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Preliminary design of a simulated counter-current chromatographic system for the separation of praziquantel enantiomers

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Abstract

An empirical design approach for the separation of praziquantel enantiomers using a simulated counter-current (SCC) chromatographic system is presented. The elution volume of the two components to be separated was determined from batch chromatography and was used to evaluate the flow conditions in each section of the SCC unit. The effects of the flow-rate and the number of columns in each section, the throughput and the feed concentration on the extract and raffinate purity of the two streams were studied. This design approach provides sufficient accuracy and an adequate representation of the SCC system. It also provides valuable insight into the main factors governing the behaviour of the system.

Keywords: Enantiomer separation; Simulated countercurrent chromatography; Praziquantel

1. Introduction

The disadvantages associated with batch chromatography have limited its application in industrial-scale separations. Batch liquid chromatography requires a significant adsorbent inventory as the adsorbent in a column is not always used efficiently. The other major drawbacks of this scheme of operation are high consumption of solvent and discontinuity of operation. These problems can be overcome by counter-current contact of liquid and solid phases. However, the physical movement of solids leads to significant complications, such as particle attrition and the difficulty of maintaining strict plug flow of both solid and liquid phases [1].

The simulated counter-current chromatographic (SCC) system overcomes these potential flow distribution problems by simulating the counter-current movement of solid and liquid phases. The continuous movement of the solid adsorbent can be simulated in a multiple fixed-bed system by an appropriate flow-switching sequence. This can be achieved by changing the inlets of the feed and desorbent and the outlets of the product streams, after a specified interval of time, referred to as the switch time, to the next column in the direction of the liquid flow. This will result in a counter-current flow of the liquid and the adsorbent. This continuous pro-

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cess allows the most efficient use of the adsorbent and avoids the problems in circulating the solid adsorbent.

This SCC or simulated moving bed (SMB) technique was originally developed by UOP [2]. In the past decade, this technique has been applied in a number of separations involving carbohydrates [3–11] and other water-soluble materials [12–16]. Most of these studies have been carried out on dilute solutions where the equilibrium isotherms are often linear. Even when dealing with high concentration, establishment of the adsorption isotherms has not been a problem as the individual components in the mixture to be separated are generally commercially available. Thus, the optimization of the performance with theoretical models of such systems is therefore possible.

However, reports on SCC for the separation of racemic mixtures are still limited [17–19], in spite of the increasing interest in chiral separations in various scientific disciplines and the industrial relevance of SCC operation. This could probably be attributed to the fact that the design principles of such a system have remained within the purview of the engineering field, making it difficult for chromatographers to appreciate the operating principles of the technique. Besides, there are added complications with preparative chiral chromatographic systems compared with the achiral systems. The higher cost of the packing materials, the low loadability of the columns and the limited choice of compatible mobile phases have always made the large-scale separation of enantiomeric mixtures a tedious process. Furthermore, these materials usually have low solubility in the mobile phase and the adsorption isotherms are usually non-linear. As the enantiomerically pure compounds are usually not available commercially, the determination of adsorption isotherms and the theoretical modelling pose great problems.

In this paper, an empirical approach to the design of the separation of a racemic mixture using SCC is presented. The compound used in this study was an anthelmintic racemic drug, praziquantel. Praziquantel was recommended as the drug of choice in the treatment of the parasitic disease schistosomiasis in 1977 [20]. (−)-Praziquantel has the advantage of high efficacy and low toxicity compared with *rac*-praziquantel as the therapeutic effect of praziquantel resides in its (−)-isomer [21]. As the enantiomerically pure compound was not available before the start of this study, the adsorption isotherm was not determined. The initial experimental conditions were selected based on the chromatogram obtained from a batch separation. From the concentration profiles obtained in the SCC runs, the experimental parameters were further optimized. This approach, which provides an easily understandable picture of the effects of the process variables, also serves to show, in its simplest way, how an SCC system works. With this understanding, a preliminary design can be performed and an initial set of operating parameters can be obtained which could then be optimized through both experiments and sophisticated modelling.

2. Design of SCC separation

Fig. 1 shows a chromatogram obtained for the separation of two components, A and B, through

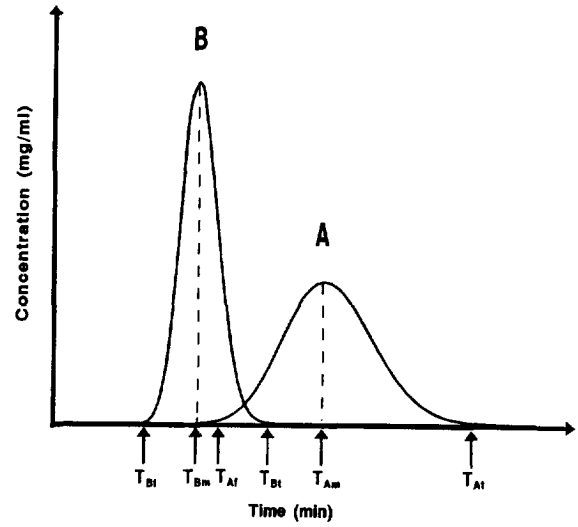

Fig. 1. Chromatogram of two components to be separated obtained by concentration pulse chromatography with a single chromatographic column.

a batch experiment (A denotes the preferentially adsorbed component and B the less adsorbed component).

