ELSEVIER

Journal of Chromatography A, 827 (1998) 143–160

JOURNAL OF CHROMATOGRAPHY A

Review

Simulated moving bed processing: escape from the high-cost box

Bruce Pynnonen[1]

Liquid Separations, The Dow Chemical Co., 1691 North Swede Road, Midland, MI 48674, USA

Abstract

The prime objectives of analytical chromatography are compact equipment, complete peak separation, speed, accuracy, precision, sensitivity and minimum sample waste. Processing compounds versus analyzing compounds via chromatography is much simpler, yet much more complex. The objective of chromatography as a manufacturing process step is to minimize cost. Product purity and production capacity are unchanging and are determined by the needs of the organization for the product. Constraints of GMP and product recovery are not part of the decision process for which process to choose since the costs of achieving these are incorporated as components of the objective function to be minimized, the cost. When process designers adopt without question the ''truths'' derived from the assumptions and boundary constraints appropriate to the regime of analytical chromatography, process chromatography is the expensive operation of last resort. Some of the keys to unlock the invisible door of the high-cost box are presented by examining a real separation and the projected costs of performing the separation in different modes.

Keywords: Simulated moving bed chromatography; Preparative chromatography; Process chromatography; Reviews

Contents

[1]Fax: +1 517 6389944; E-mail: pynnonen@dow.com

0021-9673/98/$ – see front matter
PII: S0021-9673(98)00732-8

1. Introduction

Separation of compounds by chromatography has been known for decades. Although the use of chromatographic processes for manufacturing of chemicals was evaluated as early as the 1950s [1–4] chromatography has flourished and developed largely in the field of quantitative analysis of mixtures, especially complex mixtures [5–8]. Industrial scale preparative separations as a manufacturing operation took a giant leap forward in the 1960s when UOP introduced and commercialized the Sorbex family of simulated moving bed (SMB) processes [9–15]. SMB technology reduced the volumes of stationary phase and mobile phase required to achieve a specified separation. The resulting cost savings made many chromatographic separations economically feasible; major commodity applications are found in the petroleum industry [8–15], the corn wet milling industry [16–21], and the beet sugar industry [22–31].

The use of chromatography in manufacturing processes in the pharmaceutical and fine chemical industries has grown steadily but slowly. There is significant resistance to the use of chromatographic separation in a manufacturing process because of the perceived high costs of purification using these processes. In the last five years there has been an explosion of interest in chromatographic separation processes, especially SMB processes, fueled by the market trend toward chirally pure therapeutic compounds [32–38]. This market trend is being driven by competitive advantages achieved by patents on chirally pure materials and by regulatory pressures. Since conventional SMB operation is a binary separation process, the separation of two chemically identical but stereochemically different compounds would seem to be an ideal application for the strengths of SMB chromatography.

Extensive information is available on the fundamentals of the SMB process [39,40]. Mathematical models of varying complexity have been used to investigate the performance and design of SMB processes to separate different mixtures. However, any company contemplating a manufacturing process which would use a SMB, the literature is sparse. Only a few papers discuss the practical details of designing, building, and operating a process scale SMB [41–43]. Little is available on the engineering economics of building and operating an SMB process with the objectives of making a product for sale and producing a profit for the owner organization. In fact, only limited information is available on the costs of any individual chromatographic separations [44–48].

In the design of any chemical manufacturing process, the design choices made very early on can have very large impacts on the cost of the product manufactured [49,50].

Effective chemical process design uses feed-forward (anticipate costs of design choices) and iterative (modify design based on total manufacturing cost)

optimization to minimize manufacturing cost [48–50]. Manufacturing processes are integrated processes wherein design choices which lead to lower costs in one process section may increase costs in another portion of the plant; therefore, costs to be minimized must incorporate all of the processing requirements inherent in each specific design choice [44,45,49,50].

The objective of this paper is to point out some very expensive design choices normally made without much awareness of the cost impact of that choice. In particular, the use of a stationary phase with a small particle size very similar to the stationary phase used for analytical chromatography results directly in the high costs normally associated with chromatographic purification processes. Once made, this choice locks the process chromatographer into a box which contains only options of high costs. An alternative approach of using a stationary phase with a much larger bead size will be proposed.

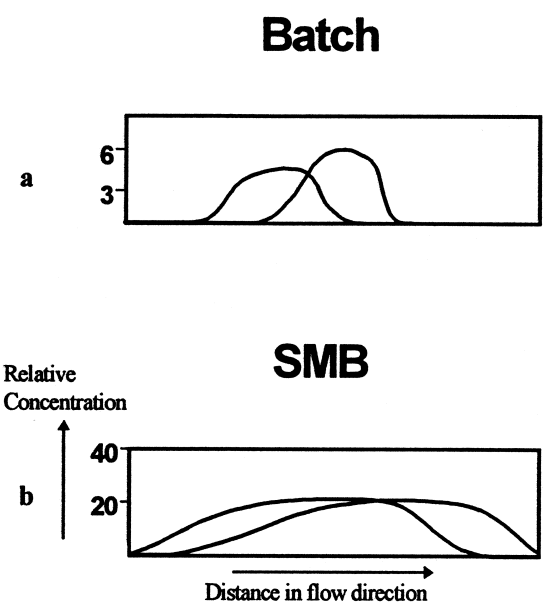

Fig. 1. Binary component process chromatographic separation in (a) a batch (or ''elution'' or ''pulse'') mode and in (b) a simulated moving bed mode.

2. Background and concepts in process chromatography

Chromatographic processing can be done in a batch (elution) mode, with integrated or sidestream recycling, in an SMB mode, or in various hybrid modes. There are major process design decisions to be made which impact on the fully integrated economic costs of chromatographic purification. First, we will cover the ways in which SMB operation reduces chromatographic separation costs for binary separations. Then we will examine other process design parameters which impact on the processing costs, whether using elution mode or SMB. Finally, we will estimate costs of chromatographic separation under various scenarios of scale and process design.

2.1. Economic comparisons, elution compared to SMB modes

There are economic advantages to SMB processing. Fig. 1 shows the component profiles of a chromatographic separation in elution (a) and SMB modes (b). There are several important features to note. First, the component profile for the SMB process has very low resolution. The peaks overlap over a very large part of the entire process. Second, upstream of and downstream of the peaks being separated in the elution chromatography column there are large sections which contain only packing and elution solvent. The stationary phase and columns represent a significant part of the separation costs. Yet the majority of that investment is wasted most of the time, functioning only as a very expensive conduit to convey elution solvent to and take it away from the peaks of interest.

Also, the overlapping portion of the peaks will eventually reach the column exit. This material is normally not lost, but is saved in a vessel for recycling back into the column to recover more of the desired material. However, the front edge of this material has had costs invested and was separated almost enough to take as part of the cut of the faster-moving component. The back edge of the recycle cut has also had a partial purification take place. When it reaches the exit of the column, not the material itself but the separation is ''thrown away'' by mixing it with the front edge of the recycle cut.

