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Optimization of productivity in solvent gradient simulated moving bed for paclitaxel purification

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ABSTRACT

The isocratic and solvent gradient SMBs for paclitaxel purification were optimized to maximize productivity under constraints of product purities and zone flow rate. The solvent composition in the feed and in the desorbent, zone flow rates, and switching time were optimized using non-dominated sorting genetic algorithm with elitism and jumping genes (NSGA-II-JG) and rate model simulations. The highest productivity is achieved using the highest solvent concentration in the desorbent and the lowest solvent concentration in the feed. The optimal solvent gradient SMB was found to have 11-fold of the productivity and 21% of the desorbent requirement, compared to the optimal isocratic SMB. The productivities of the optimal isocratic SMBs were limited by mass-transfer efficiency (or column efficiency). By contrast, the productivities of the optimal gradient SMBs were limited by zone flow rate constraint. The productivity of the optimal solvent gradient SMB without any zone flow rate constraint is 17-fold that of the optimal isocratic SMB. If the gradient SMB had a relatively small difference in ethanol concentration in the adsorption and desorption zones, the highest flow rate occurred in zone I, as in a conventional isocratic SMB. By contrast, if the gradient SMB had a sufficiently large solvent gradient, the highest flow rate occurred in zone III.

1. Introduction

Chromatography has been a versatile separation tool for the purification of various chemicals and biochemicals. Multiple adsorption mechanisms and mild operating conditions are the major advantages of chromatography. Conventional batch chromatography, which has only one inlet port and one outlet port, has been widely used in preparative and large-scale applications. This process, however, has a major limitation in throughput because a feed mixture is loaded in a discontinuous mode. By contrast, simulated moving bed (SMB), which uses multiple chromatographic columns and multiple inlet/outlet ports, is operated in a continuous counter-current mode. Due to such a difference in the operation mode, SMB can achieve higher throughput than batch chromatography [1–6].

SMB was originally developed at UOP for petrochemical separations in the 1960s [7]. Since 1980s, SMB was used to produce high fructose corn syrup (HFCS) [8]. Since 1990s, many SMB processes have been developed for chiral pharmaceutical separations [9]. Recently, SMB processes have been developed for the purification of ketoprofen enantiomer [10], sugar alcohol [5], loxoprofen enantiomer [11], and paclitaxel [12].

Paclitaxel has been regarded as one of the best cancer drugs that has emerged in the last 25 years [13–16]. Due to its novel anticancer activity, paclitaxel has been approved by the U.S. Food and Drug Administration as a treatment for refractory ovarian, breast, and other cancers [14–16]. One of the important tasks for commercializing the paclitaxel production is to develop an efficient paclitaxel purification process in order to meet the demand for high-purity product in a pharmaceutical market. Several attempts have been made to apply a chromatographic technique to the purification of paclitaxel [12,13]. One of the noteworthy purification processes is a low-pressure liquid chromatography developed by Wu et al. [13], in which a polymeric adsorbent and an environmentally benign solvent (mixture of water and ethanol) were employed. Although this process can achieve high paclitaxel purity and yield, it gives a low productivity and high solvent consumption, which are inherent in the batch chromatography mode. To overcome this limitation, Wu et al. [12] developed a four-zone SMB process for paclitaxel purification while using the same mobile and stationary phases as in the aforementioned low-pressure liquid chromatography.

Fig. 1 shows a schematic diagram of the four-zone SMB to separate paclitaxel from its major impurity, cephalomannine [12].

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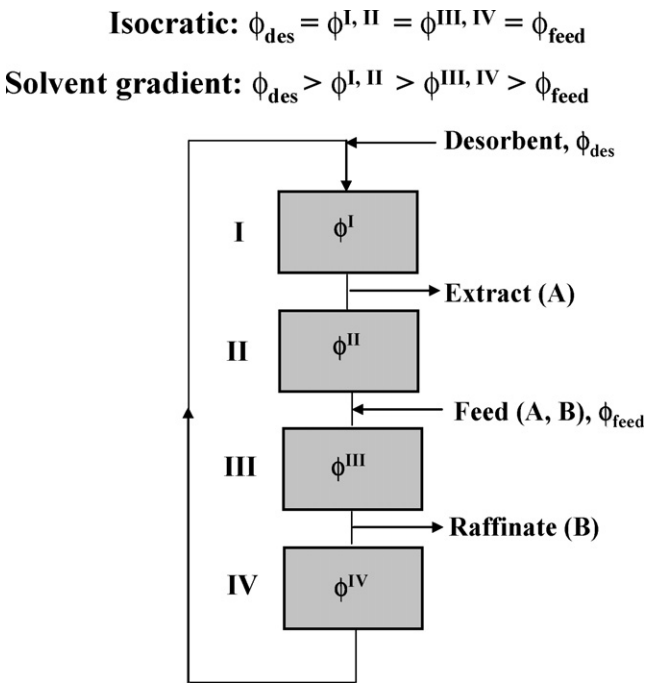

Fig. 1. Isocratic and solvent SMBs for the separation of paclitaxel (A) and cephalomannine (B). Switching of ports in the SMB is not shown. ϕ_{des}, ethanol fraction in the desorbent; ϕ_{feed}, ethanol fraction in the feed; ϕ^{j}, ethanol fraction in the mobile phase in zone j.

