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Journal of Chromatography A, 760 (1997) 159–162

JOURNAL OF CHROMATOGRAPHY A

Short Communication

Evaluation of simulated moving bed chromatography for pharmaceutical process development

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Abstract

Simulated moving bed chromatography is a new technology to the pharmaceutical industry and its usefulness has yet to be established. To properly determine its potential, we arranged an evaluation using the enantioseparation of a drug candidate as the example. A laboratory-scale system was set up and operating within two days and was able to separate 125 g of the racemic mixture per day. At this throughput, each enantiomer was isolated in high purity (greater than 97.5% enantiomeric excess) and in greater than 98% (w/w) recovery.

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

1. Introduction

Simulated moving bed (SMB) chromatography was patented in the early 1960s [1] and developed for the petrochemical industry where it is used to separate *para*-xylene from a mixture of C_8 hydrocarbons on a 100 000 tons per annum scale. Other uses include the production separation of linear chain hydrocarbons from branched and cyclic hydrocarbons, alkenes from alkanes and fructose from corn syrup [2]. All these systems have essentially linear adsorption isotherms that make calculation of the operating parameters of the system relatively simple. More recently, a number of publications have shown that the technique is being considered by the fine chemical and pharmaceutical industries where the non-linear adsorption isotherms make calculation of the operating conditions difficult [3–7]. A theoretical basis for the design of a SMB separation has been described [8].

All pharmaceutical companies are endeavouring to shorten drug development times. SMB offers many advantages over conventional preparative chromatography, especially for the separation of isomers and enantiomers, and could assist in reducing cycle time for development if the system can rapidly process relatively small amounts of material (10–100 g) and then produce the larger quantities required to support development programmes. That is to say, we need a system that can be quickly and easily set up and have a high throughput. In order to assess the potential of SMB chromatography within this context, an evaluation was arranged at SmithKline Beecham (Harlow, UK). Of the commercial systems considered, only those from Novasep (Vandoeuvre-les-Nancy, France) were supported by software that could predict the optimum operating conditions without a lengthy, iterative change of the system's parameters. The laboratory-scale Licosep 12-26 was chosen for this evaluation.

PII S0021-9673(96)00903-X

2. Experimental

2.1. Analytical chromatography

Analysis of the product streams was carried out on a 250×4.6 mm Chiralpak AD (10 μm) column (J.T. Baker, Deventer, Netherlands) and was eluted at 1 ml/min (Merck-Hitachi L6000A pump, Merck, Poole, UK) with 5% (v/v) 2-propanol in hexane (both from Romil, Waterbeach, UK) with UV detection at 275 nm (Model 991 photodiode array detector, Waters, Watford, UK).

2.2. Choice of substrate

The separation chosen for the evaluation was that of the enantiomers of a drug candidate, which, at that time, was proving difficult to separate by conventional crystallisation methods. There was therefore interest in evaluating SMB chromatography for the manufacture of the drug. The compound chosen is a potent partial agonist at muscarinic receptors (Fig. 1) and a good analytical separation of the enantiomers ($\alpha = 1.8$) had been obtained on Chiralpak AD. At no time prior to the start of the evaluation were the vendors given any information about the chromatographic or chemical properties of the compound.

2.3. Column packing

Bulk Chiralpak AD (20 μm) was obtained from Daicel (Dusseldorf, Germany) and packed into eight 26 mm Superformance columns that were obtained from Merck. Each column contained 30 g dry mass of the stationary phase and gave a bed length of about 105 mm. For the SMB chromatograph to work efficiently, it is important that the columns are closely matched for retention time (<2% deviation). Over the eight columns, the retention time of a test compound, measured at a flow-rate of 11 ml/min, was 4.54±0.05 min.

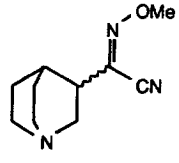

Fig. 1. Substrate used for the evaluation.

2.4. Choice of mobile phase

The mobile phase used for the analytical separation on which the SMB separation was based comprised 0.1% diethylamine and 2% 2-propanol in hexane. To simplify product isolation, it was preferable to remove the diethylamine modifier and the variation of k' and α (determined on a 50×4.6 mm column packed with 10 μm Chiralpak AD) with mobile phase composition is shown in Table 1.

In consultation with Novasep, a mobile phase containing 5% 2-propanol in hexane was selected to give a robust system.

2.5. Determination of adsorption isotherm

In order to set the SMB system parameters, it is necessary to determine the adsorption isotherms of the components. This potentially tedious and time-consuming task is greatly simplified in those cases where there is baseline separation between the components. The software from Novasep is able to accurately model the adsorption isotherm from the change in retention time with increased loading.

One of the columns to be used in the SMB system was set up in a conventional chromatograph (Delta-Prep 4000, Waters) and eluted with 5% (v/v) 2-propanol in hexane at 10.29 ml/min. Increasing volumes of a 100-mg/ml solution of the racemic mixture in the mobile phase were injected and the retention times of the two peaks were measured. The results obtained are shown in Table 2.

