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Coupling of simulated moving bed chromatography and fractional crystallisation for efficient enantioseparation

Heike Lorenz[a], Patrick Sheehan[b], Andreas Seidel-Morgenstern[a,b,*]

[a]*Max-Planck-Institut für Dynamik komplexer technischer Systeme, Leipziger Strasse 44, Zenit-Gebäude, D-39120 Magdeburg, Germany*
[b]*Otto-von-Guericke-Universität Magdeburg, Institut für Verfahrenstechnik, Universitätsplatz 2, D-39106 Magdeburg, Germany*

Abstract

An optimised coupling of liquid chromatography and fractional crystallisation is suggested for efficient enantioseparation. As a first stage, a chromatographic separation, preferably simulated moving bed (SMB) chromatography, is applied to achieve an enantiomeric enrichment sufficient for a subsequent crystallisation. First results of the experimental and modelling work for the model system (+)-/(−)-mandelic acid in an aqueous solution are described. Chromatographic investigations involve the estimation of adsorption isotherms on a suitable chiral stationary phase and the simulation and optimisation of a corresponding SMB process. From the ternary phase diagram measured for the (+)-/(−)-enantiomer/solvent system, the conditions required to crystallise a pure enantiomer from an asymmetric mixture can be derived. The productivity gains achievable from the combined process compared to the application of chromatography alone are discussed.

Keywords: Simulated moving bed chromatography; Crystallization; Enantiomer separation; Mandelic acid; Organic acids

1. Introduction

Much evidence relating to pharmaceutical products which occur in two enantiomeric forms now exists regarding the advantages of administering only that enantiomer with the desired physiological effect. In many cases, the other, non-beneficial enantiomer has no or possibly even a detrimental effect. Regulators increasingly demand that such drugs are administered in optically pure form. All of this has concentrated research efforts on the production of enantiomerically pure products, either via the synthesis of but one of the two enantiomers or through the subsequent enantioseparation of racemic mixtures [1]. In this paper, only the latter approach will be considered. Thus, it will be assumed the typical situation is that the product stream leaving a prior reactor is of racemic composition, and that the separation of this stream into enantiomerically enriched or pure fractions is the goal.

Several approaches to performing enantioseparations are known [2]. Often only chromatographic methods using suitable chiral stationary phases [3] can achieve the high purities required for pharmaceutical substances. In order to increase the productivity of chromatographic separation processes, conventional batch elution is increasingly being

*Corresponding author. Tel.: +49-391-671-8644; fax: +49-391-671-2028.

E-mail address: andreas.seidel-morgenstern@vst.uni-magdeburg.de (A. Seidel-Morgenstern).

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replaced by more sophisticated operation modes. Besides the application of discontinuous recycling techniques [4], continuous chromatographic processes are on their way to becoming a standard tool for enantioseparation. It has been proved in recent years that the simulated moving bed (SMB) process in particular is capable of separating a wide range of racemic mixtures in a reliable manner, leading to enantiomers of high purities [5]. The success of SMB chromatography is mainly due to the considerable improvements that have been achieved in the theoretical understanding of multicomponent band propagation in single chromatographic columns [6] and the availability of reliable strategies and tools to design multicolumn processes [7].

Alternatively, crystallisation from a solution of the two enantiomers offers the possibility to achieve enantiomeric enrichments. Compared to chromatography, crystallisation methods are usually cheaper. Among the crystallisation techniques potentially applicable are: the manual sorting of conglomerate crystals; resolution by entrainment; separation via formation of diastereomeric salts and crystallisation from optically active solvents [8]. Finally, an examination of the solubility diagram of a two enantiomer/one solvent system reveals the possibility to attain both partial and complete enantiomeric enrichments, once a certain minimum enrichment has been delivered by a previous process [9]. Indeed, whether any of these crystallisation methods yields a successful enantioseparation is determined by the composition of the feed to the crystalliser and the form of the equilibrium phase diagram exhibited by the two enantiomer (binary) or two enantiomer/solvent (ternary) system in question (crystallisation from the melt or from solution).

In this contribution, we examine the possibility of conducting efficient enantioseparations in a two stage process. Chromatography in general and SMB chromatography in particular are used to deliver a partially enriched stream for a subsequent crystallisation step, which should then yield enantiomerically pure products. The potential advantages of these (and other) separation technologies have been indicated by Blehaut and Nicoud [10]. A first attempt to realise such a combination has been published by Lim et al. for the Praziquantel system [11,12]. To evaluate quantitatively the potential of such a hybrid process, suitable objective functions should be formulated and optimised for the individual processes alone and for the combined process. It is known and will be demonstrated below that the productivity of separation processes usually falls off as higher purities are demanded. A critical task here in designing an efficient hybrid process is the identification of an optimal intermediate ''crossover'' purification between the chromatography and crystallisation operations.

Before analysing the hybrid process, basic principles and suitable models for the two individual processes of chromatography and crystallisation are introduced briefly.

2. Enantioseparation via chromatography

The first and most essential step in developing a chromatographic process for enantioseparation is to find an appropriate system of mobile phase and chiral stationary phase. Screening experiments on an analytical scale are usually performed. Mathematical models are then available to carry out further scale-up and for optimisation of the operating parameters [6,13].

2.1. Model of a chromatographic column

The following mass balance representing the equilibrium dispersion model has proved to be a powerful tool for the description of separation processes in chromatographic columns [6,14]. In the particular case of an enantioseparation dealt with here, the index i can represent either the (+) or (−) enantiomer.

$$\frac{\partial c^i}{\partial t} + \frac{1-\epsilon}{\epsilon} \cdot \frac{\partial q^i(c^{(+)},c^{(-)})}{\partial t} + u \cdot \frac{\partial c^i}{\partial z} = D^i_{\mathrm{ap}} \cdot \frac{\partial^2 c^i}{\partial z^2} \tag{1}$$

In this equation, equilibrium between the two phases is assumed. Thus, the most important design parameters are those of the adsorption isotherms. A possible form of the isotherm relationship is given by the competitive Langmuir model:

$$q^i = \frac{a^i c^i}{1 + b^{(+)}c^{(+)} + b^{(-)}c^{(-)}} \quad \text{for } i = (+) \text{ or } (-) \quad (2)$$

To describe band broadening effects, the apparent dispersion coefficients, D^i_{ap}, must additionally be known. For small dispersion effects, the well-known relation to the number of theoretical plates, N_i, holds:

$$D^i_{ap} = \frac{u\,L}{2\,N_i} \quad (3)$$

2.2. Principle and modelling of SMB chromatography

Besides discontinuous modes of operation such as elution and recycling chromatography, the continuously operated SMB process is now widely applied for many separation problems. The SMB principle was developed in the early 1960s by Universal Oil Products [15] for large scale separations (e.g., the separation of xylene isomers or of fructose and glucose). Intensive systematic studies were first undertaken in the 1980s [16–18]. Currently, there exists tremendous interest in applying the principle in the pharmaceutical industry to more difficult separations of value added products [5].