An additional point of interest is that the total concentration of either material can be much higher

in the SMB case, minimizing the volume of stationary phase required. A SMB process can use a higher concentration of solute in the feed than a batch process. Any comparison of a batch process to a SMB process which does not examine a higher feed concentration for the SMB case than for the batch case may be imposing an invalid constraint on the SMB. The higher concentration at the product cut also results in the conclusion that a lower volume of solvent is used than in the elution process. The same effect can be derived from the fact that there is only a very small fraction of the profile where there is exclusively elution solvent. The savings in solvent consumption from using a SMB process typically range from a factor of 3–10 when compared to elution chromatography.

One point which is not evident from Fig. 1 is that for a conventional SMB, the feed is continuous, as are the product take-off flows. This means that the process runs around the clock, producing the desired product 24 h a day without significant operator intervention. This maximizes the production capacity and minimizes the labor required to produce a purified product.

Fig. 2 shows the desired characteristics of an ideal separation. The ideal separation for analytical purposes involves injecting a small volume of a dilute feed. The total mass injected each time is extremely small compared to the size of the column. This mode of operation results in a high degree of resolution between two peaks. The ideal output can be seen as peaks separated by a large volume or time, with a rectangular shape. The height (concentration) and the base of the ''peak'' (in volume) should be the same as they were in the volume element of fluid in the injection pulse. The ideal process separation uses a large injection volume. This maximizes production rate and minimizes cost. Yet the ideal outlet peak width is still the same as the injection width. In contrast the ideal process separation exhibits no separation between the last molecules of the faster peak and the first molecules of the slow peak. While impossible to achieve, this ideal would allow 100% recovery at 100% purity and with very little dilution. This impossible target helps to keep the correct goal in mind. Low dilution implies reduced solvent consumption which implies reduced solvent costs. The solvent ahead of and behind the peaks could be recycled directly to elute the next injection. Note that the characteristics of the low resolution SMB component profile come closer to the process ideal than the elution component profile.

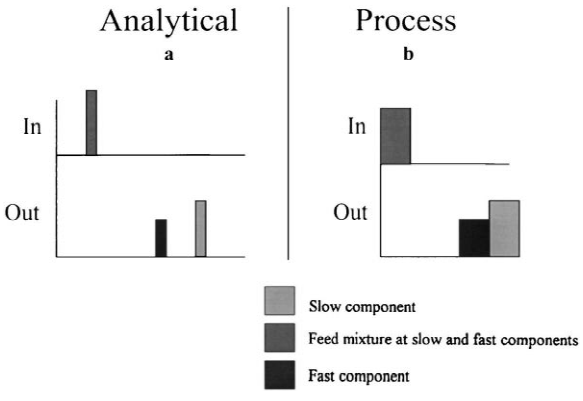

Fig. 2. Representation of the ideal separation for (a) analytical purpose and (b) process operation. Note the lack of separation between the slowest ''fast'' component and the fastest ''slow'' component. Note also the wider input and output for the ideal process case.

An important advantage of SMB operation is that the separation column is in effect ''stretched'' by the nature of the SMB. The average molecule inside the process loop passes through the same distance or through the same volume of stationary phase multiple times. The internal recycling in the process exposes the solutes to multiple passes through each section of the loop. To the solutes, the column set appears to be many times its actual size. The ''stretched'' column set performs as a longer column set, resulting in better separation. This advantage is achieved without the expense of larger volumes of stationary phase. Only if the selectivity of the stationary phase is very high and its saturation capacity very low will an SMB not result in a large savings in the volume of stationary phase required to perform a given separation. This effect is lost if the SMB is not operated in a SMB mode, that is, without a high internal recirculation rate in the slowest zone.

A higher internal recirculation rate in an SMB process reduces the volume of stationary phase required by multiplying the contacts of the solutes with the stationary phase. This benefit is achieved at the cost of a higher solvent consumption. The higher

solvent consumption is derived from the following fact. With the internal recirculation, movement through the separation columns can be accomplished without fresh elution solvent. The purpose of the elution solvent is now to accelerate the average movement rate of the more heavily retained component so as to keep its profile moving at the same rate as the profile of the fast-moving component. It is obvious that a separation would start to occur if the loop were only recirculated; however, the fast component would begin to catch up to and overlap with the slow-moving component.

Finally, SMB operation saves time and time is money. Time to market for a new produced is reduced. Provided a pilot plant is large enough to avoid wall effects and is carefully engineered to keep the important design parameters the same, it has been shown that process scale-up from a small pilot plant to a very large commercial process is straightforward [11,15,51,52]. In the pharmaceutical industry, a design algorithm and a commercially available SMB has been used to design a process to purify a racemic mixture and separate the mixture in less than one week [38].

Some of the objectives for analytical chromatography and for process chromatography are contrasted in Table 1. Reducing the capital and operating costs of the process is the objective of process design and operation for a process scale chromatographic separation. The cost of feed material required must not be neglected [44]. It is most suitably incorporated as one of the elements for each separate design scenario. With all components of a given design choice included in the cost calculation, then each design choice must be evaluated in light of the total costs inherent in each design.

Table 1
Objectives of chromatography

Analytical	Manufacturing
Small sample quantity	Cost
Complete resolution	Low pressure = low cost
Accuracy	Large quantities
Precision	Flexibility
Speed	Energy cost
Separation in <0.5 m	Packing cost
	Reliability

3. Important considerations for process chromatography

First, we will evaluate four factors which impact on the overall integrated cost of performing process scale separation by chromatographic processes. These factors are important whether an elution or SMB process is being considered. These are: particle size of the packing; column design and operating parameters; economy of scale; and integration of the total process. If only a part of the process design is optimized, total cost is unlikely to be minimized.

3.1. Particle size effects

3.1.1. Pressure drop

Pressure drop experienced in the flow of a fluid through a packed bed has been studied extensively. For the case of laminar flow (low Reynolds number) as is encountered in liquid chromatography, the well-known Leva equation reduces to the Blake–Kozeny equation [50,53]:

$$\Delta P = \frac{150 V_0 L \mu (1-\varepsilon)^2}{D_p^2 \varepsilon^3} \quad (1)$$

where ΔP is the pressure drop through the column, V_0 is the superficial linear flow-rate, L is the column length, μ is the viscosity of the fluid, ε is the external void fraction in the column, and D_p is the particle diameter.

With the use of Eq. (1), we can conclude that we will obtain a lower pressure drop at elevated temperature (reduced viscosity of the solvent), with a shorter column, with lower flow-rates, and a dramatically reduced pressure drop with the use of a larger particle size stationary phase. There are some drawbacks and limitations to each of these. At a higher temperature, we may lose selectivity or experience degradation of the target compounds. Using a short column is current normal practice. Low flow-rates imply low production rates. Larger particles are known to result in a larger height equivalent to a theoretical plate (HETP) and a lower resolution. For all of these statements, the implied premise is: ''all other things being equal''. When it comes to manufacturing cost, all other things are not equal and the optimum separation process design must include the

integrated costs of all the implications of a choice of a given process design. This has been noted by Bauer, who succinctly describes this concept as optimizing the ''fully absorbed cost of production'' [45]. This integration of cost is discussed later.

