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Simulated moving-bed for separation of mandelic acid racemic mixtures

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Abstract−Two enantiomers that constitute a racemate have different activities when employed as pharmaceuticals. Consequently, the pharmaceutical industry has been forced to market pure enantiomers instead of the racemic mixture. Simulated moving bed (SMB) is a chromatographic process that operates continuously without losing the enantiomeric purity of outlet streams from SMB. The present work describes the enantioseparation of mandelic acid in a lab-scale SMB unit. Chiral stationary phase was made by packing Kromasil TBB (O,O′-bis(4-tert-buylbenzoyl) -N,N′-diallyl-L-tartar diamid) gel into empty columns. The outlet streams were sampled and analyzed by an analytical HPLC. Analysis indicated that purity values range from 82% to 94% according to the change of extract stream flow rate.

Key words: Mandelic Acid, SMB, Kromasil TBB Column

INTRODUCTION

There is a growing demand in the pharmaceutical industry for efficient and cost effective methods to purify optical isomers [1,2]. Continuous chromatographic processes have been used as an important tool to meet the objectives of the chemical manufacture of several chiral compounds [3]. Simulated moving bed (SMB) is a large-scale version of traditional high-performance liquid chromatography (HPLC), and it operates continuously without loss of the enantiomeric purity of the outlet streams [3]. SMB was introduced in the pharmaceutical industry in the 1990's and the SMB chromatographic separation technique is mainly applied for two-component separation problems like enantiomer separations and isomer separations. The essence of SMB is that instead of the continuous moving of stationary adsorbent phase, which leads to many problems, the moving of the stationary phase in multiple columns is simulated by valve switching between columns. The process consists of simulating the countercurrent movement of adsorbent by switching the positions of the inlet and outlet streams, producing two outlet streams, one rich in the more adsorbable component (extract stream) and the other rich in the less adsorbable one (raffinate stream), which is adequate for racemates [5].

SMB has been used by several investigators to separate components from racemic mixtures [6,7], obtaining the two enantiomers of a chiral molecule with a high purity to carry out clinical tests. The variety of chiral stationary phase and the vast numbers of racemic mixtures produced by the pharmaceutical industry make this technique a powerful tool. D-Mandelic acid is pharmaceutically active as antibacterial, antiaging and diuretics agent among D- and L-mandelic acid mixture. The aim of the present communication was to design and build a laboratory-scale unit to separate D-mandelic acid from the racemic mixture of mandelic acid. As far as authors' knowledge, this work is the first report on the mandelic acid separation in the SMB of Kromasil TBB columns.

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MATERIALS AND METHODS

1. Simulated Moving Bed (SMB) Unit

A laboratory-scale SMB unit has four stainless steel columns of 0.39 cm in diameter and 30 cm in height. The columns are distributed between four different regions containing one column each (Fig. 1). The eluent is recycled through the series of columns by an eluent recycle pump. Feed and eluent pumps supply the SMB with feed (mandelic acid racemates) and eluent streams, and raffinate and extract pumps withdraw D-mandelic acid in extract stream and L-mandelic acid in raffinate stream. Four 12-position switch valves as well as four 6-way connectors are responsible for the position change of feed, eluent, raffinate and extract lines between four col-

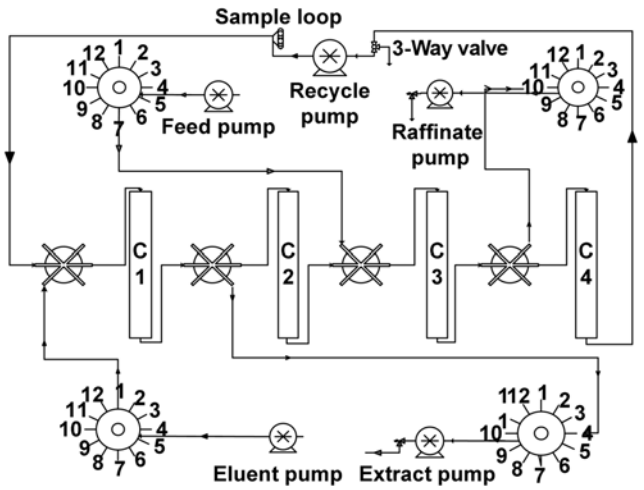

Fig. 1. Detailed P & ID of SMB.

