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Chiral separation of a pharmaceutical intermediate by a simulated moving bed process[1]

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Abstract

The chiral separation of a pharmaceutical intermediate by a simulated moving bed (SMB) system on a pilot-scale is described. The operating conditions were chosen from results simulated by the software, HELP, developed by Novasep, based upon data from a single column. The productivity of the SMB system is tested by the separation of an ester of quinoline mevalonic acid at various internal flow-rates. The eluent consumption is also discussed. The step time to switch the ports to enter or withdraw solutions is one of important factors influencing the productivity.

Keywords: Enantiomer separation; Simulated moving bed chromatography; Preparative chromatography; Pharmaceutical analysis

1. Introduction

The simulated moving bed (SMB) process was developed to separate *para*-xylene from a mixture of C_8 hydrocarbons by UOP (Des Plaines, IL, USA) in the early 1960s [1]. The SMB technology was then applied widely to produce various compounds, to separate petrochemical products and sugars, by using silica-gels or ion-exchange resins as packing materials.

We started to study the application of SMB process to the separation of chiral materials in 1989. We first tried to separate 1-phenylethylalcohol with our own SMB unit using Chiralcel OB (Daicel, Japan) as chiral stationary phases (CSP), and presented the first experimental result on chiral separations by the SMB process in 1991 [2]. Separex (now Novasep, Nancy, France) also presented their results on chiral separation at the same time [3]. After then, many papers on chiral separations, especially for the separation of pharmaceutical compounds, by the SMB process have been published [5,6,8–13]. We have also continued to develop the SMB system for the application, and to present the results, such as the separation of beta-blockers, at several symposia [4,7].

We have studied the separation of an ester of quinoline mevalonic acid, DOLE, a pharmaceutical intermediate of a cholesterol reducing agent for hyperlipidemia, by a laboratory scale SMB unit since 1994 [14]. It has been done under the joint development with Nissan (Tokyo, Japan). The points of the

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study were to check the effectiveness of modeling software to find the suitable operating conditions, the influence of long-run operation for 1 year on productivity and quality of product. The SMB unit was manufactured by UOP with 16 columns, 15×3 cm I.D., and three pumps. The operating conditions were determined by the modeling software developed by UOP based upon the data obtained by a single column. The simulation result matched the actual result in operation. The operation was continued for 1 year, and it was found to be very stable. We confirmed that the performance of CSP after 1 year of operation did not change, and it was the same as the performance before operation. We tried to increase the productivity of the useful enantiomer obtained from a raffinate solution by shortening the step time in the operation. We found that the productivity could be increased by altering the conditions. However, the productivity was lower, 0.56 kg enantiomer per kg CSP per day, than we expected, due to some mechanical limitation of the unit.

Recently, we introduced a pilot-scale SMB unit, Licosep 12–100, from Novasep. The stability of the unit in the operation, and the production capability of enantiomer was tested and confirmed by using propranolol as an evaluation sample [15].

This shows the separation of the DOLE racemic mixture by this pilot-scale SMB system. The purposes of operation of the pilot-scale SMB unit this time were to check the effectiveness of software developed by Novasep to find the suitable operating conditions, and to confirm the possibility of increasing the productivity. The main feature of this process including SMB unit itself is explained, and the results of the separation are given hereafter in comparing to a single column system (eluent chromatography) and a laboratory-scale SMB unit from the points of view of productivity and eluent consumption.

2. Experimental

2.1. Analysis

Analysis was carried out on a system comprising a Jasco 880 PU pump from Nihon Bunko (Tokyo, Japan), a Jasco 875 UV detector from Nihon Bunko, a Shimadzu CTO-6A column oven from Shimadzu (Kyoto, Japan), a Rheodyne 7125 injector (Cotati, CA, USA) and a CDS integrator from L&A soft (Tokyo, Japan).

Optical purities were analyzed by an analytical Chiralcel OF (10 μm) column (250×4.6 mm I.D.) from Daicel (Tokyo, Japan), with *n*-hexane–2-propanol (8:2, v/v) as mobile phase at a flow-rate of 1.0 ml/min, injection volume 10 μl, UV detection at wavelength 325 nm, and temperature 40°C.

2.2. Sample

The sample was an ester of quinoline mevalonic acid, DOLE, a pharmaceutical intermediate of a cholesterol reducing agent for hyperlipidemia, shown in Fig. 1. The bulk, NK-104, has been developed by Nissan. The SMB process was employed as the one process in the whole production instead of using diastereomeric crystalization method. The weaker retained enantiomer on the CSP is the useful pharmaceutical intermediate, separated in a raffinate solution. The sample was dissolved in the mobile phase *n*-hexane–2-propanol (1:1), as the feed solution, 24 g/l.

