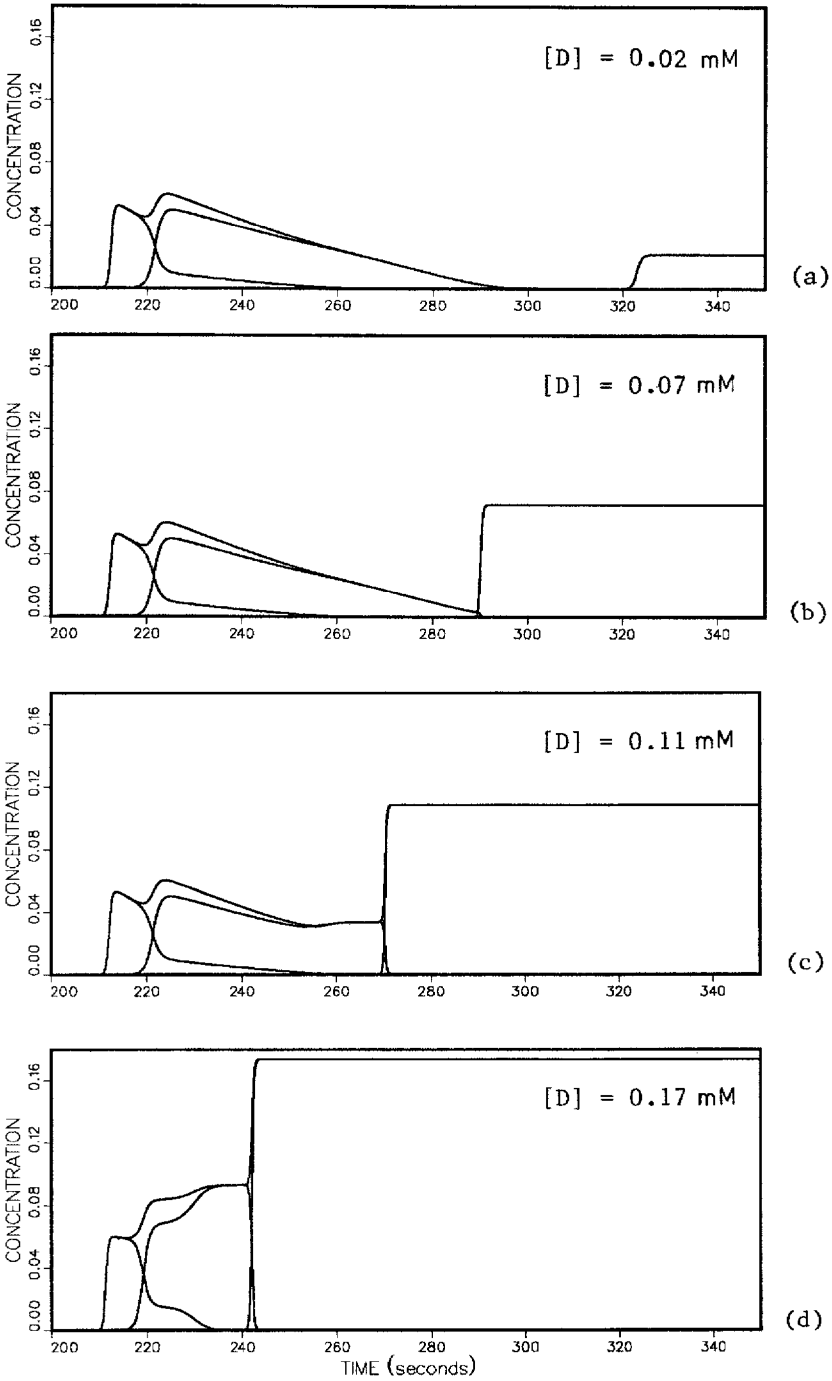

Fig. 2. Effect of the concentration of the displacer on the displacement profile at 25 cm (the abscissa scales are the same for all figures). [D]: (a) 0.02; (b) 0.07; (c) 0.11; (d) 0.17 m*M*.