The general concept of a classical four-zone SMB unit is illustrated in Fig. 1. The unit consists of a closed loop of fixed beds. There are two incoming streams, the feed mixture to be separated and fresh desorbent or eluent. Two streams leave the unit, the raffinate, which is enriched in the less adsorbed of the two components to be separated, and the extract, enriched in the more adsorbed component. The points at which these four streams enter or leave the SMB unit divide the unit into distinct four zones, numbered I, II, III and IV. Each of these four zones contains at least one fixed bed and has particular tasks to fulfil. Either by holding the fixed beds stationary and periodically shifting the inlet and outlet positions co-currently with the fluid flow (the ''moving port'' implementation) or by fixing the inlets and outlets and periodically moving the fixed beds counter-currently against the fluid flow (the ''moving column'' implementation), a counter-current between the fluid and the solid phases is simulated. In principle, both implementations are fully equivalent. The shifting time corresponds to the solid flow-rate in the true counter-current process.

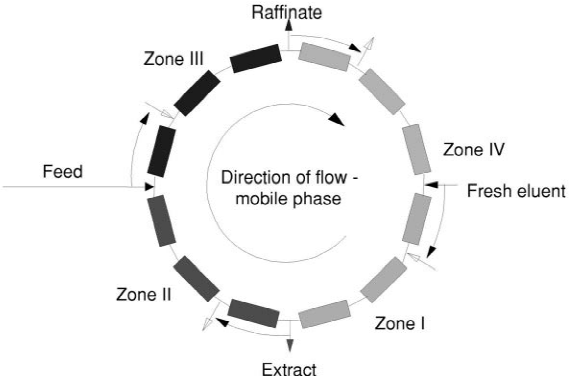

Fig. 1. Schematic illustration of the SMB process.

A more detailed design and optimisation of the SMB process can be performed using Eq. (1) formulated for each column. The numerical methods applied to solve the set of model equations are typically finite difference or orthogonal colocation schemes. In this work, an efficient explicit finite difference algorithm based on matching numerical and physical dispersion effects was applied to solve Eq. (1) together with the periodic boundary conditions characteristic for the SMB process [19,20].

2.3. Separation regions and operating points for the SMB process

The main problem in designing an SMB process is to find its optimal operating conditions. Essentially, this involves specifying relative flow-rates between the fluid and the solid phases in each of the four zones. An appropriate tool for the estimation of these parameters is offered by equilibrium theory as described by Rhee et al. [21] and Helfferich and Klein [22]. This theory neglects all mass transfer resistances and uses only thermodynamics to describe the migration of the substances in the fixed beds.

To specify the operating parameters to separate a certain binary feed mixture with a given SMB unit, five parameters have to be determined. These are the fluid flow-rates, $\dot{V}_j$ (or the corresponding velocities, u_j), in the four zones (j=I, II, III or IV) and the switching time, T^{shift}. The latter parameter is closely related to the solid flow-rate of the equivalent true counter-current process, $\dot{V}_S$. In the last few years

Morbidelli and co-workers [23–25] have contributed significantly to the treatment of this nontrivial design problem. They demonstrated that the five unknown quantities can be conveniently expressed in terms of four net flow ratios, m_j, defined as:

$$m_j = \frac{\dot{V}_j}{\dot{V}_S} - \frac{\epsilon}{1-\epsilon}, \quad j = \mathrm{I} \ldots \mathrm{IV} \tag{4}$$

Based on the similarity between true and simulated counter-current adsorption processes and neglecting all kinetic effects (i.e., assuming $D_{ap}=0$), equilibrium theory was applied to derive analytical expressions for the ranges of values of the four flow-rate ratios, m_j, which guarantee a complete separation of the binary mixture. The shape and size of the resulting regions in a m_{II}–m_{III} plot depend on the feed concentrations and on the thermodynamic parameters, i.e., on the adsorption isotherms. Explicit equations to specify the regions of complete separation in terms of the four flow-rate ratios have been reported for several isotherm models [25]. It was further demonstrated that the values of m_{II} and m_{III} are most crucial for the success of the separation. They characterise the flow-rates in the two zones located upstream and downstream of the feed position. These zones are responsible for achieving the separation.

Typical shapes of the separation regions expected for different feed concentrations are given in Fig. 2.

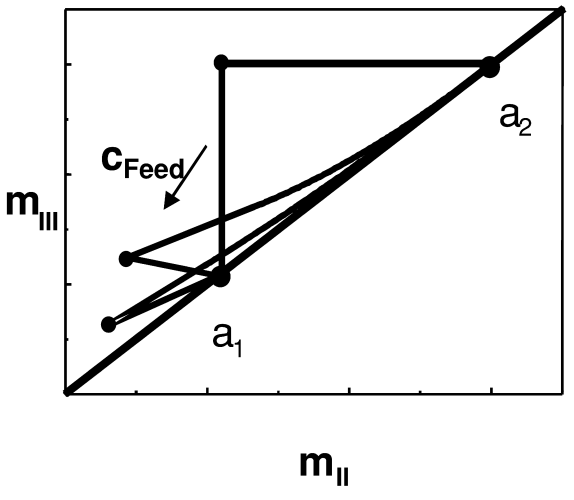

Fig. 2. Illustration of regions of complete separation [23–25].

It is noted that the shape of these regions changes and their size decreases with increasing feed concentration. In each case, as described in Refs. [23–25], the point of each region lying furthest from the diagonal is the optimal operating point, representing the maximum feed which can be processed and the minimum of eluent consumption. In general, the productivity of a SMB unit depends on the concentration of the feed stream. Thus, the feed concentration is another important design parameter.