2.3. Pilot-scale SMB unit

The SMB system, Licosep 12-100, was introduced from Novasep. It is composed of twelve 150×100 mm I.D stainless steel columns, designed by Daicel, five membrane pumps (feed, eluent, extract, raffinate

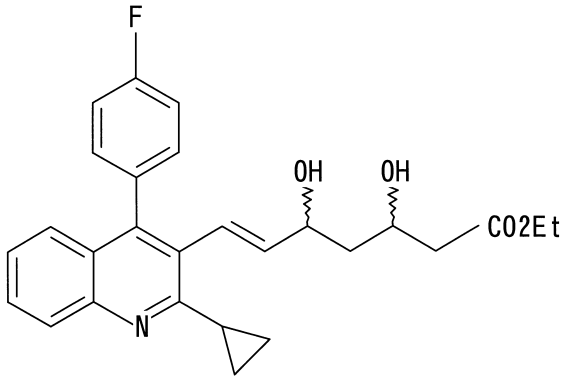

Fig. 1. Structure of DOLE.

and recycle), multiple two-way valves manufactured by Valco, and UV detector. The height of packing material in the column is adjustable between 50 and 150 mm. Also, the number of columns to be employed should be adjusted to the operating conditions simulated by HELP software, such as six columns or nine columns. Fig. 2 shows the columns in the unit, and six columns are set to each side in the unit. Operating temperature can be controlled by the heat-exchangers set in the lines of feed and

