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True moving bed chromatography: solid–liquid multi-stage counter-current extraction

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Abstract

An apparatus for solid–liquid multi-stage dual-flow counter-current extraction was created for performance of true moving bed chromatography. Using the 12-vessel apparatus, continuous adsorptive separation of methyl- and propyl-4-hydroxybenzoate was accomplished using octadecyl-silica gel as the solid phase, and a mixture of water–1-propanol (8:2) as the liquid phase. From a 1:1 mixture of methyl and propyl esters, methyl ester was extracted into the liquid phase at a purity of 98.83% and propyl ester was recovered from the solid phase by desorption with the same liquid phase to 95.89% purity.

Keywords: True moving bed chromatography; Counter-current extraction; Extraction methods; Instrumentation; Preparative chromatography; Hydroxybenzoate

1. Introduction

Along with chromatography, dual-flow counter-current extraction techniques which can perform continuous separation are an attractive separation method from the preparative point of view [1]. Although one can separate a mixture into only two fractions with this method, it is sufficient for most cases of enantioseparations. We have previously studied dual-flow counter-current extraction techniques [2,3]; however, there have been very few applications.

If dual-flow solid–liquid counter-current extraction can be performed with one of the two immiscible liquids replaced by a solid, its applicability should be expanded. Fortunately, a variety of solid stationary phases, including chiral stationary phases, have been developed for HPLC and may be useful for solid–liquid extraction.

Techniques for moving the ‘stationary’ phase in the column are known as true moving bed (TMB) technology. Counter-current adsorptive separation or ‘hypersorption’ is a TMB method, used for the separation of a mixture of hydrocarbons about 40 years ago [4]. A preliminary study on moving bed gas chromatographic separation of dichloromethane and dimethoxymethane was reported in 1962 [5]. Rotating circular chromatography reported in 1971 is also a TMB method [6]. Recently, a continuous extractive enantioseparation method via circulating a

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chiral stationary phase on a belt to perform continuous adsorptive separations [7], but not dual-flow counter-current separations, was performed. There have been no reports of true moving bed chromatography using a solid–liquid extraction apparatus.

In usual solid–liquid extraction, the targeting component is separated in one step based on large differences in distribution ratios. Most commercially available solid–liquid extraction apparatuses are not designed for circulating the solid phase and it is difficult to perform continuous separations. Thus, we manufactured a dual-flow solid–liquid multi-stage counter-current extraction apparatus. The principle of separation is similar to TMB chromatography, and we have named it 'solid–liquid multi-stage counter-current extraction' (SLMCE), because the moving of the solid phase is 'true' but still 'step-wise', and the experimental equipment can be categorized as solid–liquid extraction. The schematic operation process of SLMCE is depicted in Fig. 1. As shown in the figure, SLMCE is a good separation method for binary mixtures.

In HPLC columns, however, it is impossible to 'move' the stationary phase itself. Simulated moving