3.1.2. Equipment cost

Process equipment suitable for use at higher pressure is significantly higher in cost than equipment adequate for lower pressure operation [49,50,54]. This is especially true when going to larger equipment. The general relationship of equipment costs to operating pressure will be illustrated using only the cost for the pressure vessel which contains the chromatographic separation medium, the column. The major cost item in large pressure vessels can be attributed to the thickness of the vessel walls, and thus simply the mass of construction material used to make the vessel [54]. In addition, pumps, valves and instrumentation suitable for use at higher pressure are more expensive. Using an engineering correlation for equipment cost estimation, Fig. 3 shows the variation in cost of a column with a 1 m I.D. and length of 1 m as a function of the design pressure. The cost correlation has been updated to 1998 using Chemical Engineering's processing industry specific inflation index for the cost of installing process plants [55–58]. Fig. 4 shows the lower cost of a longer, narrower column made to contain the same volume. Fig. 5 incorporates the pressure effect calculated using Eq. (1) combined with the cost correlation to illustrate the effect on equipment cost of different particle sizes (for the case of the column with an L/D ratio of 0.5). As can be seen, inherently the choice of a small particle size results in a high equipment cost.

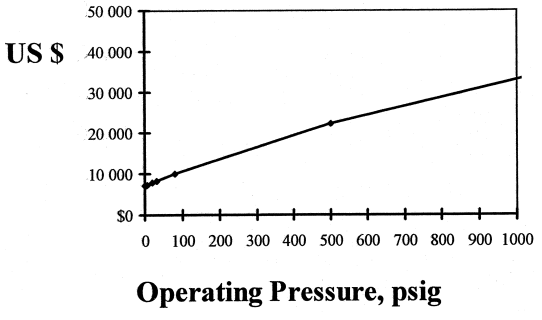

Fig. 3. Cost (1998) of a pressure vessel (a cylindrical column) of 1 m×1 m I.D. as a fraction of pressure (1 p.s.i.g=6894.76 Pa).

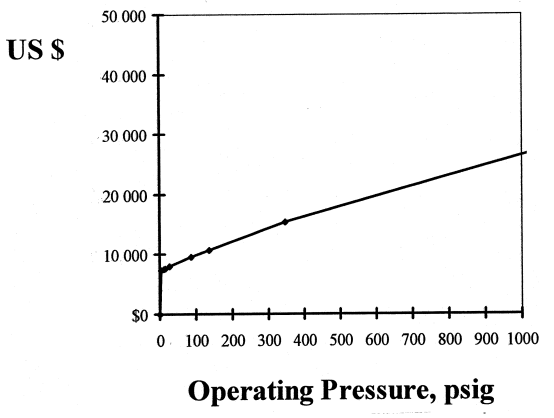

Fig. 4. Cost (1998) of a longer narrower pressure vessel (column) to contain the same volume as in Fig. 3, with ($L/D=3$).

Stationary phase costs vary widely. The cost of a stationary phase depends on many variables, including the volume in which it is produced, volume in which marketed, support type, and chemistry of the active surface or volume. Despite these other variables, a major impact on the cost of the stationary phase is the particle size of the packing (see Fig. 6). The data plotted here are actual prices of chromatographic separation stationary phases including prices from the early 1970s to 1998 and including ion-exchange, silica, carbon and alumina supports with chemistries ranging from bare support material to chiral stationary phases. As shown in the graph, there is a correlation between the average particle size and

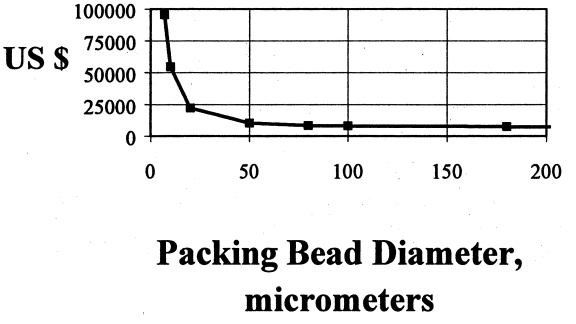

Fig. 5. Results from Fig. 3, replacing the column operating pressure with the particle size which produces that pressure on the x-axis of Fig. 3 at normal chromatographic flow rates and element viscosity.

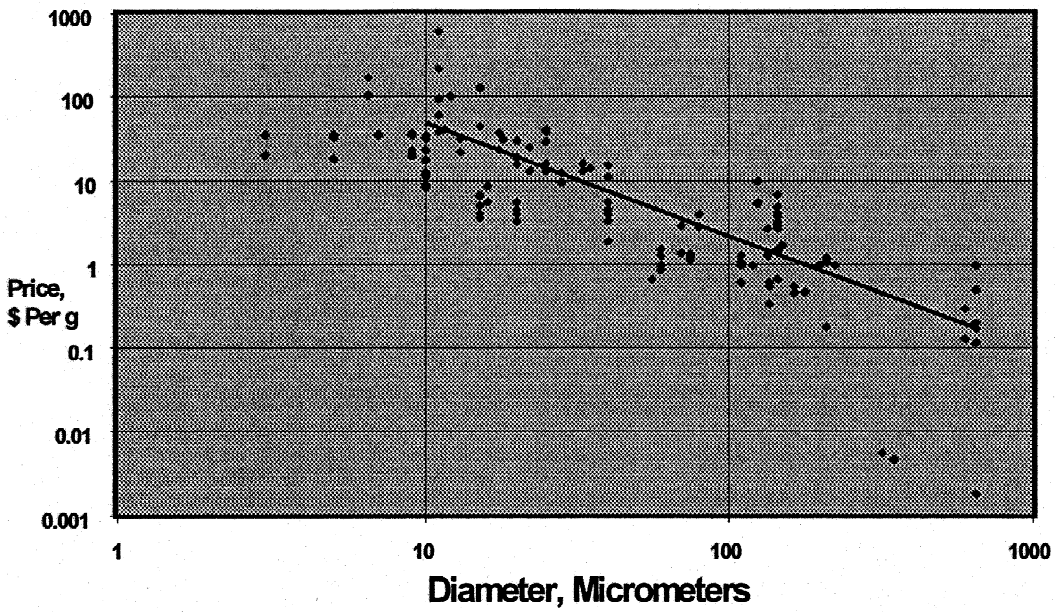

Fig. 6. Actual prices of chromatographic stationary phases (from 1972–1998) including base supports (alumina, silica, carbon), ion-exchange resins, reversed-phase bonded supports, various adsorbents and chiral stationary phases.

the cost of the separation medium, which can be represented within an order of magnitude by the following equation:

$$\text{Cost (US\$ per g)} = 3623(D_p)^{-1.675} \quad (2)$$

The exotic chemistries and low production volumes are found at the top of the envelope and the packings which have simple chemistry and which are produced in large volumes are found at the bottom of the envelope. Keeping the chemistry constant, doubling the particle size can be expected to reduce the cost for the packing by well over 50%.

3.1.3. Resolution

In light of the impact on cost of using a small particle size packing, it is desirable to examine the reasons for using a small particle size stationary phase. It is well-known that the resolution obtained in a chromatographic separation is improved by using a smaller particle size stationary phase [5,7,8,59]. The relationship between HETP and the particle size has been studied extensively. Fig. 7 is reproduced with permission from figure 7 in Ref. [59].