T_{Am} and T_{Bm} are the mean times required to elute peaks A and B, respectively, T_{Af} and T_{Bf} are the times required to elute the front of peaks A and B, respectively, and T_{At} and T_{Bt} are the times required to elute the tails of peaks A and B, respectively. Therefore,

$$V_{im} = QT_{im}$$
$$V_{if} = QT_{if}$$
$$V_{it} = QT_{it}$$

where i = A or B, Q = eluent flow-rate and V = elution volume.

In SCC operation, the more strongly adsorbed component is referred to as the extract (in this case component A) and the other component as the raffinate (component B). A schematic view of a four-section SCC system and the desired movement of the two components A and B are shown in Fig. 2. The train of columns is divided into four sections by the desorbent and feed inlets and product outlets. The function of each section is described below.

Section I, which is bounded by the desorbent inlet and extract withdrawal, is a desorption section. A fraction of the liquid leaving the top of this section is withdrawn as the extract stream while the remainder flows into section II.

Section II lies between the extract outlet and feed inlet and serves to desorb B from the adsorbent which carries both A and B as it has been in contact with the fresh feed before entering this section.

Section III is located between the feed inlet and raffinate outlet and acts as a zone for the adsorption of A and desorption of B. The liquid emerges at the top of this section, which, partially withdrawn as raffinate, contains only B.

Section IV is situated between the raffinate outlet and the desorbent inlet and functions for adsorption of component B and for recovering the desorbent. The liquid flowing out of this section should ideally contain only pure desorbent which is recirculated to the desorbent inlet for reuse.

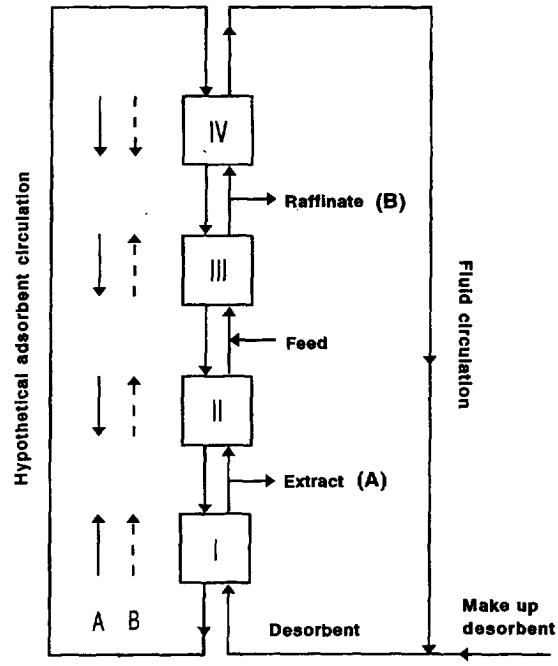

Fig. 2. Schematic diagram of a four-section simulated counter-current system and the desired movement of the components A and B.

To design the SCC separation, it is necessary to ensure operating conditions which allow components A and B to move in their desired directions as depicted in Fig. 2. For an effective separation, the permissible flow-rates in each section are closely related to the elution volumes obtained from batch chromatography based on one of the columns used in the system.

The elution volume in section I per switch time, V_I, is governed by V_{At}. However, as the number of sub-sections in this section (N_I) increases, the minimum volume required will approach V_{Am}.

For sections II and III, elution volumes which allow component B to move to the next column but retain component A are required. The recommended elution volumes, V_{II} and V_{III}, during a switch time, τ, for a good recovery and product purity of both streams are

$$V_{II} = V_X - F\tau > V_{Bm}$$
$$V_{III} = V_X + F\tau < V_{Am}$$

where F is the feed flow-rate and V_X could be approximated to be the average of V_{Af} and V_{Bf}.

If V_{II} is too small, component B will be retained in the columns in section II to an extent that results in contamination of the extract stream. The lowest advisable elution volume per switch period is governed by the mean elution volume of component B (V_{Bm}) which, in this case, requires a large number of sub-sections (N_{II}) in these sections. On the other hand, if V_{III} is too high, component A will overflow into section IV and the raffinate stream. This will result in a reduction in the purity of the raffinate product. In order to ensure no overflow of A into section IV, V_{III} should be less than the mean elution volume of component A (V_{Am}). The closer V_{III} is to V_{Am}, the larger is the number of columns required in the section to achieve a high purity of the raffinate. This also implies that the higher the feed flow-rate, the larger are N_{II} and N_{III} required for high product purity. Therefore, a lower feed flow-rate is always recommended for good separations.

If the purity of only one component is important, V_X could be varied to cater for the requirement. If the purity of a less adsorbed component is critical, a smaller value of V_X could be used, resulting in lower values of V_{II} and V_{III}. Likewise, if the purity of a more adsorbed component is critical, a higher value of V_X could be used, resulting in higher values of V_{II} and V_{III}. However, such adjustments would also lead to low recovery of the component desired.

The elution volume in section IV per switch time, V_{IV}, is governed by V_{Bf}. However, as the number of sub-sections in this section (N_{IV}) increases, the maximum permissible elution volume will approach V_{Bm} and the lowest possible make-up desorbent will be equal to the difference of V_{Am} and V_{Bm}.