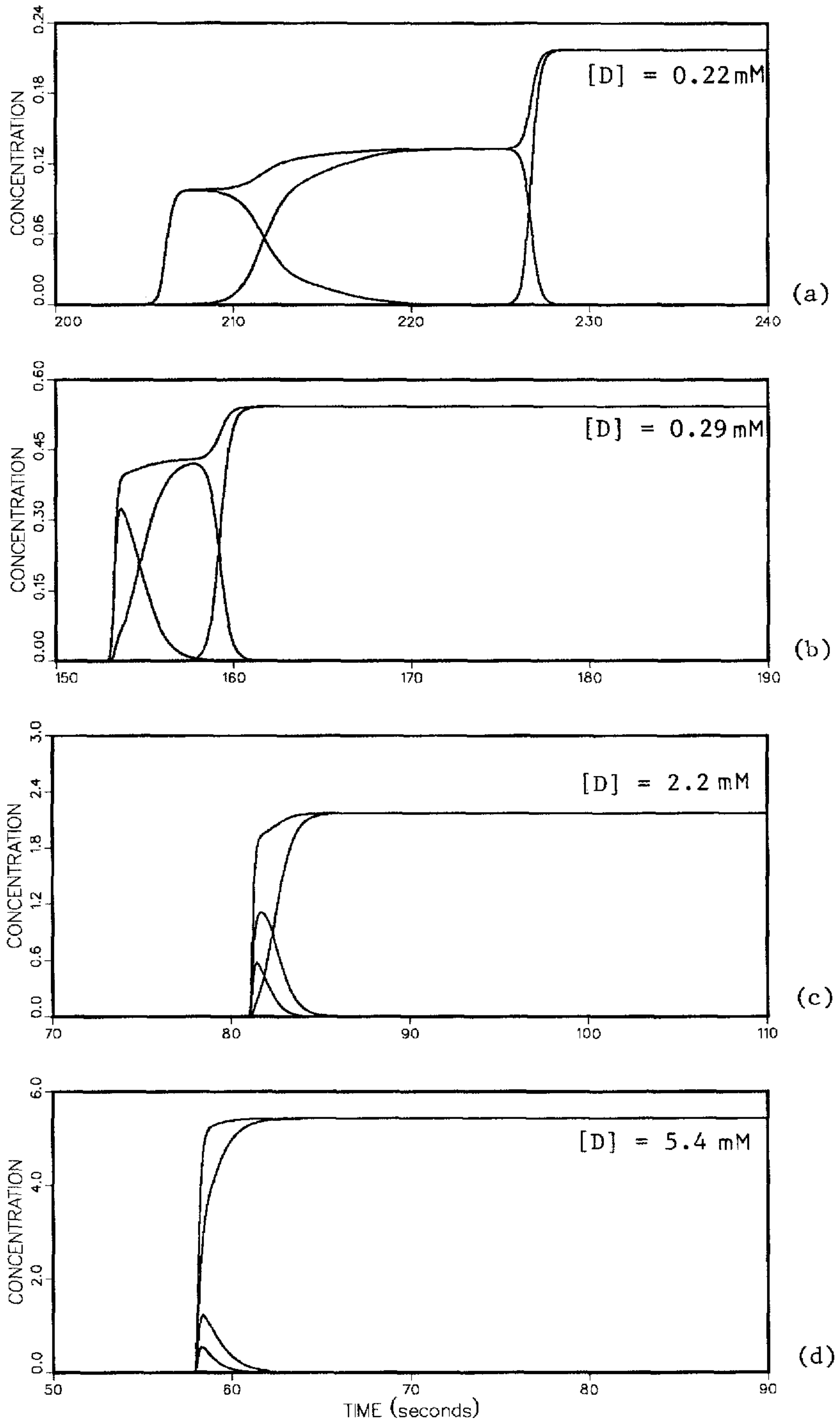

Fig. 3. Effect of the displacer concentration on the displacement profile at 25 cm (the width of the chromatogram is constant). [D]: (a) 0.22; (b) 0.29; (c) 2.2; (d) 5.4 m*M*.

displacer and the solute. As the displacer concentration is increased, the velocity of the displacer front increases; however, the retention time of the overload band remains unchanged until a critical displacer concentration, G^*, is reached. This critical concentration corresponds to the intersection of the initial slope of the second component [$(n-1)$th component] isotherm with the displacer isotherm, illustrated in Fig. 1. At this concentration the front of the displacer meets the tail of the second component just as it exits the column, hence with essentially no interference (Fig. 2b); at concentrations below G^*, components 1 and 2 propagate down the column as in overloaded elution chromatography.