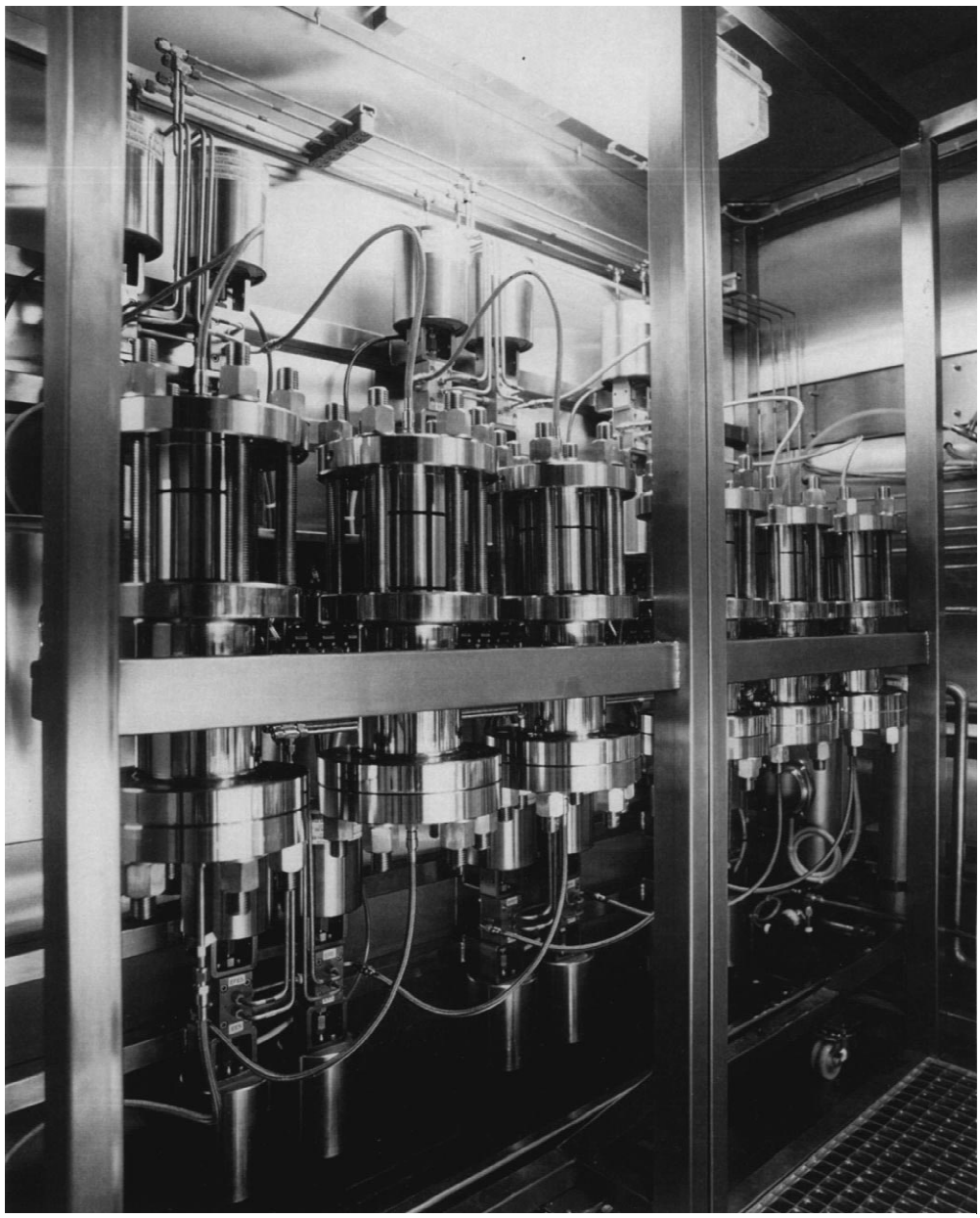

Fig. 2. SMB pilot system.

eluent solutions supplied to the unit. The temperature can be controlled between 10 and 50°C. The pressure durability of the system is up to 100 bar.

2.4. Feature of SMB separation process

The process is shown in Fig. 3. It mainly consists of SMB unit itself, several solvent tanks, two falling film evaporators (one for first condensation, another for solvent recovery process), four 20-l evaporators and a clean room for a package of the final product. The process operation is controlled by μ-XL of Yokogawa (Tokyo, Japan), and the SMB unit by Windows NT. The process can be operated under the cGMP protocol.

2.5. Columns

An eight-column SMB system was employed for the separation of DOLE based upon the simulation result. The column length of packing material, slightly modified Chiralcel OF, 20 μm (Daicel), was 100 mm. The CSP, Chiralcel OF, was packed into each column by a slurry method using 2-propanol.

2.6. Choice of mobile phase

The mobile phase for the SMB separation was different from the mobile phase used for the analytical purpose. It consisted of *n*-hexane–2-propanol (50:50, v/v). We selected this composition based on the sample solubility in the mobile phase to increase

