Journal of Chromatography, 590 (1992) 113–117
Elsevier Science Publishers B.V., Amsterdam

CHROMSYMP. 2396

Optical resolution by simulated moving-bed adsorption technology

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ABSTRACT

The application of the simulated moving bed adsorption (SMBA) technique to optical resolution using eight columns packed with chiral stationary phases was studied. The SMBA system was compared with the conventional batch system, and it was concluded that the former is better from the point of productivity and solvent recovery. In addition, it was shown that an optimum particle size of the chiral phase to attain the maximum productivity exists if a certain upper limit of the pressure drop is assumed.

INTRODUCTION

Recently, in the fields of pharmacy and agrochemicals, a racemic material tends to be substituted by an optically active material more active than the antipode. Considering the growing demand for optically active materials, we decided to develop a new technique that is more productive than a conventional batch system. The simulated moving bed adsorption (SMBA) technique is a useful means of separating large amounts of compounds as it is a continuous separation process. We therefore started this study to apply SMBA technology to the production of optically active materials. This technique was originally developed by Universal Oil Products to separate *n*-hexane and cyclohexane from their mixture [1], and recently it was applied to the separation of water-soluble materials (*e.g.*, a glucose–fructose mixture) [2]. In these instances theoretically the resolution was easy as the feed concentrations were as high as about 40% and the adsorption isotherms were linear. In contrast, our application was difficult as the solubility of the material in the mobile phase (an organic solvent) was very low and the adsorption isotherms were non-linear [3]. We are now developing computer software to simulate an SMBA system with non-linear adsorption isotherms and the results will be reported elsewhere. In this paper, we report the first separation of optical isomers by an SMBA process and demonstrate that the process has a much higher productivity than a conventional batch process.

EXPERIMENTAL

SMBA system

Fig. 1. illustrates the concept of the SMBA system for optical resolution. The umbrellas symbolize optical isomers, the conveyor belt the stationary phase and the wind the mobile phase. The open umbrellas, which are the enantiomers retained more weakly, and the closed umbrellas, which are the enantiomers retained more strongly, are on the conveyor belt. Hence we can obtain enantiomers continuously.

Fig. 2. is a schematic diagram of the experimental apparatus used. The eight adsorption columns packed with a Chiralcel OD-type packing material were connected to rotary valves. The packing materials were prepared by coating cellulose tris(3,5-dimethylphenyl carbamate) on silica gels of 20, 75 and 100 μm diameter. Each column was 15 cm × 2 cm I.D. All the adsorption column were kept at 25°C by circulating thermostated water through the jackets. The positions of the feed, raffinate, extract and desorbent were fixed, but the lines connected to the rotary valves were controlled with the system controller [Japan Spectroscopic (Jasco) Model 802-

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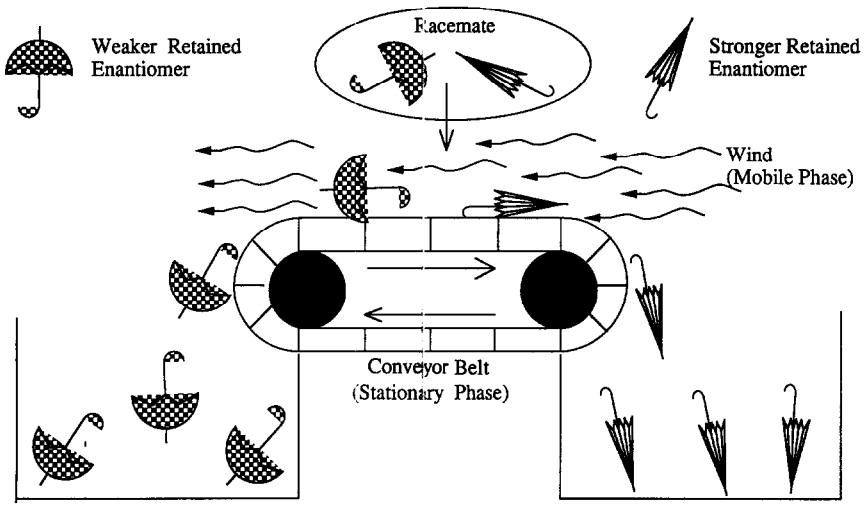

Fig. 1. Concept of the simulated moving-bed adsorber (SMBA) system for optical resolution.