As the displacer concentration is increased beyond G^*, interference occurs between the bands of the second component and the displacer, in addition to interference between the bands of the two solutes (Fig. 2c). The displacer front begins to push and sharpen the rear of the second component, giving rise to the early stages of displacement development as seen by the formation of a secondary front (Fig. 2c). When the operating line coincides with the tangent to the first component isotherm at zero concentration, the intersection is given by H^* and is illustrated in Fig. 1. Under isotachic conditions, displacer concentrations corresponding to H^* result in the first component eluting as an overloaded band or an elution band for concentrations in the linear region of the isotherm, as expected. Under non-isotachic conditions, however, Fig. 2c shows that after 25 cm the secondary front has reached the tail of the first component. For displacer concentrations higher than H^*, at 25 cm the secondary front has distorted the tail of the first component, giving rise to the displacement effect for the first component (Fig. 2d). For displacer concentrations higher than H^*, but lower than some critical value to be discussed later, isotachic displacement bands form with plateaux on both peaks on columns of sufficient length.

As the displacer concentration is increased further, beyond H^*, the tails of the bands sharpen, their width decreases and their height increases (Fig. 3a). Note that the time scales in Fig. 3 are much larger than those in Fig. 2. Moreover, in Fig. 2 the absolute scale is the same on the graphs whereas in Fig. 3 the absolute scale changes, but the relative scale is the same. However, as it is not physically possible to obtain an infinitely high concentration for an infinitely narrow band, nor would one expect to return to the initial injection conditions because of band broadening, something must occur at high displacer concentrations. As the displacer concentration is increased further, the displacer begins to squeeze components 1 and 2 whose bands interfere more and more strongly. The amount of band overlap equals the band width (Fig. 3b) and eventually neither product can be obtained with 99% purity. We call this critical displacer concentration D_c^* and define it as the displacer concentration for which the yield of 99% pure component 1 becomes zero. Under the conditions studied here, this concentration is about 4 mM (see Figs. 1 and 4). Increasing the displacer concentration still further results in very strong band interference and in the displacer overtaking the rear boundaries of the first component, such that the front of the second component coincides with the front of the first component (Fig. 3c), and then to the displacer overtaking the peak maxima of the first and second components until all of the fronts coincide (Fig. 3d).

Fig. 2a–d shows no change in the breakthrough time of the first component at lower displacer concentrations. At higher displacer concentrations it can be seen that the breakthrough time decreases, as the velocity of the displacer front increases with

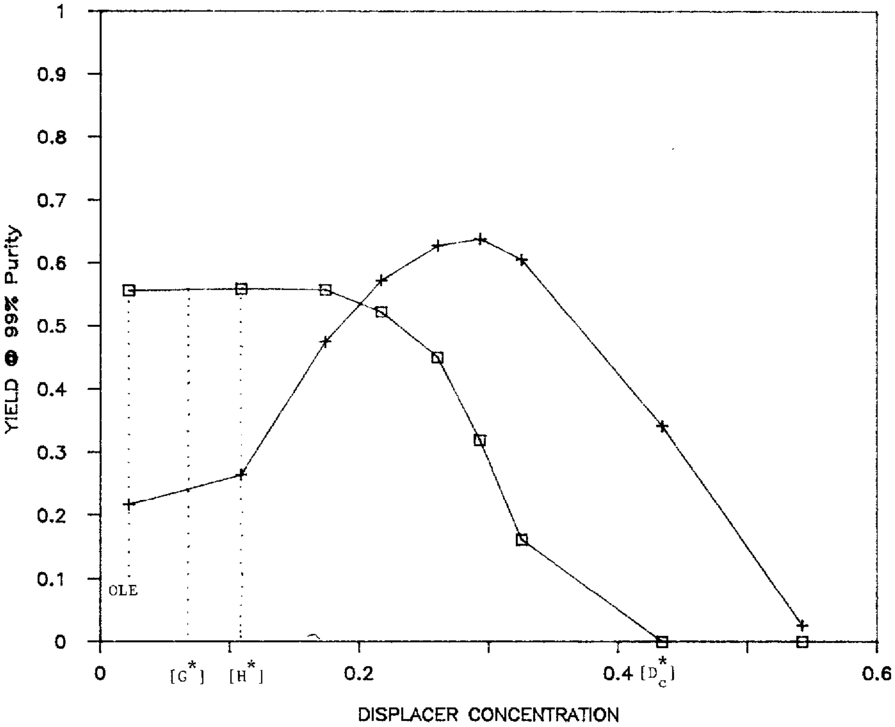

Fig. 4. Effect of the displacer concentration (m*M*) on the yield at 99% purity with a 25-cm column. □, Component 1; +, component 2. OLE = overloaded elution.