Paclitaxel (A) is recovered in the extract port while cephalomannine (B) is removed from the raffinate port. For the mobile and stationary phases employed, paclitaxel is the more strongly adsorbed component (or high-affinity component) and cephalomannine is the less strongly adsorbed component (or low-affinity component). The adsorption affinities are highly dependent on the ethanol content in the mobile phase. High ethanol concentration in the mobile phase leads to low adsorption affinities of paclitaxel and cephalomannine [12].

In the previous study [12], the SMB for paclitaxel purification employed the same mobile phase throughout the entire bed. The feed and the desorbent have the same ethanol concentration. Such an operation has been referred to as an "isocratic SMB" in the literature [17].

The isocratic SMB for paclitaxel purification has been optimized in terms of throughput per bed volume (or productivity) by Wu et al. [12]. The productivity can be further improved by operating the SMB in a solvent gradient mode [17–19], where the mobile phase composition varies along the bed. But no previous studies have addressed the issue of applying a solvent gradient in the SMB for paclitaxel purification.

The goal of this study is to investigate the potential benefits of running the SMB for paclitaxel purification in a solvent gradient mode. A solvent gradient SMB for paclitaxel purification will be designed and optimized to achieve maximum productivity. In parallel, an isocratic SMB will also be designed and optimized. The productivity, solvent consumption, and product concentration of the two optimized SMBs for paclitaxel purification will be compared. Finally, the factors which limit the productivities of the solvent gradient and isocratic SMBs will be examined.

In this study, the optimizations of the operating conditions (zone flow rates, switching time, and solvent concentrations in the desorbent and in the feed) in solvent gradient and isocratic SMBs are carried out by using rate model simulations and an optimization method, non-dominated sorting genetic algorithm with elitism and jumping genes (NSGA-II-JG) [20,21].

The concept of the NSGA-II-JG is based on the principles of genetics and the Darwinian principle of natural selection, i.e. the survival of the fittest [22]. Such principles are embodied in the NSGA-II-JG by employing a series of probabilistic operators such as reproduction, crossover, mutation, and jumping gene, all of which are inspired by natural genetics [23]. Compared to the traditional optimization methods, the NSGA-II-JG method is much more robust and thus more highly efficient in finding out the global optimal solutions.

In the optimization of this study, the column configuration of each SMB is fixed at one column per zone (or 1–1–1–1 configuration) while the other equipment conditions, such as pump capacity and column dimensions, are kept the same as in the previous study [12]. Because of the equipment conditions and the demand for high paclitaxel purity, the optimization is subject to constraints on product purities and zone flow rate. For the optimized solvent gradient SMB, the cyclic concentration wave migration (or wave dynamics) is also analyzed to confirm the product purity and productivity. In addition, significant differences in the wave dynamics between the solvent gradient and isocratic SMBs are discussed.

2. Principle of solvent gradient SMB separation

A brief summary of solvent gradient SMB separation principle is presented in this section.

A binary mixture is separated in a four-zone SMB by accomplishing a specific task in each zone as follows [24]. In zone I, the high-affinity component (A) should be completely desorbed for the regeneration of the adsorbent bed. In zone II, the low-affinity component (B) is separated from the high-affinity component (A) to allow drawing the extract product which contains only the high-affinity component (A). In zone III, the high-affinity component (A) is separated from the low-affinity component (B) to allow drawing the raffinate product which contains only the low-affinity component (B). In zone IV, the low-affinity component (B) should be confined to allow recycle of a fresh desorbent to zone I.

Since each zone must fulfill the aforementioned task, the separation in SMB is largely affected by the adsorption affinities (or isotherm parameters) of the two components. It is expected that low affinities of A and B in zones I and II will facilitate their desorption. On the other hand, high affinities in zones III and IV will allow a large amount of solutes to be adsorbed. Such variations in affinity values are expected to result in higher product purity, higher productivity, higher product concentration, and lower desorbent consumption.

Such an idea, however, cannot be achieved in an isocratic SMB where identical solvent strength is maintained throughout the bed. In such an operation mode, only the operating parameters, zone flow rates and switching time, can be optimized. Such restrictions limit the performance of isocratic SMB.

To improve the SMB performance further, one can exploit the aforementioned idea of allowing the same component to have different isotherm parameters in different zones. One way to realize such an idea is to create different solvent strengths along the bed by using different solvent strengths in the desorbent and in the feed (Fig. 1). The solvent strength is usually controlled by the concentration of an organic modifier in the mobile phase. A higher modifier concentration leads to a lower adsorption affinity (or isotherm parameter). Hence, the modifier concentration in the desorbent should be set higher than that in the feed. The SMB based on such an operation mode has been referred to as "solvent gradient SMB" in the literature [17–19].