3. Enantioseparation via crystallisation

The application of crystallisation methods for separation and/or purification of enantiomers is based on the detailed knowledge of the appropriate phase diagrams describing the melting behaviour of the two enantiomers (binary melting point phase diagram) or their solubility behaviour in the presence of a suitable solvent (ternary solubility phase diagram). According to the type of the saturation curves in the phase diagram, three fundamental types of enantiomer systems can be identified. These were first described in the pioneering work of Roozeboom [26]. Characteristic binary phase diagrams of the conglomerate, racemic compound and solid solution forming systems are shown schematically in Fig. 3.

Only 5–10% of racemates belong to the conglomerate forming group, which is the most favourable one for achieving a certain enantiomeric enrichment by fractional crystallisation from a nonracemic mixture. Of racemates, 90–95% form a compound in the solid phase, called a racemic compound or true racemate [9]. In the latter case, knowledge of the phase equilibria is even more important because the existence region of the pure enantiomers in the phase diagram (binary and ternary), which is defined by the position of the binary/ternary eutectic point (Figs. 3 and 4), is much smaller. Solid solution forming racemates (so-called ‘‘pseudoracemates’’) are relatively rare. More detailed information regarding this topic is given in the monograph of Jacques et al. [9] and in Ref. [27].

The form of the ternary (solubility) phase diagram can be deduced from the form of the binary diagrams discussed above (Fig. 3). The previous determination of the binary phase diagram also helps with predict-

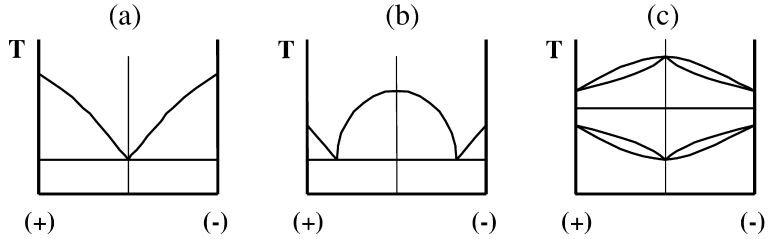

Fig. 3. Binary phase diagrams of the types of racemate: (a) conglomerate; (b) racemic compound; (c) ''pseudoracemate''.

ing rough solubility data [28]. The determination of melting point diagrams is relatively easy (e.g., using DSC methods) compared to solubility measurements for ternary systems.

In Fig. 4, a schematic solubility phase diagram for a compound forming system is presented in the most frequently used equilateral triangle form. The vertices of the triangle represent the pure components: the solvent at the top, the (+)- and (−)-enantiomers at the left and right ends of the triangle base. The triangle sides (graduated in mole or weight fraction units) represent the binary systems (+)-enantiomer/solvent and (−)-enantiomer/solvent on the left and right hand sides, respectively, and the (+)-/(−)-enantiomeric system on the triangle base with the racemic compound R at a fraction of 0.5. Each point inside the triangle sides describes a ternary mixture

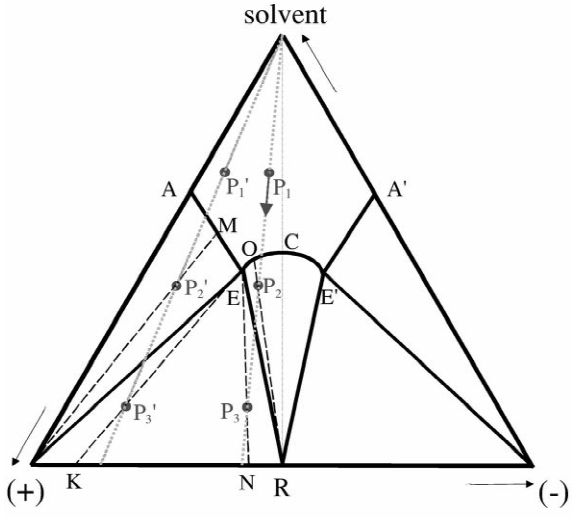

Fig. 4. Schematic ternary solubility diagram of a compound-forming enantiomeric system; T = const. (see Section 3).

consisting of all three components. The points A, A′ and C represent the solubilities of the pure enantiomers and the racemate in the solvent used at a given temperature *T* and, consequently, the curve A–E–C–E′–A′ is the solubility curve of the ternary system at this temperature. Thus, above the solubility curve (in the solvent corner), an undersaturated solution (i.e., a one-phase region) exists. The areas covered by the points A–E–pure (+) or A′–E′–pure (−) as well as by E–E′–R represent two-phase regions where a solid phase consisting of either the pure enantiomer or the racemic compound is in equilibrium with a saturated solution with a composition on the solubility curve. Phase splitting in this region is illustrated for the points P_2' and P_2 in the existence regions of the pure enantiomer and the racemate, respectively. The corresponding composition of the liquid phase is given by the points M and O, respectively. The triangular regions pure (+)–E–racemate or pure (−)–E′–racemate represent three-phase regions with two solid phases (pure enantiomer and racemic compound) in equilibrium with a liquid phase of eutectic composition E or E′. From a partially enriched solution with a composition in this region, the gain of a pure enantiomer is not possible. Saturated solutions of composition P_3 or P_3' split into a solid phase of composition N or K and, thus, a mixture of the pure enantiomer and the racemic compound is obtained. The resulting mother liquor has eutectic composition in both cases.

A pure enantiomer can only be produced by fractional crystallisation when the initial solution composition is located inside the existence region of the pure enantiomers covered by the points A–E–pure (+) or A′–E′–pure (−). Thus, for a combined process of chromatography and crystallisation, the previous chromatographic step must deliver a mini-

mal enantiomeric enrichment which exceeds that of the eutectic point in the ternary phase diagram. Subsequently, the resulting highly diluted and undersaturated solution (e.g., point P_1') has to be evaporated to reach a composition in the pure enantiomer existence region (e.g., P_2') to gain a pure enantiomer by following crystallisation step(s). Chromatographic enrichment of a racemic feed to the point P_1 (with purity less that that of point E) is insufficient, as evaporation will yield a mixture with composition such as that of points P_2 or P_3, and pure enantiomers cannot be recovered by crystallisation. If the temperature dependency of the solubility in the ternary system is known, there may be also other ways to achieve supersaturation from the chromatographically enriched solution.