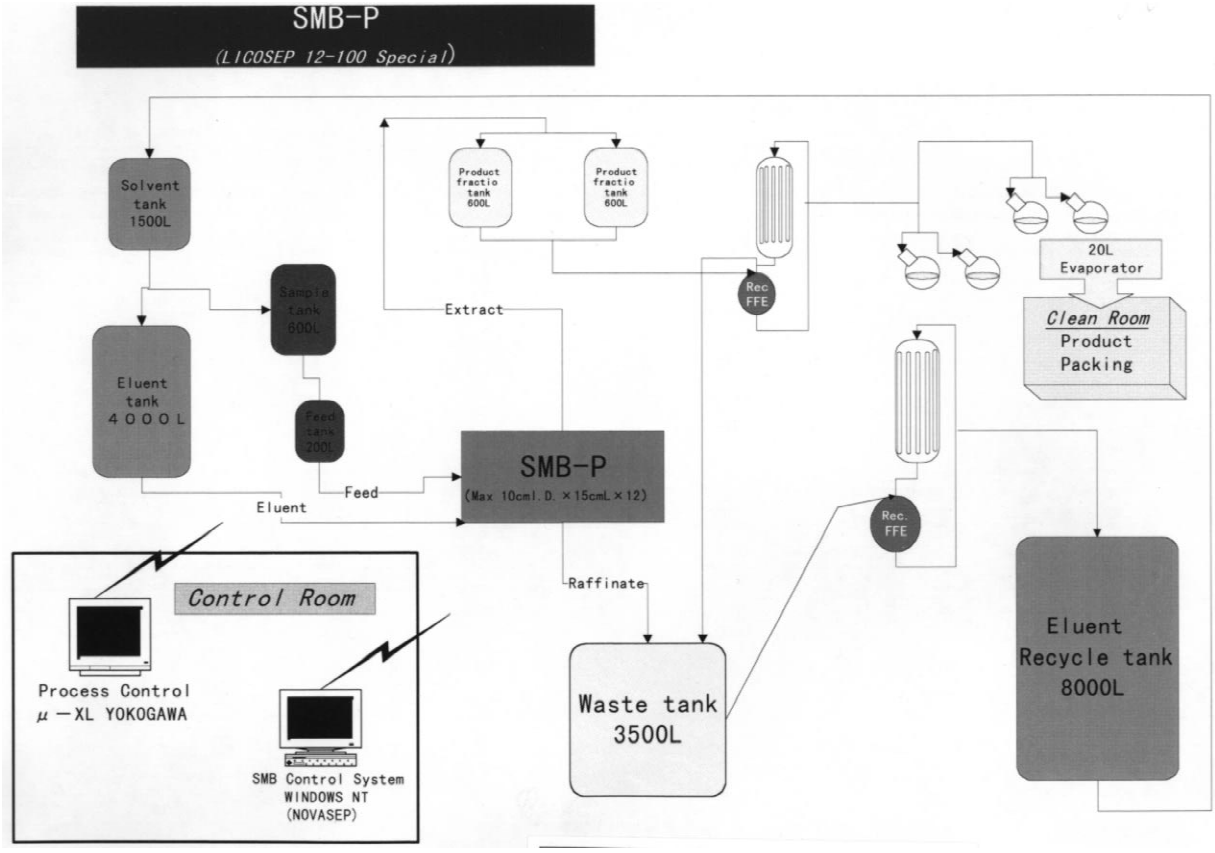

Fig. 3. Flow diagram of SMB pilot process.

the productivity, and the smaller capacity factors to decrease the eluent consumption. Both solvents were HPLC grade. Hexane was from Kanto (Tokyo, Japan), and 2-propanol was from Mitsui (Tokyo, Japan).

2.7. Specification of product

The enantiomer which is more weakly retained on CSP, in the raffinate solution from the SMB system is the target product. The required optical purity is higher than 98% enantiomer excess (e.e.).

3. Results and discussion

3.1. Simulation of operating conditions

The experiments on eluent chromatography were carried out to obtain the fundamental data for the simulation of starting operating conditions by HELP software. Two columns connected in series were used for the purpose. Each column, which was actually used in the pilot-scale SMB unit for the separation, was 10×10 cm I.D. packed with Chiralcel OF (20 μm). The racemic mixture of DOLE (100 μl) at four different concentrations, 3000, 5000, 10 000 and 24 000 ppm, were injected into the column to estimate the adsorption isotherms in the simulation software from each retention time for each sample loading. Table 1 shows the results. The calculation result by HELP software is shown in Table 2. It shows the recommended starting conditions as well as the expected concentrations and optical purities of both enantiomers obtained from the operation. The internal concentration profile in the SMB system calculated by the simulation is shown in Fig. 4.

Table 1
Variation of retention time for different sample loading

Concentration of racemic mixture injected (ppm)	t_{R1} (min)	t_{R2} (min)
3000	13.77	16.19
5000	13.74	16.12
10 000	13.64	15.98
24 000	13.64	15.95

Conditions: CSP, Chiralcel OF (20 μm), column size, 10×10 cm I.D.×2 columns, mobile phase, *n*-hexane–2-propanol (1:1, v/v), sample injection volume, 100 l; flow-rate, 150 ml/min; temperature, 40°C; detector 325 nm.

Table 2
Operating conditions of simulation result

Number of columns	8
Column specification	10×10 cm I.D.
Column configuration	2:2:2:2
Flow rates: Feed	1.78 (l/h)
Raffinate	3.33 (l/h)
Extract	5.92 (l/h)
Eluent	7.47 (l/h)
Step time (cycle time)	2.2 min (17.6 min)
Optical purity: raffinate	98.0% e.e.
Extract	92.0% e.e.
Concentration: raffinate	6.20 g/l
Extract	3.50 g/l

Fig. 5 shows the chromatogram obtained under the following conditions; column size 10×10 cm I.D., sample concentration of racemic mixture 24 g/l, mobile phase *n*-hexane–2-propanol (50:50, v/v) flow-rate 150 ml/min, temperature 40°C.

3.2. Standard operation

The operation of the SMB system was started in accordance with the conditions from the simulation result. As the result, the optical purity of enantiomer, effective compound, obtained from the raffinate solution was very low, 31.7% e.e. To accomplish a complete separation, higher than 98% e.e., the flow-rates of raffinate, extract, and recycle in the conditions were gradually changed. Table 3 shows the operating condition and related optical purity of both enantiomers obtained from the solutions of raffinate and extract as well as the productivities.

Finally, we reached 98.8% e.e. for the enantiomer in the raffinate and 97.0% e.e. in the extract. The productivity of enantiomer in the raffinate was 0.123 kg enantiomer per kg CSP per day. It was a little lower than the simulated result, 0.133 kg enantiomer per kg CSP per day. The operation was continued for over 500 cycles, and it was very stable. Fig. 6 shows