These data were entered into the Novasep software

Table 1
Variation in capacity factor and separation with mobile phase composition

2-Propanol in hexane (%)	$k'(1)$	$k'(2)$	α
5	2.234	4.234	1.90
10	1.254	2.316	1.70
15	0.915	1.475	1.61
20	0.712	1.085	1.52
25	0.593	0.881	1.49

Table 2
Variation of retention time with sample loading.

Amount of racemic mixture injected (mg)	t_{R1}(min)	t_{R2}(min)
1	11.1	17.1
1	11.0	17.0
10	10.4	15.6
50	9.75	14.3
100	9.40	13.4
200	9.05	12.5
300	8.80	11.8

to determine the adsorption isotherm and SMB operating conditions.

2.6. Separation of 75 g/day of racemic mixture

A 300-g batch of racemic mixture was available for the evaluation and the Licosep 12-26 to be used for the evaluation was available for four days. An initial throughput of 75 g/day of racemate was therefore chosen for the system. The Novasep software was used to determine the required operating parameters which were as follows: Feed concentration=20 g/l; feed flow-rate=2.6 ml/min; eluent flow-rate=23.4 ml/min; raffinate flow-rate=7.0 ml/min; extract flow-rate=19.0 ml/min; recycle flow-rate=52.1 ml/min and column shift period=3.52 min.

The Licosep 12-26 was started with these parameters and after one complete cycle (28 min), the collection of raffinate and extract streams was started. The system was allowed to run overnight and the streams produced were then analysed.

Both product streams were essentially pure, giving complete separation and complete recovery of both enantiomers.

2.7. Separation of 125 g/day of racemic mixture

New system parameters to separate 125 g/day of the racemic mixture were then calculated: Feed flow-rate=4.3 ml/min; eluent flow-rate=23.7 ml/min; raffinate flow-rate=7.0 ml/min; extract flow-rate=21.0 ml/min; recycle flow-rate=52.1 ml/min and column shift period=3.52 min. The Licosep 12-26 was restarted with these parameters and allowed to run for 36 h. During this time, samples were collected from between the columns and analysed so that the internal concentration profiles around the system could be determined. The comparison of predicted and experimental concentrations is shown in Fig. 2.

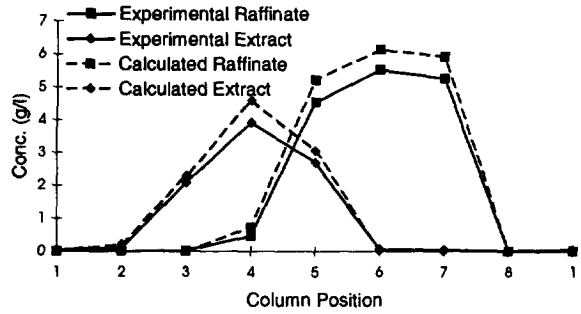

Fig. 2. Comparison of calculated and experimental concentration profiles.

Clearly, from this data, there is good agreement between the experimental and predicted concentrations and this is reflected in the quality of the products obtained. Analytical traces from the extract and raffinate streams are shown in Fig. 3.

The enantiomeric excesses (e.e.) of the raffinate and extract streams were 99.5 and 97.8%, respectively. In both cases, the recovery of material was greater than 98%.

3. Conclusion

The example used for this evaluation presented the system with a relatively simple task, but separations as good as this are often achieved on modern chiral

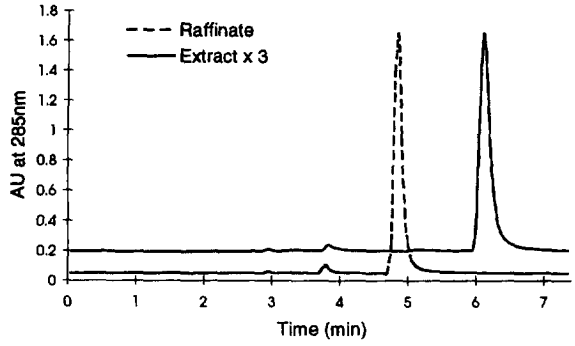

Fig. 3. Analysis of raffinate and extract streams at 125 g/day.

phases. The Licosep 12-26 demonstrated its ability to produce over 60 g/day of each enantiomer with an e.e. of greater than 97.5% and a recovery rate exceeding 98%. Setting up the system to achieve this throughput took only two days.

SMB chromatography can be operated in a way that is advantageous to a pharmaceutical development department. With the support of appropriate software, a system can be set up to produce useful quantities of material with good purity and recovery in a very short time. The efficiency of the system compared to conventional isomer separations has an impact on the resources required for drug development by allowing correspondingly smaller amounts of precursors to be synthesised.

Acknowledgments

SmithKline Beecham would like to thank Novasep (Vandoeuvre-les-Nancy, France) and E. Merck (Darmstadt, Germany) for providing the equipment and expertise used in this evaluation.

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