increasing concentration for a Langmuir isotherm. At the same time the degree of interference between neighboring bands increases and the yield decreases (Figs. 2d, 3a and 3b). There is an optimal concentration that lies between H^* and D_c^* that would lead to maximal production of the desired product(s). For the conditions in this investigation, the displacer concentration at G^*, H^* and D_c^* are 0.071 m*M* (Fig. 2b), 0.109 m*M* (Fig. 2c) and 0.4 m*M*, respectively. Although the results presented here are for a specific set of conditions, similar peak profiles are seen at other values of the parameters. This specific problem is used to illustrate some of the basic stages in displacement development.

Investigation of the effect of the displacer concentration on the separation yields for components 1 and 2 at 99%, 98% and 95% purity shows that the yield of component 2 can always be increased with the use of a displacer (Figs. 4 and 5). This is not always true for component 1. The displacer concentration for which the yield of component 2 is a maximum is slightly higher when the required purity is higher. At 99% purity (Fig. 4), the yield of component 1 at first remains constant and equal to the yield achieved in overloaded elution, and then decreases with increasing displacer concentration. At 98% and 95% purity the yield of component 1 goes through a weak maximum (Fig. 5). The increase in yield at 98% purity is small but for 95% purity it is more pronounced. The result arises from the fact that component 1 has a tail and the amount to be recycled is reduced when the purity demanded is decreased.

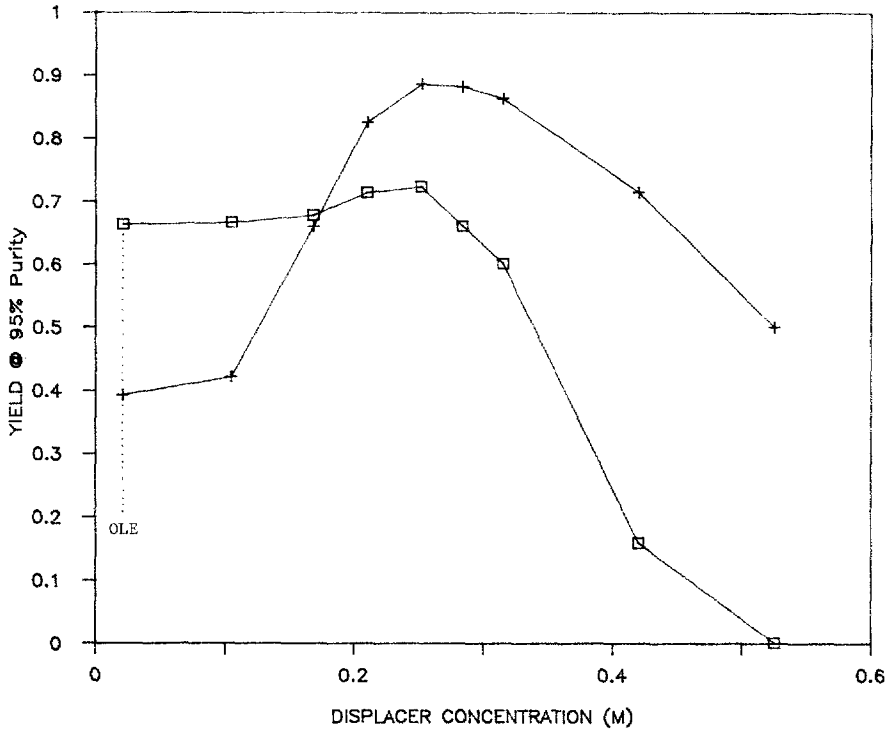

Fig. 5. Effect of the displacer concentration (mM) on the yield at 95% purity with a 25-cm column. Symbols as in Fig. 4.

The effect of the displacer concentration on the production was also investigated for 99%, 98% and 95% purity for both components 1 and 2 (Fig. 6). In this work, production is defined as the amount of product at a specified purity recovered per run. A more realistic production rate would require an estimate of the time needed to regenerate the column. As the production is the product of the yield and the amount of feed, the trends are the same as for the yield. Fig. 6 illustrates the effect of production for components 1 and 2 at 98% purity. The key point is that the production of component 2 increases considerably with displacer concentration (more than 3-fold).