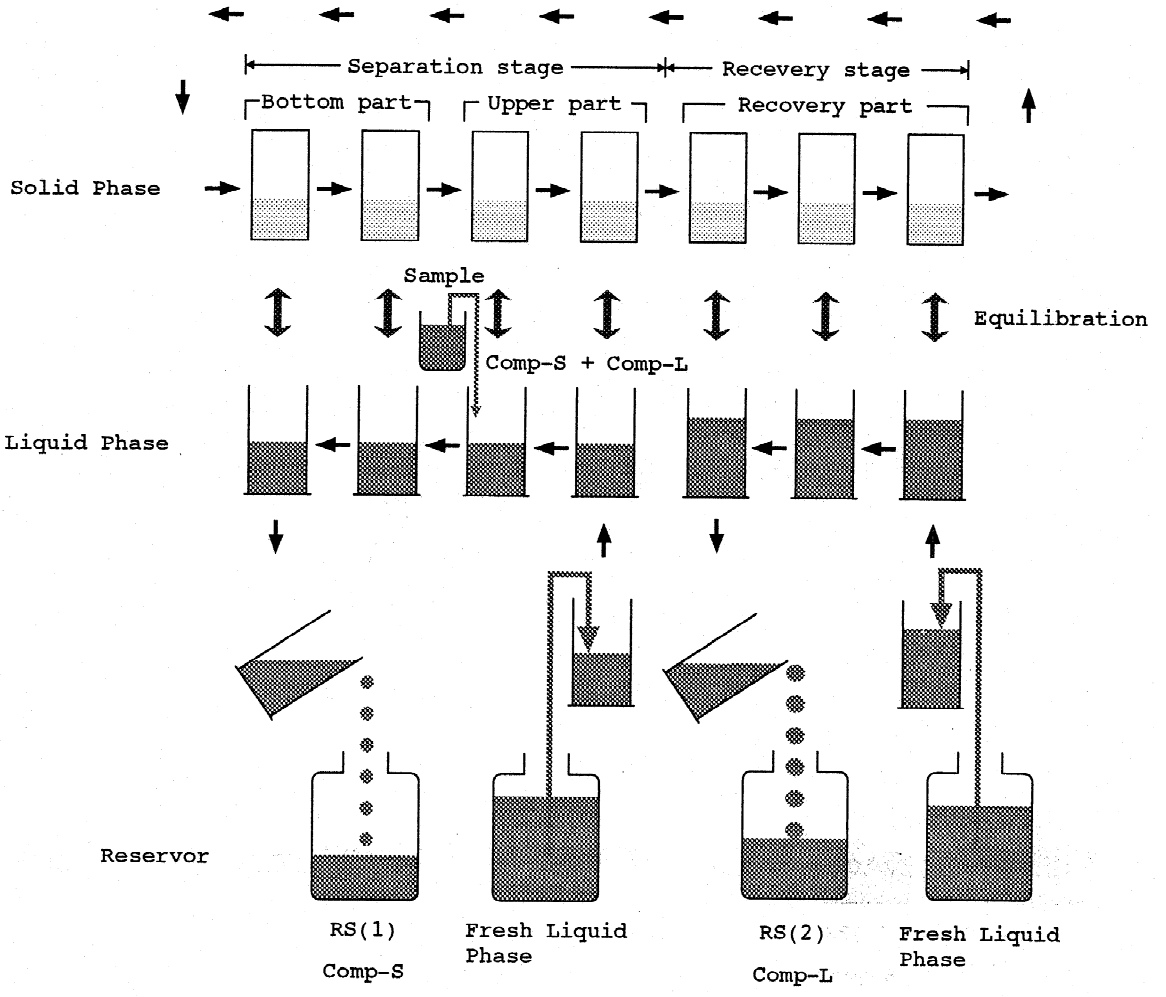

Fig. 1. Schematic separation process of a binary mixture by dual-flow solid–liquid multi-stage counter-current extraction. The component with the smaller distribution ratio (Comp-S) is extracted into the liquid phase, which is collected to RS(1). The other component (Comp-L) is adsorbed by the solid phase which is recovered (desorbed) by the same liquid phase and collected to RS(2), and the solid phase is recycled.

bed (SMB) chromatography is an alternative technique. There have been numerous theoretical and experimental investigations on SMB techniques [8–14]. In enantioseparations, SMB methods may have the following advantages [13,14]: (1) efficient use of the stationary phase; (2) the concentration of the component in the eluent is much higher than in the single column chromatography; (3) the amount of solvent is reduced to about one-half to one-tenth that used for the single-column chromatography; (4) a component yield of over 90%; (5) easily adjusted purity levels for different enantiomers. These advantages may also be true for TMB and SLMCE.

In the SMB method, the stationary phase does not actually move, but is simulated to 'move' by moving the sample inlet and outlet by systematically arranging several fixed beds and switching valves. Thus, the SMB method requires time-programmed complex valve switchings executed by a computer-aided control system of the pumps and valves. And separation is executed intermittently. However in SLMCE, the position of the sample inlet and outlet are fixed and its operation is much easier and separation is executed continuously. SLMCE can be utilized for laboratory-scale separations, as well as large-scale preparations.

In usual solid–liquid extraction, the desorption solvent is much stronger than the adsorption solvent. In SLMCE, regeneration of the solid phase after desorption is quickly performed with using a stronger solvent for the desorption of the strongly adsorbed sample in the recovery process, though further reconditioning steps should be required in order to recycle the solid phase. Here we describe an improved apparatus for dual-flow SLMCE for performing TMB chromatography, and the continuous extractive separation of a binary mixture of methyl- and propyl-4-hydroxybenzoate as model compounds.