The selection of the switch time, τ, is governed by a few factors. One of the advantages of shorter period is a higher throughput. However, this will result in a higher pressure drop across the system owing to the higher flow-rate in each section. A lower flow-rate will enhance the separation if the process experiences a high mass transfer resistance. The flow-rate across each section i (i = I–IV) is

$$Q_i = V_i/\tau .$$

The flow constraints in each section described above share the same principle as the γ concept [5–7] or the McCabe–Thiele diagram [3,4]. However, the present representation involves only the chromatogram of the components to be separated, with an operating principle easily appreciated by both engineers and scientists. To account for the non-linear or/and interacting adsorption isotherms, further adjustment to the flow-rate has to be made. This will be illustrated in this paper.

3. Experimental

3.1. Chemicals

The adsorbent used was microcrystalline cellulose triacetate (MCTA) (Merck, Darmstadt, Germany) with a particle size of 25–40 μm. The adsorbent was allowed to swell completely in ethanol for 30 min. It was then packed into the column using the slurry method. The desorbent used was HPLC-grade methanol (Fisher Scientific, Pittsburgh, PA, USA). The eluent for concentration pulse chromatography and the feed for SCC were prepared by dissolving *rac*-praziquantel (Sigma, St. Louis, MO, USA) in methanol.

3.2. Concentration pulse chromatography

The various elution volumes of the praziquantel enantiomers in batch chromatography were determined by concentration pulse chromatography. One of the chromatographic columns in the SCC set-up (dimensions 445 × 12.5 mm I.D.) was used for this study. The temperature of the chromatographic column was kept constant at 24°C by circulating water from an external thermostatic bath through the thermostat jacket around the column. The column was first equilibrated with the eluent by a solvent-delivery unit (Waters Model 610; Millipore, Milford, MA, USA). A 50-μl volume of (+)- or (−)-praziquantel at a concentration infinitesimally greater than

the plateau concentration was then injected into the column with a Rheodyne (Cotati, CA, USA) Model 7125 syringe-loading valve. The effluent from the column was monitored by a Waters Model 410 refractive index detector. The output signal from the detector was converted to digital form with the aid of an AD/DA card interfaced with a microcomputer for data storage and processing. The experiment was repeated with a series of eluent concentrations of *rac*-praziquantel.

3.3. Simulated counter-current chromatographic system

The set-up of the SCC system is shown in Fig. 3. The system consisted of eight chromatographic columns. To each of the interconnected stationary columns, five solenoid valves (ASCO, Florham Park, NJ, USA) were attached: at the column inlet, the desorbent and feed valves, and at the outlet, the extract and raffinate valves and a transfer valve. The transfer valves connected two adjacent columns together through a short flow line. To prevent back-flow of the liquid, a non-return valve was included after each valve.

The flow-rates of the feed and desorbent were controlled by two solvent metering pumps, a Varian (Palo Alto, CA, USA) Model 2510 and Waters Model 510. Flow meters were installed at the outlet of extract and raffinate streams to control and monitor the extract and raffinate flow-rates. A needle valve was also installed at the outlet of extract stream to control the flow-rate further. The on/off of the solenoid valves was operated in an appropriate sequence by a programmable logic controller.

Counter-current contact between the adsorbent and the liquid was simulated by advancing all the valve functions by one column unit in the direction of the liquid flow after each switch time (Fig. 4). Operation was continued for several cycles until the concentration profiles showed to significant changes between successive cycles.

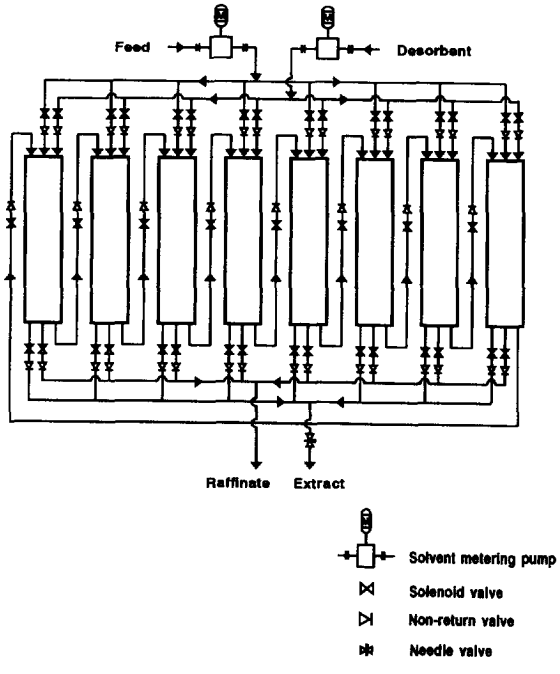

Fig. 3. Schematic diagram of the SCC system.

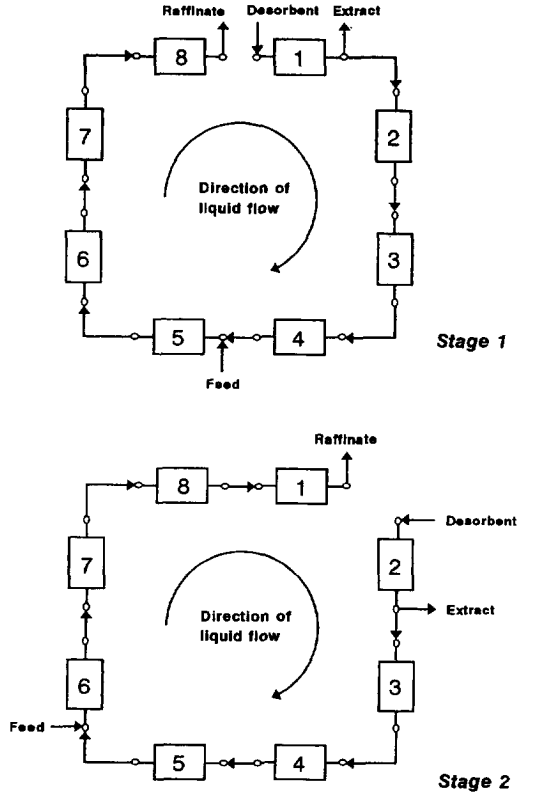

Fig. 4. The first two switches in the sequential operation of the simulated counter-current chromatographic system.