The effect of the displacer concentrations on the isotachic length (*i.e.*, the column length at which an isotachic train is formed) was studied semi-quantitatively by comparison of the peak profiles obtained at various column lengths. The results show that the length required to reach isotachic conditions decreases with increasing displacer concentration. For example, at displacer concentrations of 0.2, 0.3 and 0.5 *M*, the isotachic lengths are approximately 45, 35 and 25 cm, respectively.

Effect of column length

The effect of column length, with all other parameters held constant, was investigated at the displacer concentration corresponding to the maximal production of component 2. Fig. 7 illustrates the effect of the column length on the peak profiles at a displacer concentration of 0.3 *M*. In the first 5 cm, the rectangular injection plug

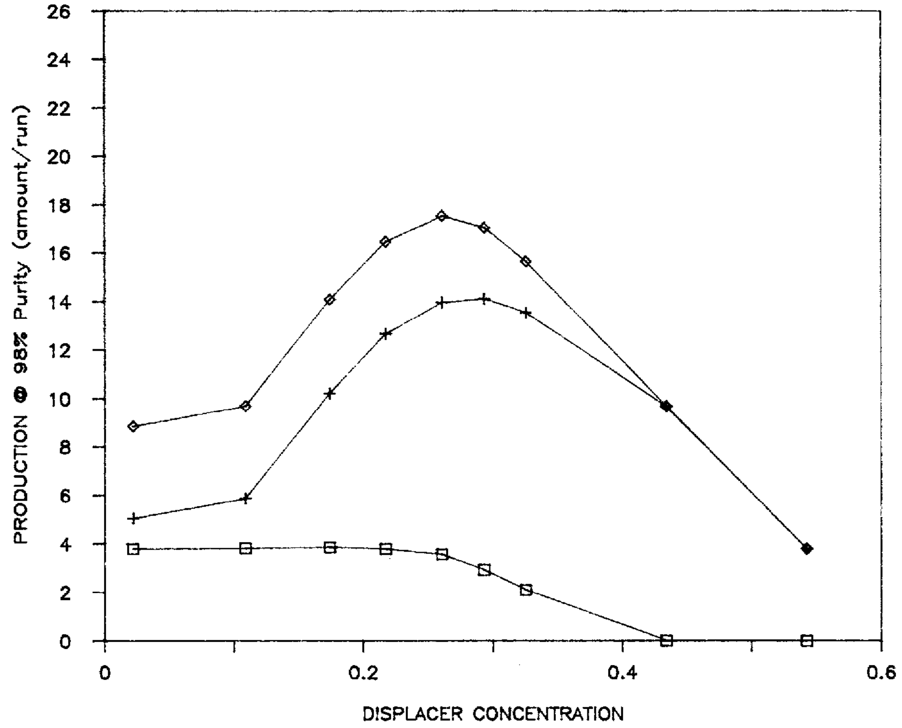

Fig. 6. Effect of the displacer concentration (m*M*) on the production at 98% purity with a 25-cm column. ◇, Total; □, component 1; +, component 2.

having a height of 217 and a width of 0.11 s collapses to a band having a height of about 2 and a width of about 15 s (Fig. 7a). This illustrates the early stages of the displacement effect indicated by the formation of the secondary front on component 2 which begins to push the tail of component 1. At 15 cm (Fig. 7b), the rear boundary has already sharpened considerably, the tail of component 1 is less important and the fronts of the two zones are well separated. At 25 cm (Fig. 7c), the bands are almost totally resolved with increased sharpening of the rear boundary of the first component. At 35 cm (Fig. 7d), isotachic conditions have been reached, giving the maximum yield possible under the specified conditions. The band of component 2 exhibits a wide plateau, but not the band of component 1. The interference zone is reduced. The cut points corresponding to 99% purity are shown for the 25- and 35-cm columns (Fig. 7c and d). The area between the first two vertical lines represents the amount to be recycled.

The effect of column length on the yield and production at 99% purity for components 1 and 2 are shown in Figs. 8 and 9. As the column length increases, the yield increases and tends towards a limit reached for about 35 cm for 99% purity (Fig. 8). The same result is observed for production (Fig. 9) as a function of column length. When isotachic conditions are reached, there is no further increase in the production or the yield. It is clear from the Figs. 6 and 9 that there is an optimal column length and an optimal displacer concentration that will maximize the production at a specified