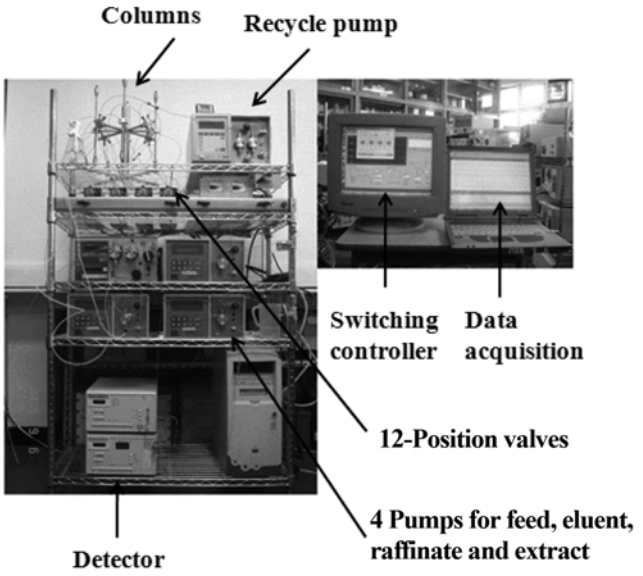

Fig. 2. Photographs of the laboratory SMB unit.

umns at preset switch times. These valves are connected to four high pressure liquid chromatographic pumps and columns. In Fig. 2 some details of the complete setup are shown. 12-position valves (Valco Instruments Co.) are electrically commanded and linked to a computer by a data-acquisition board. Each valve automatically operates the unit at the selected flow rates by a program developed by a local software company.

The unit also contains a sampling valve connected to one of the columns of the series, which allows collection of internal samples. Analysis of these samples enables determination of the internal profile of concentrations of D and L enantiomers, which illustrates the dynamics of separation inside the series of columns.

2. Racemic Mixture Used for Separation

A racemic mixture of mandelic acid was purchased from Sigma. The structure of the mandelic acid molecule is depicted in Fig. 3.

The mandelic acid molecule has chirality and was separated in a column of Kromasil column [8], using hexane and ter-butylmethylether (tBME) as the mobile phase. The D enantiomer is the one of interest, due to its antibacterial activity, and must be separated from the L enantiomer.

3. Column Packing and Mobile Phase

TBB, the stationary phase, has been considered for the resolution of mandelic acid racemic mixtures. It was purchased from Eka Chemical. The mobile phase used was HPLC-grade hexane and tBME (85/15% v/v), in which mandelic acid is dissolved up to 0.1 mg/mL. The columns (3.9 mmD×300 mmL) were slurry-packed following the protocol described [9].

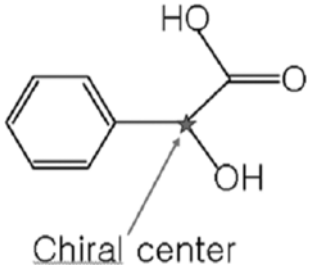

Fig. 3. Chemical structure of mandelic acid.

4. Determination of Purity by HPLC

To ensure the purity of the streams, samples were collected throughout the experimental run, for subsequent analysis in an HPLC system, which furnishes the values of purity averaged over the time of collection. The column used for the HPLC tests is 250 mm high with an ID of 4.6 mm. Extract purity (D-mandelic acid) is referred to as P_D and raffinate purity (L-mandelic acid) as P_L. The concentration of solute in raffinate and extract is determined with an analytical HPLC equipped with commercial Kromasil TBB column [8].

5. Porosity Measurements

Porosity of the bed of TBB packed in the columns was measured following the protocol described by [9]. Each of the four columns necessary for operation of the SMB unit, containing the TBB, was individually coupled to the HPLC system, and 1,3,5-Tri-tert-butylbenzene was injected into each one of them. This compound does not interact with the adsorbent and hence residence time throughout the bed is proportional to total bed porosity. The relation between porosity and residence time is

$$t_0 = \frac{\varepsilon V}{Q}.$$

where ε is the total bed porosity including the particle pores, t_0 is the residence time of Tri-tert-butylbenzene flowing throughout the bed, Q is the liquid flow rate and V is the total volume of the bed.

6. Isotherms Parameters from Chromatographic Experiments

Before running the SMB unit, it was necessary to know the interactions between the enantiomers of the racemic mixture and the chiral stationary phase. This information can be obtained by injecting racemic mandelic acid into each of the four columns of the SMB unit. Then the retention time of each enantiomer is measured, which allows determination of the linear isotherms, valid for dilute systems. The isotherms are represented by the Henry constants [9].

$$H_i = \frac{t_i^R - t_0}{t_0}\left(\frac{\varepsilon}{1-\varepsilon}\right)$$

where t_i^R is the retention time of the i enantiomer.