3.4. Concentration and purity analysis

The concentrations of the extract and raffinate streams for each stage were analysed using a standard analytical liquid chromatographic system. The system consisted of a Waters Model 610 fluid unit, a Waters Model 717 autosampler and a Varian Model 2070 spectofluorimeter with excitation and emission wavelengths set at 270 and 300 nm, respectively. The chromatographic column used was Chiralpalk AD (Daicel Chemical Industries, Tokyo, Japan). The eluent was a mixture of HPLC-grade hexane and 2-propanol (80:20) (Fisher Scientific). The purity as defined in this study referred to the optical purity. The extract purity is defined as the ratio of the concentration of the (+)-isomer in the extract stream to the concentration of both the isomers in the same steam. The raffinate purity is defined as the ratio of the concentration of the (−)-isomer in the raffinate stream to the concentration of both the isomers in the same stream. The recovery of a component is defined as the ratio of the amount obtained in a product stream to the amount fed into the column.

4. Results and discussion

From concentration pulse chromatography, the elution volumes at different eluent concentration of *rac*-praziquantel were calculated from the chromatogram, the more adsorbed component being the (+)-isomer and the less adsorbed being the (−)-isomer. It was found that as the concentration of the praziquantel enantiomers in the eluent increases, the mean elution volumes of the two enantiomers drop exponentially (Fig. 5a and b). From these figures, it can be seen that the ease of separation decreases as the concentration increases. However, from the results it is not possible to deduce the mean elution volumes of the enantiomers when one of the enantiomers is dominant in the liquid phase, which is always the case in the SCC system.

As this study was based on existing instrumentation, the first step was to distribute the eight columns available in the system among the four sections. The main aim of the present separation was to achieve a raffinate with little contamination with the (+)-isomer and with maximum recovery of the (−)-isomer. To obtain a high concentration product stream would be considered secondary. In order to achieve good separation, the number of columns in sections II and III must be maximized since sections I and IV would not be utilized for the separation. The sole purpose of sections I and IV is to conserve the desorbent to produce high-concentration product streams.

The liquid leaving section IV has to be devoid of components A and B. In our case this can be

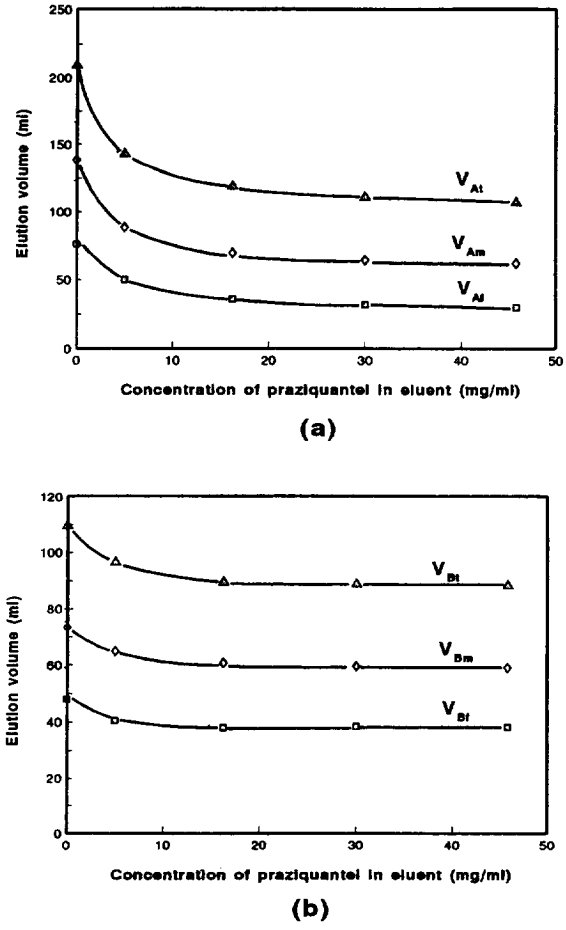

Fig. 5. Various elution volumes for (a) (+)- and (b) (−)-praziquantel by concentration pulse chromatography at different concentrations of *rac*-praziquantel in the eluent.

achieved if V_{III} is less than V_{Bf}. Since V_{Bf} is small compared with V_{At}, the allowable V_{IV} would be very small compared with V_I. Therefore, recycling of V_{IV} does not seem to be attractive, especially when there is a limitation on columns available. It was therefore decided to have a system which consists of three sections and with a configuration of one, three and four columns in the three sections, respectively.