2. Apparatus for solid–liquid multi-stage counter-current extraction

The extractor vessel is composed of a cylinder piston and an outer cylinder made of stainless steel pipes. The bottom of the outer cylinder (105×50.00 mm I.D., 2.5 mm thick; the capacity is about 80 ml) is welded to a stainless steel plate (2.5 mm thick). The bottom of the cylinder piston (120×49.80 mm O.D., 2.5 mm thick) is welded to a sintered stainless steel filter (20 μm mesh), and a piston ring made of tetrafluoroethylene is set 5 mm from the bottom (Fig. 2). These vessels were prepared by Shiraishi Kogyo (Tokyo, Japan).

The present apparatus has 12 sets of extraction vessels. The 12 outer cylinders for the liquid phase are fixed on the base plate, and the 12 cylinder pistons for the solid phase are hooked on the top plate which can be moved up and down by a screw motor. When the pistons are retracted, both the base and top plates can be rotated. The step-wise rotation of the top plate with cylinder pistons (solid phase, counterclockwise), and the base plate with outer cylinders (liquid phase, clockwise) produces the dual-flow counter-current motion of the two phases. The stroke range is set to keep the solid phase soaked in the liquid. Equilibration is achieved by the up and down strokes of the pistons. The speed of the stroke is about 0.5 cm/s. The number of strokes for equilibration, the range of the strokes, and the rate of strokes are electronically controlled. The equipment was manufactured by Suction Gas Kikan (Tokyo, Japan) (Fig. 3).

3. Experimental

3.1. Chemicals

4-Hydroxybenzoic acid *n*-propyl ester was purchased from Tokyo Kasei Kogyo (Tokyo). 4-Hydroxybenzoic acid methyl ester, 1-propanol and HPLC solvents were obtained from Wako (Osaka, Japan).

3.2. HPLC conditions

An HPLC system 980 (Jasco, Tokyo) equipped with an ODS column (Wakosil-II $5C_{18}$, 5 cm×4 mm, Wako) and a Rheodyne sampling valve (20 μl) was used. The eluting solvent was a mixture of water–1-propanol (8:2), and the eluent was monitored at 254 nm.

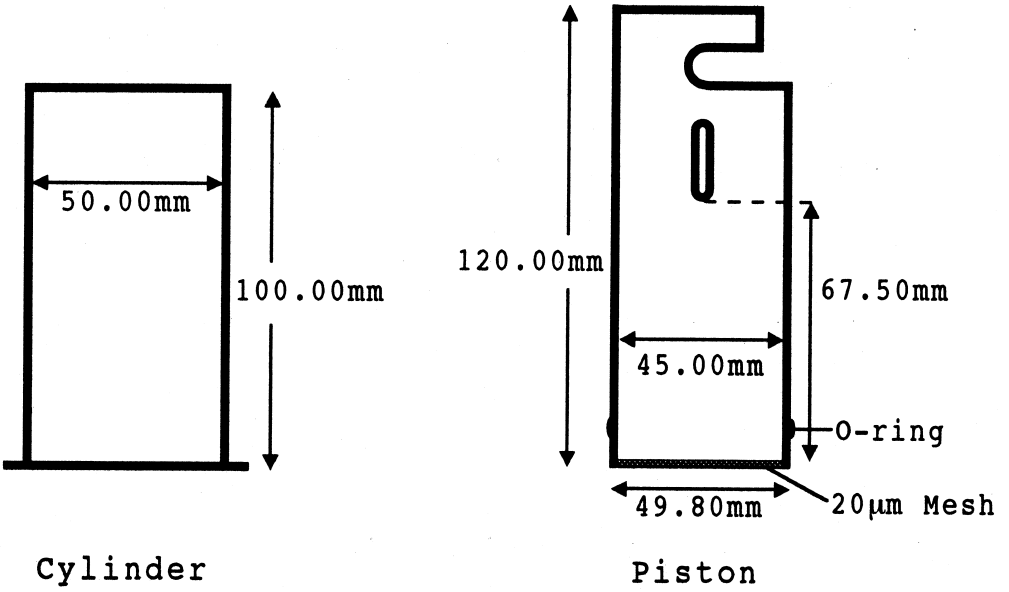

Fig. 2. The structure of the outer cylinder and the piston (the unit vessel of the extractor).

