YOUNG LIN APPLICATION LETTER

Application note No. : YL-APP-2001001

Subject : Application of Young Lin HPLC to Simulated Moving Bed System

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Abstract

SMB is a continuous process in which a solvent and the compounds to be separated are injected into and withdrawn from a ring of chromatographic column at rotating point between the columns. This technique simulates movement of the chromatographic packing material, or bed, against the solvent stream and allows for continuous recovery of the desired compound.

1. Introduction

Chirality has become vitally important in the pharmaceutical, chemical and agricultural industries. The differences which make compounds chiral can produce critically different pharmaceutical effects in biological systems. As a result, demand for stereoselective separation techniques and analytical assays to evaluate the enantiomeric purity of chiral compounds, has increased. Chiral chromatographic separation has become a necessary tool not only for the analytical determination of enantiomeric purity, but also for isolation and production of pure enantiomers. Younglin 9600 HPLC is used for the development of separation and purification technology of chiral Intermediate, racemic mixtures. Chromatographic separation and purification is a simple, economical and high purity process.

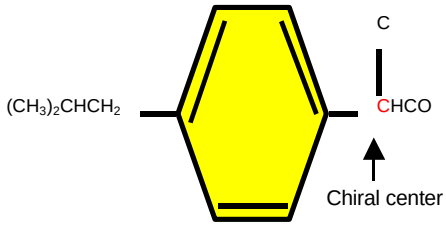
2. Research

Following researches have been performed.

1. Research on local manufacturing of column packing materials for chiral medicines separation, and optimization for separation and purification by HPLC.
2. Determination of the parameters for separation columns which are being scaled-up: 4.6 mm ¡ æ10 mm ¡ æ25 mm.
3. Development of lab-scale SMB chromatographic process for chiral medicine separation by using 8 columns of 4.6 mmD x 150mmL.
4. Development of industry-scale SMB process by using 8 columns of 25 mmD x 150mmL.

3. Scale-up of the Separation Columns

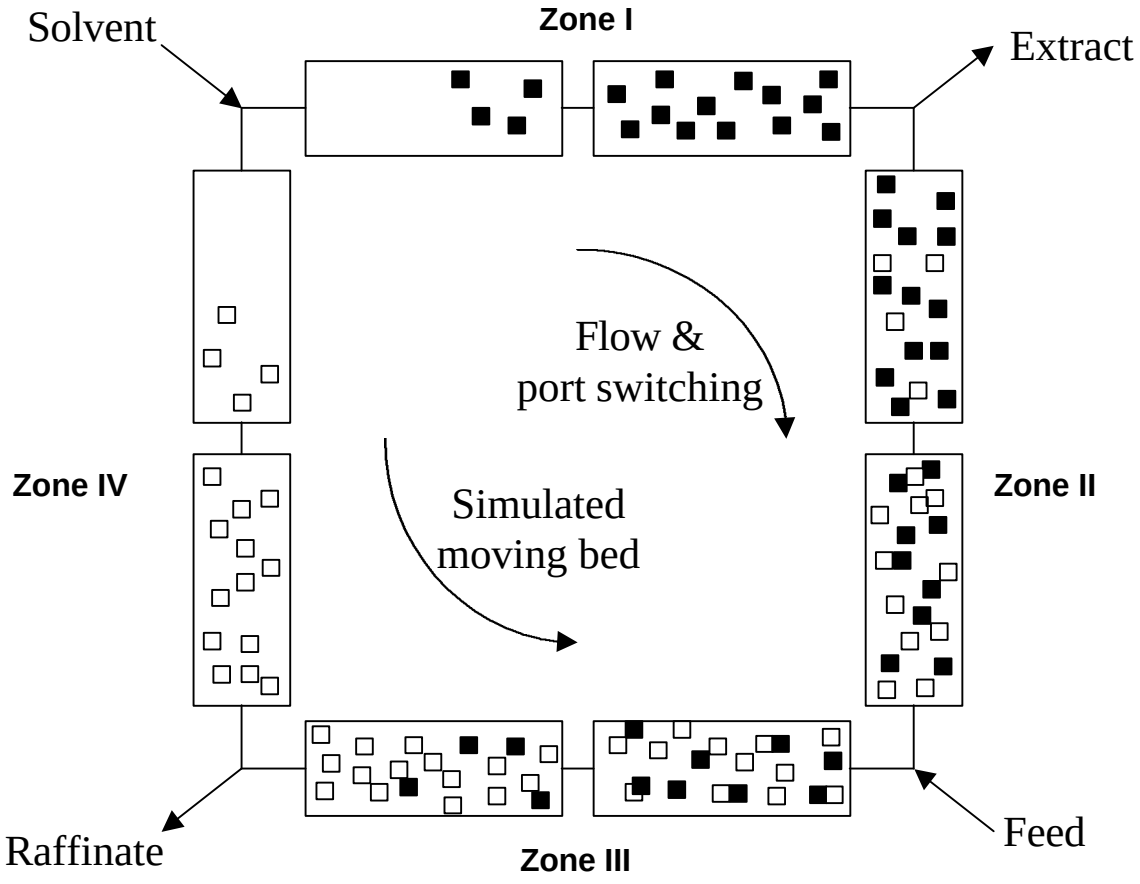
The scale-up process has been made by the database which include chiral absorbent, eluent composition, pressure drop, resolution, No. of theoretical plates, capacity factor and adsorption isotherm. The chiral medicine separated is ibuprofen(S, R) <see in Figure 1>. It is an anti-inflammatory agent which resides the pharmacological activity in the (S)-(+)-entiomer only. However, (R)-(-)-entiomer has many side effects such as stomach discomfort, stomach ulcer, coagulation problem, possible bleeding, and kidney damage.