From Fig. 5a and b, we deduced that the elution volumes of the two enantiomers are dependent on the concentration of the enantiomers in the liquid phase. However, the concentration of the enantiomers in each column of the SCC system cannot be predicted. As an initial estimate, the following elution volumes per switch period were selected, based on the results obtained from concentration pulse chromatography with an eluent concentration at 20.0 mg/ml and the number of columns used in each section: $V_I = 195.0$ ml, $V_{II} = 68.0$ ml, $V_{III} = 80.0$ ml, feed concentration = 20.0 mg *rac*-praziquantel/ml of methanol and switch period $\tau = 1$ h. Thus, the operating flow-rates were desorbent = 3.25, feed = 0.20, extract = 2.12 and raffinate = 1.33 ml/min.

The cyclic steady state was reached after approximately fifteen cycles of operation. The extract and raffinate purity were analysed to be 83.5% and 98.5% with a recovery of the (−)-praziquantel of 82.6%. The column outlet concentration profiles for the eight columns at equal time interval throughout the switch time under these conditions are shown in Fig. 6. These profiles were obtained by sampling the outlet solution at column 8 for eight consecutive switches after the cyclic steady state had been reached. The sample collected for the first switch represented the column outlet concentration of column 8, the second switch column 7, and so on. The first collection for each switch was performed at 5 min after the switch and the subsequent collections at 10-min intervals. An analysis of these concentration profiles showed that columns 5, 6 and 7 were not utilized fully. The recovery of the (−)-praziquantel and the extract purity could therefore be improved by increasing V_{II} and V_{III}.

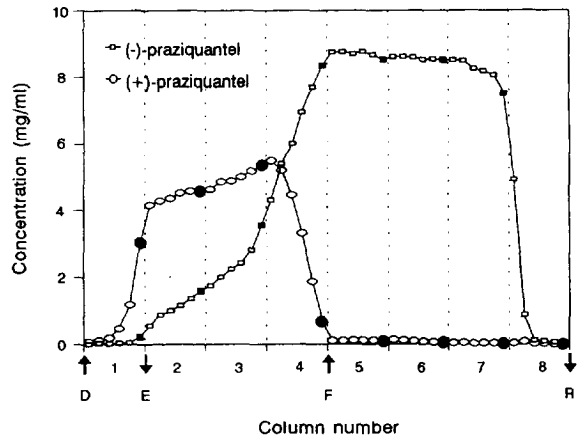

Fig. 6. Column outlet concentration profiles for the eight columns. The first sampling of each column was 5 min after the switching of valve function, indicated by shaded symbols, and subsequent sampling was at 10-min intervals. Column configuration = 1–3–4; desorbent flow-rate = 3.25 ml/min; feed flow-rate = 0.20 ml/min; extract flow-rate = 2.12 ml/min; raffinate flow-rate = 1.33 ml/min; feed concentration = 20.0 mg/ml; $\tau = 60$ min; $V_I = 195.0$ ml; $V_{II} = 68.0$ ml; $V_{III} = 80.0$ ml.

The relationships of extract and raffinate purity, and the recovery of (−)-praziquantel with the elution volume, V_{III}, are shown in Fig. 7a and b. The feed flow-rate and concentration and the desorbent flow-rate were kept constant. This graph shows that the optimum conditions with respect to the raffinate purity and recovery of (−)-praziquantel are ca. 73.0 and 85.0 ml for V_{II} and V_{III}, respectively. Under these optimum conditions, the column outlet concentration profiles throughout the switch period are as shown in Fig. 8, from which it was observed that columns 6 and 7 were not fully utilized in separating the isomers. However, with a slight increase in the elution volumes, V_{II} and V_{III}, the (+)-isomer would emerge in the raffinate stream and result in a lower purity of the raffinate stream (Fig. 7a). Therefore, there exists a critical elution volume where the raffinate purity drops drastically above this value. If an elution volume slightly greater than this critical value is used, more (+)-isomer would enter section III. This increase in concentration would result in a lower volume of liquid required to elute the isomer. As a result, more (+)-isomers would enter section

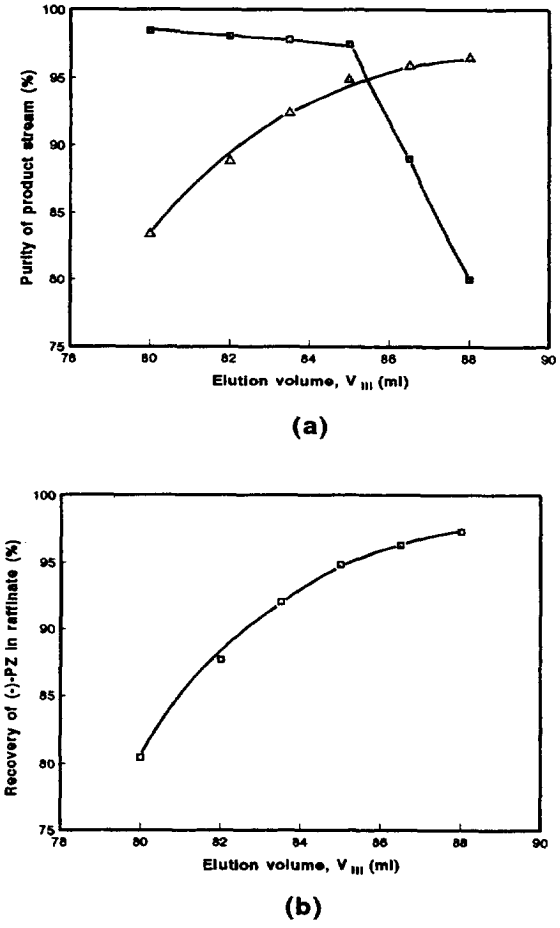

Fig. 7. Effect of elution volume, V_{III}, on (a) the extract and raffinate purity and (b) the recovery of (−)-praziquantel in the raffinate stream. Column configuration = 1–3–4; desorbent flow-rate = 3.25 ml/min; feed flow-rate = 0.20 ml/min; feed concentration = 20.0 mg/ml; τ = 60 min; V_I = 195.0 ml; $V_{II} = V_{III}$ − 12.0 ml.

