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Theoretical study of preparative chromatography using closed-loop recycling with an initial gradient

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ABSTRACT

Complementing classical isocratic elution, several more sophisticated operating modes have been proposed and are applied in preparative chromatography in order to improve performance. One such approach is gradient elution, where the solvent strength is altered by varying the fraction of a modifier added to the mobile phase to enhance selectivity and to achieve faster elution. Another useful technique is closed-loop recycling, allowing better peak resolution and increased yields. This study focuses on a modified new scheme which incorporates the advantages of both gradient elution and closed-loop recycling for the separation of a ternary mixture where the intermediately eluting component is the target. A parametric study was carried out using typical adsorption isotherm parameters to elucidate the effects of varying loading factors and parameters specific to the two basic operational modes on production rates and yields. A comparison was also made between the proposed scheme and conventional techniques. It was found that the studied scheme could exploit increased column loadings and offers significantly higher production rates.

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1. Introduction

Preparative chromatography is an important process for the isolation and purification of value added components from complex mixtures. Hereby, the first important step in solving a specific separation problem is to find a suitable combination of stationary and mobile phases. This selection is usually performed based on the results of screening experiments at an analytical scale. Once the chromatographic system is fixed, there are several degrees of freedom which should be exploited in an optimal manner. In classical isocratic elution, in the first row these degrees of freedom are the column dimensions, the injected amounts and the flow rates [1]. It has been demonstrated frequently, that classical elution is not always the most attractive mode of operation [2]. Often production rates and yields achievable using this mode are not sufficient. For this reason several alternatives have been suggested and implemented. A comprehensive overview is given in [1].

An attractive alternative to single pass elution is closed-loop recycling chromatography [3,4]. Fig. 1 shows a schematic illustration of the concept practiced commonly today [5]. The strategy involves repeated recycling of certain parts of the elution profile containing the target component until the required separation is reached. As simulated for a model system in Fig. 1(c), the fraction containing the target component can be finally collected, e.g. at the end of the fourth cycle with high purity and yield. The closed-loop recycling principle was successfully implemented based on isocratic conditions for example by Bombaugh and Levangie [3] and Biesenberger et al. [6]. Duvdevani et al. [7] suggested the principle of "alternate pumping and recycling" to avoid the periodic destruction of achieved separation by repeatedly transporting the part of the profile recycled through the pump. Bailly and Tondeur [8,9] and Crary et al. [10] simulated recycling chromatography using the ideal model of chromatography considering also injections of fresh feed in every cycle. The key advantage of recycling relies on the fact, that the available number of theoretical plates can be increased, i.e. additional separation could be achieved without increasing the actual length of the chromatographic column [4,11–13]. Another significant advantage of closed-loop recycling is that no fresh solvent is required during the recycling periods, offering the potential to reduce the overall solvent consumption [14].

Frequently encountered problems in chromatographic processes are high retention factors of some of the components and thus long overall retention times. In this context, solvent gradients can be used, which lower the retention times gradually by a monotonic increase of the elution strength [15,16]. Fig. 2 illustrates a typical scenario where a solvent gradient is used to accelerate

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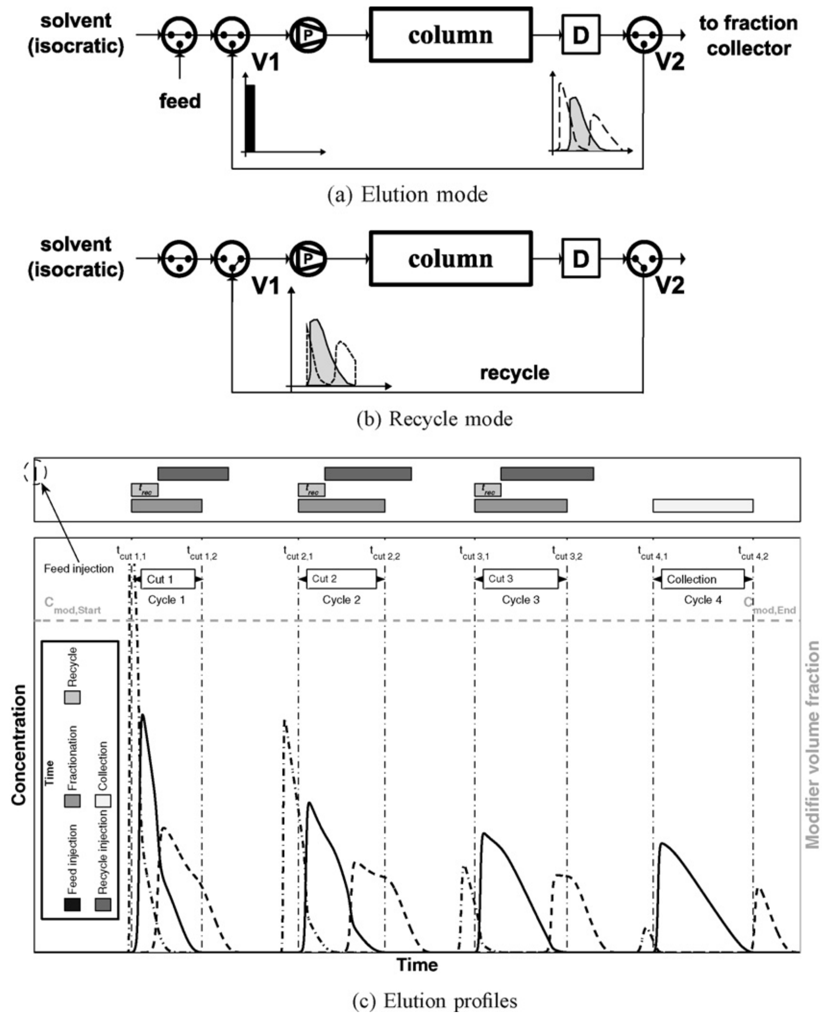