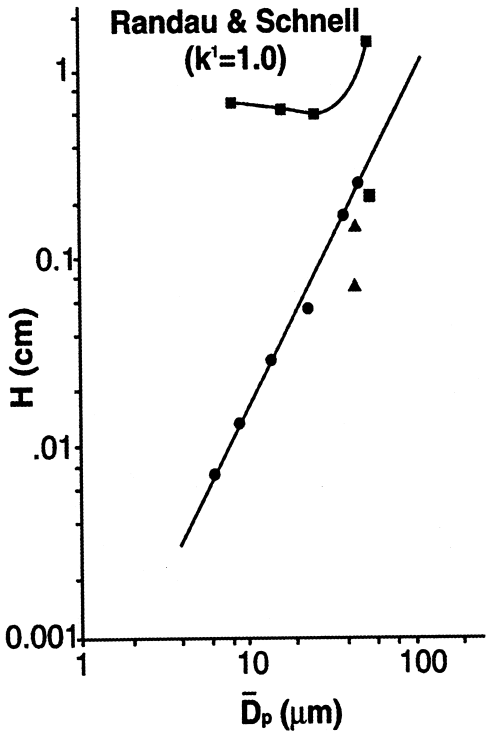

Fig. 7. Effect of particle size on the HETP obtained in a 25 cm column. From Ref. [59] with permission.

Therefore, all other things being equal, a small particle stationary phase will give a better separation. However, engineering economics dictates that all other things be allowed to vary in order to reduce costs; specifically, a longer column does not keep all other things equal (see below).

3.1.4. Column packing procedures

Uneven packing in a column can quickly waste the separation developed by chromatography. Extensive care is taken in using low dead volume connecting fittings. Small particles in particular are difficult to pack uniformly and special column packing procedures were developed to achieve in practice the high resolution which was theoretically predicted [59]. Companies which supply pre-packed analytical columns have a large part of their operating costs expended in the labor and equipment to pack columns and validate the effectiveness of the packing operation on each column. These costs also become a part of the picture for process chromatography as labor to pack production scale columns and as non-productive downtime of the stationary phase, the column, and other equipment while a column is being packed. Columns with larger particle size packings are much easier to pack and result in less expensive hardware and lower labor costs.

3.2. Column design and operating conditions

3.2.1. Column length

In elution or batch chromatography, a large number of plates is needed to obtain a good separation. *N*, the number of plates is related to HETP as follows:

$$N = L/\mathrm{HETP} \tag{3}$$

Better separation (more plates) is achieved by a longer column [7,8,59,60]. A good estimate of the length required to compensate for changes in particle size is [60]:

$$L_{\mathrm{new}} = L_{\mathrm{old}}(D_{\mathrm{p,new}}/D_{\mathrm{p,old}})^{1.5} \tag{4}$$

If one doubles the particle size of the packing, the resolution can be restored by using a column which is less than three-times as long. For analytical work in a lab setting, when improving resolution by increasing column length, column dimensions quickly get out of hand and the column will not fit in a normal column oven; this can be overcome by linking smaller columns together [59,60]. In a production mode, very long columns present no significant obstacles and long columns are common. In addition, splitting the total column length into smaller sections is still an attractive option. A long column of the same diameter can be used (using a larger volume of stationary phase) or the column diameter can be decreased (keeping the total column volume constant).

3.2.2. Column flow-rate

HETP is known to follow the van Deemter relationship, where under particle conditions, the HETP increases as the flow velocity increases. At flow-rates well above the van Deemter minimum, this effect has been represented by

$$\mathrm{HETP} = DV_0^n \tag{5}$$

where D and n are constants and V_0 is the superficial linear velocity. Since n is usually less than one, the effect of increased flow-rate is beneficial [44,59,60]. With an increase in flow-rate, the production rate increases faster than the peak broadening.

3.2.3. Feed volume and concentration

Production rates are dramatically influenced by the feed volume and feed concentration used. In a given time, if more mass of solute mixture can be loaded onto the column and still be separated, the production rate is higher. The penalty of loading larger quantities of feed material is broader profiles (lower resolution). The effect is more severe when the large quantity of solute is contained in a large volume of solvent. The mathematical derivation of the HETP, in fact, breaks down when the injection volume becomes non-negligible with respect to the outlet peak width. Not only will the peak be spread from ''overloading'' the packing, the peak starts broad as a result of the volume of feed added to the column. The total exit profile width is influenced by a number of factors, only one of which is attributable to the column packing itself. Total system spreading is a combination of the effects from the connections in the plumbing prior to the column, the distributor of the flow at the beginning of the column, the original

peak width of the injected feed, the collector at the end of the column, and the exit piping. The effects combine as a total variance which is the sum of the individual variances:

$$W_T^2 = W_i^2 + W_f^2 + W_e^2 + W_d^2 + W_c^2 + W_p^2 \quad (6)$$

where: W_T = width of the peak (total spreading), W_i^2 = variance of injection system, W_f^2 = variance of fittings located downstream of injector and upstream of detector, W_e^2 = variance of connecting lines, W_d^2 = variance due to detector and collector system, W_c^2 = variance due to column and W_p^2 = variance of the original injection pulse.

Therefore, for a fixed mass of solute to be fed in a given time period, a higher concentration of solute contained in a smaller volume will produce a better separation. If the solubility of the components in the feed is high, the feed can be pre-concentrated prior to injection onto the column. A SMB process can handle a higher feed concentration than a batch process. An important consideration, therefore, in choice of eluent is the solubility of the feed components. This effect may be profound on the net cost of chromatographic separation. A solvent which yields a low resolution but a high solubility of the compounds of interest may result in lower costs than a very selective solvent in which the solubility of the feed components is low.

3.2.4. Distributor design

The design of distributors and collectors is extremely important for process chromatography. A very large dispersion of the collected peaks can be produced by poor performance of a flow distributor or collector [43,61,62]. This problem is the source of many scale-up failures in process chromatography.

3.3. Economies of scale

3.3.1. Capital equipment

In engineering economics it is well-known that the capital and operating costs of a production process are not linear with the manufacturing capacity of a plant. Generally, for custom-designed operations, the costs follow an exponential rule [49,50], where

$$\text{Capital cost} = C_1 + C_2(\text{Capacity})^n \quad (7)$$

While the n varies for different types of processes, it is generally less than 1.0. For very rough estimation of the capital cost of a plant in the absence of more specific data for that type of process, engineers assume the ''six-tenths rule,'' and n is taken to have a value of 0.6. For large-scale plants, the constant C_1 becomes negligible.

3.3.2. Labor

For many processes, labor required is the same, whether the plant is large or small. In this instance, labor costs follow the ''zero-tenths rule''. Documentation and analytical costs respond similarly.

3.3.3. Dramatic range of cost variability with scale

Over large orders of magnitude, the price per unit mass of chromatographically purified products will change quite dramatically, independently of the difficulty of the separation. It would be an error to assume that high-volume, lower-cost therapeutic compounds cannot afford the costs of a chromatographic separation without evaluating the purification costs at large scale. Commodities which are purified in large scale by chromatography sell for pennies per kilogram. Surely their chromatographic purification costs are less than their sales prices. The effect of scale will be illustrated in the discussion of the example separation.