III. This would lead to a further increase in concentration and a further decrease in volume required to elute the isomers. Consequently, the (+)-isomer would emerge from the raffinate stream. It was observed that the effect of the concentration of the (+)-isomer on the decrease in elution volume of both isomers is significant. The build-up of the (+)-isomer in section III at a V_{III} above the critical value is a slow process, and more than 20 cycles might be required to reach the cyclic steady state. Therefore, a material balance is required to ascertain the establishment

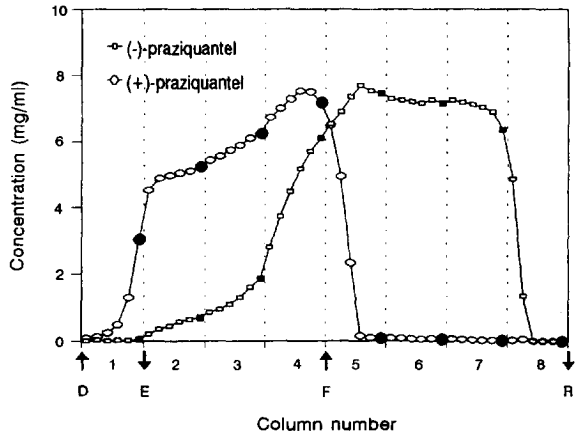

Fig. 8. Column outlet concentration profiles for the eight columns. The first sampling of each column was 5 min after the switching of valve function, indicated by shaded symbols, and subsequent sampling was at 10-min intervals. Column configuration = 1–3–4; desorbent flow-rate = 3.25 ml/min; feed flow-rate = 0.20 ml/min; extract flow-rate = 2.03 ml/min; raffinate flow-rate = 1.42 ml/min; feed concentration = 20.0 mg/ml; τ = 60 min; V_I = 195.0 ml; V_{II} = 73.0 ml; V_{III} = 85.0 ml.

of the cyclic steady state. From this observation, it was deduced that a larger number of subsections in section III may not be necessary. The extract purity and hence the recovery of the (−)-praziquantel could be increased by increasing the number of sub-sections in section II. It was therefore decided to use a 1–4–3 instead of a 1–3–4 configuration. This resulted in an increase in the extract purity to 97.0% and in the recovery of the (−)-praziquantel to 97.0%. The raffinate purity dropped slightly to 97.5%.

To increase the throughput, the switch time was reduced from 1 h to 30 min. The flow-rates of the feed, desorbent, extract and raffinate streams were doubled. Therefore, instead of separating 240 mg/h of *rac*-praziquantel, the system was able to separate 480 mg/h of the racemic mixture. From the experimental results, there was no significant difference in the extract and raffinate purities. However, a further decrease in the switch period resulted in a high pressure drop which may not be tolerated by the chiral stationary phase used.

The effects of the feed concentration and flow-rate on the performance of the SCC system were also studied. For the same V_{II} and V_{III}, the

product purity dropped as the concentration of the feed increased. This behaviour indicated the existence of a limited capacity of MCTA which led to a drop in separation efficiency when the concentration of the enantiomers in the liquid phase increased. In order to achieve the same purity of (−)-praziquantel (97.5%) in the raffinate stream, V_{II} and V_{III} were reduced by increasing the extract flow-rate. For comparison, the feed flow-rate was kept constant at 0.40 ml/min. As V_{III} decreases with an increase in feed concentration, the recovery of (−)-praziquantel also decreases. However, there exists a feed concentration where the amount of (−)-praziquantel recovered per hour is the maximum, which was found to be ca. 50.0 mg/ml (Fig. 9).

With the throughput kept constant at 1200 mg/h and the switch period at 30 min, the effects of feed concentration and feed rate on the recovery of (−)-praziquantel were studied. The results showed that the product purity dropped when the feed concentration was decreased (or when the feed rate was increased). The elution volumes, V_{II} and V_{III}, required to obtain a raffinate purity of 97.5% for varying feed concentration are shown in Fig. 10a and the recovery of

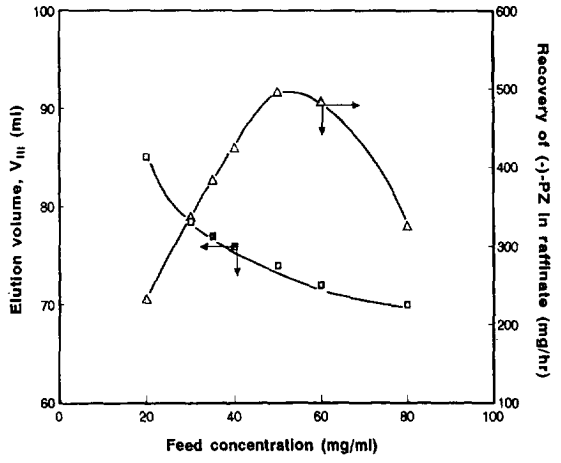

Fig. 9. Effect of feed concentration on elution volume, V_{III}, and the amount of (−)-praziquantel recovered in the raffinate stream per hour with raffinate purity kept constant at 97.5%. Column configuration = 1–4–3; desorbent flow-rate = 6.50 ml/min; feed flow-rate = 0.40 ml/min; τ = 30 min; V_t = 195.0 ml; $V_{II} = V_{III} - 12.0$ ml.