RESULTS AND DISCUSSION

1. Bed Porosity and Henry Constants

Total porosity was as 0.68 determined from the pulse experiments for the four columns (Table 1). The average values of Henry con-

Table 1. Determination of bed porosities and Henry constants of four columns

Col. no.	ε	Henry constant	
		L-form	D-form
1	0.680	9.597	10.36
2	0.685	9.800	10.62
3	0.687	9.746	10.53
4	0.681	9.592	10.43
Average	0.683	9.684	10.48

stants are; H_L=9.68 and H_D=10.48.

2. Continuous Runs in the SMB Unit

After determination of the Henry constants, the procedure described by Mazzotti et al. [10] allowed choice of the operational conditions for SMB unit operation. The triangle theory is useful to select points where m2 and m3 are located and flow rates of feed, eluent, raffinate and extract can be determined. It was assumed that the system operates under conditions dilute enough to be correctly represented by the linear isotherms.

The conditions chosen for the experimental runs are summarized in Table 2.

Switching time was determined as the average value of the retention time of L-mandelic acid (13.45 min) and D-mandelic acid (14.36 min).

The experimental runs under three conditions in Table 2 were chosen, and their results will be presented in order to illustrate how SMB operation is assessed in Figs. 4, 5, and 6, respectively, for the concentration of the extract and raffinate streams in the experimental runs. The numbers in the abscissa indicate the outlet ports of the column positions that are 1, 2, 3, 4 and 5 representing eluent, extract, feed, raffinate, and eluent respectively. Number 5 is the same position as number 1 for convenience in graphing. Feed was supplied to the inlet of column 3 and raffinate stream was sampled at the outlet of column 4 as in Fig. 1. The position of raffinate stream is periodically changed to the right direction in Fig. 1, and consequently raffinate samples are taken in the next switch time at the outlet of column 1 and so on. After four switch times, the raffinate port returns to the start position. Analysis of these samples in batch HPLC system allows determination of an internal concentration profile through four columns. The profiles show that steady state was established after ten cycles. The cyclic steady state was decided when the sample concentrations from extract and raffinate streams did not change. A shift of profiles is observed as the extract flow rate Q_{EX} decreases. The profiles in Fig. 4 are observed to move right to the column 4 in comparison with Figs. 5 and 6 as the Q_{EX} decreases from 0.4 to 0.2 ml/min. D-mandelic acid concentrations at 4 become higher from 0.004 to 0.008 and the purity of raffinate stream (L-mandelic acid) decreases. On the other hand, the purity of extract stream (D-mandelic acid) at 2 increases.

The purity of D-mandelic acid increases from 80% to 94% as Q_{EX} decreases (Fig. 7). As Q_{EX} decreases, Q_{II} and Q_{III} in Table 2 increases due to the lower output in front of zone II. As a result, internal concentration profiles of D-,L-mandelic acid are moving to the raffinate port (no. 4) because the feed (50/50 mixture of D-/L-mandelic acid, no. 3) port highly influences the raffinate port due to relatively

Table 2. Summary of SMB operation conditions and results of SMB experimental runs

	Case1	Case2	Case3
Q_{feed} (ml/min)	0.2	0.2	0.2
Q_{eluent} (ml/min)	0.8	0.8	0.8
$Q_{extract}$ (ml/min)	0.4	0.3	0.2
$Q_{raffinate}$ (ml/min)	0.6	0.7	0.8
Q_I (ml/min)	1.3	1.3	1.3
Q_{II} (ml/min)	0.9	1.0	1.1
Q_{III} (ml/min)	1.1	1.2	1.3
Q_{IV} (Recycle) (ml/min)	0.5	0.5	0.5
Δt (ml/min)	13.45	13.45	13.45

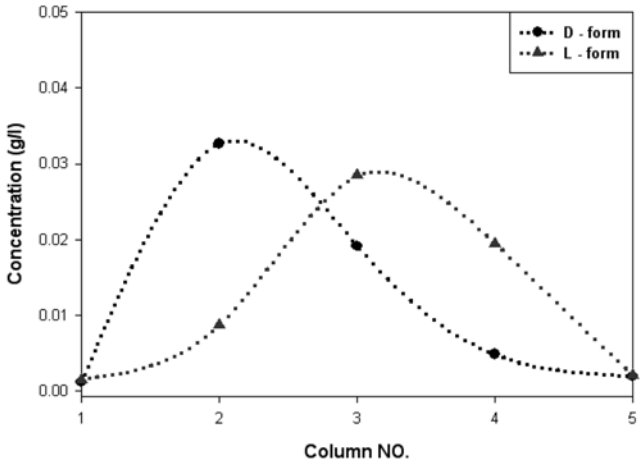

Fig. 4. Internal concentration profiles at Q_{EX}=0.4 ml/min.