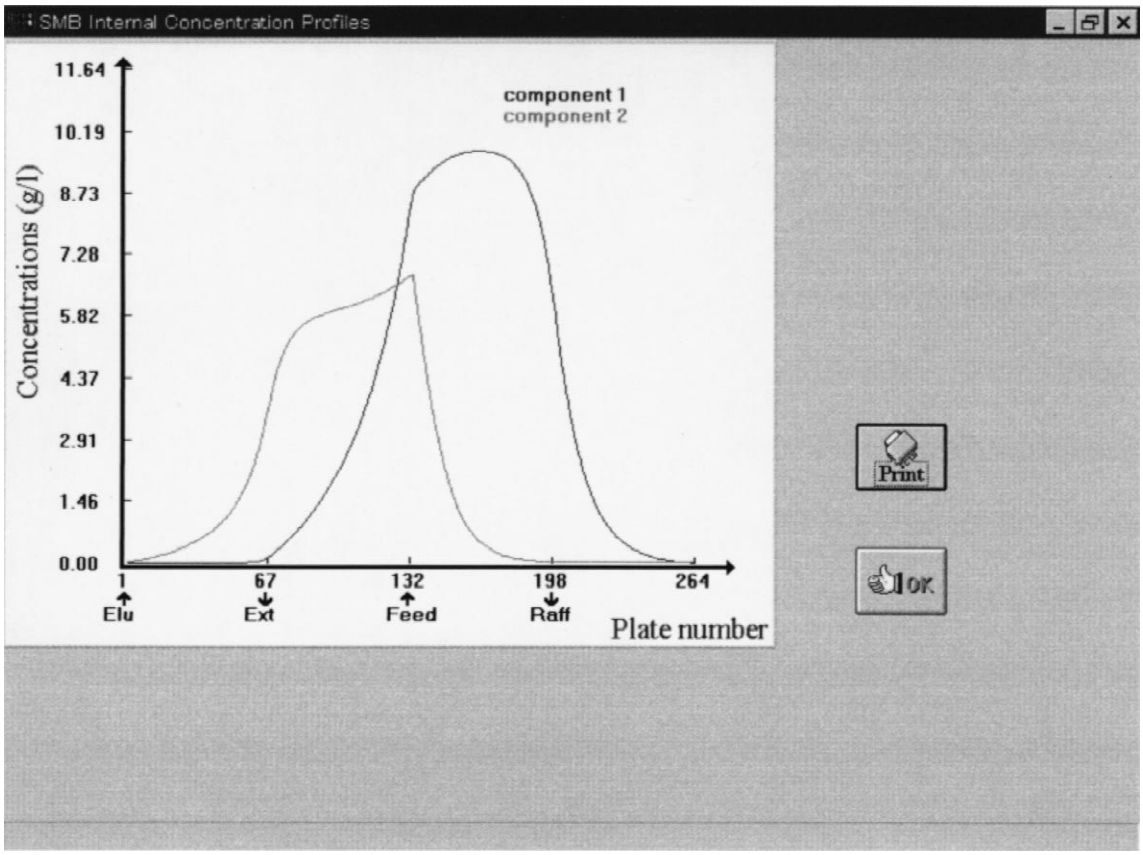

Fig. 4. Internal concentration profile in the SMB system calculated by the software.

the optical purity of the product obtained under each operating condition.

3.3. Increase of productivity

In accordance with the simulation results, 2.2 min was used as the step time. To increase the productivity, we tried shortening the step time to 1.1 min, half of standard condition. Each flow-rate was increased to twice the standard, and then it was adjusted gradually to accomplish the required optical purity. As a result, 99.4% e.e. enantiomer in the raffinate was obtained. All conditions and the results are shown in Table 4.

The productivity of the enantiomer was 0.268 kg enantiomer per kg CSP per day, finally. This was 2.2 times larger than the standard. Solvent consumption was 440 l/kg enantiomer, and it was a little less than the standard. In the case of the shorter step time operation, the flow-rates of zone 2 and 3 were very high, in the range of 50 to 60 l/h. However, the separation capability of the CSP (Chiralcel OF) was maintained under such higher internal flow-rates conditions. No changes of performance of the CSP were observed using 1.1 min as step time. The maximum loading capacity under the higher flow-rate may be beyond this conditions. So, the higher internal flow-rates used, the higher productivity we can expect. It depends upon the mechanical limitation of system equipment, such as valves, pumps, and parts of larger columns. Fig. 7 shows the change of optical purity for each operating condition.