4. Coupling of chromatography and crystallisation

Based on the above considerations, it appears to be attractive to combine the two separation processes, i.e., to use chromatography to achieve a certain enrichment and then to turn to fractional crystallisation. In Fig. 5, a possible two-step operation scheme is shown schematically. A 50:50 feed is separated continuously by SMB chromatography into raffinate and extract streams enriched partially in one and the other enantiomer, respectively. The partial enrichments given in the figure are but guidelines, the actual enrichments achievable depend upon the adsorption isotherms of enantiomers on the CSP used and the flow-rates set, and are subject to overall mass balances. However, in general, the enrichments will be different for raffinate and extract streams. In the figure, the required creation of supersaturation between the two processes is also indicated.

The two partially enriched streams are then fed to two continuously operated crystallisers, where solid phases consisting only of one or other enantiomer may be collected. Solid–liquid phase equilibrium will usually not be completely established in continuous crystallisers. In any case the mother liquor contains some of both enantiomers and should be recycled. This liquor is, however, partially enriched compared to the starting racemic feed, and to decide in which way the mother liquor can most favourably be remixed with the feed is a nontrivial task and is outside the scope of this work.

The overall process suggested here is a coupling of two units with complex thermodynamics and kinetics which are connected by recycle streams, and it is seen that the modelling and optimisation of the whole is a complex task. A quantitative analysis of

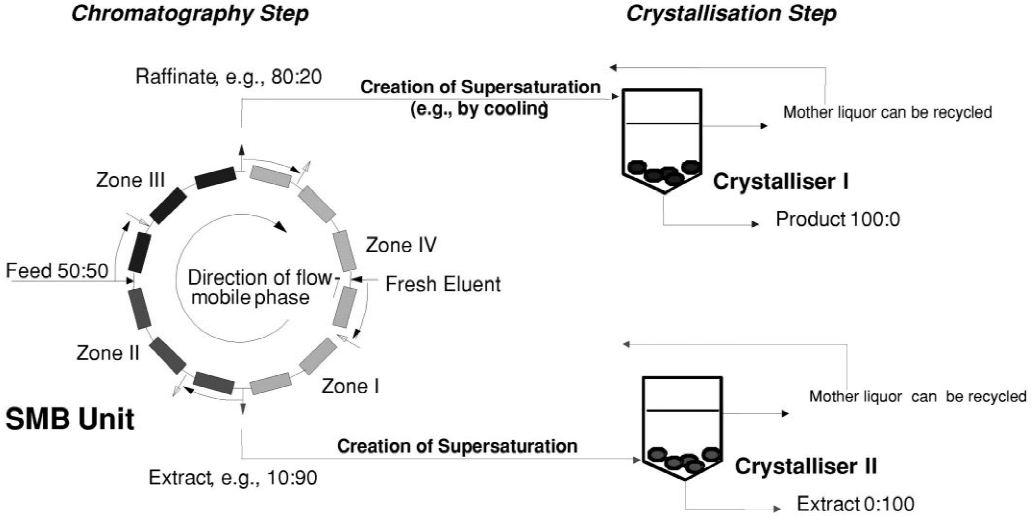

Fig. 5. Possible two-step operation scheme for enantioseparation.

the overall process requires the definition of suitable objective functions.

At this stage, the two quantities purity and productivity should be defined in relation to chromatographic separations. Firstly, purity is here defined as the percentage of concentration of the dominant enantiomer in a given stream with respect to the sum of the concentrations of each enantiomer.

$$\mathrm{Pur}_j = 100 \cdot \frac{c_j^i}{c_j^{(+)} + c_j^{(-)}} \quad \text{for } i = (+) \text{ or } (-)$$

$$\text{and } j = \text{stream} \tag{5}$$

Here, the index i refers to whichever of $(+)$ or $(-)$ has the larger concentration. The index j refers to stream in question. Thus, a racemic mixture has Pur = 50%; a mixture with $c^{(+)} = 3$ g/l and $c^{(-)} = 1$ g/l has Pur = 75%. This definition of purity is usual in the literature of chromatography and SMB, and differs from the conventional notion of enantiomeric purity [9].

The productivity of a chromatographic separation step is defined here as the mass flow of a particular product (fulfilling specified purity requirements) per unit volume of stationary phase used.

$$\mathrm{Prod}_{i,j} = \frac{\dot{V}_j c_j^i}{V_{\mathrm{s,tot}}} \quad \text{for } i = (+), (-) \text{ and } j = \text{stream} \tag{6}$$

Fig. 6 illustrates schematically the motivation for this investigation, namely, that there is a productivity gain to be achieved by demanding but an intermediate purity of a chromatographic separation and then crystallising, as compared to demanding a high purity of the chromatographic process alone. This possibility arises from the fall-off in productivity of chromatographic processes as represented by the curve ''chromatography alone''.

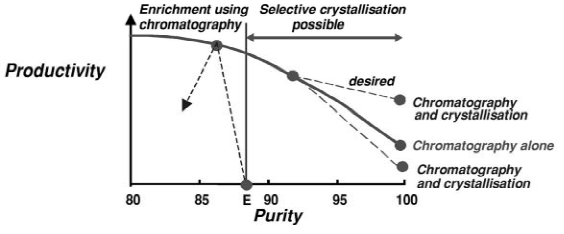

Fig. 6. Dependence of productivity on purity (two-step process).

It has already been explained in Section 3 that, in the case of enantioseparations, there is a minimum purity (i.e., that of points E and E′ in Fig. 4) which must be delivered by the chromatographic step before the crystallisation step can yield an enantiomerically pure product. This is represented in Fig. 6 by the vertical line at purity E. Crystallisations from solutions of purity higher than E may yield enantiopure crystals, as indicated by the straight dashed lines jumping from the ''chromatography alone'' curve to points at 100% purity. However, the productivity gain depends also on the productivity of the crystallisation step, and hence more than one such line is shown. Optimising the crystallisation step will deliver the most favourable performance (the ''desired'' path shown). Crystallisations from solutions of purity less than the critical value E cannot yield enantiopure crystals (see Section 3), and thus, the crystallisation paths in Fig. 6 which start on the left hand side of E reach points of purity less than E. It is a general goal of this work to establish the form of Fig. 6 for a concrete case — to describe the productivity–purity curve for chromatography, to establish the value of the critical ''border'' purity at E, and finally to determine from the shape of the crystallisation paths whether the two-step process does indeed perform the enantioseparation more efficiently and to quantify this improvement.