SC system controller]. The feed and drainage pumps were used as the pumps for the high-performance liquid chromatographic (HPLC) system (Jasco 887-PU). The intermittent rotation of the rotary valves produced counter-current movements of the adsorbent phase to the liquid stream in the system. In Fig. 1 the stationary phase is moving, but in the real equipment the feed line, desorbent feed line, raffinate line and extract lines are moving intermittently. The desorbent was a *n*-hexane–isopropanol (9:1). The racemate used was 1-phenylethanol. The raffinate and extract were collected at certain in-

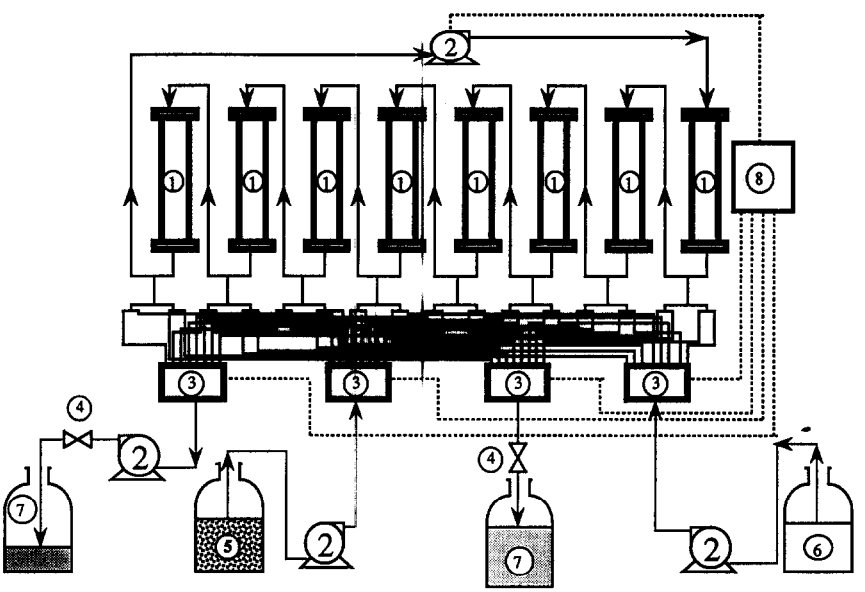

Fig. 2. Schematic flow diagram of SMBA system for optical resolution. 1 = Column, 150 mm × 20 mm (I.D.), packed with Chiralcel OD (20 μm, 75 μm, 100 μm); 2 = HPLC pump; 3 = rotary valve (8-port type); 4 = back-pressure valve; 5 = feed (racemate) reservoir; 6 = desorbent reservoir; 7 = extract and raffinate collector; 8 = system controller.

tervals (*e.g.*, 1 h) and their optical purities were measured by HPLC. A Shimadzu LC-6A HPLC system equipped with a Chiralcel OD column (25 cm × 0.46 cm I.D.) (Daicel) and a Model SPD-6AV detector was employed. The eluent *n*-hexane–isopropanol (9:1) at a flow-rate of 1.0 ml/min. 1-Phenylethanol was detected of 260 nm and determined by the external standard method.

Conventional batch system

The column size was 50 cm × 1 cm I.D., the column temperature was 25°C, the eluent was *n*-hexane–isopropanol (9:1) at a flow-rate of 4.7 ml/min and a 50-μl aliquot of the sample solution (2%, w/w, in the above-mentioned mixture) was injected every 8 min.