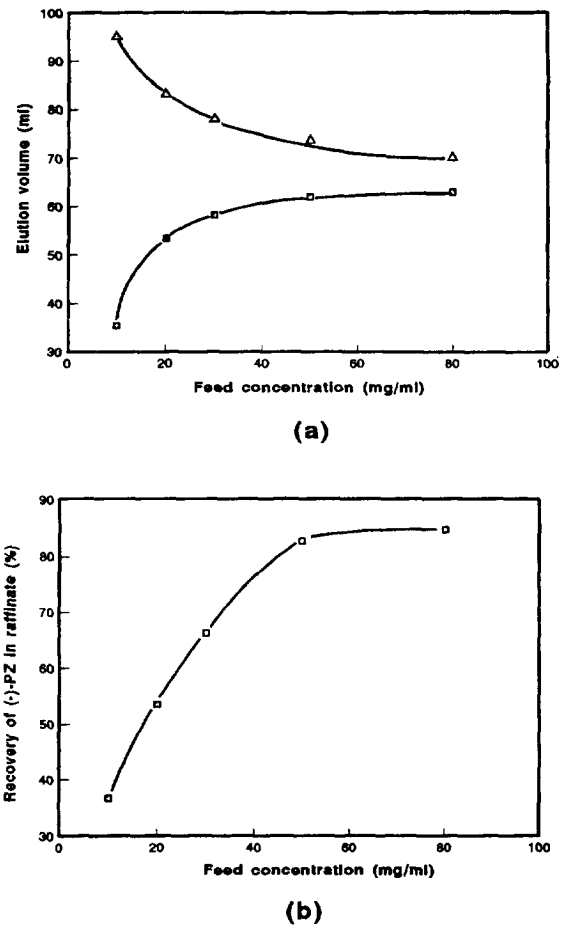

Fig. 10. Effect of feed concentration on (a) elution volumes, V_{II} and V_{III}, and (b) recovery of (−)-praziquantel in the raffinate stream with throughput kept constant at 1200 mg/h and raffinate purity at 97.5%. Column configuration = 1–4–3; desorbent flow-rate = 6.50 ml/min; τ = 30 min; V_t = 195.0 ml.

(−)-praziquantel is shown in Fig. 10b. The decrease in the recovery of (−)-praziquantel with a decrease in concentration or increase in feed rate was due to a greater difference between V_{II} and V_{III}. The effect of this difference in elution volumes on the performance of the SCC system has been discussed earlier. Although a slightly higher recovery of (−)-praziquantel could be obtained in the raffinate stream at a feed concentration of 80.0 mg/ml, the use of this operating condition was discouraged as problems arose in the operation of the solenoid valves with a high feed concentration.

At a feed rate of 0.40 ml/min and a feed concentration of 50.0 mg/ml, further experiments were carried out by varying V_{II} and V_{III} to determine the optimum conditions in terms of the raffinate purity and the recovery of (−)-praziquantel. The results (Fig. 11a and b) show the same trend as observed in Fig. 7a and b where a higher V_{III} leads to a lower raffinate purity and a higher recovery of (−)-praziquantel. A critical V_{III} of ca. 74 ml was also observed in this graph. The purity of the raffinate drops drastically when V_{III} is greater than this value.

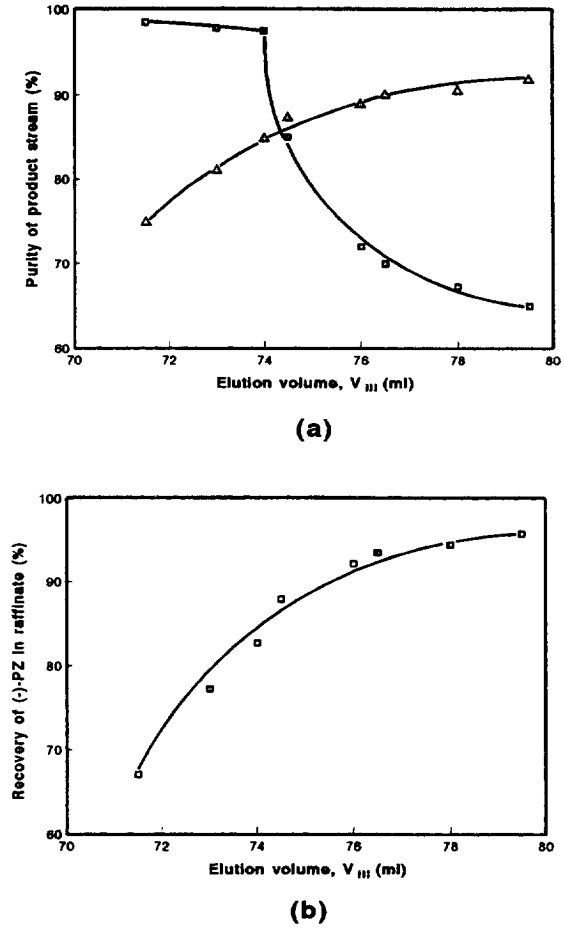

Fig. 11. Effect of elution volumes, V_{III}, on (a) the extract and raffinate purity and (b) the recovery of (−)-praziquantel in the raffinate stream. Column configuration = 1–4–3; desorbent flow-rate = 6.50 ml/min; feed flow-rate = 0.40 ml/min; feed concentration = 50.0 mg/ml; τ = 30 min; V_I = 195.0 ml; $V_{II} = V_{III} - 12.0$ ml.