5. Experimental

For a combination of chromatographic and crystallisation separation techniques, the separation of the enantiomers of mandelic acid dissolved in aqueous solution was chosen as a suitable model system. The two pure enantiomers are commercially available at a reasonable price, and from literature sources some data for solubility are known [29,30].

The experimental work included measurements in both the chromatographic and crystallisation areas. The chromatographic part involved the estimation of adsorption isotherms on a suitable chiral stationary phase after having set up an optimised HPLC separation method. On the other hand, the equilibrium data of the ternary system (+)-mandelic acid/

(−)-mandelic acid/water have been measured to identify the conditions where the pure enantiomers can be successfully crystallised. In the following, the experimental methods applied are described.

5.1. Chromatographic measurements

Chromatographic separation of the mandelic acid enantiomers can be carried out on a β-cyclodextrin chiral stationary phase (200/4 Nucleodex β-OH, Machery-Nagel). The mobile phase composition was 50 m*M* NaH_2PO_4/acetonitrile (95:5, v/v) buffered to pH 3. Measurements with one analytical column (20×0.4 cm) have been performed at a flow-rate of 0.5 ml/min and at 20°C. A Hewlett-Packard 1100 HPLC-system with a UV photodiode array detector was applied. The UV signal was recorded at a wavelength of 220 nm. To estimate column efficiencies and capacity factors, small sample sizes were injected (1 μl of a 0.1% mandelic acid in eluent solution). The column porosity was estimated from the retention time of an acetonitrile pulse. The eluents used were of HPLC grade (LiChrosolv), the mandelic acid enantiomers {(*S*)-(+)-mandelic acid, (*R*)-(−)-mandelic acid and the racemic (±)-mandelic acid} supplied from Merck or Aldrich were of synthesis grade (>99% purity). To estimate the adsorption isotherms, elution profiles under overloaded conditions have been recorded and analysed using the elution by characteristic point (ECP) method [6].

5.2. Solubility measurements and estimation of the ternary phase diagram

Solubility measurements were carried out using a static isothermal method with phase separation and subsequent analysis. An excess of either pure enantiomer or a mixture of known composition of both enantiomers was added to a certain amount of solvent in a closed glass container. This container was then immersed in a double- or triple-walled thermostatted equilibrium apparatus and the solution was then electromagnetically stirred at the desired temperature (temperature controlled to within ±0.02 K) until equilibrium was achieved (at least 4 h). The time required for establishing the solid–liquid equilibrium was determined in a separate experiment, withdrawing and analysing samples of the mother liquor after different time intervals during dissolution studies. It was shown that at 25°C the equilibrium has already been attained after 20 min for both the (+)-mandelic acid enantiomer and the racemate. For ternary sample systems containing the (+)- and (−)-mandelic acid enantiomers and water, both the liquid and solid phase (saturated solution and undissolved solid) were analysed to determine their composition. The amount of solute in the saturated solution was determined by evaporation of the solvent in a rotary evaporator. The (+)- to (−)-enantiomer ratio both of this solute and of the original undissolved solid was analysed by HPLC. The quality of the results was assessed from an overall mass balance. For binary systems consisting of a pure enantiomer and the solvent, only the liquid phase was examined taking a liquid sample using a pipette after allowing the solid phase to settle and then evaporating the liquid sample. Repeatability measurements showed that the maximal error of the solubility data in the temperature range reported was below 2.5%. About 60 points in the ternary phase diagram (+)-mandelic acid/(−)-mandelic acid/water have been measured allowing the determination of solubilities at temperatures between 0 and 40°C covering the whole range of enantiomeric purity.

6. Results and discussion

6.1. Chromatography

From single injection experiments conducted under linear conditions, numbers of theoretical plates of the order 4000–5000 were observed for the cyclodextrin columns for both enantiomers of mandelic acid. The total column porosity was found to be $\epsilon = 0.793$. Fig. 7 shows overloaded elution profiles for separate injections of the single solutes used to determine the slopes of the adsorption isotherms. Due to the high column efficiency, it was justified to take these slopes from the tails of the chromatograms (equilibrium theory, ECP method [6]). From these slopes, the parameters of the Langmuir isotherm equation (Eq. (2)) were fitted and the parameters obtained are presented in Table 1. The form of the

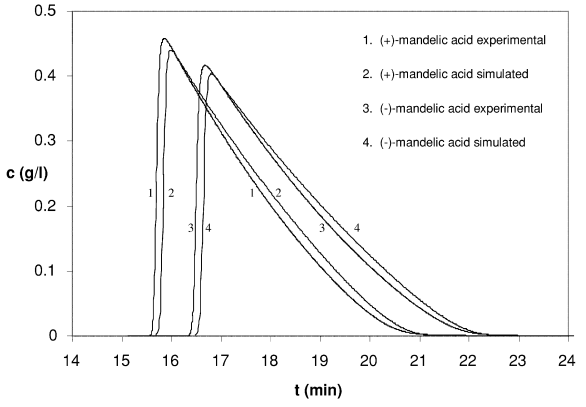

Fig. 7. Elution profiles of the two single enantiomers under overloaded conditions.

Table 1
Parameters of the Langmuir equation (Eq. (2))

$a^{(+)}$	19.443
$a^{(-)}$	20.864
$b^{(+)}$ (l/g)	0.370
$b^{(-)}$ (l/g)	0.415

corresponding isotherms is plotted in Fig. 8. The separation is seen to be a difficult one, the separation factor under linear conditions being 1.073. Also shown in Fig. 7 are peaks generated from simulations based upon Eq. (1) using the fitted isotherm parameters. The agreement between the experimental and simulated peaks validates the procedure within the limits of accuracy obtainable from the ECP method.

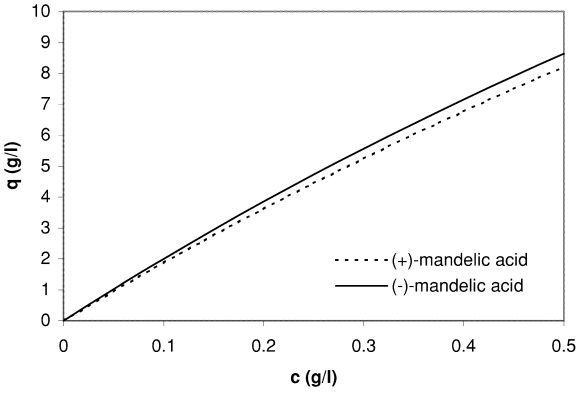

Fig. 8. Adsorption isotherms of the enantiomers as fitted to Langmuir equation (Eq. (2)).