3.3. Liquid phase

A mixture of water–1-propanol (8:2) was used as the liquid phase. The volume of the liquid phase for the separation stage was 20 ml (19.39 g), and that for the recovery stage was 60 ml (58.16 g).

3.4. Solid phase

Octadecylsilica gel (ODS, 300 mesh, 40–100 μm, Tokyo Kasei Kogyo) was used as the solid adsorbent. First, 1.70 g of ODS were placed in the cylinder piston, and the piston was push down to soak the gel in the liquid phase (20 ml) in the cylinder bath. The solid phase increased 3.17±0.13 g on average.

3.5. Sample solution

Methyl- and propyl-4-hydroxybenzoate (0.40 g each) were dissolved in 100 ml of the liquid phase.

3.6. Measurement of the distribution ratios

Using four sets of vessels, the distribution ratios of the benzoates were measured in an air-conditioned room (24±1°C), using 4.87 g of wet solid phase and 20 ml of sample solution (4 mg/ml in water–1-propanol, 8:2). Distribution equilibrium was attained in five complete strokes of the piston. The concentration of the sample in the liquid phase (C_e) was then measured by HPLC. The increase in solid-phase mass after soaking was added to the liquid phase mass (total mass of the liquid phase became 22.56±0.13 g). The amount of sample absorbed per unit mass of the dry solid phase (S_a, mg/g) was then calculated from the initial amount of sample (A_0, mg) and C_e.

$$S_a = (A_0 - 22.56C_e)/1.7 \quad (1)$$

And the distribution ratio (D) is expressed as:

$$D = \frac{S_a}{C_e} \quad (2)$$

The obtained values of D were 5.67±0.36 (methyl ester) and 21.49±1.45 (propyl ester) on average. Because the concentration dependency of the distribution ratios can be neglected in the concentration range of 0.1–4 mg/ml, these values were used for further calculations. The measurements of the distribution ratios of the samples can be performed by