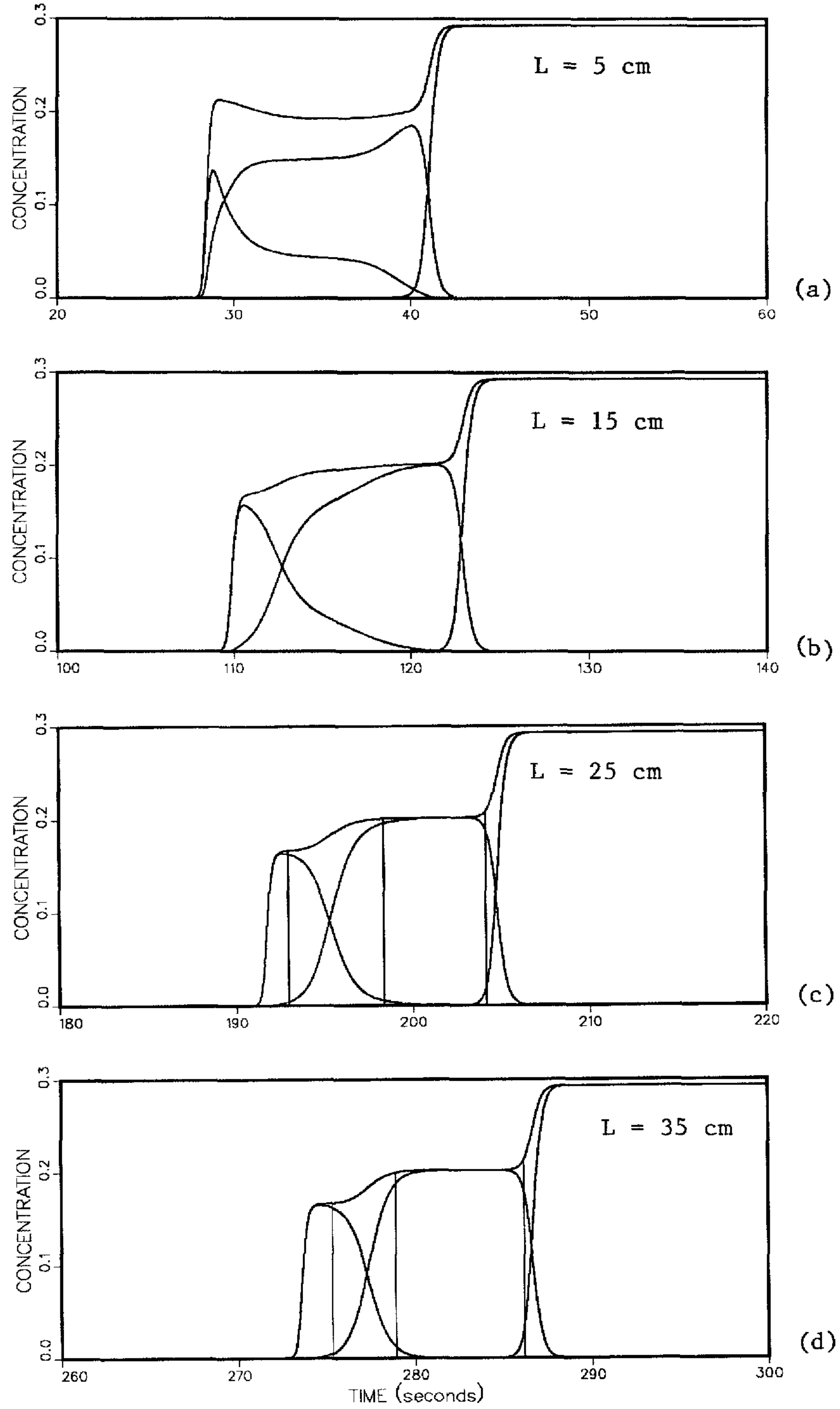

Fig. 7. Displacement profiles as a function of column length at maximal production for displacer concentrations of 0.3 m*M*. (a) 5; (b) 15; (c) 25; (d) 35 cm column.