3.4. Economic optimization

3.4.1. Process integration

Engineering economics recognizes that unit operations in a manufacturing plant are not independent. One operation is fed by a previous step and in turn feeds another operation. If costs are minimized in one step, it may result in much higher costs for a preceding or following step [43–45,49,50]. Plant design and economics are so linked that textbooks in this branch of engineering discuss equipment design and equipment costs in parallel.

3.4.2. Solvent purchase versus solvent recycle

In chromatography, an example would be the costs of elution solvent. At a small scale, labor is a large component of purification cost. It is less expensive to buy fresh solvent than to pay labor costs to attempt

to purify and recycle the solvent. At a very large scale, it is much more cost-effective to put capital equipment in place to recover and recycle the solvent [10–12,45–47]. Even where the solvent used is water, one of the cheapest solvents available, a large fraction of the capital equipment and operating costs are represented by the product recovery section of the process, where the water is evaporated to recover the desired product and recycle the water [46–48].

3.4.3. Chromatographic enrichment combined with crystallization

Some mixtures of isomers crystallize very poorly when both isomers are major components. One isomer may crystallize readily to a high purity when the other isomer is present at a low concentration. In such a case, crystallization by itself will not work at all, much less work economically. Yet, achieving a very high purity by chromatography alone may be very expensive, since each additional point in purity is more and more expensive to obtain. In such a case, a combination of bulk refining by chromatography to achieve a moderately high purity followed by crystallization under those conditions which play to the strengths of crystallization can be far less expensive than chromatography alone.

3.4.4. Racemization with recycle

An additional case arises where conditions exist to be able to control a reversible racemization or isomerization. While chromatography can be used (if the individual isomers are stable) to purify the racemate into two very pure isomers at high recovery, it may be far more economical to operate under low-cost conditions which provide the desired enantiomer in high purity and moderate yield, but accept the undesired enantiomer in high recovery but moderate purity. This fraction can be re-isomerized to the equilibrium mixture and recycled. If this recycling cost is lower than the additional chromatographic costs of obtaining both isomers in high purity and high yield, then the net production costs are reduced. In addition, the process operation will often be more robust and forgiving.

3.4.5. High purity of only one product cut

If the feed material is not expensive or the chromatographic separation very expensive, the ''optimum'' described in the literature of pure extract and pure raffinate may not be the economic optimum. If the desired product is contained primarly in the raffinate stream, the economic optimum may involve separating in the pure raffinate only region of the m_2/m_3 plane.

3.4.6. Stationary phase volume zone allocation

Most analyses and simulations in the literature show the stationary phase equally distributed in the four zones of the SMB process. This equal distribution of volumes has no theoretical basis and is unlikely to be the economic optimum. The function of each zone is different and the difficulty of performing each separate function is different and may vary from application to application. Logically, an uneven distribution of a fixed volume of stationary phase should provide superior performance of an SMB separation process. The allocation of the discrete volumes of stationary phase is an important degree of freedom in the design economics of chromatographic separation.

3.4.7. Summary of process integration

Every separation problem is unique. Each process case must be considered for possible options and a total cost analysis made of all the related and necessary options.

4. The example separation and its projected costs

To illustrate these concepts, the separation shown in Fig. 8 will be used. This is the separation which is achieved on an analytical HPLC column. In addition to the two formulaic isomers, there are two additional undesired impurities. The desired isomer is more strongly retained on the stationary phase. For all cases the desired isomer is to be recovered at 97% purity and 98% recovery.

Various cost scenarios are presented in Tables 2–7 and in Fig. 9.

4.1. Analytical column used in a production mode

Table 2 contains the operating parameters for the case of producing very small quantities of the desired

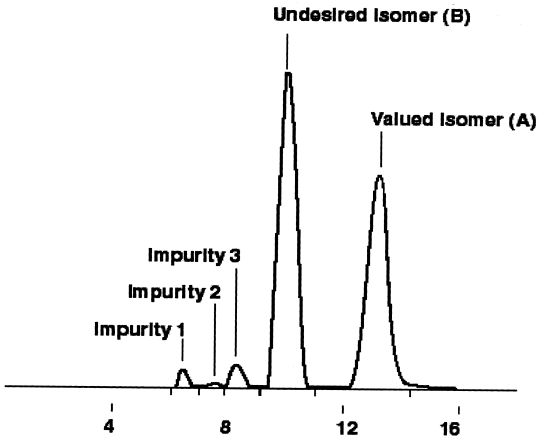

Fig. 8. Analytical chromatogram of the example separation. Injection: 20 μl of 5% (w/w) 42% purity commercial high fructose corn syrup. Eluent: degassed deionized water 0.6 ml/min. *T*: 85°C, column: Bio-Rad Aminex HPX87C (0.78 cm×30 cm), RI. Detection: Dynamax Model RI-1. *x*-Axis: time in min.

isomer by elution or pulse chromatography on the analytical column in an economically correctly loaded (''overloaded'' by analytical definitions) condition. The overwhelming cost item is the labor to operate the process. The costs for materials and even stationary phase are low because of the low volumes of material being processed, but the labor is fixed and is spread over a very, very small quantity. The net cost of chromatography is over US$ 15 000 per kilogram. Fig. 9a shows the distribution of costs. At this small scale, the overriding cost is the labor to perform the separation.

4.2. Batch mode, larger columns, small particle stationary phase

Tables 3 and 4 present the assumptions and allocated costs for scaling up the same separation to 100× and to 10 000× the scale of the laboratory preparation. The larger scale represents approximately 10 metric tons (MT) per year of the desired isomer. The chromatographic purification cost has decreased to US$ 789 and US$ 266 per kilogram of desired isomer, respectively. At the larger scale, the total labor has not increased significantly and is spread over a much larger amount of product produced. The majority of the cost comes from cost of the stationary phase (Fig. 9b Fig. 9c), despite the fact that a dramatic price reduction (from economy of scale of production of the stationary phase) has been assumed. At 100×, the stationary phase cost used is US$ 40/g and at 10 000× US$ 10/g. In this case, the solvent cost is low, because the solvent (demineralized water) is very inexpensive. The alloca-

Table 2
Conditions and economic bases of process separation on an analytical column

Process conditions		
Feed concentration	100 g/l	
Feed purity	45%	
Recovery	98%	Column volume: three columns of 14.3 ml
Injection volume	0.715 ml	
Injection period	15 min	
Flow-rate	1.0 ml/min	
Costs		Annualized allocated cost (US$)
Columns	Incorporated in stationary phase costs	–
Stationary phase	US$ 83/g, three columns, two changes/year each	4200
Labor	0.1 person/year at US$ 100 000/year	10 000
Energy	US$ 200/year	200
Solvents and chemicals	US$ 500/year	500
Other capital	19 000 10 year S.L.	1900
Annual production		
g/day	3.0	
kg/year	1.06	
Net chromatography cost, US$/kg		15 857