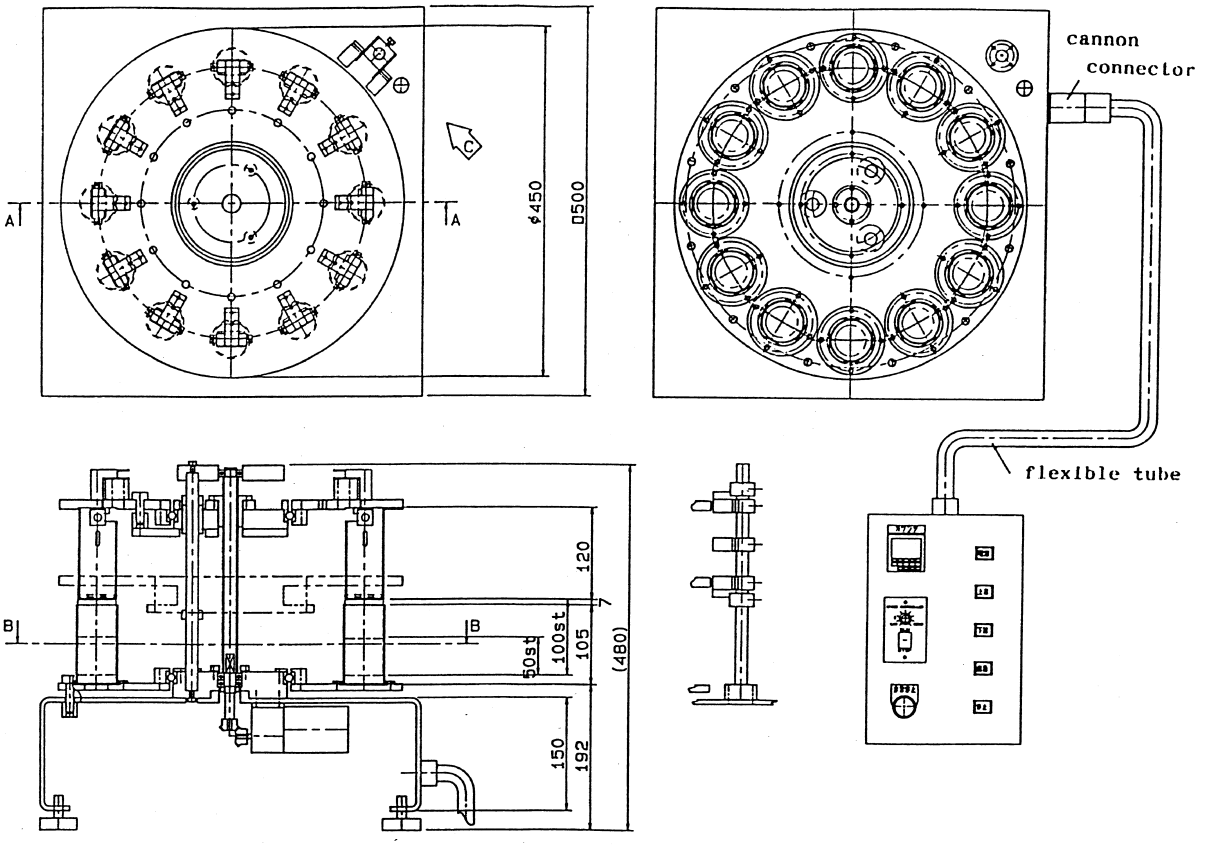

Fig. 3. Plans of the apparatus. (A) Top view (top left), a sectional plan (A–A, bottom left), a sectional plan (B–B, top right), a view of the pole with sensors (bottom middle, a view from the arrow C), and the control panel (bottom right).

an HPLC method using a column packed with the same solid phase and eluting with the same liquid phase, however, the concentration dependency of the distribution ratios of the samples can be easily determined by this method.

3.7. Operation procedure

The solid phase (ODS, 1.70 g of dry mass) was introduced to cylinder pistons, and was wetted with liquid phase. Then, 20 ml of the initial sample solution were placed in the cylinder bath at the fourth position. The liquid phase (20 ml) was set in the other seven (from first to eighth, except for fourth) separation cylinder baths, and 60 ml of the liquid phase was set in the four (from fourth to 12th) recovery cylinder baths. The following protocol was followed: (1) perform five strokes of equilibration (step 1); (2) transfer all the solid phases to the next stage (rotate the top plate counterclockwise); (3) perform five strokes of equilibration (step 2); (4) remove the liquid in the first [L(1)] and the ninth [L(9)] position cylinder baths to the collection reservoirs, RS(1) and RS(2), respectively; (5) supply fresh liquid phases to the first (60 ml) and ninth (20 ml) positions; (6) add sample solution (4 mg each ester in 1 ml) to the liquid phase of the fifth position; (7) transfer all the liquid phases to the next stage (rotate the base plate clockwise; the position of the sample addition comes to the fourth position again). The above steps (1–7) of procedures are counted as one extraction operation unit. (8) Repeat steps 1–7 for the desired total operation time.

The solid phase is recycled throughout the experiment. When the total operation times (t_{op}) becomes very large, continuous separation can be achieved by

continuous feeding of the sample and recycling of the solid phase.

3.8. Simulation program

The computational program was written in N-88 BASIC on MS-DOS, using a PC-9801US (i386, 32-bit) microcomputer (NEC, Tokyo, Japan). The amount of component in the solid phase in the Ith stage, S(I) and that in the liquid phase L(I) are calculated by the following equations (see Nomenclature). At equilibration step 1, from the stage $I=1$ to ND,

$$S(I) = (D \cdot SS + LA)[L(I-1) + S(I)]/(SL + LA + SF + D \cdot SS) \quad (3)$$

$$L(I) = (SL + SF) \cdot [L(I-1) + S(I)]/(SL + LA + SF + D \cdot SS) \quad (4)$$

from the stage of $I=ND+1$ to $ND+NU$,

$$S(I) = (D \cdot SS + LA) \cdot [L(I-1) + S(I)]/(SL + LA + D \cdot SS) \quad (5)$$

$$L(I) = (SL + SF) \cdot [L(I-1) + S(I)]/(SL + LA + D \cdot SS) \quad (6)$$

from the stage of $I=ND+NU+1$ to $ND+NU+NC$,

$$S(I) = (D \cdot SS + LA) \cdot [L(I-1) + S(I)]/(CL + LA + D \cdot SS) \quad (7)$$