Based on the adsorption isotherms as determined, a simulation study was carried out to predict the performance of a SMB unit consisting of only four analytical columns of the type and size described above [$V_{s,tot}=4\cdot(1-\epsilon)\cdot V_{col}=2.08$ ml]. The purpose of this study was to identify regions of complete and partial separation within the $m_{II}-m_{III}$ plane for the concrete chromatographic system (Fig. 2). In each case, appropriate values of m_I and m_{IV} were assumed based on the critical values obtained from equilibrium theory [23–25] including an additional safety factor of 10%. Simulating the SMB unit over the range of reasonable values of m_{II} and m_{III} for a feed of given concentration allowed one to identify regions where both raffinate and extract streams had at least a specified purity (not necessarily 100%). For each SMB run simulated, the purities delivered when the cyclic steady state had been established were analysed.

Due to the fact the efficiency is of minor importance in SMB chromatography, in the simulations a reduced plate number of $n=300$ was assumed to be valid for both components and independent of flow-rate. This increased the speed of simulations. Shown in Fig. 9a are the regions in the $m_{II}-m_{III}$ plane delivering both raffinate and extract streams at purity of 70% or greater for a range of feed concentrations. In each case, c_f represents the concentration of each enantiomer in the feed stream, with $c_f=c_f^{(+)}=c_f^{(-)}$, as necessary for a racemic feed stream. As indicated in Fig. 2 earlier, the regions become smaller with increasing concentration.

Fig. 9b is obtained by taking the vertex of the region as the optimal operating point for each case and plotting the productivity (Eq. (6)) of the SMB process at this point versus the feed concentration. This is done by converting the values of the m-ratios back into actual flow-rates, then calculating productivity, in this case the sum of the productivities of the (+)- and (−)-enantiomers. It is seen that the productivity depends upon feed concentration and that the productivity–concentration curve exhibits a maximum around $c_f^{(+)}=c_f^{(-)}=0.3$ g/l.

The form of the dependences shown in Fig. 9a will also depend upon the purity limit (70% above) at which this analysis is performed. Taking the low feed concentration $c_f^{(+)}=c_f^{(-)}=0.001$ g/l, Fig. 10a

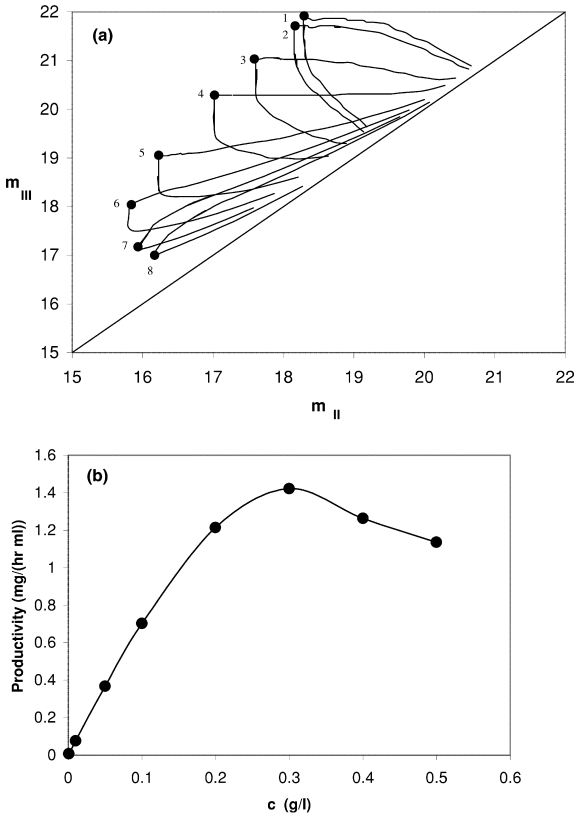

Fig. 9. (a) Regions in the $m_{II}-m_{III}$ plane guaranteeing 70% purity of both raffinate and extract streams for the following feed concentrations: (1) $c_f=0.001$ g/l; (2) $c_f=0.01$ g/l; (3) $c_f=0.05$ g/l; (4) $c_f=0.1$ g/l; (5) $c_f=0.2$ g/l; (6) $c_f=0.3$ g/l; (7) $c_f=0.4$ g/l; (8) $c_f=0.5$ g/l. The points mark the optimal operating condition for each region. (b) Productivities at the optimal operating points of the regions shown in (a).

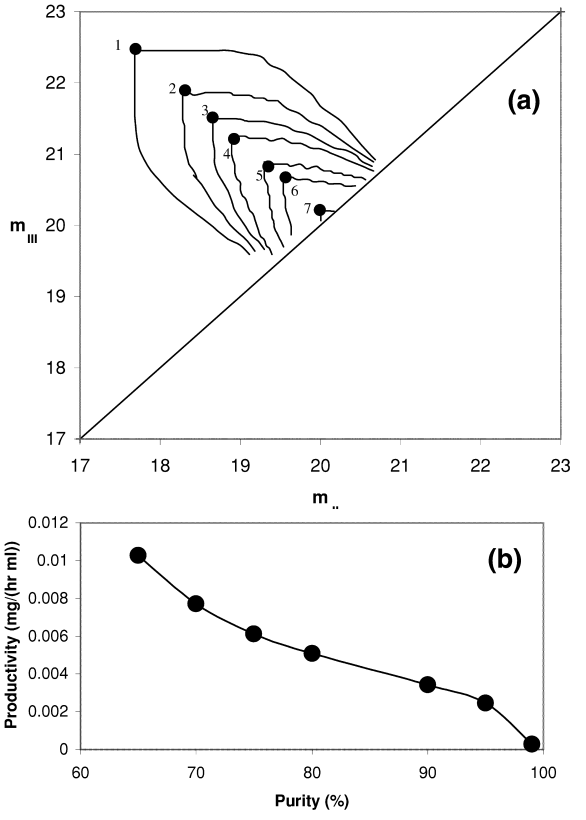

Fig. 10. (a) Regions in the $m_{II}-m_{III}$ plane guaranteeing, for $c_f=0.001$ g/l, raffinate and extract streams with purity: (1) Pur>65%; (2) Pur>70%; (3) Pur>75%; (4) Pur>80%; (5) Pur>90%; (6) Pur>95%; (7) Pur>99%. The points mark the optimal operating condition for each region. (b) Productivities at the optimal operating points of the regions shown in (a).