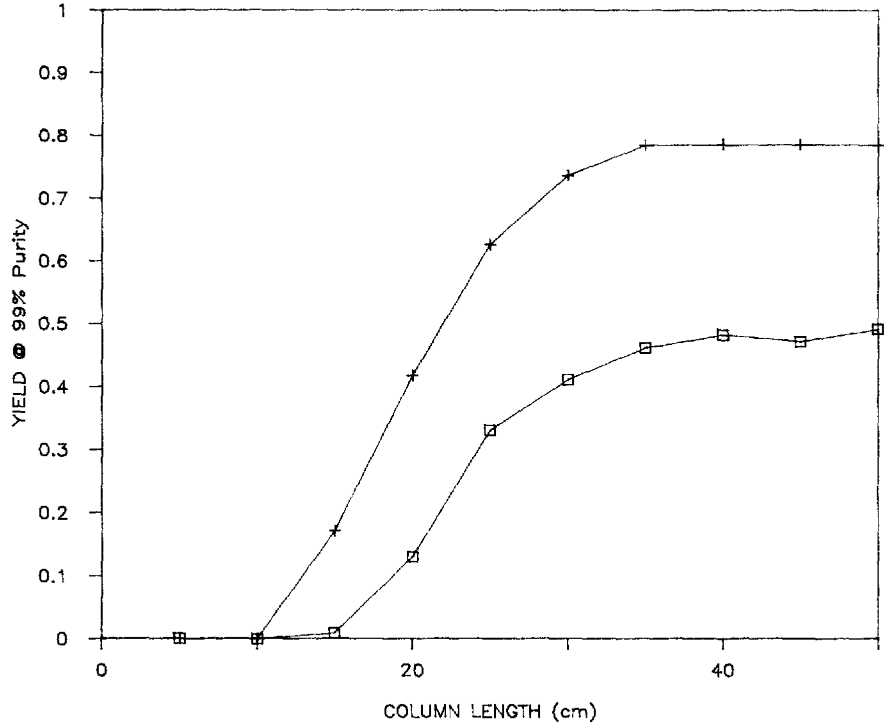

Fig. 8. Effect of column length on the yield at constant displacer concentration and 99% purity. Symbols as in Fig. 4.

purity. Obviously, these values depend on the sample size, velocity of the mobile phase, particle size and column efficiency, which will be discussed elsewhere[41].

Comparison with experimental results

Semi-quantitative agreement can be found between the intermediate profiles predicted by the numerical solution and data in the literature. Horvath *et al.* (ref. 7, Fig. 12) have published intermediate profiles for the separation of 3,4-dihydroxyphenylacetic acid from 4-hydroxyphenylacetic acid with phenol as the displacer, together with the parameters of the single component isotherms of these two compounds. The single component isotherms for components 1 and 2 were employed in a competitive Langmuir model (eqn. 3) and an isotherm was assumed for the displacer. The experimental conditions for 2:1, 1:2 and 2:2 mixtures were used in our model and the peak profiles predicted are shown in Fig.10a, b and c, respectively. Good agreement is seen between the chromatograms shown in Fig. 10 here and in Fig. 12 in ref. 7, with similar breakthrough times, similar values for the peak maxima and similar waves appearing on the tails of the bands. Slight discrepancies are seen, for example, in Fig. 10c, where the second component exhibits a plateau between the two humps, whereas in ref. 7 it rather shows a deep minimum and no plateau. This can be explained by the fact that our assumption of competitive Langmuir isotherms modeled

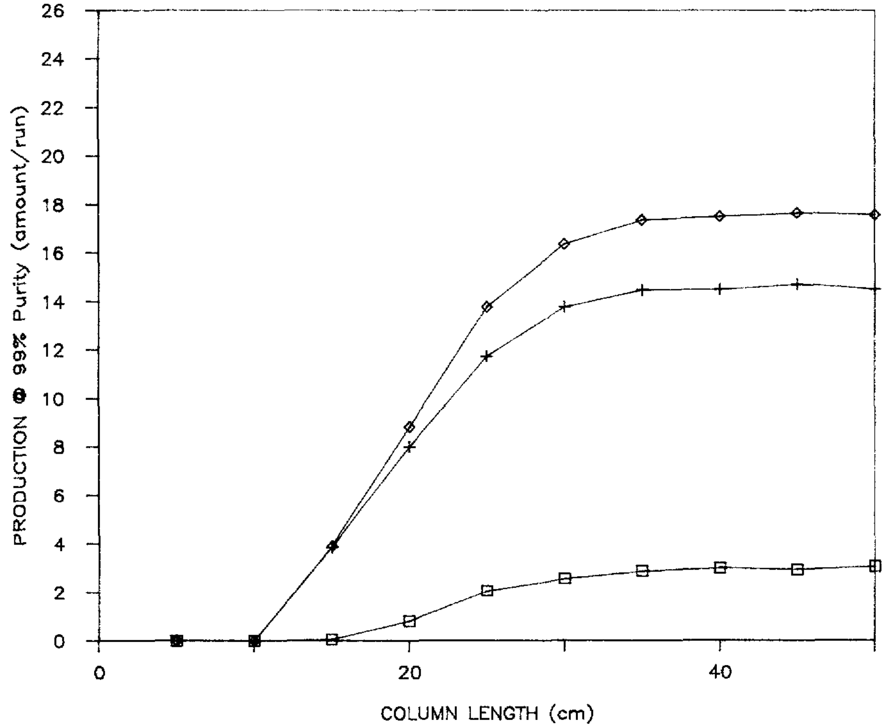

Fig. 9. Effect of column length on production at constant displacer concentration and 99% purity. Symbols as in Fig. 6.

