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HIGH-EFFICIENCY LIQUID EXTRACTOR FOR ISOLATION OF A DESIRED MATERIAL FROM COMPLEX ORGANIC MIXTURES[a]

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SUMMARY

A novel counter flow liquid extraction system is described that offers major potential advantages for the purification of fine chemicals and biochemicals. This system utilizes the flexibility of liquid extraction to provide a much more effective operating mode than is possible in elution chromatography. It is based on a novel contactor design which provides highly effective mass transfer, and is operated via a control system which facilitates process optimization.

The apparatus is a multi-stage liquid extractor with provision for independent control of each stream rate and also the feed schedule. It can therefore be operated in a wide variety of processing modes, including both transient and steady-state operation. One particularly useful mode for the batch purification of complex mixtures is described in detail. A transient feed to the centre of the column is combined with a stream rate ratio which reduces the migration velocity of the desired product to zero. All other species then pass out at one or other end of the column and operation is continued until dispersion begins to result in leakage of the desired material. It is shown by an extension of the plate theory of Martin and Synge that such an operation is much more efficient than that used in elution chromatography, and that its advantage increases with increasing difficulty of the separation. The column design is also an important feature in providing much higher resolution than conventional liquid extractors. Another important feature is a computer-controlled valving system which simplifies optimization and control of stream flows. The accessibility of sampling ports over the entire length of the extractor greatly facilitates control of the separation process.

INTRODUCTION

The increasing need for the purification of complex chemical species not amenable to crystallization has led to increasing interest in chromatographic

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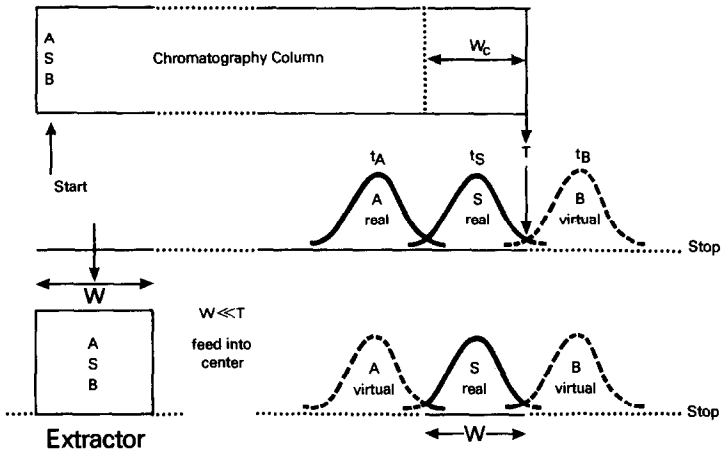

Fig. 1. Qualitative comparison of conventional elution chromatography with the proposed counterflow extraction system. Shown is the end of separation of a 1:1:1 mixture of closely related species A, S and B: Typically, the chromatographic peak width W_c, *i.e.*, the column length occupied by the wanted species S, is much smaller than the total column length T but similar to the total length of the extractor. Ideally, the extractor length and extractive peak width W are identical. The evident saving of equilibrium stages, expressed by $W << T$, reflects the superiority of dual- over single-flow operation.

techniques. These can achieve a very high resolution, but column packings are expensive, and the chromatographic mode does not use these packings efficiently. Column inefficiency arises in large part from the need to keep the solid phase stationary. In liquid extraction, this restriction can be relaxed in such a way as to reduce the required number of stages substantially. This point is illustrated in Fig. 1, where the separation of a 1:1:1 mixture A–S–B by conventional elution chromatography up to the beginning of elution of S is compared with the same separation by a transient counter-flow liquid extraction process.

We begin by contrasting these two processes qualitatively. To do this, we consider a chromatographic column and an extractor in which "plates" and "stages" are drawn to the same scale (*cf.*, Fig. 1). In normal elution chromatography, a narrow band of mixed solutes migrates from the feed end of the column and gradually separates into the partially overlapping bands at peak positions t_A, t_S and t_B (imaginary), shown at the upper right section. In the process, the entire column volume is used at one time or another, but at all times most of it is essentially solute free and contributes nothing to the separation. The total number of plates required for this separation is T, but the maximum portion of the column occupied at any instant by S is the much smaller number of plates W_c.

In the extraction process, performed with W stages, the feed mixture is introduced to the central region of the separator, and the centre of mass of the desired solute, S, is stationary. Unwanted solutes, A and B, are discharged from the two ends of the column as indicated in the lower right section, and all stages of the extractor are helping to effect the separation, except at the very early stages. Operation is now continued until product leakage begins. To a first approximation, valid under the usual conditions of chromatographic separation, the total number of stages W required is now approximately W_c, the same number as those occupied in the chromatograph at

the end of the separation. The difference $N = T - W_c$ may be considered the number of non-working plates in the chromatographic column.

Later we provide mathematical descriptions for these two processes, which provide the basis for quantitative comparison, and we show that the advantage of the proposed extraction mode increases with increasing difficulty of the separation. This is basically because the number of non-working plates N increases in proportion to the time required for separation while the number of working plates W increases only with the square root of time. First, however, we point out that a large number of stages, W, is required even for the extractor and therefore that there is a need to provide multi-stage operation at low capital cost. The solution we recommend for this purpose is the apparatus described in Figs. 2 and 3. We also note in this introductory section that an effective control system is needed for transient operations of this type. The approach that we use for this purpose is described under Apparatus.

ANALYSIS

We need a means of describing the migration of the centre of mass of each species and its spatial distribution about this centre. Here we provide such a description in the context of the apparatus shown in Figs. 2 and 3, and we introduce approximations to simplify the description and emphasize the key features of the system behaviour.

The column consists of two or more rotating cylinders (Fig. 3), each divided into a number of discrete stages by partitions perpendicular to the column axis (Fig. 2). Each stage has a total volume, v, of which a portion v_L is occupied by the lower phase L, and a portion v_U by the upper phase U. Each stage is totally liquid filled so that

$$v = v_L + v_U \tag{1}$$

and we define the hold-up ratio by

$$r = v_U/v_L \tag{2}$$

The upper phase is taken as moving to the right and the lower phase to the left. Rates of flow are defined by ${}^0V_U$, ${}^0V_L$ = volume of upper and lower phase, respectively, fed to the column per unit time. These volumetric flow-rates will be assumed to be constant over position and time during the analysis, neglecting volume changes accompanying the redistribution of solutes. In practice, however, the flow-rates will be manipulated during operation to establish the stationarity of the desired peak.

Analysis will be made in terms of *ideal* stages, defined as producing thermodynamic equilibrium between the two streams leaving each stage, but it is recognized that the physical stages in Figs. 2 and 3 may not be as effective as ideal stages. Therefore, we define a stage efficiency factor f by the relation

$$W_{real} = W_{ideal}/f \tag{3}^a$$

[a] The same ratio f exists between the final volumes of the respective product solutions, and between the amounts of solvents required in the ideal and the real processes that effect the same resolution; *cf.*, footnote to eqn. 11. Depending on the operating conditions, the observed values of f range from 0.3 to 0.8.

where W_{real} = the number of real extractor segments needed to perform the same resolution as W_{ideal} ideal stages (*cf.*, *Extractor and column lengths*).

It will be assumed that f is a constant, but in reality it is expected to depend on the flow-rates of the streams and other operating conditions. In general, f may be significantly different for each species, but we will not consider such a refinement here. Ideal operation corresponds to assuming complete mixing and equilibrium within each stage but no mixing between stages.

Solutes injected into the centre of the column are subject to transport by the flowing phases. Their migration rates depend only on the volumetric stream rates and their ratio,

$$R = {}^0V_U/{}^0V_L \tag{4}$$

the hold up ratio, r (eqn. 2), and the respective partition coefficients, K. K_X of solute X is defined by

$$K_X = [X]_U/[X]_L \tag{5}$$

the brackets and subscripts denoting equilibrium concentrations of X in the upper and the lower phase, respectively[a].

We describe the migration rates as displacements Δ (in terms of stage numbers) of the centre of mass produced on feeding volumes V_U and V_L of the upper and lower phases, respectively:

$$\Delta_X = \Delta_{U,X} - \Delta_{L,X} \tag{6}$$

where

$$\Delta_{U,X} = (V_U/v_U)(1 - Q_X); \qquad \Delta_{L,X} = (V_L/v_L)Q_X \tag{7}$$

and the probability of residence of X in the lower phase is

$$Q_X = 1/(1 + K_X r) \tag{8}$$

The concentration ratio K_X, which depends on the physical properties of solute X and the phases involved in the distribution of X, shares its impact on that distribution with the volume ratio r of the said phases within the system (hold-up ratio) (*cf.*, eqns. 2 and 8). The mass distribution of X between the phases is thus a function of the product $K_X r$, the reciprocal of which in partition chromatography is termed "capacity factor", and denoted by k'_X.