RESULTS AND DISCUSSION

Measurement of the basic physical properties

In the SMBA system eight columns were connected in series, so the pressure drop becomes very high. We therefore chose packing materials with some larger particle sizes (20,75 and 100 μm) and compared their performances and the pressure drops in the SMBA systems. Table I shows the number of theoretical plates of a single column (25 cm × 1 cm I.D.).

Results of SMBA experiments

The results of the SMBA experiments are shown in Figs. 3–6. As shown in Fig. 3, we divided eight columns into four zones. Zones 1 and 4 have one column each, zones 2 have four columns and zone 3 has two columns. In ordinary set-ups each zone has two columns, but in our case the above arragement gave better results. This means that the role of zones 2 and 3, which was the separation of the racemate, was more important than the role of zones 1 and 4, which was washing the column. The feed concentration was very low compared with the above-mentioned water-soluble compounds as the solubility of the racemate in the mobile phase was low. In spite of these unfavourable conditions, we could eliminate the racemate with a high efficiency [99% enantiomer excess (e.e.)].

Fig. 4. shows the effect of the flow-rate of the extract on the purity of the product enantiomers.

TABLE I

NUMBER OF THEORETICAL PLATES

Experimental conditions: column, 25 cm × 1 cm I.D.; mobile phase, *n*-hexane–isopropanol (9:1, v/v); flow-rate, 4.7 ml/min; temperature, 25°C; sample, *trans*-stilbene oxide, 5000 ppm; sample loading, 20 μl.

Particle size (μm)	No. of theoretical plates
20	1673
75	262
100	120

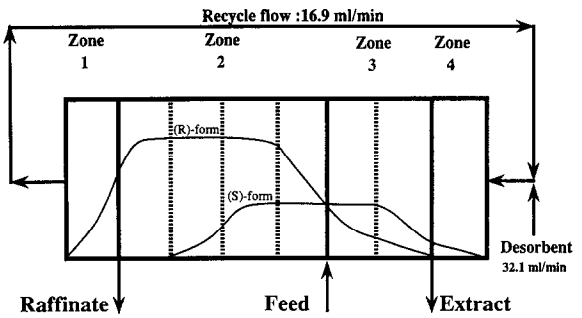

Fig. 3. Experimental results of optical resolution with the SMBA system. Conditions: packing, Chiralcel OD, particle diameter 20 μm; column 150 m × 20 mm I.D. (× 8); sample, 1-phenylethanol; mobile phase, *n*-hexane–isopropanol (9:1, v/v); cycle time; 2.9 min; temperature; 25°C. The distribution of the two enantiomers is shown conceptually. Feed: racemic 1-phenylethanol, 0.5 ml/min, 39 100 ppm (racemate); raffinate: (*R*)-(+)-1-phenylethanol, 5.4 ml/min, 1728 ppm (99% e.e.); extract: (*S*)-(−)-1-phenylethanol, 27.2 ml/min, 360 ppm (92% e.e.).

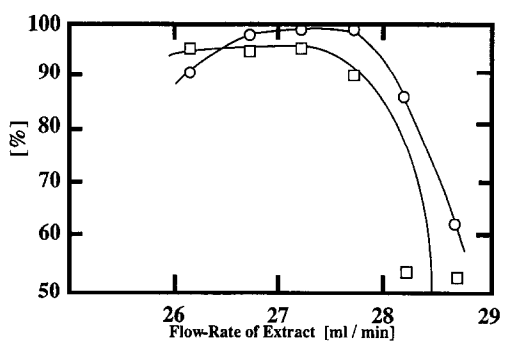

Fig. 4. Effect of the flow-rate of the extract on the purity of the product enantiomers. Experimental conditions as in Fig. 3 except for the flow-rate of the raffinate and extract. □ = (*S*)-(−)-phenylethanol in extract (%); ○ = (*R*)-(+)-phenylethanol in raffinate (%).