$$L(I) = (CL + SF) \cdot [L(I-1) + S(I)]/(CL + LA + D \cdot SS). \quad (8)$$

At the equilibration step 2, from the stage $I=1$ to ND,

$$S(I) = (D \cdot SS + LA) \cdot [L(I) + S(I+1)]/(SL + LA + SF + D \cdot SS) \quad (9)$$

$$L(I) = (SL + SF) \cdot [L(I) + S(I+1)]/(SL + LA + SF + D \cdot SS) \quad (10)$$

from the stage of $I=ND+1$ to $ND+NU$,

$$S(I) = (D \cdot SS + LA) \cdot [L(I) + S(I+1)]/(SL + LA + D \cdot SS) \quad (11)$$

$$L(I) = (SL + SF) \cdot [L(I) + S(I+1)]/(SL + LA + D \cdot SS) \quad (12)$$

from the stage of $I=ND+NU+1$ to $ND+NU+NC$,

$$S(I) = (D \cdot SS + LA) \cdot [L(I) + S(I+1)]/(CL + LA + D \cdot SS) \quad (13)$$

$$L(I) = (CL + SF) \cdot [L(I) + S(I+1)]/(CL + LA + D \cdot SS). \quad (14)$$

where L(0) is the fresh liquid phase. And S(ND+NU+NC+1) is to be recycled as S(1).

3.9. Experimental operation conditions

By inputting extraction conditions, the separation results can be calculated as shown in Table 1.

Because the apparatus has 12 vessels, the total number of the vessels (ND+NU+NC) must be 12. Here we chose ND=4, NU=4 (eight vessels) for separation, and NC=4 (four vessels) for recovery. The amount of the liquid phase for the recovery stage (CL) was set as 60 ml, and the amount of the solid phase for the separation stage (SS) was set at 1.70 g. The initial amount of both esters were 80 mg in the liquid phase, and the additional sample scale (MS and ML) was 4 mg dissolved in 1 ml of the liquid phase (SF). The sample addition times (TF) were set at 19, and the total operation times (t_{op}) were set as 20. Then, the amount of the liquid phase (SL) was varied from 17 to 21 ml under the above conditions (Table 1, Nos. 1–5). The experimental condition was determined as No. 4 (SL=20 ml) in Table 1.

4. Results and discussion

4.1. Comparison of the calculated and experimental results

Under the optimal conditions of No. 4 in Table 2, continuous extractive separation of the mixture was

Table 1
Calculated results under selected extraction conditions and experimental results[a]

No.	Liquid phase, SL (g)	Operation times, t_{op}	Extracted amount (mg)					
			Extraction liquid phase			Desorption liquid phase		
			Me	Pr	Purity (%)	Me	Pr	Purity (%)
1	16.48	20	46.72	0.49	98.97	5.47	94.23	94.52
2	17.45	20	53.79	0.53	99.02	3.94	90.63	95.83
3	18.42	20	60.62	0.60	99.02	2.85	86.80	96.82
4	19.39	20	67.11	0.69	98.98	2.06	82.76	97.57
5	20.36	20	73.20	0.82	98.89	1.50	78.57	98.13
Exp.	19.39	20	66.04	0.78	98.83	3.81	88.82	95.89

[a] Other conditions for calculations are: SS = 1.70 g; LA = 3.167 g; CL = 54.926 g (60 ml), ND = 4; NU = 4; NC = 4; A(1) = 80; MS = 4; ML = 4; SF = 0.969 g (1 ml); and TF = (t_{op} − 1). Above values of SL correspond to volumes of 17, 18, 19, 20 and 21 ml.

performed (Exp. in Table 2). The experimental results agreed well with the calculated results (No. 4). The distribution of the materials in each separation and recovery vessels were analyzed by HPLC and calculated by the same program, they also agreed very well. The differences between the experiments and the calculated values may be due to slight deviations (~10%) in soaked liquid amounts, vaporization of the liquid, and slight temperature dependency of the distribution ratios of the components (especially propyl ester). The extraction vessels were not thermostatted, although the experiments were performed in an air-controlled room (23–25°C).