<Figure 1> Chial structure of Ibuprofen.

4. Principle of HPLC-SMB Process

SMB, Simulated Moving Bed is composed of total 8 separation columns and is divided into 4 zones. Each zone includes 2 columns between Feed and Raffinate, Raffinate and Solvent, Solvent and Extract and Extract and Feed. Zone ¥ °is for solvent regeneration and Zone ¥ ±and ¥ ²are for separation, while zone ¥ ³is for adsorbent regeneration. The schematic diagram of the process is given in <Figure 2>.



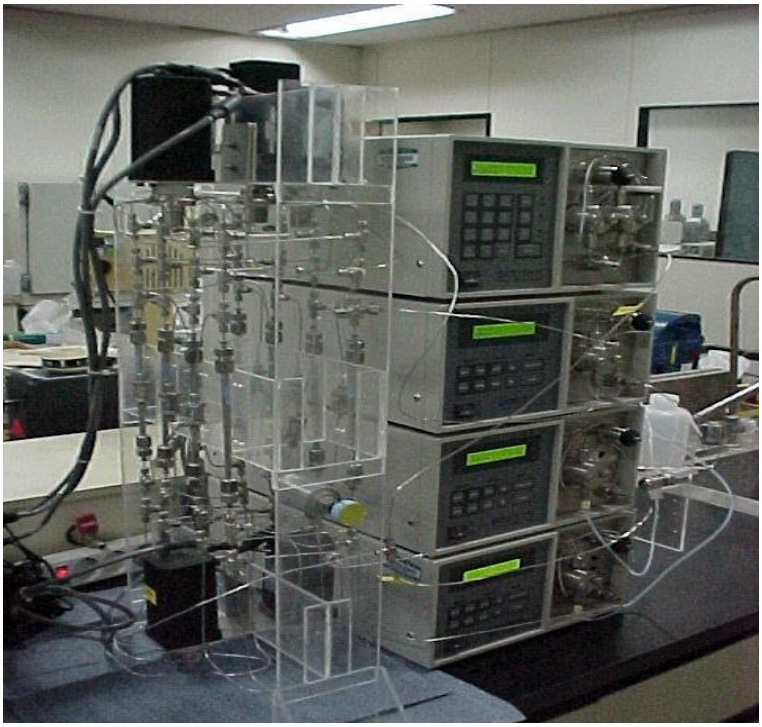
<Figure 2> Principle of HPLC-SMB Process.

5. Separation and purification of Ibuprofen racemate

Ibuprofen racemate was separated and purified by lab-scale SMB system at KIST <Figure 3>.