Considering the equal weights of K and r in eqn. 8, and the increase in descriptive

[a] In partition chromatography, K_X is defined by the ratio of concentrations of X in the moving (numerator) and in the stationary (denominator) phase, whereas in adsorption chromatography K_X would be related to the reciprocal of the adsorption coefficient. For convenience it is assumed that K_X is independent of the overall concentration. Clearly, partition coefficients in liquid–liquid and in liquid–solid systems depend on different mechanisms and generally cannot be expected to be of the same order.

and experimental range covered by their product, we adopt

$$K_X r = 1/k'_X \tag{9}$$

as the operating variable actually governing the overall behaviour of X in the distribution process. Treating K_X as the variable would unduly reduce the role of r to that of a parameter and unnecessarily complicate the following discussion.

It must be emphasized in this context that the hold-up ratio r is to some extent, depending on the type of apparatus, amenable to choice by the operator. Thus, within the constraints defined by physical realities (stage geometry, flow mechanics, bulk phase mixing), there exists an important degree of freedom with respect to optimization of the numerical value of k'_X.

Dispersion of solutes about the centre of mass for an idealized system can be obtained very simply by extending the concept of equilibrium stages introduced by Martin and Synge[1] to motion of both phases. This is because the Poisson distribution of a solute X derived for the motion of a single phase is determined completely by the variance σ_X^2, which in turn is just equal to the net displacement of X. Since variances due to individual disturbances in a linear system are additive, one may then write for any solute X that the variance for motion of both phases is just the sum of those for the individual motions:

$$\sigma^2_{X,\text{ideal}} = \Delta_{U,X} + \Delta_{L,X} \tag{10}$$

with

$$\sigma^2_{X,\text{real}} = \sigma^2_{X,\text{ideal}}/f \tag{11}^a$$

where it should be noted that both contributions Δ are now positive. Note that both $\Delta_{U,X}$ and $\Delta_{L,X}$, the magnitudes of migrations resulting from the motions of X by the individual phases in terms of numbers of ideal stages, are dimensionless, as is σ_X^2.

The description of the solute distributions may be simplified by noting that Poisson distributions can be adequately approximated by the normalized Gaussian probability distribution function

$$\varphi(u)\Delta u = (2\pi)^{-1/2} \exp[-u^2/2]\Delta u \tag{12}$$

with

$$u = w_X/\sigma_X \tag{12a}$$

$$\Delta u = (1/\sigma_X)\Delta w_X \tag{12b}$$

where w_X = distance, on either side, from the maximum of peak X, in terms of the respective number of plates, where $\varphi(u)$, the probability density for a deviation between u and $u+\Delta u$ from the maximum, is to be determined; σ_X = standard deviation of the Poisson distribution; *cf.*, eqn. 10; $\Delta w_X = 1$ (width of one plate).

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[a] Eqn. 11 reflects the ratio $\sqrt{f}$ of the widths of calculated and observed mass distributions in ideal and real systems that are effected by throughput of the same amounts of solvents; *cf.*, footnote to eqn. 3.

Eqn. 12a provides a convenient means of defining the width of a solute band in a chromatographic column or an extractor. Thus, the width of the S peak in Fig. 7 may denoted by

$$W = 2u\sigma_S \tag{13}$$

where u is the number of standard deviations on either side of the peak considered to comprise a major fraction of the solute band. Numerically, the respective fraction corresponds to the area A enclosed by the curve $\varphi(u)$ and the abscissa within $u = \pm u$, and is given by

$$A = 2\int_0^u \varphi(u)\mathrm{d}u \tag{14}$$

Values of A are tabulated in any treatise on statistics: limits $u = 2$ or 2.33 define areas representing 95.45 or 99% of the total peak area, which is defined by the limit $u = \infty$.

We shall show (*cf.*, eqn. 20a), for a desired solute S, that the displacement Δ_S becomes zero when the flow ratio R (*cf.*, eqn. 4), is set to

$$R = 1/K_S \tag{15}^a$$

Assume that we have a stationary peak, formed under this condition, finally extending over the whole length of the extractor. Assume that length corresponds to $u = 2$ or 2.33 standard deviations on each side of the peak centre. On the basis of the notions above, we conclude that the mass of S represented by this peak corresponds to 95 or 99% of the total S distributed in the operation. We can therefore quantitatively express S recoveries from distributions, observing that missing material is not lost, but recoverable from the eluates collected during the operation.

Assume we have (Fig. 7) an extractor containing sufficient plates to accommodate the stationary S peak assumed above and, in addition, the migrating peaks A and B, emerging from peak S, on the grounds of the presence of contaminants A and B, where $K_B > K_S > K_A$, and the respective weights are $m_A = m_S = m_B$. The separation of species S from contaminant B is readily observed as a distance between peak centres S and B, $\Delta_B - \Delta_S$, which can be expressed as a multiple u of the sum $\sigma_B + \sigma_S$. Thus,

$$\Delta_B - \Delta_S = u(\sigma_B + \sigma_S) \tag{16}$$

When $u = 2$ or 3, we speak of 4- or 6-σ separations between S and B. On the basis of the notions above, the 4-σ separation, followed for example by stagewise withdrawal and pooling of the extractor contents from extractor stage 0 (centre of S peak) up to stage $+2\sigma_S$ (approximate site of the S peak front), corresponding to that half of the S peak facing the B peak, would provide a recovery of an S fraction representing 47.5% of all

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[a] The formalism of diffusion leads to the same general conclusion, verified by experiment[2].

S originally present, with an S content of 95% and a B content of 5%. The opposite half of the peak would obviously provide an S fraction with an S content of 100%.

The number u, characteristic of the degree of a given separation (recovery, purity), will be denoted as the "separation parameter".

An approximate estimation of peak widths in terms of standard deviations is possible in practice by concentration measurements at various distances from the peak centre, considering that the concentration in the extractor of solute X at $u = 2$ or 3 is about 10 or 100 times smaller than at $u = 0$ [*cf.*, the respective ordinates $\varphi(u)$ of the Gaussian probability distribution function].

APPARATUS

Separation unit

The extractor consists essentially of two or more serially connected horizontal cylinders of the kind shown schematically in Figs. 2 and 3. They rotate about their axes, and each is divided into a large number of narrow segments, which act as the separation stages. To provide these segments the cylinder is coaxially partitioned by tightly fitting circular discs, held in place by PTFE gaskets. A small opening at the periphery of each disc provides for inter-segment communication. Aligning these openings yields a channel for flow of liquid throughout the entire cylinder. Each cylinder end bears a cover perforated at its centre to accommodate a non-rotating piping system. It provides separate access to the lower and upper section of the adjacent segment (Fig. 2).

Neighbouring cylinder ends are connected by means of their respective piping. The piping at the outer cylinder ends serve for throughput of U, *e.g.*, from left to right, and for throughput of L in the opposite direction, assuming the separation unit is completely filled with a partially miscible solvent pair. Clearly, such throughput requires the channels of serial cylinders to be aligned and to be immersed in the same particular phase which is going to be transferred. Phase throughput is timed by the cylinders' rotation and, consequently, pulsed.

The upper section of Fig. 3 shows a transient position of the communicating holes above the phase boundary, allowing for throughput of a pulse of upper phase U. The opposite situation, allowing for throughput of a pulse of lower phase L, is pictured in the lower section. Onset and shutdown of the pulses are programmable as a function of periodically attained angular positions of the communicating holes[3]. Fig. 3 shows

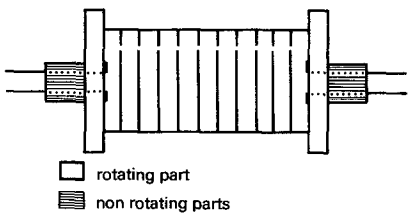

Fig. 2. Separation cylinder (schematic) with inlets and outlets for the flowing phases, and holes in the partitioning walls which provide for interchamber communication. Not shown are additional holes in the cylinder wall which allow samples to be drawn. At least two such cylinders are aligned to form the basic element of the extractor (*cf.*, Fig. 3).

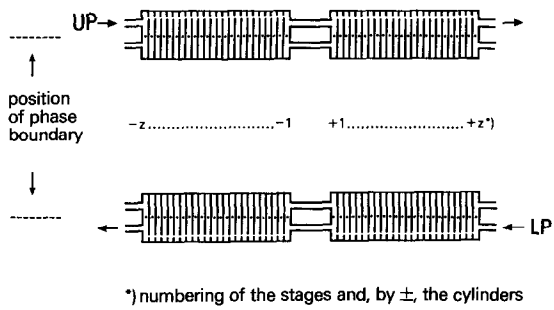

Fig. 3. Phase transfer coupled to cylinder rotation: periodic passage of the communicating holes through space occupied by UP and LP, respectively, allows for alternate pulsed throughput of solvent streams coming from opposite ends of the system, and thus effects a quasi-continuous counterflow.

also the serial numbering of the elements ± 1, ± 2, ..., $\pm z$, the numbers and the cylinders left or right from the centre bearing a negative or positive sign, respectively. The centre of the system coincides with the location of the feed (*cf.*, Fig. 4).

Owing to differing surface tensions, the walls of the segments (glass, PTFE or stainless steel) become unequally wetted by U and L. The better wetting phase tends to form a film which, on rotation, is drawn through the lesser wetting phase. Back in its mother phase this film is replenished. This concept was introduced by Signer[4].