shows $m_{II}-m_{III}$ regions for a range of purity requirements ranging from 65% purity of both raffinate and extract to 99% for both (with the four columns assumed here no complete separation was possible). Larger regions are found as the purity requirements are relaxed. This means larger feed streams could be treated. This is observed from the productivities possible for the SMB unit seen in Fig. 10b, where the possible productivity of the SMB unit is plotted as a function of purity requirement at the optimal operating points of each region in Fig. 10a. The fall-off in productivity was anticipated in the shape of the ''chromatography alone'' curve in Fig. 6 above. Indeed, Fig. 10b now shows the shape of this curve for our case. The implication of the higher SMB productivities and $c_f=0.001$ g/l possible at lower purity requirements will be discussed in Section 6.3 below.

6.2. Crystallisation

In order to identify the conditions where the pure enantiomers can be crystallised from a solution which has been previously enantiomerically enriched, experimental measurements of the phase equilibrium data of the system consisting of both enantiomers and solvent have been carried out. The results of the measurements are presented in Figs. 11 and 12.

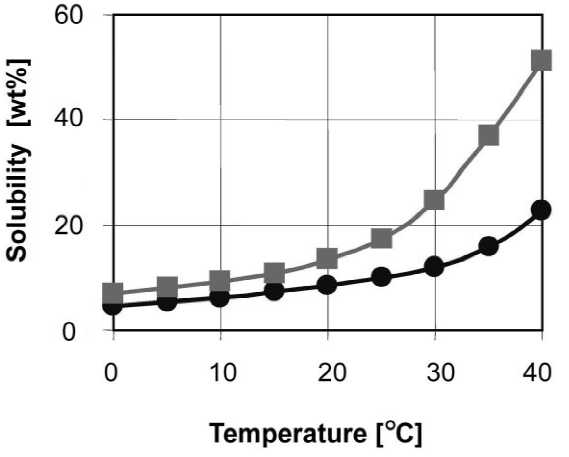

Fig. 11. Temperature dependence of the solubility of mandelic acid in water: (■) (±)-mandelic acid; (●) (+)-mandelic acid.

Fig. 11 shows the solubility of both racemic mandelic acid and its (+)-enantiomer in water as a function of temperature. In both cases, the solubility increases in a roughly exponential manner with the temperature. Corresponding to the melting points (120.2°C for the racemate, 131.6°C for the enantiomers, according to our measurements), the solubility of the racemate is higher than that of the pure enantiomer. Furthermore, a significant difference in the temperature dependency of the solubility can be observed, this being considerably stronger for the racemic mandelic acid than for the pure enantiomer. Thus, in the temperature range between 20 and 40°C, the solubility of the racemate rises from 13.3 to 51.3 wt% compared to an increase from 8.4 to 22.6 wt% for the pure enantiomer. From a practical point of view, this implies that cooling crystallisation is possible for both the racemate and the pure enantiomers. However, the knowledge of the pure enantiomer and racemate solubilities alone, as given in Fig. 11, does not allow the specification of suitable conditions under which crystals of pure enantiomer can be recovered from a partially enriched solution. These data are also not sufficient to decide whether

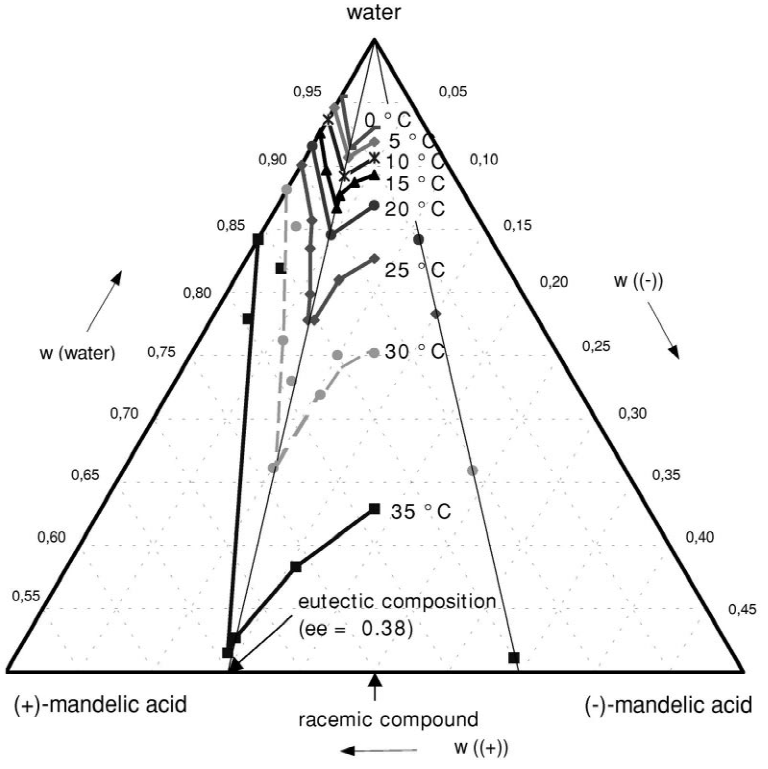

Fig. 12. Ternary solubility diagram of the two enantiomers of mandelic acid in water for the temperatures given.

the mandelic acid system is a compound/forming system or a conglomerate/forming system.

In Fig. 12, the ternary phase diagram of the system (+)-mandelic acid/(−)-mandelic acid/water is presented in the equilateral triangle form described above in Section 3. It contains the equilibrium data measured for various temperatures between 0 and 35°C represented by isotherms in the diagram. Most of the points measured refer to an excess of the (+)-enantiomer; for mixtures containing the (−)-enantiomer in excess, only a few experiments have been carried out to confirm the symmetry of the isotherms about the line of mixtures of racemic composition. This symmetry was indeed observed within the limits of experimental error and thus, the isothermal saturation lines in the triangle (−)-mandelic acid–racemic compound–water may be constructed by reflection of the (+)-mandelic acid–racemic compound–water triangle about the racemic compound–water line. As already discussed with reference to Fig. 11, the exponential upward trend of the solubility with the temperature and the higher solubility of the racemic compound compared to the pure enantiomers can also be observed here. Furthermore, a mixture with a solubility maximum (i.e., a eutectic point) can be identified between the pure enantiomer and the racemic composition, thus giving the saturation line the typical shape of a compound forming system. Thus, racemic mandelic acid may be identified as a true racemate. The solubility data determined are in agreement with the few literature data available [29,30].