4.2. For better separations

The present apparatus has 12 extraction vessels; however, much better separations can be performed with more vessels. Thus, trial calculations were executed with 30 vessels, where ND = 10, NU = 10,

Table 2
Distribution of methyl- and propyl-4-hydroxy-benzoate in 1–12 cylinders (mg in the liquid phase)[a]

Position of cylinder			Calculated		Found		
			Me	Pr	Me	Pr	
		Recovery liquid					
CL = 4	12	↓	0.000	0.503	0.004	0.547	
3	11		0.001	1.43	0.007	1.57	
2	10		0.015	3.06	0.022	3.18	
1	9		0.235	5.62	0.222	5.53	→Rs(2)
		Fresh liquid					
NU = 4	8	↓	0.737	3.48	0.646	3.22	
3	7		2.10	3.99	1.91	3.48	
2	6		4.59	3.91	4.41	3.14	
1	5		9.07	3.78	9.05	2.78	
ND = 4	4		13.1	1.92	12.7	1.38	
3	3		12.2	0.490	11.4	0.280	
2	2		9.80	0.156	8.74	0.097	
1	1		4.54	0.061	3.92	0.061	→Rs(1)

[a] For calculations, conditions used are the same as in No. 4 in Table 1. The volume of the liquid phase were 20 ml (19.39 g, from ND = 1 to NU = 4) or 60 ml (from CL = 1 to 4), respectively. Sample was fed at the fourth position (ND = 4). Fractions of ND = 1 and CL = 1 were collected.

Table 3
Trial calculations with 30 vessels[a]

No.	Liquid phase, SL (g)	Operation times, t_{op}	Extracted amount (mg)					
			Extraction liquid phase			Desorption liquid phase		
			Me	Pr	Purity (%)	Me	Pr	Purity (%)
6	19.39	20	2.44	0.00	100.00	0.00	7.98	100.00
7	19.39	50	76.66	0.00	100.00	0.04	143.98	99.97
8	19.39	100	267.46	0.02	99.99	0.15	346.58	99.96

[a] Other conditions for calculations are: SS = 1.70 g; LA = 3.167 g; CL = 54.926 g (60 ml); ND = 10; NU = 10; NC = 10; A(1) = 80; MS = 4; ML = 4; SF = 0.969 g (1 ml); and TF = (t_{op} − 1).

and NC = 10 (Table 3, Nos. 6–8). Separations with over 99.9% purities can be attained.

By the calculation with the program, a separation of a binary mixture (α = 1.2, D1 = 10 and D2 = 12) with over 98% purities can be achieved with the apparatus which has 50 + 50 vessels for the separation and five vessels for the recovery stage, respectively[1].

4.3. Limitations on the direct application of the stationary phase and eluent system in HPLC to SLMCE

Though the present apparatus has a 20-μm mesh filter at the bottom of the piston cylinder, the filter mesh must be reduced to 2 μm in order to use the fine (3–5 μm) stationary phases used in HPLC. In SLMCE, however, it is not necessary to reduce the particle size in order to increase the HETP, because the transfer step is separated from the equilibration step, and the transfer of the stage is executed after equilibration.

When the solid phase is not favorably wetted with the liquid phase, it may be difficult to soak the fine particles of the solid phase with the liquid without pressure, limiting the choice of solvent that can be used with this apparatus.

5. Conclusion

An improved apparatus for dual-flow solid–liquid multi-stage counter-current extraction was manufactured. Using a mixture of methyl- and propyl-4-hydroxybenzoate as model compounds, it was demonstrated that true moving bed chromatographic separation of a binary mixture can be performed with the apparatus. Further, the separation results were satisfactorily simulated by a calculation program.

6. Abbreviations

CL	amount of the liquid phase in each outer cylinder of the recovery stage
D	distribution ratio
L(I)	amount of a sample in the liquid phase of Ith position
LA	average amount of the liquid soaking the solid phase
MS, ML	amount of the sample added after the second feed (mg)
NC	number of cylinders used for the recovery process
ND	number of cylinders in the bottom part of the extractor; this indicates the position of the sample feed
NU	number of cylinders in the bottom part of the extractor
t_{op}	total operation time
S(I)	amount of a sample in the solid phase of the Ith position (mg)
SF	amount of liquid phase used for the sample feed after the second feed (g)
SL	amount of the liquid phase in each outer cylinder of the extraction stage (g)
SS	dry mass of the solid phase
TF	total number of the sample feed

[1] This calculation is supported by the previous experiments [3].

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