The film and its immediate surroundings represent a mixing zone, and the bulk phases constitute the conjugate settling zone. No additional stirring is required to promote solute transport between the phases. Such transport is admittedly slower than in a dispersion of droplets, but this is partly compensated for by the system's insensitivity to the presence of emulsifiers.

Permissible rates of rotation must still be determined by practical experience, but satisfactory operation has generally been obtained over a range of 0.3–2 rad/s ($\approx$3–20 rpm). Mixing between phases becomes a problem at too low a speed, and film detachment (with excessive formation of droplets) when the system is rotating too fast. Some of the segments, equidistant from each other, are equipped with sampling holes (ports) drilled into the cylinder wall.

This design offers important advantages. The horizontal orientation of the column makes it possible to stop the operation for sampling purposes and solves many of the problems associated with flooding. Together with the valve controls discussed below, it makes possible the accurate control of phase ratios. The gentle motion of the rotating disk surface minimizes emulsification and at the same time provides good bulk mixing within each compartment.

Valve and piping systems

Computer-controlled on–off valves are provided for each inlet and outlet stream, as indicated in Fig. 4. These valves permit the input and output flows of both solvents and feed streams to be controlled. They can be used for withdrawal of product from the central region of the extractor after a transient separation process, and to compensate for flow ratio changes between the right and left extractor sections, relative to the feed point, in the case of repeated feeds.

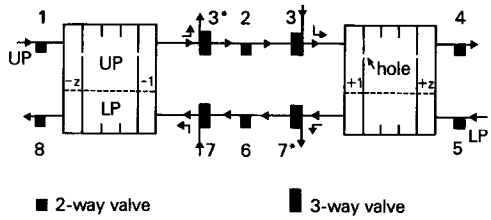

Fig. 4. The inner valving system. Valve functions and respective valve conditions are summarized in Table I.

Pumps P1 and P5 in Fig. 5 operate continuously on the U and L reservoirs shown, to pump liquid from the reservoirs to valves 1A and 5A. These valves then provide either input or circulation of the phases (valve 1A, upper phase; valve 5A, lower phase). Valves 1L and 5L are used to readjust the phase boundary levels as needed. Thus, if the boundary in stage $-z$ (Fig. 5) is too low it can be raised by energizing valves 5A, 5, 6, 1 and 1L, which is a single programmable operation (*cf.*, Table I).

Figs. 4 and 5 show the valve positions and functions needed for column operation. It must be recognized that there are two types of valves used: (1) two-way valves, indicated by a single black square can only provide straight-through flow and are either open (energized, +) or closed (de-energized, −); (2) three-way valves, shown as black oblongs, can provide flow in either of two directions, as indicated by arrows. When not energized (−) they provide what shows as straight-through flow in the figure. When energized (+) they provide the branched flow indicated.

The various valve positions needed for extractor operation are summarized in Table I.

Control unit

The complex sequence of valve sequences needed for operation of this apparatus is automated by an electronic control unit which performs the following functions:

(1) All of the valve positions listed in Table I are automatically synchronized.

(2) Operation is based on a master cycle which corresponds to one rotation of the cylinders, and the time periods for each set of valve positions are determined by the

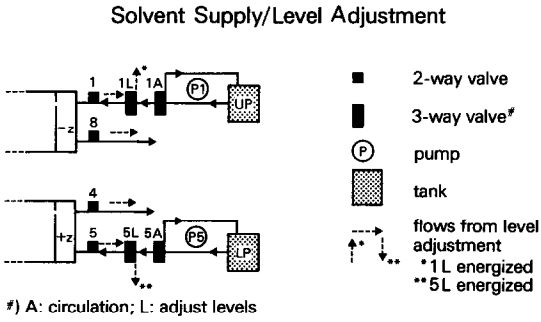

Fig. 5. The outer valving system: see caption to Fig. 4.

TABLE I

VALVE CONDITIONS FOR EXTRACTOR OPERATION

Function	*Valve conditions (+ or −)*													
	1	*2*	*3*	*3**	*4*	*5*	*6*	*7*	*7**	*8*	*1A*	*1L*	*5A*	*5L*
Throughput of U	+	+	−	−	+	−	−	−	−	−	+	−	−	−
Throughput of L	−	−	−	−	−	+	+	−	−	+	−	−	+	−
Input of feed in U[a]	−	−	+	−	+	−	−	−	−	−	−	−	−	−
Input of feed in L[a]	−	−	−	−	−	−	−	+	−	+	−	−	−	−
Output of product in U[b]	+	−	−	+	−	−	−	−	−	−	+	−	−	−
Output of product in L[b]	−	−	−	−	−	+	−	−	+	−	−	−	+	−
Pressure build up (U input)	+	+	−	−	−	−	−	−	−	−	+	−	−	−
Pressure release (U output)	−	+	−	−	+	−	−	−	−	−	−	−	−	−
Pressure build up (L input)	−	−	−	−	−	+	+	−	−	−	−	−	+	−
Pressure release (L output)	−	−	−	−	−	−	+	−	−	+	−	−	−	−
Increase of r in stage $-z^c$	+	−	−	−	−	−	−	−	−	+	+	−	−	−
Decrease of r in stage -1, $-z^c$	+	−	−	−	−	+	+	−	−	−	−	+	+	−
Increase of r in stage -1, $-z^c$	+	−	−	−	−	+	+	−	−	−	+	−	−	+
Decrease of r in stage $+1$, $+z^c$	+	+	−	−	−	+	−	−	−	−	−	+	+	−
Increase of r in stage $+z$, $+1^c$	+	+	−	−	−	+	−	−	−	−	+	−	−	+
Decrease of r in stage $+z^c$	−	−	−	−	+	+	−	−	−	−	−	−	+	−
All flows stopped	−	−	−	−	−	−	−	−	−	−	−	−	−	−

[a] By gravity; transient and continuous process.
[b] Transient process.
[c] See Figs. 3, 4 and 5 for numbers and locations of stages.

angular positions of the communicating holes in the discs. Both the initiation and duration of each setting are programmable to specify:

(i) throughput of the upper and lower phases;

(ii) input of feed, which may be dissolved in either solvent (batch or continuous operation);

(iii) withdrawal of product, again from either phase (only batch operation);

(iv) withdrawal of upper or lower phase (reflux, in case of continuous operation);

(v) input of upper or lower solvent without concomitant output (pressure adjustment);

(vi) output of upper or lower phase without concomitant input (pressure adjustment);

(vii) reversal of sense of rotation (to eliminate any propeller effect, no valves are affected);

(viii) vacant: all flows stopped.

The present controller can produce any desired combination of program steps (up to 80) within any one program cycle. The "zero" point (beginning) of the master cycle is programmable and must be set to coincide with the crossing of the communicating holes from the lower to the upper phase.

SAMPLE CALCULATIONS

Extractive mode

We now illustrate operation of the extractor by showing how one may isolate a desired species S from a solution contaminated with closely related species A and B, using the extractive mode described briefly above.

Operating principle

We start the separation by dissolving as much as possible of the mixture A–S–B in the phase which is the better solvent, avoiding, however, viscosities that prevent easy flow through the piping and valves which lead the solution into the stage assembly. The volume of the feed solution should not exceed one tenth of the extractor volume. The equilibrated extractor is set in rotation, and phase throughput is initiated at a flow ratio $R = 1$ or, if K_S is approximately known, $R \approx 1/K_S$.

The extractor is now ready for input of the feed. This input is pulsed, the feed pulses replacing totally or partly the pulses of the respective phase throughput (*cf.*, Fig. 3). Any desired sequence of the two sorts of pulses can be programmed. This program is changed to replace feed pulses by solvent pulses when the feed solution is used up. The operation is then continued until the distribution of S broadens to the point of noticeable leakage of S from the ends of the extractor.

Clearly, replacement of ideal (= instantaneous) by gradual feed input as described above is not without effect on the mass profile of the final solute distribution. However, calculations and practice show that the distortion of the ideal Poisson profiles is moderate enough to be neglected in the prediction and control of experimental separations.

We do not need an exact knowledge of K_S and its dependence on solution composition. Instead, we can find the required flow ratio R by trial and error, *i.e.*, by monitoring the evolution of the S distribution through the sample ports and making heuristic adjustments of the solvent streams as the separation proceeds. We do this by making a series of semi-quantitative measurements of relative concentrations of S along the entire length of the extractor.

This is indicated in Fig. 6, which refers to an actual example, the isolation of a cyclosporin derivative from 200 g of raw material in an extractor composed of 200 segments containing a total volume of 20 l. Shown here are spots on three thin-layer chromatograms obtained from samples drawn at three different states of the operation, defined by the respective *total* solvent throughputs V_1, V_2, V_3 where $V_i = (V_U + V_L)_i$, and *overall* flow ratios R_1, R_2, R_3 where $R_i = (V_U/V_L)_i$.