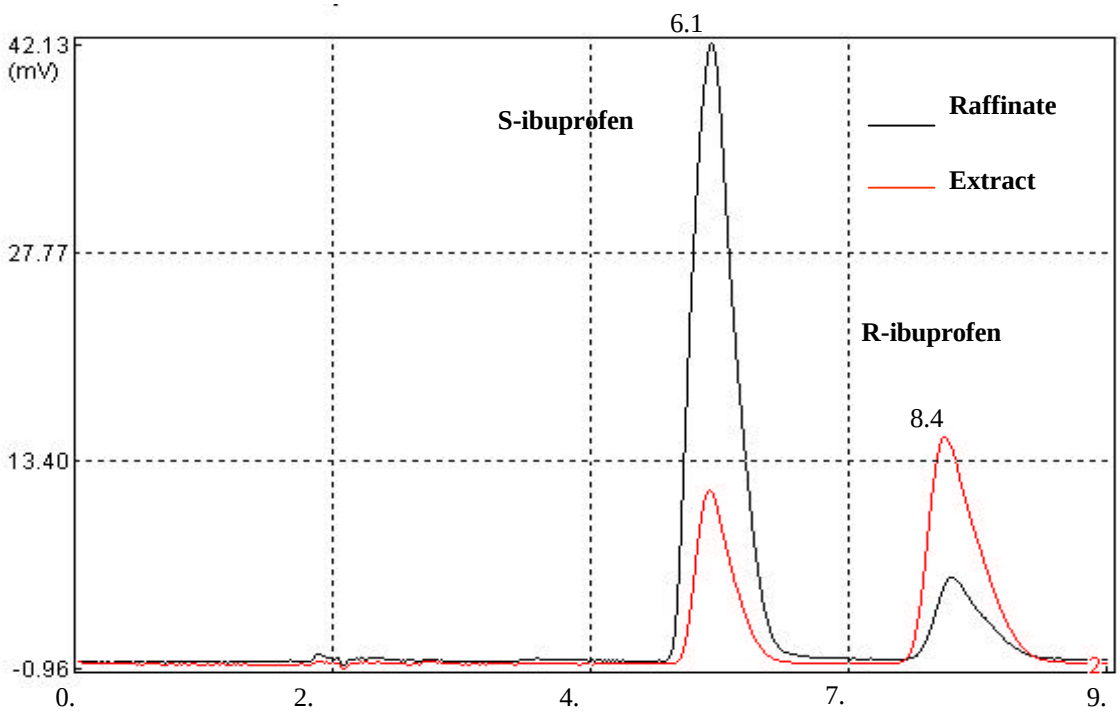
Experimental conditions

System : Laboratory-scale SMB consisting of 8x4.6mmD separation columns
Sample : Ibuprofen racemate
Concentration : 50,000 ppm
Solvent composition : hexane/tert-butylmethyl ether/acetic acid (75/25/0.1, v/v%)
Desorbent flow rate : 0.64 ml/min
Extract flow rate : 0.44 ml/min
Feed flow rate : 0.04 ml/min
Raffinate flow rate : 0.24 ml/min
Recycle flow rate : 0.24 ml/min
Switching time : 10 min

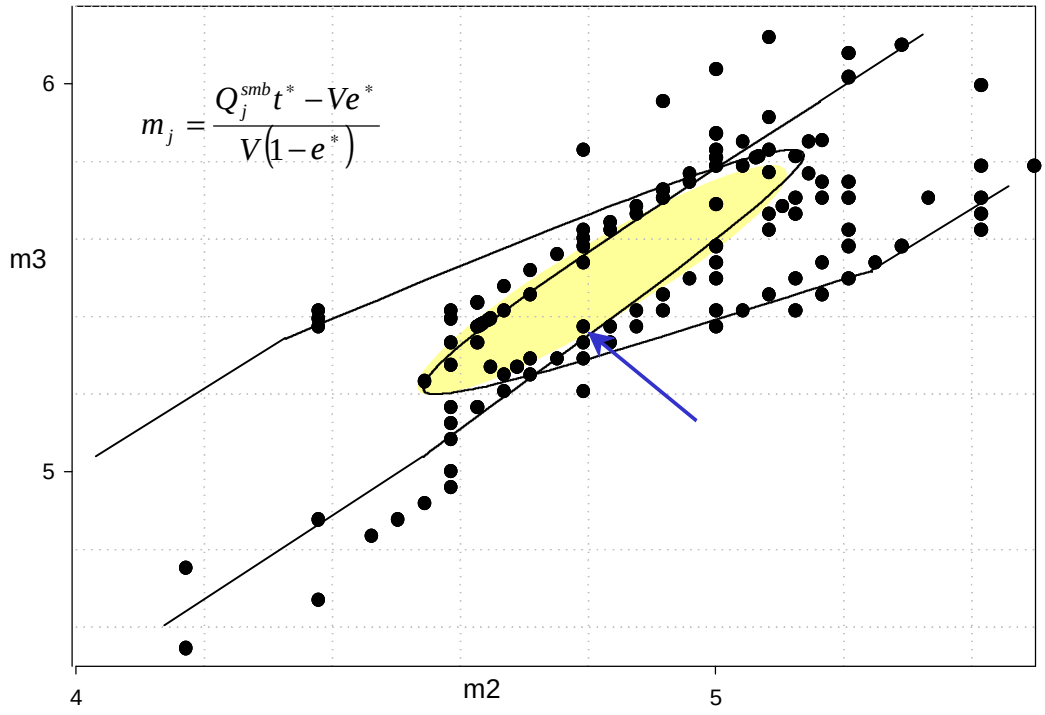


<Figure 3> HPLC-SMB System used at KIST.

Typical example of optical separation pattern of ibuprofen racemate in lab-scale SMB is shown in Figure 4. The behavior of chromatographic system is related to the three basic phenomena such as the adsorption thermodynamics, the column hydrodynamics and the mass transfer kinetics. Mass balance equations, taking into account the three basic phenomena are written for all the components involved in an infinitesimal slice of the column. The set of partial differential equations derived from the mass balance equations is solved numerically by adding boundary and initial conditions. Thus the behavior of chromatographic system of SMB can be predicted. Figure 5 shows the simulated possible operating range of SMB.



<Figure 4> Separation of ibuprofen by SMB Process.



<Figure 5> Simulated results of separation zone ¥ ±and ¥ ²

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6. Conclusion

Recently, the chiral drugs market increases rapidly by almost 10 percent per year and the amount of sales over the world surges toward $100 billion per year within a few years (source C&E News, October 11,1999). SMB is an attractive technology because it gives high selectivity, high yield, and saves the development time and cost for enantiomer production. Thus, most of pharmaceutical makers are already looking on SMB as a standard technology for producing enantiomers. To meet the emerging chiral drug market, Younglin has developed the manufacturing technology for industrial-scale SMB with the cooperation of KIST. Based on the experimental running of KIST, Younglin HPLC is proved to be an effective part for SMB.

ACKNOELEDGEMENT

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