



# Steady state recycling chromatography with solvent removal—Effect of solvent removal constraints on process operation under ideal conditions



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## ABSTRACT

Steady state recycling chromatography (SSR) offers a means to reduce eluent consumption and increase productivity in preparative and production scale chromatographic separations. Even better performance is obtained with an integrated process by coupling solvent removal unit to the chromatographic separation unit. Here a design method for SSR with an integrated solvent removal unit (SSR–SR) is presented. The method is more practical than previous work as the effect of physical constraints, such as solubility or viscosity, imposed on the amount of solvent removed is included. The method holds under ideal conditions for binary systems with competitive Langmuir isotherm model. The design equations allow calculation of the regions of feasible operating parameters when either the maximum concentrations in the solvent removal unit or of the solution fed into the chromatographic column is restricted. The method was applied to analyze the performance of different SSR–SR configurations in two case studies: the separation of mandelic acid enantiomers and the separation of EMD 53986 enantiomers. The benefits of SSR–SR are relatively small under ideal conditions but the design method developed here can give a good starting point for designing SSR–SR processes under non-ideal conditions.

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## 1. Introduction

Preparative liquid chromatography is one of the most selective separation techniques in the pharmaceutical, fine chemical and food industries. It is applied successfully for the separation and purification of a wide range of substances such as enantiomers, other isomers, sugars and proteins. The most common process schemes are single-column batch chromatography and multi-column simulated moving bed (SMB) chromatography. The batch mode is versatile and provides multiple product fractions, but usually suffers from low productivity, high eluent consumption and/or low recovery yield. As to the SMB, high productivity, low eluent consumption, and high yield are counterbalanced by high investment costs and a high degree of complexity.

Many single column recycling techniques are known to enhance the performance of classical batch chromatography with significantly lower investment costs than SMB processes [1–3]. The most promising concepts are steady state recycling schemes where the sufficiently pure leading and trailing sections of the elution

profile are collected as product while the unresolved middle part is recycled into the column. A constant amount of fresh feed is added to the recycle fraction, which causes the process to attain a periodic steady state. The process can be operated in different injection modes. In the mixed-recycle scheme [4], the recycle fraction is mixed with the fresh feed before re-injection. In the closed-loop mode [5], the recycle fraction and the fresh feed are introduced separately in order to preserve the already achieved partial separation.

An advanced process concept, SSR–SR, where the performance of conventional steady-state recycling process is improved by integrating it with a solvent removal unit, e.g. membrane filtration or evaporation unit, has recently been introduced [1]. A similar approach for concentrating internal process streams has been proposed also for SMB chromatography [6,7]. In addition, various hybrid process concepts where either single column [8] or SMB [9,10] chromatography is combined with an enzymatic racemization and membrane filtration for solvent removal have received increased attention.

The solvent removal unit can be placed in different positions of the SSR–SR process. Solvent can be removed from: (I) the fresh feed, (II) the recycle fraction, and (III) the stream that is fed into the column (obtained by mixing the fresh feed and the recycle fraction). Siitonen et al. [1] investigated various SSR–SR configurations by

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using the equilibrium theory of chromatography and created the theoretical background for analysing and designing the process. A method was developed to choose *a priori* the relevant cut times for fractionating the outlet stream of the chromatography column and the capacity of the membrane filtration unit such that arbitrary purity constraints are satisfied. In addition, it was shown that the three SSR–SR configurations have identical performance with the same operating parameters. In contrast, the configurations differ with respect to the maximum amount of fresh feed as well as the range of feasible volumes of feed pulse into the column.

In practice, the extent of solvent removal is often limited by various factors. Firstly, the maximum concentration achievable in the solvent removal unit may be limited by solubility of the components since precipitation is not acceptable. On the other hand, if the solubility is high, osmotic pressure in membrane filtration or vapour pressure in evaporation may limit the operation. Secondly, the maximum concentration introduced into the chromatographic column may be limited by solubility, viscosity, or pressure drop.

Recently, Hellstén et al. [11] studied the effect of solvent removal constraints on the performance of SSR–SR process under non-ideal conditions by numerical simulations. Separation of glucose and galactose was used as a model case for a large scale biorefinery application of steady-state recycling chromatography. It was found that an optimized SSR–SR process yields always higher productivity than a conventional SSR chromatography or a batch process that employs a similar solvent removal unit. The most advantageous SSR–SR configuration depends on the fresh feed concentrations and the solvent removal constraint.

In this work, the theory of SSR–SR chromatography developed by Siitonen et al. [1] is extended to the case when practical solvent removal constraints affect the SSR–SR operation. A design method is developed for calculation regions of feasible volume of feed pulse into the column and volume of fresh feed. The approach is based on the equilibrium theory of chromatography and is applicable for binary systems that follow competitive Langmuir adsorption isotherm model. The performance of the three SSR–SR configurations is compared with the performance of (1) classical batch chromatography, (2) batch process with solvent removal, and (3) conventional SSR process without solvent removal with two case studies.