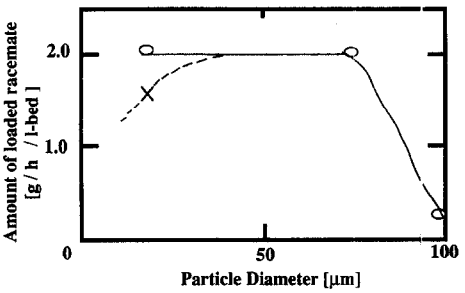

Fig. 5. Relationship between particle diameter and sample loading.

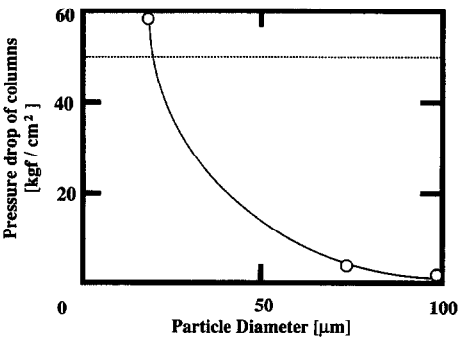

Fig. 6. Relationship between particle diameter and the pressure drop of the columns.

The conditions of the experiments except the flow-rates of the raffinate and the extract were the same as those in Fig. 3. A satisfactory optical purity of the raffinate (98% e.e.) could be obtained only in a limited range of the flow-rate ratio of the raffinate and the extract. This severe limitation may be rationalized as follows. When the extract flow-rate was too low, the flow-rate in zone 2 became too large, causing the elution of the *S*-form in the raffinate; when the extract flow-rate was too high, the flow-rate in zone 2 became too large, causing too much *S*-form to remain in zone 4, which was incompletely washed out to contaminate the raffinate. Both factors seem to be the outcome of the low resolution of the enantiomers on the columns.

Fig. 5. shows the relationship between the particle size and the load calculated from the maximum feed concentration, which kept the purity of the raffinate higher than 98% e.e. Fig. 6 shows the relationship between the particle size and the total pressure drop of all columns. Fig. 5 clearly shows that the amount of the loaded racemate decreased when the particle size was larger than 75 μm. On the other hand, the total pressure drop sharply increased when the particle size decreased. If the upper limit of the total pressure drop of the system is assumed to be 50 kgf/cm^2, the amount of loaded racemate should follow the broken line in Fig. 5 and the presence of the optimum particle size is predicted. To determine the optimum particle size, a more de-

TABLE II

COMPARISON OF THE CHARACTERISTICS OF THE SMBA SYSTEM WITH A CONVENTIONAL BATCH SYSTEM IN THE OPTICAL RESOLUTION OF 1-PHENYLETHANOL BY CHIRALCEL OD (20 μm)

Parameter	Conventional batch operation	SMBA system	SMBA/Batch
Loading of racemate (g/h · l bed)	0.13	2.05	16:1
Productivity of (*R*)-(+)-enantiomer (g/h · l bed)	0.016	0.981	61:1
Amount of used solvent [l/g (*R*)-(+)-enantiomer]	463.4	5.3	1:87
Concentration of refined (*R*)-(+)-solution (p.p.m.)	8.7	1728.4	200:1
Enantiomer excess of the product (% e.e.)	99.0	98.7	1:1
Yield of (*R*-(+)-1-phenylethyl alcohol (%)	24.6	95.5	4:1

tailed study must be conducted with particle sizes between 20 and 75 μm. If the upper limit is 100 kgf/cm^2, the amount follows the solid line in Fig. 5.

We compared the SMBA system and a conventional batch system and the results are given in Table II. The SMBA system was apparently superior to the conventional batch system in the following two respects: the productivity per unit amount of the packing material was 61 times larger, and the amount of solvent used was on 87th and the concentration of the raffinate was 200 times higher. Hence the cost of solvent recovery is much lower with the SMBA system.

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