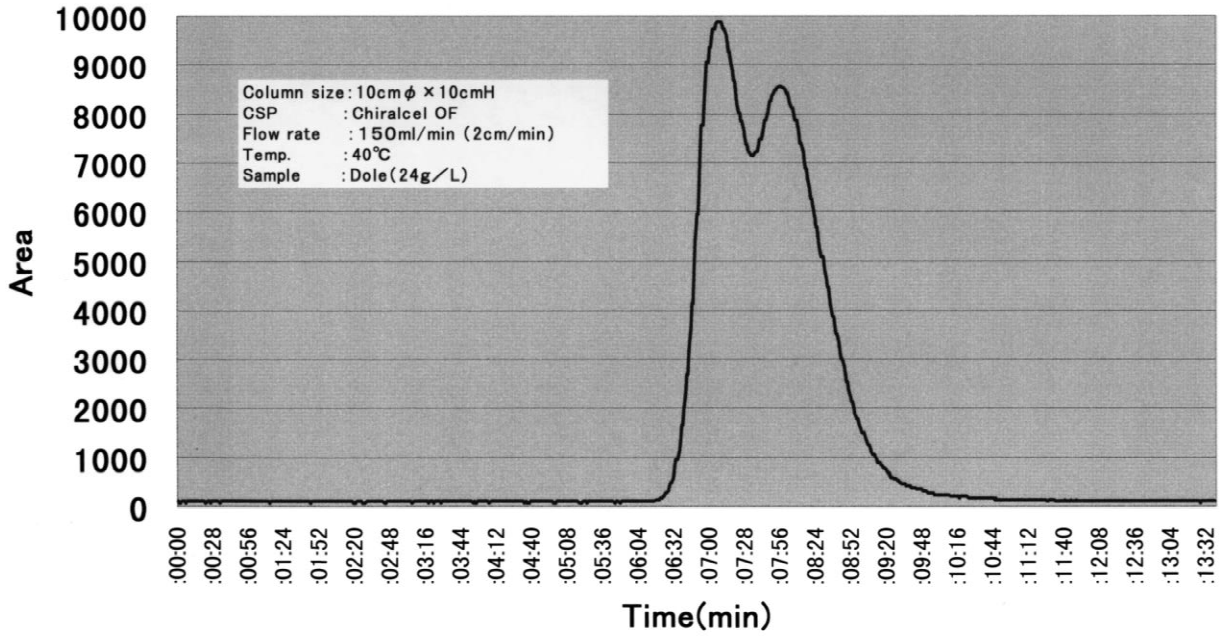

Fig. 5. Column chromatogram.

3.4. Comparison of productivity and eluent consumption

We have compared the results to the previous ones from the point of productivity and eluent consumption for the separation of racemic DOLE. The following four cases were compared; LC is an eluent chromatography by a single column system, SMB-L is a laboratory scale SMB system manufactured by UOP, SMB-P-1 is a pilot scale SMB system operated in the step time of 2.2 min, and SMB-P-2 is operated in the 1.1 min step time. SMB-L and SMB-P are

Table 3
Conditions and results of standard operation

Run number	HELP	1	2	3	4	5
Conditions						
Feed (l/h)	1.78	1.78	1.78	1.78	1.78	1.78
Raffinate (l/h)	3.33	3.33	3.23	3.13	3.13	3.13
Extract (l/h)	5.92	5.92	5.92	6.12	6.12	6.12
Eluent (l/h)	7.47	7.47	7.47	7.47	7.47	7.47
Zone 3 (l/h)	30.13	30.13	28.13	27.93	28.13	28.33
Step time (min)	2.2	2.2	2.2	2.2	2.2	2.2
Results						
Raffinate (% e.e.)	98.0	31.7	98.4	97.8	98.8	98.8
Extract (% e.e.)	92.0	97.2	95.3	88.6	95.4	97.0
Productivity (kg per kg CSP per day)	0.133	0.109	0.104	0.063	0.109	0.123

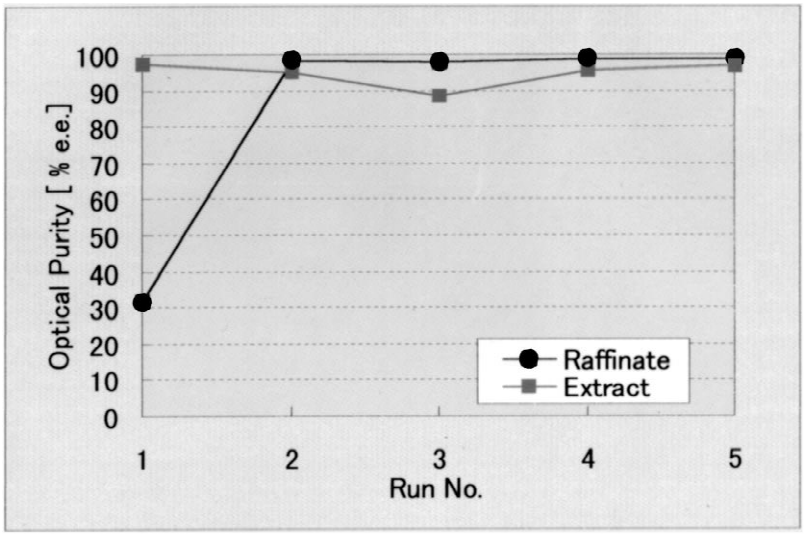

Fig. 6. Change of optical purity of each enantiomer under standard operation.