Fig. 1. The principle of closed-loop isocratic recycling: (a) elution mode: valves V1 and V2 in open loop configuration to facilitate one pass elution, (b) recycle mode: V1 and V2 switched to realize closed-loop formation and (c) Elution profiles: illustration of simulated column outlet concentrations for four consecutive cycles. The intermediate part of the profile containing the target component is recycled until the required purity and yield are achieved.

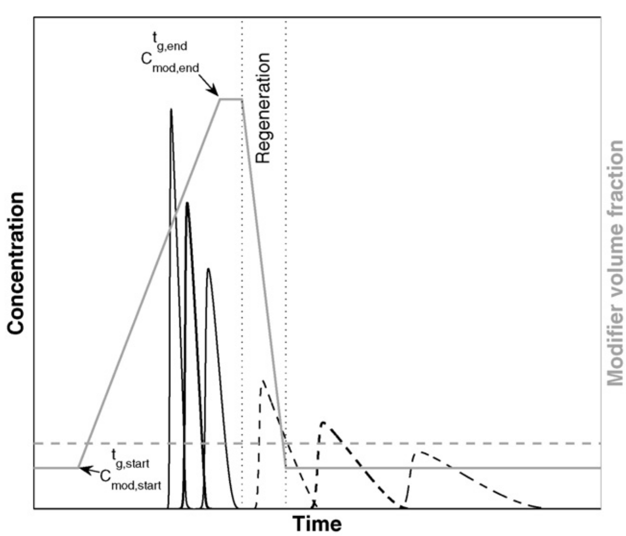

Fig. 2. Simulated column outlet concentration profiles for isocratic elution of a ternary mixture (dashed lines) compared to elution with a linear solvent gradient (solid lines), the modifier concentration changes between $t_{g,start}$ and $t_{g,end}$ from $C_{mod,start}$ to $C_{mod,end}$.

elution. The required change in the elution strength of the mobile phase is typically achieved by varying the volume fraction of a modifier from a certain lower starting value ($C_{mod,start}$) at $t_{g,start}$ to a higher value ($C_{mod,end}$) at the gradient end time ($t_{g,end}$). After the elution of the components, typically the column is immediately regenerated rapidly to bring it back to the starting state.

By varying the solvent strength, the slowly migrating components can be speeded up, thus making way for more frequent sample injections and thereby better productivity. In addition to shorter cycle times, gradient elution also allows for higher product concentrations compared to isocratic elution. There exists a number of ways to change the elution strength with time. Most widely used are linear and stepwise gradients.

It should be emphasized that the better separation performance achievable by employing alternative operation modes is due to additional specific degrees of freedom compared to classical elution. For example, in the closed-loop recycling mode, variables like the number of cycles and concentration threshold for fractionation could be additionally optimized. In linear gradient elution, the variables $C_{mod,start}$, $C_{mod,end}$, $t_{g,end}$ and $t_{g,start}$ could be selected to improve the performance of the process.

The objective of this study was to evaluate theoretically the potential of combining the advantages of both modes described above. More specifically, an attempt was made to investigate if a scheme which exploits closed-loop recycling combined with

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