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Trapping multiple dual mode centrifugal partition chromatography for the separation of intermediately-eluting components: Throughput maximization strategy☆

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ABSTRACT

Trapping multiple dual mode centrifugal partition chromatography (trapping MDM CPC) is an alternative to isocratic pulse injections for the separation of intermediately-eluting components from complex mixtures using liquid-liquid chromatography. In this work, a throughput maximization strategy is developed and validated to investigate the full potential of trapping MDM CPC as a preparative technique. In the proposed approach, shake flask and stationary phase retention experiments are used to determine the maximum feed concentration and flow rate, respectively. A model-based parameter selection process combining a mathematical short-cut method and simulations based on the equilibrium cell model is used to obtain the column loading and step durations resulting in maximized process throughput. The proposed throughput maximization strategy is experimentally validated for the separation of a ternary model mixture of parabens. A preliminary comparison of trapping MDM CPC separation performance to that of stacked pulse injections is also made.

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1. Introduction

Liquid-liquid chromatography (LLC) is a preparative separation technique employing the two phases of a liquid-liquid biphasic system as the mobile and stationary phases. Separation is achieved as a result of the differing partitioning behavior of the sample solutes between the two phases. The stationary phase is held in place during operation by means of the column geometry and application of a centrifugal field. LLC devices can be grouped into two main categories: hydrodynamic countercurrent chromatography (CCC) units and hydrostatic centrifugal partition chromatography (CPC) ones.

The presence of a liquid stationary phase in LLC presents several advantages over conventional liquid-solid chromatography techniques, such as no irreversible sample adsorption on the stationary phase, high loading capacity, and the possibility to tailor the stationary phase composition to the desired separation. Additionally, either phase of the biphasic system (upper or lower phase) may be employed as the stationary phase, and the roles of the two phases may even be switched during operation. As a result, a high degree of operational flexibility can be achieved in LLC, which has given rise to a variety of operating modes not realizable with conventional chromatography techniques [1]. One such operating mode, trapping multiple dual mode CPC (trapping MDM CPC), was presented in a previous publication from the group [2].

Trapping MDM CPC allows the preparative recovery of an intermediately-eluting component from a multicomponent mixture, offering an alternative to isocratic pulse injections. Pulse injections often result in overlapping peaks, and, therefore, reduced yield of the intermediately-eluting target component in pure form. In trapping MDM CPC, the feed mixture is loaded between the columns of a two-column set-up. The early- and late-eluting components are obtained at opposite ends of the column during multiple cycles, with each cycle consisting of two steps. These two steps correspond to the two elution modes in LLC: descending (Des) and ascending mode (As). In Des mode, the upper phase is the stationary phase and the lower phase is pumped through the column as the mobile phase. The roles of the phases are reversed in As mode (the upper phase becomes the mobile phase), as are the flow direction and elution order of the feed components. Meanwhile, the intermediately-eluting target component remains "trapped" within the columns. After the early- and late-eluting components have fully eluted, the trapped target compound is recovered in pure form.

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The MDM technique was first introduced in [3] for the separation of a feed mixture into two product streams on a single column and has since been implemented for a wide range of (pseudo-)binary separation applications. The MDM technique was further developed for ternary separations using two-column CCC devices as described in [4,5]. In [4], the feed was injected continuously over several cycles, while in [5] injections were made repeatedly and always at the start of a new cycle. In the trapping MDM CPC technique presented in this work, column loading is performed at the start of the process and takes place during a single cycle. A short-cut method for selection of the trapping MDM CPC operating parameters (i.e., step durations) under the requirement of full recovery of the pure target was derived and experimentally validated in a previous publication from the group [2]. In order to explore the full potential of trapping MDM CPC as a preparative separation technique, the focus of this study is maximization of the process throughput. Although several recent publications have addressed throughput maximization in LLC [6–9], none of these have focused on the isolation of an intermediately-eluting component by "trapping" it on the column.

Throughput may be improved by increasing the loaded volume and/or the feed concentration. The loaded volume may be increased by performing repeated injections at certain intervals or by increasing the volume introduced during a single injection or loading step. In binary MDM separations without an intermediately-eluting "trapped" component, it has been shown that repeated loading of the feed may be used to increase the process throughput [3,10,11]. In trapping MDM CPC, repeated injections could be useful in cases where the trapped target component is present at low concentrations in the feed and the separation factors between the target and impurities are high. In this case, the majority if not all of the impurities would elute during a single cycle before the next feed introduction, avoiding the destabilizing effects of high solute concentrations on the column. However, the model mixture implemented in this work is meant to represent the situation often encountered at the end of a multistep downstream processing chain: a concentrated feed solution consisting of the target component and remaining impurities with low separation factors. In this case, repeated injections would lead to high solute concentrations within the column, especially near the site of injection.