Table 3
Conditions and economic bases of process separation, 100× analytical scale

Process conditions		
Feed concentration	100 g/l	
Feed purity	45%	
Recovery	98%	Column volume: one column of 4300 ml
Injection volume	71.5 ml	
Injection period	15 min	
Flow-rate	100 ml/min	
Costs		Annualized allocated cost (US$)
Columns	US$ 100 000 three year S.L.	333
Stationary phase	US$ 40/g, 2.5 year life	41 310
Labor	0.1 person/year at US$ 100 000/year	10 000
Energy	US$ 20 000	20 000
Solvents and chemicals	US$ 5000	5000
Other capital	US$ 35 000 five year S.L.	7000
Annual production		
g/day	303	
kg/year	106	
Net chromatography cost, US$/kg		789

Table 4
Conditions and economic bases of process separation on a large column at 10 000× analytical scale (10 MT/year)

Process conditions		
Feed concentration	100 g/l	
Feed purity	45%	
Recovery	98%	Column volume: one column of 143 l
Injection volume	7150 ml	
Injection period	15 min	
Flow-rate	10 l/min	
Costs		Annualized allocated cost (US$)
Columns	US$ 25 000 three year S.L.	8333
Stationary phase	US$ 10/g, two year life	2 065 500
Labor	0.25 person/year at US$ 100 000/year	25 000
Energy	US$ 200 000	200 000
Solvents and chemicals	US$ 500 000	500 000
Other capital	US$ 85 000 five year S.L.	17 000
Annual production		
kg/day	30.3	
MT/year	10.6	
Net chromatography cost, US$/kg		266

Table 5
Conditions and economic bases of process separation for the limit of a very large scale where only the stationary phase cost is considered

Process conditions		
Feed concentration		
Feed purity		
Recovery		
Injection volume		
Injection period		
Flow-rate		
Costs		Annualized allocated cost (US$)
Columns		
Stationary phase	US$ 10/g, two year life	
Labor		
Energy		
Solvents and chemicals		
Other capital		
Annual production		
kg/day		
MT/year		
Net chromatography cost, US$/kg		201

Table 6
Conditions and economic bases of process separation on a 50 μm bead packing in a set of 11 longer, narrower columns

Process conditions		
Feed concentration	100 g/l	
Feed purity	45%	
Recovery	98%	Column volume: 143 l
Injection volume	21 450 ml	
Injection period	45 min	
Flow-rate	10 l/min	
Costs		Annualized allocated cost (US$)
Columns	US$ 42 900 three year S.L.	14 300
Stationary phase	US$ 1.44/g, two year life	74 400
Labor	0.1 person/year at US$ 100 000/year	10 000
Energy	US$ 200 000	200 000
Solvents and chemicals	US$ 25 000	25 000
Other capital	US$ 205 000 five year S.L.	41 000
Annual production		
kg/day	30.3	
MT/year	10.6	
Net chromatography cost, US$/kg		34

Table 7
Conditions and economic bases of process separation on a commodity scale SMB using a 320 μm bead packing and capital equipment to evaporate and recycle solvent

Process conditions		
Feed concentration	764 g/l	
Feed purity	45%	
Recovery	98%	Column volume: 114 000 l
Feed flow-rate	110 l/min	
Costs		Annualized allocated cost (US$)
SMB	US$ 1.4 million ten year S.L.	140 000
Stationary phase	US$ 610 000, US$ 5.5/kg, five year life	122 000
Labor	2 person/year at US$ 100 000/year	200 000
Energy	US$ 750 000	750 000
Solvents and chemicals	US$ 7000	7000
Other capital	US$ 1.0 million ten year S.L.	100 000
Annual production		
MT/day	53.4	
MT/year	18 700	
Net chromatography cost, US$/kg		0.0705

tion for stationary phase and solvent could be reversed if the relative pricing of solvent and stationary phase were exchanged.

4.3. The limit in cost as scale is increased

If one assumes a hypothetical case of an extremely large plant and very inexpensive solvent (or solvent recycling costs) one can calculate the lowest limit in cost which can be achieved. This is the stationary phase cost alone. If one assumes a cost for the packing of US$ 10 per gram, the cost of chromatography at ''infinite scale'' is US$ 201 per kilogram. See Table 5 and Fig. 9d.

5. Grassroots design to minimize costs

In order to reduce the chromatographic separation cost below this level, there is no option but to try a new paradigm. If one designs from the beginning with cost in mind, one concludes that the following are desirable:

1. Big beads to bring the stationary phase cost down
2. Big beads to reduce the pressure drop *and equipment costs*
3. Long columns to get reasonable numbers of plates
4. Recycling of solvent (even if it costs capital initially) at larger scale
5. Reasonable resolution (high resolution implies excess cost)
6. High solubility and high feed concentration
7. Low viscosity (choice of solvent and temperature)
8. Large scale (only one processing line operated by a minimum of labor)
9. Profile preservation (i.e., SMB operation)

On this basis, we design a plant to use a 50 μm diameter stationary phase. In the absence of further information the price of the stationary phase, calculated from Eq. (2) would be US$ 5 per gram. However, the chemistry of this particular stationary phase is on the simple end of the range shown in Fig. 6. At the analytical bead size (7 μm) the price per gram would be calculated to be US$ 139, when in fact, purchased in bulk it costs US$ 40 per gram. Using this information coupled with a size ratio correction based on Eq. (2), the calculated price is US$ 1.44 per gram, which is the price used for the economic projections. Using Eq. (4) we compensate for the increased HETP of a bigger bead size by making the column approximately 19-times as long. Therefore the column is 572 cm long. In order to keep column cost down by keeping the pressure rating of the column low, we split the total column