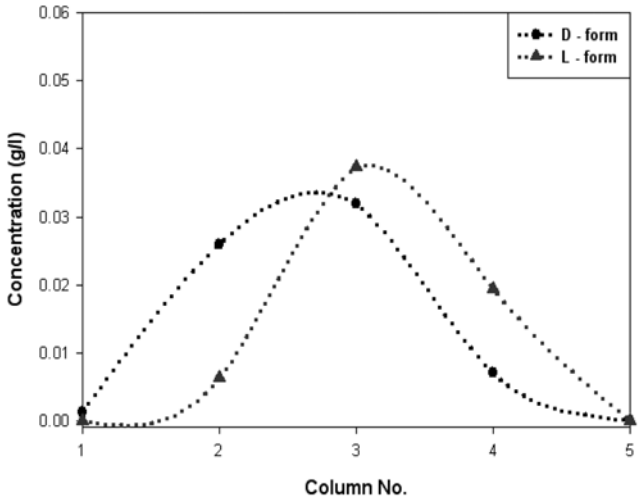

Fig. 5. Internal concentration profiles at Q_{EX}=0.3 ml/min.

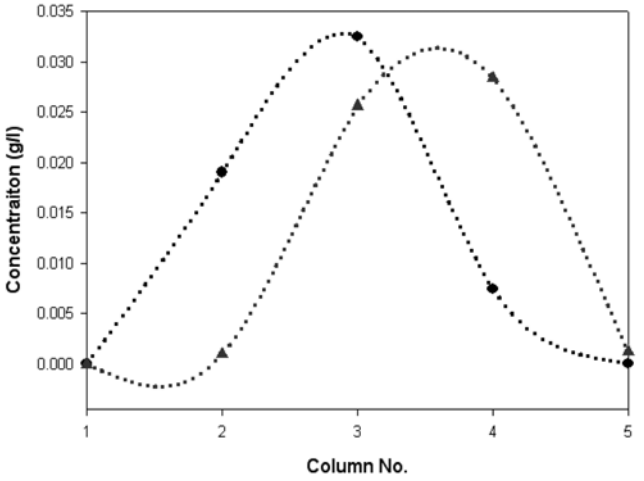

Fig. 6. Internal concentration profiles at Q_{EX}=0.2 ml/min.

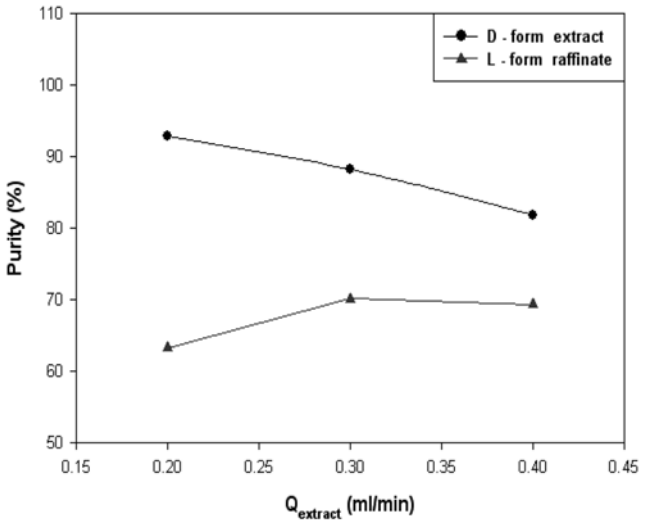

Fig. 7. Variation of puity of D-mandelic acid and L-mandelic acid.

short separation time in zone III. The moving rate of D-mandelic acid profile is lower than that of L-mandelic acid so that the raffinate purity decreases and the extract purity increases.

CONCLUSIONS

The enantiomers of racemic mandelic acid were fairly separated by the SMB unit under the conditions designed and employed. The method adopted for the design of the experimental conditions [10], as well as the assumption of linearity of the isotherms which describe the system, were adequate for the range of concentrations tested, not higher than 0.1 g/L in the feed. The levels of enantiomeric purity were high, mainly for the stream of interest, i.e., the extract, whose purity was comparable to that of the standard D-mandelic acid enantiomer. The purity of the raffinate, although not as high as that of the extract, was high enough to avoid large losses of the D enantiomer, which should be completely recovered in the extract stream.

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