by combining single component isotherms is very crude. It has been observed that competitive isotherms measured by frontal analysis are correctly accounted for by more complex equations[42].

CONCLUSIONS

It has been demonstrated that the proposed model allows the rapid optimization of the experimental conditions and a thorough investigation of the effect of the operating parameters on the separation. Preliminary results indicate that the prediction of experimental band profiles is satisfactory.

Finally, this work permits some comparison between overloaded elution and displacement chromatography. If in a two-component mixture the purification of the first component is of interest, then overloaded elution chromatography can achieve this goal satisfactorily and no significant gain in the recovery yield or production is brought by the use of a displacer. This is not the case if isolation of the second component is desired. The question is whether these gains are sufficient to compensate for the case of the displacer and the regeneration step. Work is in progress to investigate this problem[41].

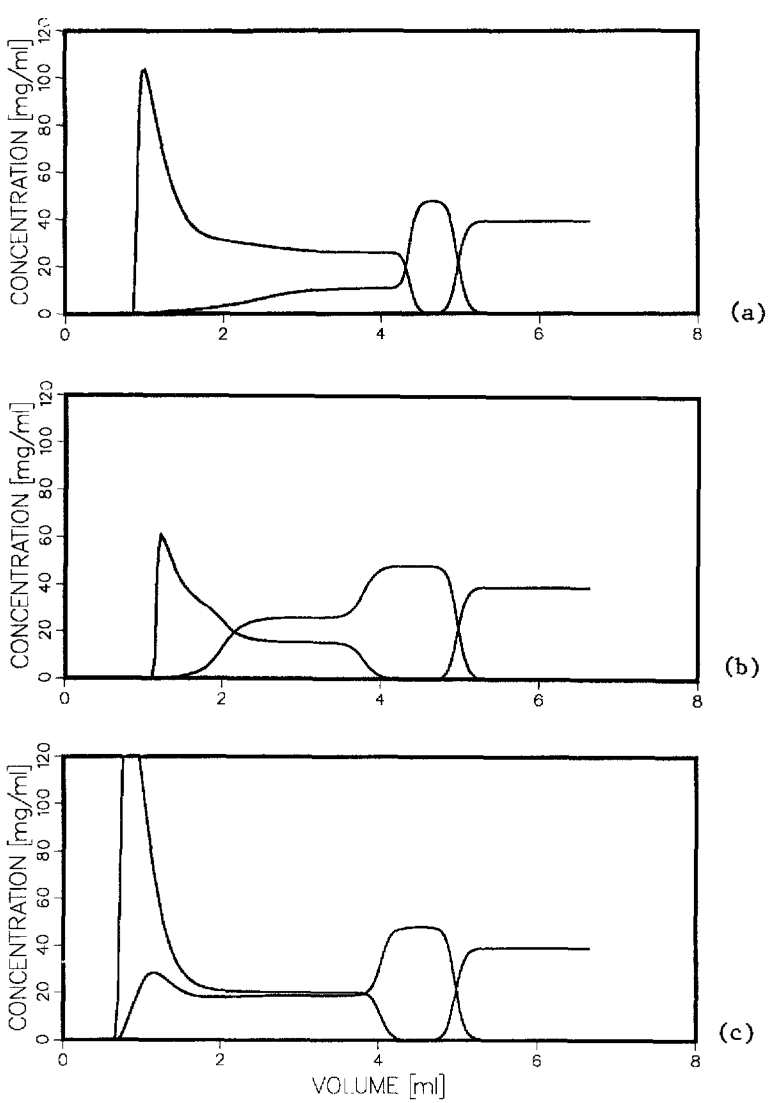

Fig. 10. Effect of sample concentration on the peak shape; comparison with experimental data in ref. 7. Ratio of amounts of components 1 and 2: (a) 114:57; (b) 57:114; (c) 114:114 (mg/mg).

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