State defined by:	Samples drawn from segments:
$V_1 = 0.297$ l; $R_1 = 1.16$	-12 to $+15$ yielded spots (top) which reveal a complex distribution of a largely unresolved mixture centered around the feed point
$V_2 = 16.915$ l; $R_2 = 1.23$	-100 to $+100$ yielded spots (centre) now revealing an advanced state of purification, with the centre of mass of the cyclosporin peak almost ideally located

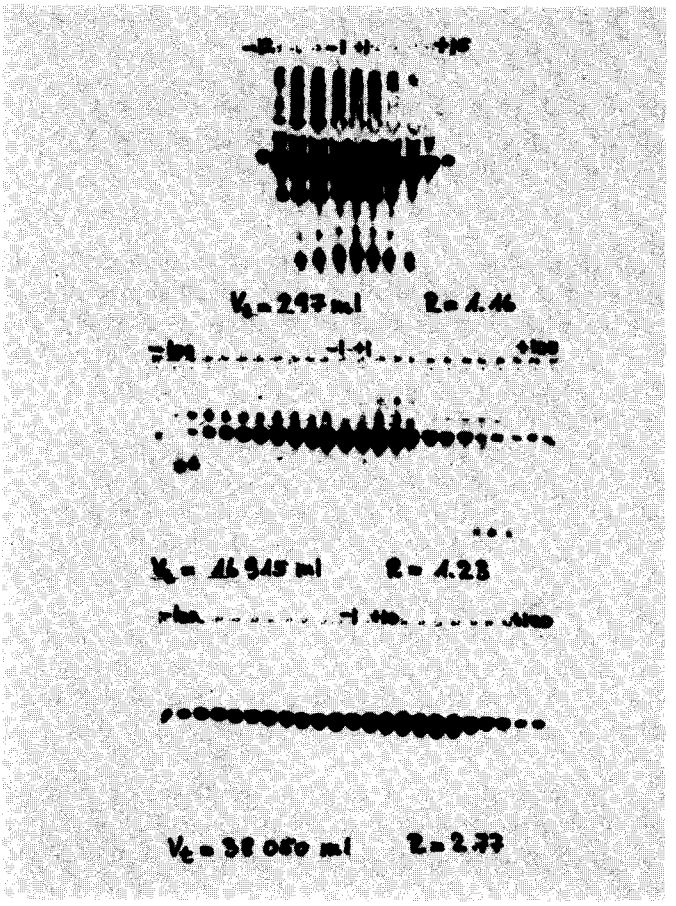

Fig. 6. Example of thin-layer chromatographic monitoring of the evolution of an extractor separation, and of heuristic manipulation thereof.

$V_3 = 38.050$ l; $R_3 = 2.77$ -100 to $+100$ yielded spots (bottom) revealing a pure cyclosporin peak, asymmetric owing to the more difficult elimination of material eluted to the left by the lower phase.

Note the continuing increase in R, first necessary to keep the wanted peak centred in the extractor, and later necessary to avoid product loss with outgoing lower phase[a].

Stage requirements

We now show how such an extractor may be designed by considering some representative hypothetical situations: we assume mixtures of equal amounts of A,

[a] Evidently, all manipulations that involve monitoring distributions and adjustment of solvent streams are amenable to full automation[5].

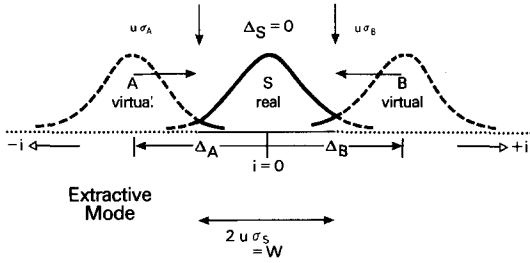

Fig. 7. Extractive mode. Ternary A–S–B (1:1:1) separated up to incipient loss of S. Shown are the elements of calculation used in the long column approximation assuming the separating system to extend beyond the actual extractor boundaries. The virtual peaks are imaginary. $\pm i$ = serial stage number; $i = 0$, location of the feed point. u = number of standard deviations σ providing a desired recovery and purity of species S. Vertical arrows point to actual extractor boundaries. The figure corresponds to $\sigma_{AS} = \sigma_{SB}$ and $k' = 1$, producing a symmetrical distribution with respect to the feed point: $\Delta_A = -u(\sigma_A + \sigma_S)$; $\Delta_B = +u(\sigma_S + \sigma_B)$. The drawing shows a resolution such that $u = 2$ on both sides of the S peak.

S and B; we consider conditions such that $K_A < K_S < K_B$, and for convenience we shall assume that

$$K_B/K_S = K_S/K_A = \alpha \tag{17}$$

where α is the separation factor; and we note that the extractor operates best with holdup ratios (eqn. 2), between 1/4 and 4, and we therefore choose as representative examples $r = 1/4$, 1 and 3.

Our purpose is to determine the number of ideal stages W_{ideal} needed for a given degree of purification in terms of the fractional removal of contaminants A and B from a ternary A–S–B mixture subjected to extraction. The number of ideal stages W_{ideal} for the separation is that which will just hold species S within the extractor at the end of the separation operation. To find that number, we first shall consider 4-σ separations of S from binaries A–S and S–B as examples. The extension to corresponding 6-σ separations will then be quite obvious.

Binaries A–S and S–B. We base calculations on the mathematical assumption that the extractor is infinitely long, as suggested in Fig. 7. Then the calculated required length of the actual extractor needed, in terms of the number of chambers, is given by eqn. 13, with the proviso that σ_x^2 (*cf.*, eqn. 10), is known, which by eqn. 7 calls for a knowledge of the turnover numbers V_U/v_U and V_L/v_L. These are interrelated by the holdup and volume ratios r and R, and related to the sums $V = V_U + V_L$ (the total volume throughput) and $v = v_U + v_L$ (the total plate volume) in the following manner:

$$V_U/v_U = (V/v)[(R/(1 + R)][(1 + r)/r] \tag{18}$$

$$V_L/v_L = (V/v)[(1 + r)/(1 + R)] \tag{19a}$$

For convenience, V_L/v_L as expressed by eqn. 19a, is termed the "volume factor",

$$V_L/v_L = \Phi \tag{19b}$$

Now note (Fig. 7 and eqn. 6), that

$$\Delta_S = \Delta_{U,S} - \Delta_{L,S} = 0$$

or, from eqns. 2, 7, 15, 19a and 19b

$$= \Phi_S(K_S R - 1)Q_S \tag{20a}$$

= [volume factor][mobility factor]

where Φ_S so far is indeterminate, but (eqn. 15), $K_S R = 1$ and (eqns. 8 and 9),

$$Q_S = k'/(1 + k') \tag{21a}$$

where, for convenience, k' is an abbreviation defined by

$$k' = k'_S \tag{22}$$

Note further (eqn. 10), that

$$\sigma_S^2 = \Delta_{U,S} + \Delta_{L,S}$$

$$= \Phi_S(K_S R + 1)Q_S \tag{23a}$$

while (eqns. 15 and 17),

$$\Delta_A = \Phi_A[(1/\alpha) - 1]Q_A < 0 \tag{20b}$$

and

$$\sigma_A^2 = \Phi_A[(1/\alpha) + 1]Q_A \tag{23b}$$

where (eqns. 8, 9, 17 and 22)

$$Q_A = \alpha k'/(1 + \alpha k') \tag{21b}$$

and

$$\Delta_B = \Phi_B(\alpha - 1)Q_B > 0 \tag{20c}$$

$$\sigma_B^2 = \Phi_B(\alpha + 1)Q_B \tag{23c}$$

with

$$Q_B = k'/(a + k') \tag{21c}$$

where all Φs are still indeterminate. However, as may be seen from Fig. 7,

$$\Delta_A = \Delta_{AS} = -u(\sigma_A + \sigma_S) \tag{24a}$$

determining a simultaneous value Φ_{AS} for Φ_A and Φ_S;

$$\Delta_B = \Delta_{SB} = +u(\sigma_S + \sigma_B) \tag{24b}$$

determining a simultaneous value Φ_{SB} for Φ_B and Φ_S.

On the basis of these equations, especially remembering the condition expressed by eqn. 15, we derive expressions for the volume factors Φ_{AS}, Φ_{SB} (*cf.*, Appendix, eqns. 40 and 41) and for V_{AS}, V_{SB} in eqns. 19a and 19b, and hence arrive at the following approximations for W:

Case 1: separation A–S:

$$W = W_{AS} = 2u\sigma_{AS}$$

(*cf.*, eqn. 13), which from eqns. 15 and 23a

$$= 2u(\Phi_{AS} \cdot 2Q_S)^{0.5} \tag{25}$$

$$= W_{AS}(u^2, \alpha, k')$$

(*cf.*, Appendix, eqn. 25a, and Fig. 8).

Case 2: separation S–B:

$$W = W_{SB} = 2u\sigma_{SB}$$

$$= 2u(\Phi_{SB} \cdot 2Q_S)^{0.5} \tag{26}$$

$$= W_{SB}(u^2, \alpha, k')$$

(*cf.*, Appendix, eqn. 26a, and Fig. 8).

When $k' = 1$, then eqns. 25 and 26 reduce to

$$W_{AS} = W_{SB} = 4u^2 \cdot \frac{\alpha + 1}{\alpha - 1} \tag{27}$$

Eqn. 27 represents a useful approximation of eqns. 25 and 26 because, within the accessible range, the k' dependence of W is moderate.