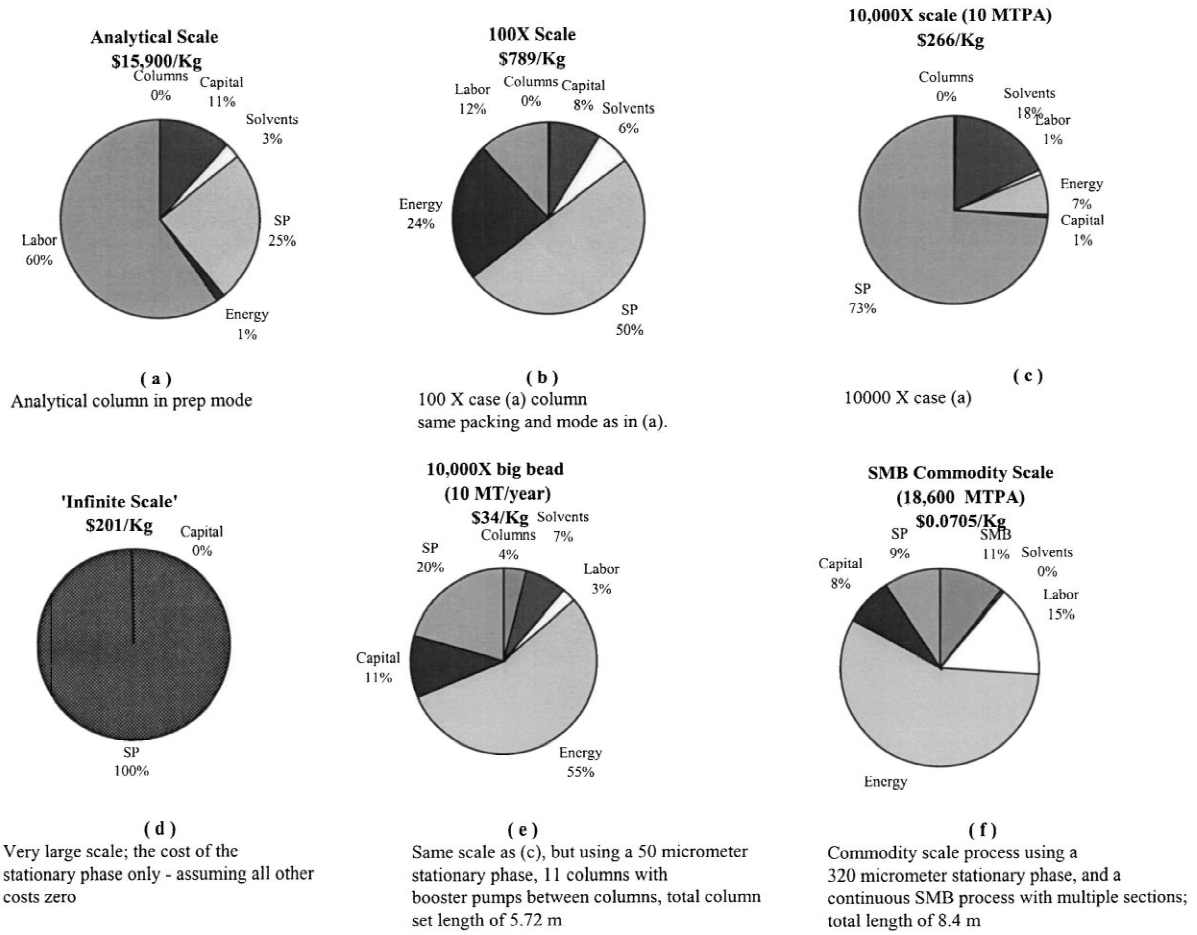

Fig. 9. Distribution of cost components for process separation at various scales and with the indicated process scenarios.

into 11 sections with inexpensive centrifugal pumps in the conduit piping between adjacent columns. Even after the increase in pressure drop from using a longer column, the total pressure drop with the bigger bead size is estimated to be 2600 kPa. By breaking the total column into 11 sections, the pressure drop per column is 236 kPa, which dramatically reduces the cost of the column sections and the cost of the pump or pumps required. In addition, it makes packing of the system with stationary phase much easier [59].

To improve the HETP by increasing diffusion kinetics and to keep the pressure drop low, we operate at elevated temperature. The column has a higher L/D ratio which makes the column less expensive and which makes the problem of flow distribution more tractable. The columns are US$ 1300 each. Including distribution and piping (ratio of installed cost to purchased cost of 3.0), the price for the entire set of columns is US$ 43 000.

We recycle the solvent, which increases the capital cost of the integrated plant. The reduction in cost of solvent purchased more than offsets the capital, energy and labor costs of the recycling operation. With this mode of operation, we calculate the fully absorbed cost of chromatographic purification to be US$ 34 per kilogram. The operating conditions and economic performance for the 50 μm bead in a set of long narrow columns are summarized in Table 6. Fig. 9e presents the distribution of costs for this case. Adding SMB operation to the design approach used above would decrease the total costs by a factor of

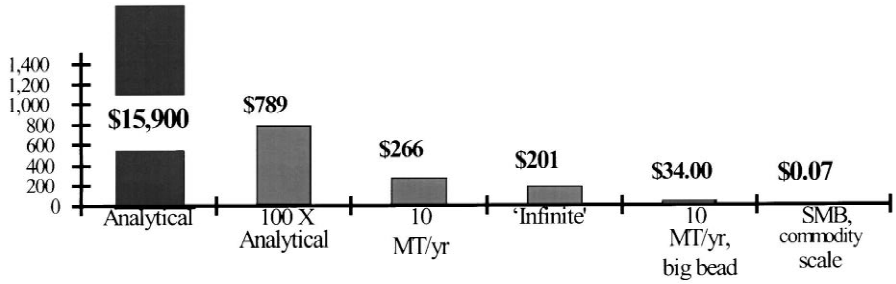

Fig. 10. Fully adsorbed costs of production in the various scales and modes examined.

two or three. The primary cost reductions would be in stationary phase and energy savings.

6. Economics at a commodity scale

Table 7 and Fig. 9f present the situation for a very large scale scenario, which is far beyond the scale of most fine chemicals or therapeutic compounds. The commodity scale scenario uses an SMB process, a stationary phase with a very large bead size (320 μm), a total column length of 8.4 m, solvent recycle, very high (60%, w/w) solute concentrations in the SMB feed, and is highly automated, requiring very little labor. The economic conditions are given in Table 7. The fully absorbed economic cost of chromatographic separation is US$ 0.07 per kilogram.

7. Summary of costs for various scenarios

Fig. 10 summarizes the total costs (excluding the cost of the feed) for performing this separation under the various scenarios considered.

8. Conclusions

Chromatographic separation on a process scale is different from analytical chromatography and has very different objectives. The process chromatographer has many degrees of freedom in choice of design of the separation process. Factors which are unimportant for analytical work but extremely important to the cost of process separation are high solute solubility in the eluent, length of the column, temperature of operation, labor to pack columns, particle size of the stationary phase, ease of solvent recycling, and, of course, scale of the equipment. The use of large particle size packings in long columns with continuous operation of an SMB process can reduce chromatographic separation costs by orders of magnitude. A one- dimensional view of what constitutes good chromatographic separation locks the chromatographic separation process designer into a high cost mode. The key to unlocking low cost operation requires a simple, but dramatically difficult paradigm shift in the mind, primarily involving the use of large particle size packings, ''overloaded'' conditions, and low resolution. In elution chromatography, high purity and high recovery cannot be achieved with low resolution. In SMB chromatography, it can be done, is a reality, and has been practiced for over three decades.

Acknowledgements

The author wishes to thank The Dow Chemical Company for its support and permission to publish this work, colleagues Alan Greenberg, Daryl Gisch and Larry Nicholson for their helpful suggestions, and Ronald Majors, the Journal of Chromatographic

Science, and Preston Publications for permission to use Fig. 7.