The feed concentration is limited by the sample solubility as well as the effects of the presence of the solutes on both the thermodynamic equilibrium of the solvent system and the column hydrodynamics. High solute concentrations can result in changes of the partition coefficients and the volumes of the phases. In more extreme cases, a single or third phase (liquid or solid) may be formed. These effects, coupled with the accompanying changes in the phases' physical properties (e.g., density, viscosity, interfacial tension), affect the hydrodynamics within the column and can lead to stationary phase loss [8,12,13]. Prediction of the cumulative effects of the abovementioned changes would require full characterization of the system thermodynamics and hydrodynamics as a function of solute concentration. This task would require extensive experimental effort and/or the development of complex mathematical models. Therefore, in this work, a simplified approach for the selection of the column loading parameters was developed.

In addition to the column loading parameters, the flow rates and step durations during the trapping MDM CPC separation must also be selected. In the interest of processing the largest feed solute quantity in the shortest amount of time, flow rates should be as high as possible while still maintaining stable operating conditions (e.g., no stationary phase loss, not exceeding pressure drop limitations). The short-cut method derived in [2] can be used to facilitate selection of the step durations. Although a helpful starting point in trapping MDM CPC design, the short-cut method is fully valid only under ideal conditions (i.e., in the absence of band broadening effects). Separation performance under real conditions must be determined experimentally or predicted with the use of models taking band broadening effects into account.

Various models have been used for the description of LLC processes in the presence of band broadening, such as the equilibrium cell model of Martin and Synge [14–16], the countercurrent distribution model [17], the non-equilibrium (longitudinal mixing) cell model [18], and the plug flow with axial dispersion model [19,20]. In this work, simulations based on the equilibrium cell model were employed to evaluate separation performance with the parameters determined by the short-cut method.

The objective of this work is to provide a structured approach to selection of the operating parameters leading to maximized throughput in trapping MDM CPC. Completion of this objective comprised the following tasks:

- Experimental determination of the maximum applicable feed concentration and corresponding maximum applicable flow rate.
- Development of a model-based throughput maximization strategy incorporating the short-cut method for operating parameter selection introduced in [2] and simulations based on the equilibrium cell model.
- Experimental validation of the proposed model-based design approach.
- Comparison of trapping MDM CPC performance to that of isocratic pulse injections.

A model feed mixture consisting of three parabens (methyl paraben, ethyl paraben, and propyl paraben) was used to facilitate the theoretical development of the throughput maximization strategy. The parabens differ only in their alkyl chain lengths and represent a "difficult" separation (low separation factors). Ethyl paraben was the intermediately-eluting target component to be trapped and later recovered.

2. Theory

2.1. Principle of trapping MDM CPC

The principle of the trapping MDM CPC operating mode is described in detail in [2] and is revisited here for convenience.

The separation objective in trapping MDM CPC is the recovery of an intermediately-eluting target component from a complex mixture in pure form. This separation can be viewed as a pseudo-ternary separation represented by the components A, B, and C, with B as the intermediately-eluting target. The partition coefficients of the three components can be relatively defined as $K_A^{Des} < K_B^{Des} < K_C^{Des}$ in Des mode or $K_A^{Asc} > K_B^{Asc} > K_C^{Asc}$ in As mode. B will remain trapped inside the CPC unit while A and C elute from the two column ends in Des and As mode, respectively, allowing the recovery of pure B at the end of the process.

Due to the cyclic nature of the trapping MDM CPC process, a unit consisting of two hydrostatic CPC columns and four pumps (two for mobile phase and two for feed; one of each running in each mode) is used. Trapping MDM CPC consists of three process stages: column loading, separation, and product recovery. A schematic representation of the process (first appearing in [2] and re-printed here for clarity) is found in Fig. 1.

In the loading stage (Fig. 1a), the feed is introduced between the two columns during a single cycle, designated as Cycle 0. In Des mode, the lower phase feed solution is fed into the left-hand column, while in As mode, the upper phase feed solution is pumped into the right-hand column. There is no accompanying flow of pure mobile phase during feed introduction.

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