The enantiomeric composition of the eutectic point is found to be almost invariant with temperature, having a (+)- to (−)-mandelic acid ratio of about 69:31 (or vice versa). This value corresponds well with the only available literature data of Nishiguchi et al. [29] with 69:31 and of Fouquey and Jacques [31] with 70:30 (derived from the binary melting point diagram). The region of existence of crystals of enantiomerically pure mandelic acid can now be identified for a given temperature as the region formed from the pure enantiomer corner, the pure enantiomer solubility at a given temperature and the appropriate eutectic point at this temperature. As discussed at the end of Section 3, the eutectic point specifies a minimum enrichment required from the chromatographic step in a process coupled with crystallisation step. This is the significance of the point E in Fig. 6. Thus, for the example considered here, the SMB process must deliver a stream with an enantiomeric enrichment greater than 69:31 to make possible a successful subsequent crystallisation of the pure enantiomer. This motivated the choice of the purity 70:30 in the study reported on in Fig. 9, this value being just above the minimum necessary to attain pure enantiomers upon crystallisation.

At this point it should be noted that the chromatographic separation studied here was performed using not pure water as the solvent, but from an aqueous solution containing a certain amount of phosphate buffer at a defined pH. The solubilities of the racemic and the pure enantiomeric mandelic acid in this eluent were determined to be slightly higher than in water alone due to the pH shift. However, the typical deviation here was found to be less than 5%. A possible influence of the phosphate buffer on the purity of the mandelic acid crystallised from the appropriate solution will be studied in future work.

6.3. Coupled process

To summarise the key information established thus far on the way to reproducing the form of Fig. 6 for our sample system: the form of the chromatography productivity curve has been established for a four-column SMB unit; the position of the eutectic point gives the minimum purity which must be delivered by the chromatography step, thus, the position of the vertical line in Fig. 6 beyond which a selective crystallisation may be successfully conducted.

Yet to be established is the form of the crystallisation pathways given in Fig. 6. The productivity to be expected of crystallisation carried out after chromatographic enrichment depends upon a number of factors. Referring to Fig. 5, there is the necessity to create supersaturation. Cooling is one possible approach here, and the costs of creating supersaturation should be taken into account when estimating the productivity of a crystallisation step. Also to be considered are the kinetics of the crystallisation itself, which will determine the sizing and design of the crystalliser and the duration of the process for batch processing or the residence time for continuous processing. The degree of supersaturation created not only gives the driving force for the crystallisation but

also influences the yield which can be expected from the crystalliser. Returning to Fig. 4, the higher the degree of supersaturation, the further the point P_2' is ''driven'' towards the vertex of the ternary diagram representing pure (+)-crystals. In accordance with the classical lever rule, the possible yield of crystals is then specified, with the maximum yield occurring for a given degree of supersaturation when the contents of the crystalliser are allowed to reach equilibrium. The degree of supersaturation will also influence the composition of the mother liquor. The composition of the mother liquor determines whether further selective crystallisations are possible (multi-stage processing), and also affects the recycling of mother liquor to the chromatography unit. It may be remarked that the precise specification of the performance of a crystalliser and the subsequent optimisation of this process are complex issues. These have not yet been addressed in the work reported upon in this paper, and form part of the future work to be undertaken.

From Fig. 10b, one can see the possible increase in productivity of the SMB unit which can be gained by demanding lower purities compared to the high purities often demanded (>99%). It is seen from the results in Section 6.2 that crystallisation from SMB product streams of 69:31 purity or greater can yield crystals of pure enantiomer. For example, demanding purities of 70 or 80% of both outlet streams of the SMB unit sees possible throughput which are increased by factors of about 28 and 18, respectively, compared with the throughput when 99% pure streams are demanded. Thus, the two-step process enables one to take advantage of these substantial increases in productivity and this is offered as a first indication of possible gains to be achieved by implementing the two-step process suggested here.

7. Conclusions

In this paper, the possibility of a coupling of chromatography and crystallisation for the efficient separation of enantiomers has been analysed. It was attempted to describe essential parts of both processes with simple models. A main objective was to find a way to specify a reasonable ''border purity'' between the two processes.

The analysis performed for the particular separation of racemic mandelic acid dissolved in an aqueous solution revealed the potential of using β-cyclodextrin chromatographic columns to achieve an enrichment exceeding that of the eutectic point of the two enantiomer/solvent system, which has been shown to be a critical value and lies for our model system around 69:31 (or 31:69) over a broad temperature range.

In addition to the measurements of the underlying adsorption isotherms and the ternary solubility diagrams and the SMB simulations, a complete quantitative analysis of the suggested process also requires knowledge of crystallisation kinetics and of the expenditures related to the creation of the supersaturation required for crystallisation. Regarding this latter step, one should be careful to avoid creating too much supersaturation, thereby entering and then leaving again the region of pure crystals, (as per the point P_3' in Fig. 4).

Regarding future work, the issue of the possible inclusion of buffer components in crystals should be analysed. Adsorption isotherms at different temperatures will be measured. The analysis of SMB processes with more than four columns is planned. A detailed examination of the design and optimization of the crystallisation step will also be undertaken.

8. Nomenclature

a	parameter in Langmuir isotherm (–)
b	parameter in Langmuir isotherm (l/g)
c	concentration in mobile phase (g/l)
d	inner diameter of chromatographic column (m)
D_{ap}	apparent dispersion coefficient (m^2/s)
L	length of a column (m)
m	flow-rate ratio as defined in Eq. 4 (–)
N	number of theoretical plates (–)
q	concentration in stationary phase (g/l)
t	time (s)
T^{shift}	shift time of the SMB process (s)
u	(superficial) velocity (m/s)
V	volume (m^3)
$\dot{V}$	liquid flow-rate (ml/min)
w	weight fraction (–) or wt%
z	length along a column (m)

Subscripts

col	column
f	feed
s	solid (i.e., chiral stationary phase)
tot	total

Superscripts

(+), (−)	refers to (+) or (−) enantiomer

Greek

ϵ	porosity (–)

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