References

[1] D. Simpson, W. Bauman, Ind. Eng. Chem. 46 (1954) 1958.
[2] D. Asher, D. Simpson, J. Phys. Chem. 60 (1956) 518.
[3] R.M. Wheaton, W.C. Bauman, Ind. Eng. Chem. 45 (1953) 228.
[4] G.E. Prielipp, H.W. Keller, J. Am. Oil Chem. Soc. 33 (1956) 103.
[5] A Users Guide to Chromatography – Gas, Liquid, TLC, Regis Chemical Company, Morton Grove, IL, 1976.
[6] J.H. Knox, J. Chromatogr. Sci. 15 (1977) 352.
[7] H. Engelhardt, High-Performance Liquid Chromatography, Springer-Verlag, New York, 1979, Ch. 2.
[8] L.R. Snyder, J.J. Kirkland, Introduction to Modern Liquid Chromatography, Wiley, New York, 2nd ed., 1979.
[9] D.B. Broughton, C.G. Gerhold, US Pat., 2 985 589 (1961).
[10] D.B. Broughton, Chem. Eng. Prog. 64 (1968) 60–65.
[11] D.B. Broughton, R.W. Neuzil, J.M. Pharis, C.S. Breasley, Chem. Eng. Prog. 66 (1970) 70.
[12] A.J. de Rosset, R.W. Neuzil, D.J. Korous, Ind. Eng. Chem. Proc. Des. Dev. 15 (1976) 261.
[13] D. Broughton, Chem. Eng. October (1977) 49.
[14] M. Seko, H. Takeachi, T. Inada, Ind. Eng. Chem. Prod. Res. Dev. 21 (1982) 656.
[15] D.B. Broughton, Sep. Sci. Tech. 19 (1984) 723.
[16] L. Lefevre, US Pat, 3 044 905, 17 July (1962).
[17] H. Hongisto, Int. Sugar J. 79 (1977) 100–104.
[18] H. Hongisto, Int. Sugar J. 79 (1977) 131–134.
[19] Illinois Water Treatment Company, IWT ADSEP System, Advanced Technology in Liquid Processing, Making Waves in Liquid Processing, Public Brochure, Vol., 1, No. 1, 1982.
[20] B. Burris, R. Szilagyi, T. Swanson, 211th American Chemical Society National Meeting, Symposium on Industrial Scale Process Chromatographic Separations, New Orleans, 27–28 March, 1996.
[21] J. Corbett, D. Burke, The 211th American Chemical Society National Meeting, Symposium on Industrial Scale Process Chromatographic Separations, New Orleans, 27–28 March, 1996.
[22] L. Norman, G. Rorabaugh, H. Keller, J. Am. Soc. Sugar Beet Technol. 12 (1963) 363.
[23] R. Gadomski, Sugar Azucar October (1990) 17.
[24] H.J. Hongisto, P. Laakso, 20th General Meeting, American Society of Sugar Beet Technologists, San Diego, 26 February–2 March, 1978.
[25] X. Lancrenon, D. Herve, Sugar Technol. Rev. 14 (1988) 207.
[26] M. Kearney, Oral presentation, 50th Anniversary Conference, Sugar Processing Research Institute, San Francisco, 29 May–1 June, 1990.
[27] M. Buckley, G. Norton, Int. Sugar J. 93 (1991) 226–228.
[28] V. Kochergin, M. Kearney, 28th General Meeting of the American Society of Sugar Beet Technologists, New Orleans, 8–11 March, 1995.
[29] J. Pope, 211th American Chemical Society National Meeting, Symposium on Industrial Scale Process Chromatographic Separations, New Orleans, 27–28 March, 1996.
[30] F. Matsuda, Symposium on Industrial Scale Process Chromatographic Separations, 211th National ACS Meeting, New Orleans, 27–28 March, 1996.
[31] Paananen, Hannu, Workshop on Separation Processes in the Sugar Industry, Sugar Processing Research Institute, New Orleans, 18 April, 1996.
[32] M. Gattuso, B. McCulloch, J. Priegnitz, presented at the symposium Chiral Europe 1994.
[33] M. Gattuso, B. McCulloch, D. House, W. Baumann, presented at the symposium Chiral USA 1995.
[34] S.C. Stinson, Chem. Eng., News 9 (1995) 44.
[35] E. Kusters, G. Gerber, F.D. Antia, Chromatographia 40 (1995) 387.
[36] A.E. Rodrigues, Z.P. Lu, J.M. Loureiro, L.S. Pais, J. Chromatogr. A 702 (1995) 223.
[37] E. Francotte, P. Richert, M. Mazzotti, M. Morbidelli, J. Chromatogr. A 796 (1998) 239.
[38] D.W. Guest, J. Chromatogr. A 760 (1997) 159–162.
[39] C.B. Ching, D.M. Ruthven, K. Hidajat, Chem. Eng. Sci. 40 (1985) 1411.
[40] G. Cox, Symposium on Industrial Scale Process Chromatographic Separations, 211th National ACS Meeting, New Orleans, 27–28 March, 1996.
[41] F. Charton, R. Nicoud, J. Chromatogr. A 702 (1995) 97.
[42] B. Pynnonen, Symposium on Industrial Scale Process Chromatographic Separations, 211th National ACS Meeting, New Orleans, 27–28 March, 1996.
[43] B. Pynnonen, Symposium on Industrial Scale Process Chromatographic Separations 211th National ACS Meeting, New Orleans, 27–28 March, 1996.
[44] R.M. Nicoud. H. Colin, LC·GC 8 (1990) 24.
[45] J.E. Bauer, A.K. Chandhok, B.W. Scanlan, S.A. Wilcher, Proceedings PrepTech 97, Orlando, FL, September, 1997.
[46] I. Jaferey, 211th American Chemical Society National Meeting, Symposium on Industrial Scale Process Chromatographic Separations, New Orleans, 27–28 March, 1996.
[47] J. Pope, 211th American Chemical Society National Meeting, Symposium on Industrial Scale Process Chromatographic Separations, New Orleans, 27–28 March, 1996.
[48] B. Pynnonen, Workshop on Separation Processes in the Sugar Industry, Sugar Processing Research Institute, New Orleans, 18 April, 1996.
[49] M.S. Peters, K.D. Timmerhaus, Plant Design and Economics for Chemical Engineers, Chemical Engineering Series, McGraw-Hill, New York, 4th ed., 1991.
[50] R.H. Perry, C.H. Chilton (Eds.), Chemical Engineers' Handbook, McGraw-Hill, New York, 5th ed., 1973.
[51] H. Bieser, A. deRosset, Starke 29 (1977) 392.
[52] B. Burris, R. Szilagyi, T. Swanson, 211th American Chemical Society National Meeting, Symposium on Industrial Scale Process Chromatographic Separations, New Orleans, 27–28 March, 1996.
[53] R.B. Bird, W.E. Stewart, E.N. Lightfoot, Transport Phenomenon, Wiley, New York, 1960, p. 199.

[54] A. Mulet, A.B. Corripio, L.B. Evan, Chem. Eng. 5 (1981) 145.
[55] P.M. Kohn, Chem. Eng. 8 (1978) 189.
[56] T.H. Arnold, C.H. Chilton, Chem. Eng. 18 (1963) 143.
[57] Chem. Eng., March (1980).
[58] Chem. Eng., April (1998) 180.
[59] R.E. Majors, J. Chromatogr. 11 (1973) 88.
[60] S.R. Rudge, M.R. Ladisch, Biotechnol. Prog. 4 (1988) 123.
[61] A. Alaska, PrepTech '97, Orlando, FL, September, 1997.
[62] M. Kearney, Symposium on Industrial Scale Process Chromatographic Separations, 211th National ACS Meeting, New Orleans, 27–28 March, 1996.