fundamentally different systems each other. SMB-L consists of 16 columns, three pumps (feed, eluent, extract), and rotary valves to switch columns. It is a three zones/three pumps system without recycle flow line. It may take larger eluent consumption than SMB-P to obtain a weaker retained enantiomer in the raffinate solution.

Table 5 shows each specification of system, operating conditions, and the results of operations. Figs. 8 and 9 show clearly that the productivity and eluent consumption of SMB system is much better than that of LC system. The productivity in the case of SMB-P-2 is twenty-two times larger than the LC system. Also, the eluent consumption of SMB system is less than one twentieth that of LC.

4. Conclusions

Chiral separation of a pharmaceutical intermediate of cholesterol reducing agent for hyperlipidemia, racemic DOLE, by a pilot scale SMB system was studied. It was confirmed that the SMB system was very effective for the production of enantiomer, and

Table 4
Operating conditions and results for increase of productivity

Run no.	1	2	3	4	5
Conditions					
Feed (l/h)	3.56	3.56	3.56	3.56	3.56
Raffinate (l/h)	6.26	6.26	6.26	6.26	6.26
Extract (l/h)	12.24	12.44	12.44	12.44	12.24
Eluent (l/h)	14.94	15.14	15.14	15.14	14.94
Zone 3 (l/h)	56.26	56.06	60.06	56.26	60.26
Step time (min)	1.1	1.1	1.1	1.1	1.1
Results					
Raffinate (% e.e.)	96.90	98.50	98.00	98.10	99.40
Extract (% e.e.)	91.30	89.50	89.80	89.80	94.80
Productivity (kg per kg CSP per day)	0.241	0.276	0.247	0.256	0.268

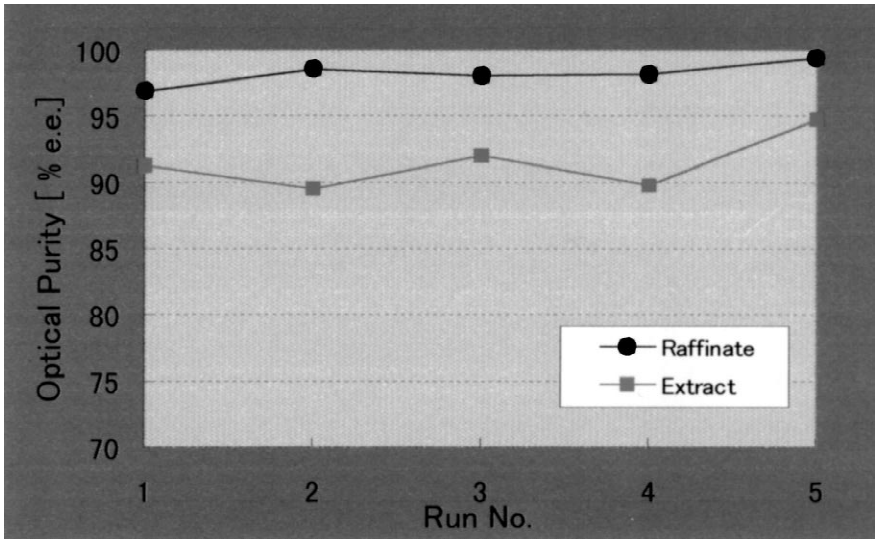

Fig. 7. Change of optical purity in the condition selected for the increase of productivity.

that it was much superior to the LC system as regards both productivity and eluent consumption. The productivity of the SMB system is twenty times larger than LC one, and the eluent consumption is less than one twentieth.

It was also confirmed that the higher flow-rate, shorter step time, can bring about larger productivity within the limitation of mechanical durability of equipment. Chiralcel OF has never indicated the limit of loadability for racemic DOLE in the range of operating conditions which we have taken.

In addition, the pilot scale SMB system can be operated stably, and the HELP software developed by Novasep is a useful tool to find the starting operating conditions.