Ternaries A–S–B. Assuming equal amounts of the components A, S and B, and using eqns. 25 and 26, one must choose the larger of the two values to obtain the desired separation of S with respect to neighbouring A or B. The separation of S from the opposite neighbour B or A is then better than estimated from the value of u. Thus, the plate requirement for the separation of a 1:1:1 ternary with separation factors $\alpha_{AS} = \alpha_{SB}$ is conveniently read from graphs of the type shown in Fig. 9, which is derived

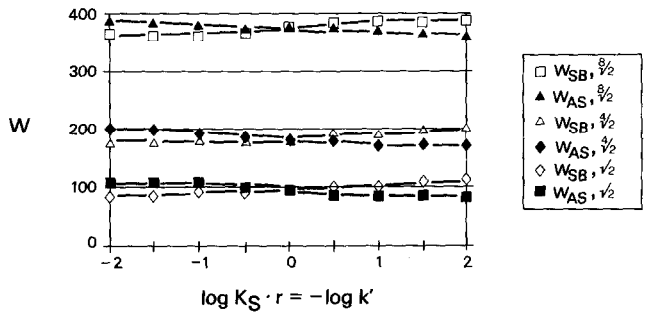

Fig. 8. Extractive mode: binaries. Stage number requirements, W_{AS} and W_{SB}, for desired separations (4σ) of binaries A–S or S–B (1:1), retaining S and eluting A by LP, or B by UP. Data based on separation factors $\alpha_{AS} = \alpha_{SB} = 2^{1/2}, 2^{1/4}, 2^{1/8}$.

from data in Fig. 8. If the separation factors for the two binary pairs A–S and S–B are different, then the above calculation of W may tentatively be made only for the smaller factor. Caution is indicated.

Evaluation of the separation of ternaries composed of unequal weights of A, S and B can also be based on eqn. 14. However, overlaps cannot be estimated in terms of overlapping peak areas, with the u-scale on the abscissa, unless the individual peaks of A, S and B are drawn on individual ordinate scales $\varphi(u)$ that are proportional to the underlying masses m_A, m_S and m_B.

Separating power of a given set of W stages. In practice, the separation power of an extractor is fixed by the number W of its stages. Suppose $W = 120$, and a binary A–S distributed until S appears in the effluents from stages -60 and $+60$. What is then the degree of separation of S from A in terms of $u = u'$, when $\alpha = \sqrt{2}$ and $k' = 10^{1.5}$?

One way to find the answer comes from inspection of the algebraic form of eqn.

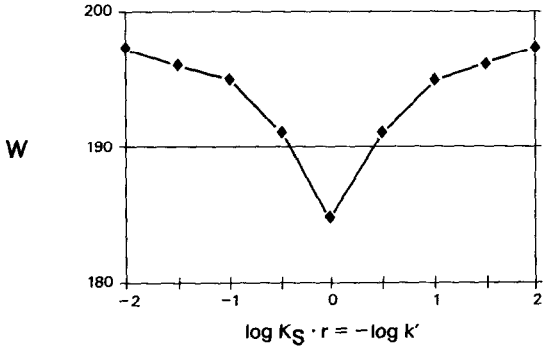

Fig. 9. Extractive mode: ternaries. Stage number requirements, W, for desired separations (4σ) of ternaries A–S–B (1:1:1), retaining S and eluting A by LP, and B by UP. Data based on separation factors $\alpha_{AS} = \alpha_{SB} = 2^{1/4}$, and taken from Ws for binaries in Fig. 8, selecting the larger value within each pair W_{AS}, W_{SB} as explained in the text.

25, using calculated values of W_{AS}. Accordingly, 105 stages would provide a 4-σ separation, *i.e.*, $u = 2$. Therefore, with 120 stages available,

$$(u')^2 = 2^2(120/105)$$

and $u' = 2.14$.

Recoveries and purity

The boundaries of the extractor affect the system behaviour, because solutes cannot be returned to the system by non-existent streams. The error introduced into the calculation of the distribution of S by assuming an infinite extractor is small, because loss of S is negligible. The errors for A and B, however, are significant, but proper allowance for them is difficult mathematically[6]. We therefore content ourselves here by noting that the long-column approximation overestimates the contamination of S by A and B, and therefore provides a conservative estimate.

Chromatographic mode

We now turn our attention to the extraction analogue of elution chromatography, to justify the comparison already shown in Fig. 1.

Operation principle

Note that the extractor described above can be operated in a chromatographic mode and then provides a system which simulates partition chromatography; we just shift the feed point to the stage next to the inlet of either of the phases, the upper phase for example, and then suppress the flow of the lower phase. Accordingly, stage numbering t becomes unidirectional and begins at the feed point. Finally, using chromatographic language, stages become plates (*cf.*, Figs. 1 and 10).

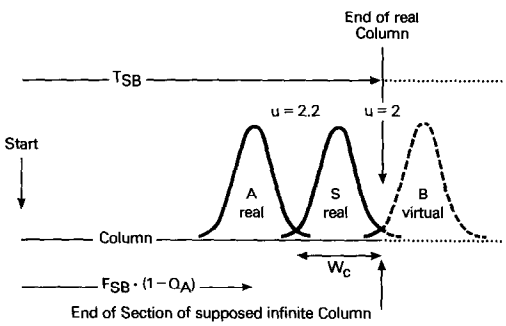

Fig. 10. Extractor in chromatographic mode. Ternary A–S–B (1:1:1) separated up to incipient loss of S. Shown are the elements of calculation used in the long column approximation, assuming the column to extend beyond its actual length, T_{SB}, in terms of ideal plates. The virtual peak is imaginary. $u = 2$, number of standard deviations σ_S and σ_B providing the desired resolution between species S and B; $u = 2.2$, measure of the resulting resolution A–S, due to inherent distribution asymmetry; W_c, width of the S peak; F_{SB}, turnover number of the mobile phase per plate which brings the front of the S peak up to T_{SB}; $F_{SB}(1 - Q_A)$ is the concomitant displacement Δ_A. The figure corresponds to $\alpha_{AS} = \alpha_{SB} = 2^{1/2}$ and $k' = 1$.

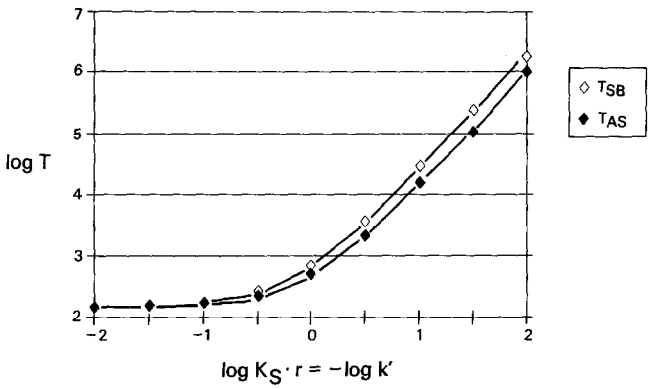

Fig. 11. Chromatographic mode: binaries. Stage number requirements T_{AS} and T_{SB} for desired separations (4σ) of binaries A–S or S–B (1:1), retaining A and eluting S, or retaining S and eluting B. Data based on separation factors $\alpha_{AS} = \alpha_{SB} = 2^{1/2}$.

Plate requirements

We base the discussion on Fig. 10, in which the situation at the end of the chromatographic process in a column with T_{SB} plates is shown; peak B would be present in a hypothetical column of infinite length. The column length, in terms of its number of plates T needed for the separation of binaries, can be derived in the manner used above by combinations of displacements Δ_c from the origin and standard deviations $\sigma_c = \sqrt{\Delta_c}$, the suffix c referring to the chromatographic mode. The procedure, familiar to chromatographers, is outlined in the Appendix (*cf.*, eqns. 27a–34).

Binaries A–S and S–B. The column length needed for the separation of A from S (not shown in Fig. 10), or S from B (*cf.*, Fig. 10) is described by eqn. 32 or 33. The peak width of S after removal of B[a] is given by eqn. 34.

Graphs of eqns. 32–34, when $\alpha_{AS} = \alpha_{SB}$, are shown in Figs. 11 and 12. T_{AS} is always slightly smaller than T_{SB}. It may be recalled at this point that there was no such fixed relation between W_{AS} and W_{SB}. Both T_{SB} and W_{SB} represent column lengths required for S–B separations with retention of S and removal of B. There is no such symmetry between T_{AS} and W_{AS}: the former refers to removal of S with retention of A, the latter to removal of A with retention of S.

Ternaries A–S–B. Assuming equal amounts of A, S and B in a ternary, and $\alpha_{AS} = \alpha_{SB}$, the stage requirement for separation in the extractive mode was defined by the larger of the two numbers W_{AS}, W_{SB}. That number equalled the width of the S peak. Now, adopting the same assumptions with respect to the properties of the ternary, we define the plate requirement for separation in the chromatographic mode by the larger number T_{SB}. The separation S–B to be expected is then characterized by the value of the parameter u which was used in calculating T_{SB} by eqn. 33. How good is the separation A–S at this stage of the process (Fig. 10)? It must be better (characterized, for example, by $u = 2.2$), since the A–S separation could have been achieved with a shorter column (*cf.*, Fig. 11).