In our study of the crystallization of the praziquantel enantiomeric system [22], we found that the yield of the enantiomerically pure crystals from a partially resolved mixture would be equal to the enantiomeric excess of the mixture. Therefore, the overall recovery of enantiomerically pure (−)-praziquantel crystals by coupling the two processes was calculated, and this is shown in Fig. 12. Among the several experiments runs conducted, the recovery of (−)-praziquantel in the SCC process was the highest with a V_{III} of 79.5 ml. However, this condition gave the lowest overall recovery of enantiomerically pure (−)-praziquantel crystals. This was due to the low enantiomeric excess of the solution to be crystallized.

Based on the experimental runs conducted, it was deduced that the following experimental conditions allow a high yield of enantiomerically pure (−)-praziquantel crystals: desorbent flow-rate = 6.50 ml/min, feed flow-rate = 0.40 ml/min, extract flow-rate = 4.43 ml/min, raffinate flow-rate = 2.47 ml/min, feed concentration = 50 mg *rac*-praziquantel/ml of methanol, extract purity = 85.0%, raffinate purity = 97.5%, (−)-

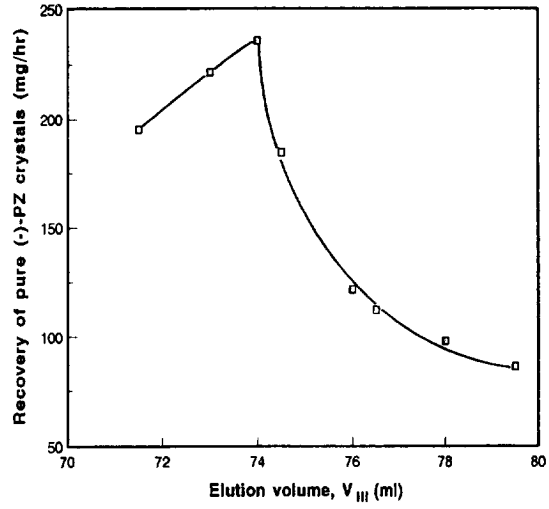

Fig. 12. Effect of elution volumes, V_{III}, on the recovery of enantiomerically pure (−)-praziquantel crystals by crystallization of the partially resolved mixture from the SCC process. Column configuration = 1–4–3; desorbent flow-rate = 6.50 ml/min; feed flow-rate = 0.40 ml/min; feed concentration = 50.0 mg/ml; τ = 30 min; V_I = 195.0 ml; $V_{II} = V_{III} - 12.0$ ml.

praziquantel recovery = 82.7% and yield of enantiomerically pure (−)-praziquantel crystal when coupled with crystallisation = 78.6% = 11.7 g/day.

As the main criterion of the present separation was to obtain high-purity products, no work was carried out to conserve the desorbent or increase the product concentration. As a three-section configuration had been used in this system, the raffinate stream was highly diluted. The extract stream was also subjected to high dilution owing to the high volume required to elute the (+)-isomer completely from the column in section I. The concentration of the product streams can be increased by collecting them at a particular interval, e.g., the first 18 min of a 30-min switch time for extract stream and the last 15 min of a 30-min switch time for the raffinate stream. As the retention time of the (+)-isomer decreases with an increase in column temperature, V_I can be reduced by increasing the operating temperature of column(s) in section I. This will help to conserve the desorbent and to increase the extract concentration. However, in the pilot unit, the additional cost of heat exchangers and switching valves associated with such system may well exceed the cost of the solvent saved. Furthermore, the solvent used in this system could be easily recovered and product concentrated by vacuum evaporation.

5. Conclusions

The advantage of the proposed approach is that the effects of changes in process variables, such as the flow-rate in each section, are easily visualized. This provides a useful initial guide for the selection of operating conditions and the prediction of system performance. This approach could be used to adapt to an existing system or could also be used to design the column configuration based on the results on the batch chromatography. However, this approach does not permit the prediction of the amount of impurity in the outlet streams. It requires experimental runs, through which the optimum flow conditions and column distribution among the four sections can be obtained from the knowledge of the concentration profiles. Nevertheless, it serves as a useful initial approach for the SCC studies and provides a better understanding of the links between batch and continuous chromatography.

For the case of the separation of a racemic mixture, large amounts of (−)- or (+)-isomer are usually not available for the study of the adsorption isotherm. This empirical approach would allow the preliminary separation of the racemic mixture to obtain pure or nearly pure enantiomers. With the achievement of these higher purity products, adsorption isotherms could be established and further optimization of the system could be performed by conventional modelling.

Symbols

F	feed flow-rate (ml/min)
N	number of sub-sections
Q	volumetric flow-rate (ml/min)
T	elution time (s)
V	elution volume (ml)
τ	switch time (min)

Subscripts

I–IV	sections I–IV of the SCC process
A	the preferentially adsorbed component
B	the less preferentially adsorbed component
f, m, t	front, mean and tail of the chromatogram

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