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Table 5
Comparison of system specification, operating conditions and results

	LC	SMB-L	SMB-P-1	SMB-P-2
Column size	50×20 cm I.D.	15×3 cm I.D.	10×10 cm I.D.	10×10 cm I.D.
No. of column	1	16	8	8
No. of zone		3	4	4
Column configuration		6:6:3:1	2:2:2:2	2:2:2:2
Amount of CSP (kg)	9.42	1.02	3.77	3.77
Feed concentration (g/l)	5	30	24	24
Mobile phase	*n*-Hex–IPA (8:2)	*n*-Hex–IPA (1:1)	*n*-Hex–IPA (1:1)	*n*-Hex–IPA (1:1)
Flow-rate: feed (ml/min)	45.5	1.66	1.78	3.56
eluent (ml/min)	760	23.04	7.47	14.94
Step time (min)		3.75	2.20	1.10
Temperature (°C)	25	40	40	40
Productivity (kg per kg CSP per day)	0.012	0.056	0.123	0.268
Eluent consumption (l/kg product)	9680	1248	479	439
Enantiomer recovery (%)	67	80	90	>90

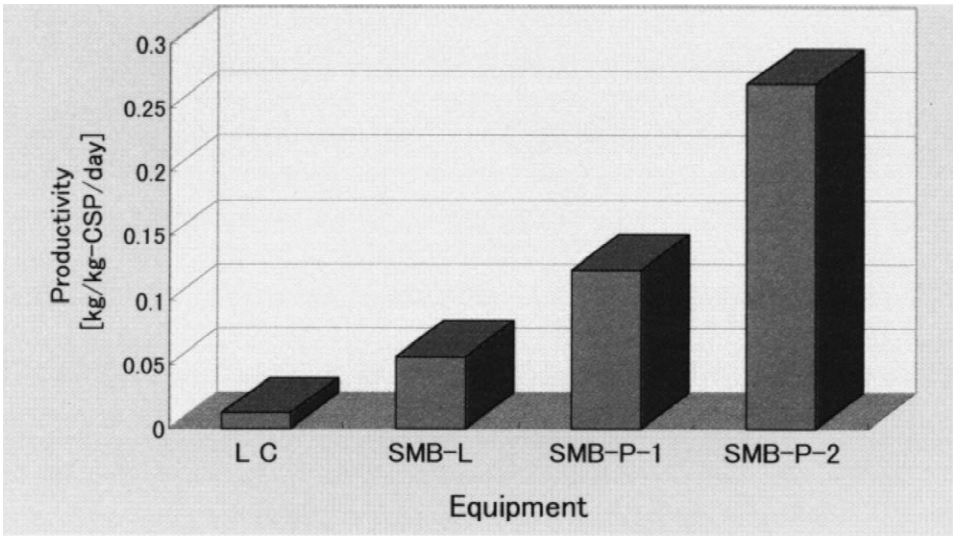

Fig. 8. Comparison of productivity among LC, SMB-L and SMB-P.

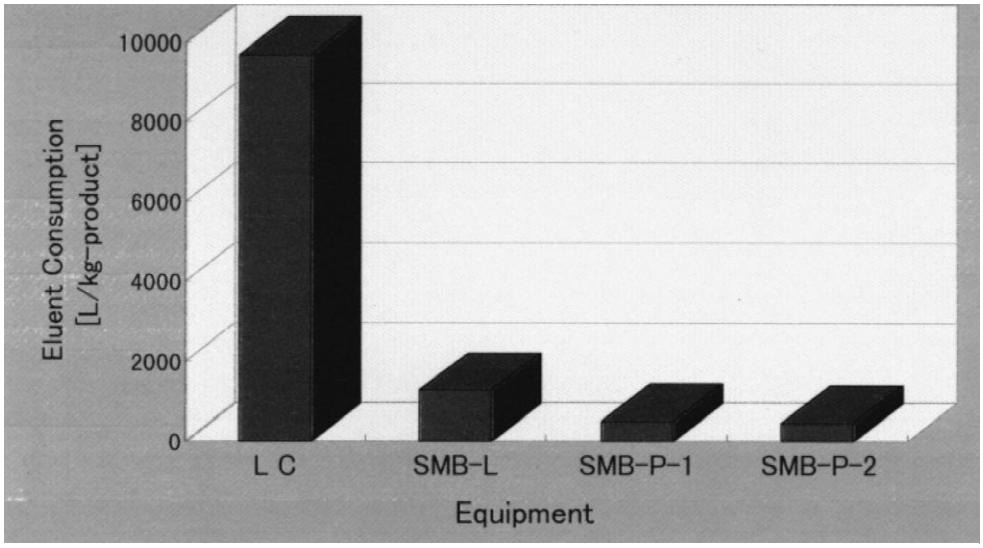

Fig. 9. Comparison of eluent consumption among LC, SMB-L and SMB-P.

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