[a] Driving B beyond the plate with serial number T_{SB} in the infinitely long column is considered as an equivalent to elution from the last plate (T_{SB}) of a finite column.

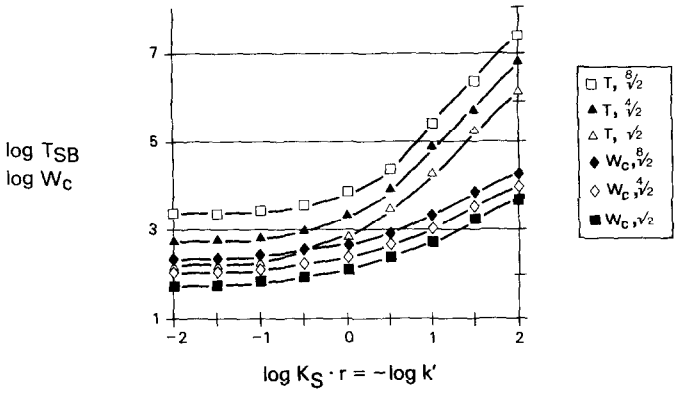

Fig. 12. Chromatographic mode: binaries. Stage number requirements, T_{SB}, and space requirement, W_c, for desired separations (4α) of binaries S–B (1:1), retaining S and eluting B (*cf.*, Fig. 1). Data based on separation factors $\alpha_{AS} = \alpha_{SB} = 2^{1/2}, 2^{1/4}, 2^{1/8}$.

EXTRACTIVE *VERSUS* CHROMATOGRAPHIC MODE

Stage and plate requirements for binary separations S–B, with retention of S

For comparison, calculated stage and plate number requirements for the separation of S from binaries A–S and S–B, and from the ternary A–S–B by the extractive and the chromatographic modes are presented in Figs. 8, 9, 11, 12 and 13 as functions of the variable $K_S r = 1/k'$, with separation factors $\alpha = 2^{1/2}, 2^{1/4}$ and $2^{1/8}$ as parameters. The lower groups of curves in Figs. 12 and 13 furnish a further comparison of corresponding peak widths W_c and W_{SB}.

All data refer to 4-σ separations, *i.e.*, to a numerical value of 2 for the separation parameter u, corresponding to about 95% recovery of S from a supposed symmetrically distributed 1:1:1 ternary. Multiplication of these data by 1.36 or 2.25 yields plate numbers theoretically required for 99 and 99.7% recoveries, respectively. Recall in this context the slight distribution asymmetry due to $W_{AS} \neq W_{SB}$, and $T_{SB} \neq T_{AS}$, and the section on *Recovery and purity*. The range of $K_S r$, chosen from 0.01 up to 100, is broader than is accessible in practice. It is assumed to illustrate trends. Also, $\alpha = 2^{1/8}$ presents a lower limit to feasibility in the extractor.

Extractor and column lengths

A straightforward comparison is based on W ($= W_{SB}$) and T_{SB} (*cf.*, Fig. 13). Clearly, there is a stage-saving effect of dual flow, and it becomes increasingly attractive with increasing difficulty of the separation. Extractors with several hundred real stages, with a stage efficiency[a] of about 50%, may well match separation by chromatography, especially when the demand on yields is lessened: minor elution (*cf.*, Fig. 7) of S from either or both of its peak ends in order to wash out contaminating peak tails of A and/or B is equivalent to an increase in extractor length. A yield-saving alternative is offered by repetition of a run after recovery and concentration of the

[a] See footnote to eqn. 3.

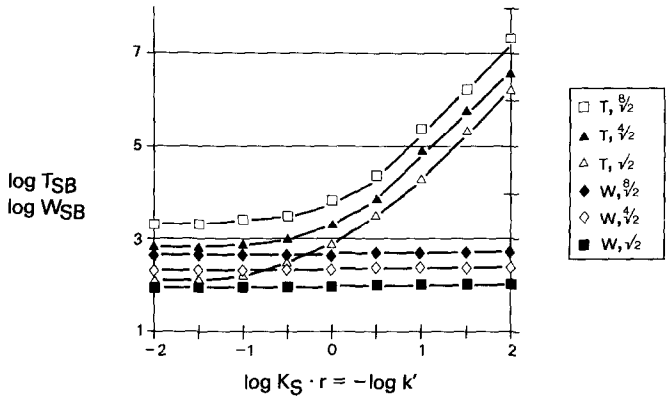

Fig. 13. Extractive *versus* chromatographic mode: binaries. Stages W_{SB} and plates T_{SB} required for desired separations (4σ) of binaries S–B (1:1), retaining S, eluting B. Data based on separation factors $\alpha_{AS} = \alpha_{SB} = 2^{1/2}, 2^{1/4}, 2^{1/8}$.

reactor contents. In fact, with each repetition the mass of contaminants A and B in the tails of the outgoing peaks will drop in geometrical progression.

Space requirements of retained S

In the Introduction, the number of extractor stages $W \rightleftharpoons (W_{SB})$ accommodating S was said to be expected to be of the same order as the number of column plates W_c occupied by S after elution of B (Fig. 1). In fact, this holds only when $k' \approx 1$. The deviations from expectation as shown by Figs. 12 and 13 appear as a consequence of the impact on peak widths of the migration mechanism. The displacement Δ of a peak and its standard deviation σ (or peak width), when effected by uni- or bidirectional flow, are based on mobility probabilities which are characteristically different.

In the chromatographic mode (*cf.*, Appendix, eqns. 27a and b and 28a and b), the standard deviation $\sigma_X = \sqrt{[F(1 - Q_X)]}$ depends, apart from the volume factor F, exclusively on the probability $(1 - Q_X)$ for residence of X in the mobile phase.

In the extractive mode (eqns. 23a–c),

$$\sigma_X = \sqrt{[\Phi(K_X R + 1)/(K_X r + 1)]} = \sqrt{[\Phi([R/r]K_X r + 1)/(K_X r + 1)]} \qquad (23d)$$

depends, apart from the volume factor Φ, on both $(1 - Q_X)$ and Q_X, the probabilities for residence of X in UP and in LP, but with weight R/r for $1 - Q_X$ and weight 1 for Q_X. Therefore, the extractive peak widths W are similar at all values of k', whereas the chromatographic peak widths W_c change rapidly with small shifts in k', even within the chromatographically preferred range of $k' = 3$–10.

Solvent consumption

The feasibility of a separation process depends on the equipment and on the solvent consumption. Comparison from this aspect of the extractive and the chromatographic modes must be done under comparable situations. For example, operations may be considered to start with a solvent-charged extractor and a conditioned column, and to end with the extractor and column ready for a restart. It

may further be considered that these conditions are met by draining the final product solution off the extractor, followed by recharging with fresh solvent on the one hand, and by total non-gradient elution of all materials from the column on the other.

It appears convenient to state solvent consumption in terms of multiples of the total volume of an extractor stage or a column plate. Of course, these multiples are related to the turnover numbers Φ and F.

Extractive mode

For the extractive separation of a ternary A–S–B, the so-defined solvent consumption is derived from the volume factor Φ (*cf.*, eqns. 19a and b and Appendix, eqns. 40 and 41) belonging to the larger value W_{AS} or W_{SB} (Figs. 8 and 9) used to perform the separation. Hence, the total relative volume V_{et}/v required in the extractive mode is given by (eqns. 19a and b, 25 and 26)

$$V_{et,\,AS}/v = V_{AS}/v + W_{AS} = \Phi_{AS}[(1 + R)/(1 + r)] + W_{AS} \tag{35a}$$

or by

$$V_{et,\,SB}/v = \Phi_{SB}(1 + R)/(1 + r) + W_{SB} \tag{35b}$$

Recall that V_{et} is biphasic, being composed of UP and LP. Note the explicit dependence of V_{et} on the holdup ratio r. It adds to an implicit dependence which via k' is hidden in Φ. There is no comparable dependence on the flow ratio R because the latter is a parameter fixed by the relationship given in eqn. 15.

Graphs combined from the functions 35a and 35b, by choice of the larger ordinate $V_{et,AS}/v$ or $V_{et,SB}/v$ at each abscissa, are shown in Fig. 14 with holdup ratios $r = 0.25$, 1 and 3 as parameters. It must be noted that the choice of r fixes the point on the abscissa corresponding to log $K_S r$ when K_S is fixed by the nature of the feed and the solvent.