## 2. Background

### 2.1. Equilibrium theory of chromatography

Within the frame of the equilibrium theory of chromatography, it is assumed that the mass transfer resistance and the dispersive effects are negligible, the fluid velocity is constant, and the packing properties are homogeneous along the column. Under these conditions, the mass balance for an individual component  $i$  is given by

$$\frac{\partial c_i}{\partial t} + u \frac{\partial c_i}{\partial x} + \phi \frac{\partial q_i^{\text{eq}}}{\partial t} = 0 \quad i = (1, 2) \quad (1)$$

where  $c_i$  is the fluid phase concentration of solute  $i$ ,  $q_i^{\text{eq}}$  is the stationary phase concentration that is in equilibrium with the fluid phase,  $\phi$  is the phase ratio ( $\phi = (1 - \varepsilon)/\varepsilon$  with  $\varepsilon$  being the total void fraction of the bed),  $u$  is the interstitial velocity ( $u = L/t_0$  with  $L$  being the column length and  $t_0$  being the retention time of a non-retained component),  $t$  is the time, and  $x$  is the column axial coordinate. For binary systems that follow the competitive Langmuir adsorption isotherm model the equilibrium relationship is given by

$$q_i^{\text{eq}} = \frac{N_i K_i c_i}{1 + K_1 c_1 + K_2 c_2} \quad (2)$$

where  $N_i$  and  $K_i$  are the saturation capacity and the equilibrium parameter of solute  $i$ , respectively. In the following discussion, it is assumed that the component 1 is the less strongly retained one. This means that  $H_2 > H_1$ , where  $H_i = N_i K_i$  is the Henry constant of component  $i$ .

To solve the model Eqs. (1) and (2), proper initial and boundary conditions are needed. In this work, it is assumed that a rectangular pulse of binary mixture with known duration,  $\Delta t^F$ , is first fed to an initially clean column and then eluted in isocratic mode. In this case, the initial and boundary conditions of Eq. (1) are

$$c_i(x, t = 0) = 0 \quad \text{for } 0 \leq x \leq L \quad (3)$$

$$c_i(x = 0, t) = c_i^F \quad \text{for } 0 \leq t \leq \Delta t^F \quad (4)$$

$$c_i(x = 0, t) = 0 \quad \text{for } t > \Delta t^F \quad (5)$$

where  $c_i^F$  is the concentration of component  $i$  in column feed.

The model forms a system of two homogeneous quasilinear partial differential equations. It can be solved analytically by the method of characteristics. The fundamentals of the solution are described extensively in the literature [12–15].

### 2.2. Principle of SSR–SR process

Various single column chromatographic processes are presented schematically in Fig. 1. The classical mixed-recycle steady state recycling chromatography process (Fig. 1a) is started by introducing a certain amount of feed mixture from the feed tank into an initially clean column. The feed pulse is then eluted isocratically with eluent  $E$ . The initial state of the feed reservoir can be, for example, a fresh feed mixture, a diluted fresh feed mixture, or a solution whose composition corresponds to the steady state feed.

An example of the concentration profiles at the SSR column outlet is shown in Fig. 2. The actual SSR cycle starts at time  $t_{A1}$ , when the first component breaks through. The column effluent is directed to product fraction  $A$  to collect the leading section of the chromatogram containing an excess of the less adsorbed component 1. Between times  $t_{A2}$  and  $t_{B1}$  the unresolved fraction is collected and recycled. In the mixed-recycle mode, the whole recycle fraction is collected in the feed reservoir, mixed with fresh feed and then introduced back into the column. After time  $t_{B1}$ , the product fraction  $B$  containing an excess of the more retained component 2 is collected until the chromatogram is eluted completely at time  $t_{B2}$ .

The above procedure is repeated while keeping the time intervals between the fractionation valve switching events constant. This forces the process into a periodic steady state in which the elution profiles and the average product compositions do not vary from cycle to cycle.

In an SSR–SR process, the performance of MR–SSR chromatography is improved by integrating it with a solvent removal unit, e.g. a membrane filtration unit or an evaporation unit. As already mentioned, there are several options to position the solvent removal unit. In this work, the design and performance of the following three configurations are discussed: (I) solvent is removed from the fresh feed (Fig. 1b), (II) solvent is removed from the recycle fraction (Fig. 1c), and (III) solvent is removed from the actual feed solution entering the column (i.e., solution obtained by mixing the fresh feed and the recycle fraction) (Fig. 1d).

The steady state operation of SSR chromatography and the three SSR–SR process options are conveniently presented on the hodograph plane as shown in Fig. 3. In this work, it is assumed that the solvent removal unit works ideally such that the relative composition of the solution is not changed in the unit. The operating line of the solvent removal unit is thus a straight line on the hodograph plane, and solvent removal corresponds to moving upwards on that line.

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