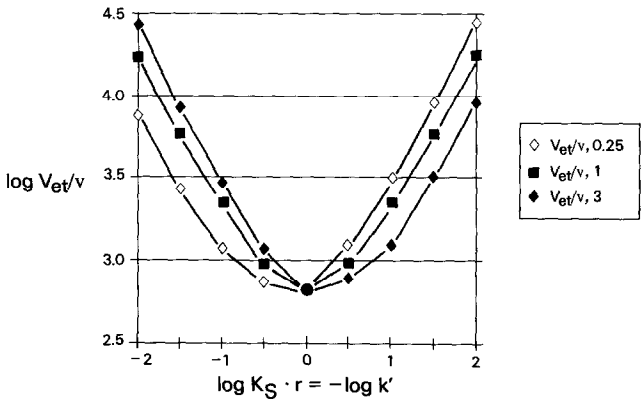

Fig. 14. Extractive mode: solvent consumption. Desired separations (4σ) of ternaries A–S–B (1:1:1), based on W stages, where W is the larger value selected from the pair W_{SB}, W_{AS} (*cf.*, Figs. 8 and 9), require a total solvent volume V_{et} as defined in the text. This figure shows relative volumes V_{et}/v at holdup ratios $r = 0.25$, 1 and 3, when $\alpha_{AS} = \alpha_{SB} = 2^{1/2}$.

Minimizing the solvent consumption is seen to involve just a shift via r of the product $K_S r$ as close to 1 as is physically possible in view of the hydrodynamics of the system. This shift will be accompanied by another advantage, *i.e.*, a slight simultaneou s decrease in the stage number requirement (*cf.*, Fig. 9). Adaptable holdup ratios thus prove to be a valuable feature of the equipment presented in this paper.

Chromatographic mode

Turning to the chromatographic mode, proceeding up to complete elution of the slowest moving species A (at least 3σ with respect to the tailing half of the peak), we must remember that it is always eqn. 33 which determines the column length (separation of S with respect to neighbouring B). Complete elution of A from a column of T_{SB} plates requires at least the volume

$$V_{ct} = V_{R,A} + 3V_{R,A}/\sqrt{T_{SB}} \tag{36}$$

where

$$V_{R,A} = T_{SB}v[r/(1 + r)]/(1 - Q_A) \tag{37}$$

is the retention volume of A, and

$$\sigma_{V,A} = V_{R,A}/\sqrt{T_{SB}} \tag{38}$$

is the standard deviation about $V_{R,A}$. Hence (eqn. 21b),

$$V_{ct}/v = (r/1 + r)(1 + \alpha k')(T_{SB} + 3\sqrt{T_{SB}}) \tag{39}$$

Recall that V_{ct} is monophasic. Note again the explicit dependence on the phase ratio r.

Graphs of the function 39 are shown in Fig. 15 with holdup ratios r = 0.25, 1 and 3 as parameters. Note the differences when compared with Fig. 14: there is no

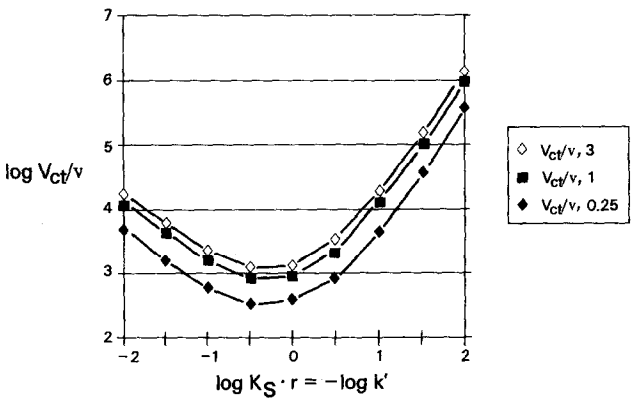

Fig. 15. Chromatographic mode: solvent consumption. Desired separations (4σ) of ternaries A–S–B (1:1:1), based on T_{SB} plates (*cf.*, Fig. 12), require a total solvent volume V_{ct} as defined in the text. This figure shows relative volumes V_{ct}/v at holdup ratios r = 0.25, 1 and 3, when $\alpha_{AS} = \alpha_{SB} = 2^{1/2}$.

curve crossing, and the minima are displaced to log $K_S r < 0$. However, the remarks with respect to the evaluation of Fig. 14 apply, and the minimization rule remains valid.

Extractive versus *chromatographic mode*

With the proviso of identical holdup ratios in the extractor and the chromatographic column, we deduce from Figs. 14 and 15 that the latter, within the range of k' accessible to chromatography, offers a slight advantage with respect to solvent consumption. However, the adaptability of the holdup ratio, characteristic of the extractor, is largely non-existent with columns, and the estimate of V_{ct}/v according to the previous section is highly conservative.

HARDWARE AND APPLICATIONS

Several units of the type described above have been built and put into operation. The smallest, shown in Fig. 16 (Mechanische Werkstätte Max Kohler, Basle, Switzerland) consists of two glass cylinders, each 15.26 m × 5 cm I.D. Each consists of 282 stages and five interdispersed sampling chambers. The former (latter) have a width of 0.4 (1) cm and contain about 7.7 (19) ml of liquid. The cylinders are arranged parallel to each other, with U-turns for the flows and a feed port in each line. The unit is equipped with a motor and a controller, located near stages ± 1, with two solvent reservoirs, two receiving flasks and two ceramic pumps, located near stages ± 282. The supporting bench is movable.

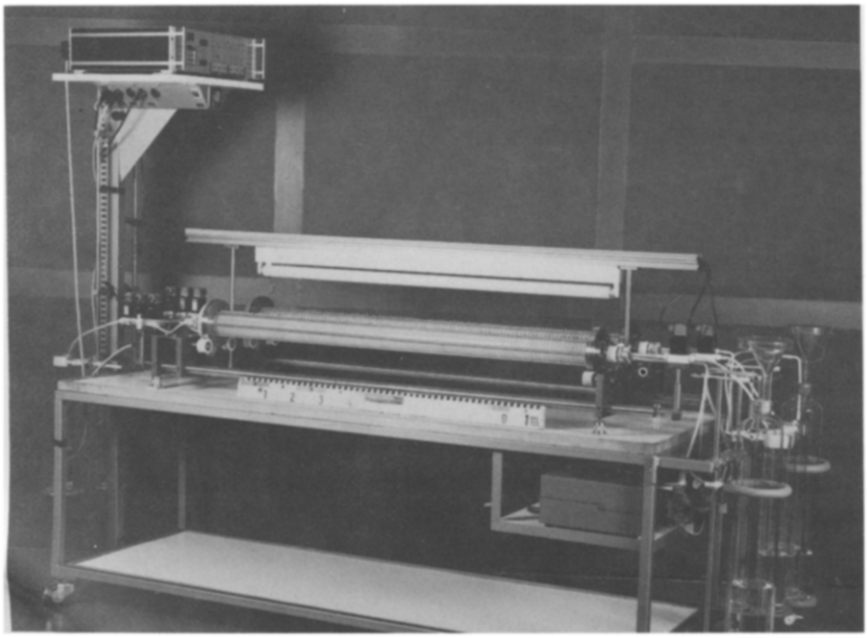

Fig. 16. Laboratory-scale extractor. Volume, 4.5 l; feed $\leq$ 450 ml; motor and controller near feed point, pumps, solvent reservoirs and receiving flasks at opposite end, movable bench.

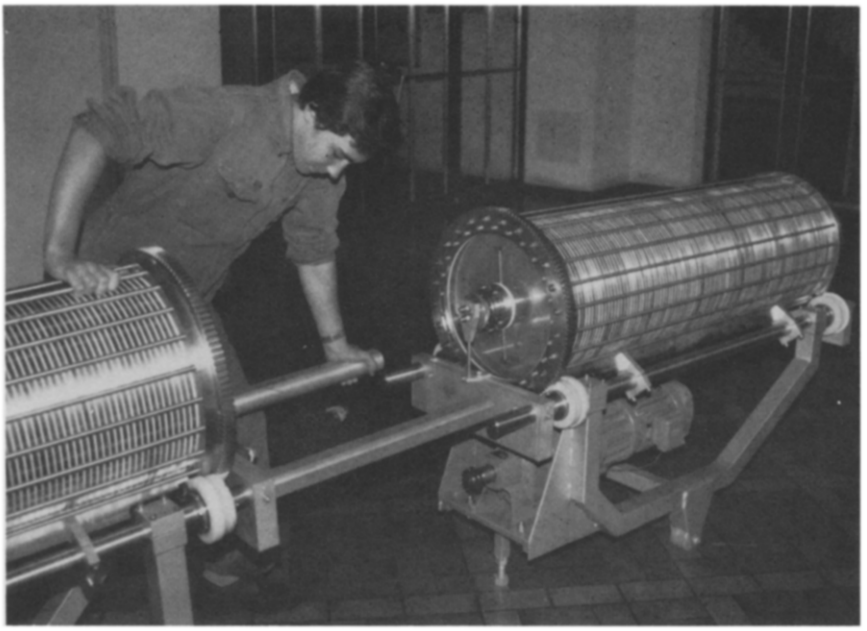

Fig. 17. Assembling two cylinders, pilot-scale extractor. Volume, 250 l; feed $\leqslant$ 25 l; explosion-proof motor underneath, other accessories located in a separate room; movable.

The larger, shown in Fig. 17 (Mechanische Werkstätte Max Kohler), is intended for pilot-scale operation and has an I.D. of 40 cm. It consists of two cylinders (stainless steel) mounted end to end, each with 100 inner stages of width 1 cm and two outer stages with terminating glass walls. Each inner stage is accessible through a sampling hole.

Results obtained on peptide purifications with the smaller unit were reported by a group from Smith Kline and French Laboratories[7]. A more detailed discussion of that work will be provided in a forthcoming paper.

SYMBOLS

A	area defined by the normalized Gaussian probability distribution function; eqn. 14
A	contaminant of S, with smaller affinity to upper phase than S
A′	contaminant of S, with smaller affinity to upper phase than A
α_{ij}	separation factor K_S/K_A or K_B/K_S; $\alpha_{ij} = K_i/K_j > 1$
B	contaminant of S, with greater affinity to upper phase than S
B′	contaminant of S, with greater affinity to upper phase than B
Δ_X	total displacement from the origin of the centre of mass of the migrating species X
$\Delta_{L,X}$	displacement from the origin of the centre of mass of the migrating species X, effected by flow only of LP
$\Delta_{U,X}$	displacement from the origin of the centre of mass of the migrating species X, effected by flow only of UP

f	an empirical efficiency factor, relating for a given degree of resolution, W_{real} to W_{ideal}; *cf.*, eqn. 3; for a given throughput of solvent, by $\sqrt{f}$, real (= observed) and ideal (= theoretical) peak widths; *cf.*, eqn. 11
$\varphi(u)$	ordinates in the normalized Gaussian probability distribution function
F_{ij}	volume factor (chromatographic mode); eqns. 28 and 29
Φ_{ij}	volume factor (extractive mode); eqn. 19b
$\pm i$	serial numbering of reactor stages; *cf.*, Figs. 3–5
k'	chromatographic capacity factor for species S, synonym of $1/K_S r$
K_X	partition coefficient of species X; eqn. 5
L, LP	lower phase
m_X	mass of species X present in a mixture or, after separation, represented by the respective peak in a distribution profile
N	non-working plates in a chromatographic column
Q_X	probability of residence of solute X in the lower phase; eqns. 21a–c
r	holdup ratio v_U/v_L, *i.e.*, ratio of volumes of light (upper) and heavy (lower) phase present in a plate or stage; eqn. 2
R	flow ratio, *i.e.*, ratio of volumetric stream rates ${}^0V_L$ and ${}^0V_U$ passing through an extractor; eqn. 4
S	species to be separated from contaminants A and B present in a ternary A–S–B
σ_X	standard deviation about Δ_X
σ_X^2	variance about Δ_X; eqn. 10
σ_{ij}	standard deviation about displacement Δ of species i or j after a separation process involving i and j; eqns. 25 and 26
$\sigma_{V,X}$	standard deviation about $V_{R,X}$; eqn. 38
t	serial numbering of plates in a chromatographic column; *cf.*, Fig. 1
t_X	position of peak X in a chromatographic column; *cf.*, Fig. 1
T	total number of plates in a chromatographic column; *cf.*, Fig. 1
T_{ij}	T required for separation of species i and j by elution of the faster moving one; Fig. 13, eqns. 27a and b and 28a and b
u	variable in the normalized Gaussian probability distribution function; eqns. 12 and 14
u	separation parameter, a measure of resolution defined by eqn. 16, or a preset value of the variable u providing a desired resolution; eqns. 25, 26, 32 and 33
u'	resolution to be expected by a given number W of stages
U, UP	upper phase
v	total volume of liquid present in a plate or stage; eqn. 1
V	sum of $V_L + V_U$ = total solvent volume used during an extractive separation
V_{ij}	V needed for the separation of species i and j
${}^0V_L$	volumetric stream rate of LP
${}^0V_U$	volumetric stream rate of UP
V_{et}, V_{ct}	total solvent volumes required for extractive and chromatographic separations of a ternary, with complete recovery of the feed

$V_{m,ij}$ effluent volume of mobile phase (driving the faster component of a binary beyond a certain plate of an infinitely long chromatographic column); eqns. 28 and 29

$V_{R,X}$ retention volume of species X in elution chromatography; eqn. 37

v_L, v_U volumes of LP and UP present in a stage or plate

V_L, V_U total volumes of LP and UP used during an extractive separation process

W number of extractor stages

W_{ideal} number of ideal extractor stages required to store a wanted species S being separated from A and/or B

W_{real} $= W_{ideal}/f$ which is the real number of extractor stages required to store S; eqn. 3

W_{ij} W_{ideal} required to separate species i and j by retention of either and elution of the other one; eqns. 25 and 26

W_c peak width of species S at impending elution from a chromatographic ~~col~~umn

[X] concentration of species X in a solution

$\pm z$ ultimate serial stage numbers in reactor cylinders (+) and (−); *cf.*, Figs. 3–5

APPENDIX

Stage requirements

From eqns. 20b, 21a and b and 24a

$$(\Phi_{AS})^{1/2} = u \cdot \frac{[(\alpha k' + 1)/k']^{1/2}\{(\alpha + 1)^{1/2} + [2(\alpha k' + 1)/(k' + 1)]^{1/2}\}}{\alpha - 1} \tag{40}$$

From eqns. 20c, 21a and c and 24b

$$(\Phi_{SB})^{1/2} = u \cdot \frac{[(\alpha + k')/k']^{1/2}\{(\alpha + 1)^{1/2} + [2(\alpha + k')/(k' + 1)]^{1/2}\}}{\alpha - 1} \tag{41}$$

From eqns. 25 and 40

$$W_{AS} = u^2 \cdot \frac{2\{2(\alpha k' + 1)/(k' + 1) + [2(\alpha + 1)(\alpha k' + 1)/(k' + 1)]^{1/2}\}}{\alpha - 1} \tag{25a}$$

From eqns. 26 and 41

$$W_{SB} = u^2 \cdot \frac{\alpha\{2(\alpha + k')/(k' + 1) + [2(\alpha + 1)(\alpha + k')/(k' + 1)]^{1/2}\}}{\alpha - 1} \tag{26a}$$

Plate requirements

For the binary A–S separation we have (*cf.*, Fig. 10)

$$T_{AS} = \Delta_{cS} - u\sigma_{cS} = F_{AS}(1 - Q_S) - u[F_{AS}(1 - Q_S)]^{0.5} \tag{27a}$$

$$= \Delta_{cA} + u\sigma_{cA} = F_{AS}(1 - Q_A) + u[F_{AS}(1 - Q_A)]^{0.5} \tag{27b}$$

where

$$F_{AS} = (V_{m,AS}/v)[(1 + r)/r] \tag{28}$$

F_{AS} is the "volume factor" separating A–S, and has the dimension of a total turnover number of the mobile phase present in a plate;
$(1 - Q_X)$ = probability of residence of X in the mobile phase (UP); it represents in this context the "mobility factor" of species X. $Q_S = Q_S(k')$, $Q_A = Q_A(\alpha, k')$ (*cf.*, eqns. 9 and 21a and b);
$V_{m,AS}$ = effluent volume of mobile phase needed for the separation of A–S;
$vr/(1 + r)$ = fraction of the plate volume occupied by mobile phase.

For the binary S–B separation we have (*cf.*, Fig. 10)

$$T_{SB} = \Delta_{cB} - u\sigma_{cB} = F_{SB}(1 - Q_B) - u[F_{SB}(1 - Q_B)]^{0.5} \tag{28a}$$

$$= \Delta_{cS} + u\sigma_{cS} = F_{SB}(1 - Q_S) + u[F_{SB}(1 - Q_S)]^{0.5} \tag{28b}$$

where

$$F_{SB} = (V_{m,SB}/v)[(1 + r)/r] \tag{29}$$

F_{SB} is the "volume factor", separating A–S; $F_{SB} \neq F_{AS}$, because $V_{m,SB} \neq V_{m,AS}$;
$1 - Q_X$: see comment on eqns. 27a and b; $Q_B = Q_B(\alpha, k')$ (*cf.*, eqn. 21c); $Q_S = Q_S(k')$ (*cf.*, eqn. 21b).

Each of the pairs of eqns. 27a and b and 28a and b can now be solved to obtain

$$(F_{AS})^{1/2} = \frac{u}{[1/(k' + 1)]^{1/2} - [1/(\alpha k' + 1)]^{1/2}} \tag{30}$$

and

$$(F_{SB})^{1/2} = \frac{u}{[\alpha/(k' + \alpha)]^{1/2} - [1/(k' + 1)]^{1/2}} \tag{31}$$

and these are used to determine the column lengths.

From eqns. 27b and 30

$$T_{AS} = u^2 \cdot \frac{[(\alpha k' + 1)/(1 + k')]^{1/2}}{\{[(\alpha k' + 1)/(1 + k')]^{1/2} - 1\}^2} \tag{32}$$

From eqns. 28b and 31

$$T_{SB} = u^2 \cdot \frac{[\alpha(k' + 1)/(k' + \alpha)]^{1/2}}{\{[\alpha(k' + 1)/(k' + \alpha)]^{1/2} - 1\}^2} \tag{33}$$

From eqn. 28b we deduce for the peak width W_c of species S

$$W_c = 2u[F_{SB}(1 - Q_S)]^{0.5} \tag{34a}$$

which from eqn. 29 becomes

$$W_c = u^2 \cdot \frac{2}{[\alpha(k' + 1)/(k' + \alpha)]^{1/2} - 1} \tag{34}$$

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