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Coupling Chromatography and Crystallization for Efficient Separations of Isomers

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Abstract. Within the pharmaceutical industry and in biotechnology there is an increasing need for selective and efficient separation technologies to isolate and purify value-added products. A hybrid process approach combining chromatography and fractional crystallization is studied below. The work presented is concerned with the application and evaluation of this concept in order to isolate a certain pharmaceutical intermediate from a binary mixture. A comparison with performing the same separation exclusively in a single chromatographic process is given also.

Keywords: chromatography, simulated moving bed process, crystallization, hybrid processes

1. Introduction

The preparation of pure isomers is an important issue for the pharmaceutical industry (Crosby, 1997). Time to market is typically the critical parameter and affects the selection of the technology used to produce the required products. Besides asymmetric synthesis an assortment of separation methods is used. In the last years chromatographic methods based on the simulated moving bed technology (SMB) have been increasingly proposed to perform these separations, especially for chiral systems. Schulte and Strube (2001) gave a review regarding preparative enantioseparations by means of SMB technology. Alternatively, direct crystallization such as fractional crystallization of partially resolved mixtures or preferential crystallization is widely used to obtain isomers as discussed in detail by Jacques et al. (1981). It is well known that the productivity of chromatographic methods decreases with increasing purity demands (Kaspereit et al., 2002). Thus, process combinations appear to be attractive. One possibility to perform such separations is the coupling of a chromatographic enrichment step with subsequent crystallization, as discussed for enantioseparations in

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Lim et al. (1995) and Lorenz et al. (2001). There is still a need of analyzing more examples in order to evaluate the potential of this concept.

2. Principle of the Hybrid Process

The system under consideration is a mixture of 2 diastereomers and an additional impurity. The structure of the molecules (pharmaceutical intermediates) is of no relevance to this work. Only one of the isomers is the product, the other one is recycled to earlier stages of the synthesis. Throughout this work the subscripts *P, SP* and *I* will denote the (desired) product, the (undesired) side product and the impurity, respectively. Superscripts are used below to mark the position in the hybrid process (see Fig. 1 and nomenclature).

It is widely accepted that a countercurrent chromatographic separation, usually, exploits more efficiently the stationary phase and allows for a lower eluent consumption compared to a simple batch elution process (Heuer et al., 1998). Therefore, the chromatographic separation is done in this work by means of SMB chromatography.

The considered hybrid process is illustrated in Fig. 1. Fresh feed ($F0$) is introduced to the process and mixed with a recycle stream from the crystallization step. This mixture enters an SMB process where the product P exits the SMB at the raffinate port (R). In order to crystallize the product usually some adjustments have to be done, such as a pre concentration or a solvent change. Evaporation processes will be used to perform the solvent treatment in this study. Part of the product will remain in the liquid phase of the crystallizer C (depending on the mother liquor purity). To maintain high yields of the product (as offered by a successful single SMB separation) a recycling of the mother liquor has to be established. The concentration level of this recycle stream, as well the composition of the solvent (in the case of solvents consisting of several components) may have to be adjusted again to meet the design conditions of the SMB feed. The SMB process is assumed as the performance limiting step in the hybrid process. In the following discussion product P leaving the process through the extract port (E) of the SMB will be treated as a loss, although it could be reused together with the side product *SP* in earlier stages of the synthesis.

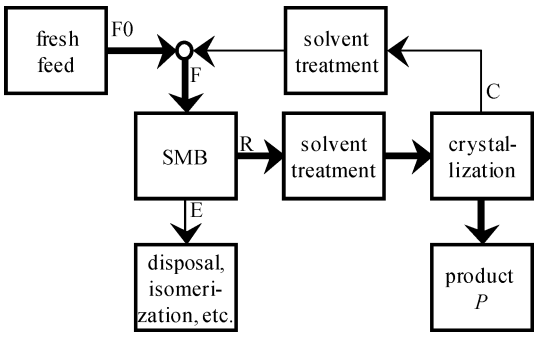

Figure 1. Scheme of the hybrid process considered.

3. Experimental

3.1. Solid Liquid Equilibria Studies

The melting temperatures of the solid isomers and their mixtures were measured with a differential scanning calorimeter (Calvet TG-DSC, Setaram, France). The solubility of the isomers and the eutectic composition were determined by means of isothermal equilibrium measurements (5, 15, 25 and 35°C) and HPLC analysis. The solvents used were ethyl acetate and two mixtures of ethyl acetate/heptane ($65/35_{v/v}$ and $55/45_{v/v}$). Different solvents were considered to account for changes of the solvent composition during pre concentration and crystallization processes.

3.2. Crystallization Studies

The crystallization of product P was studied with batch experiments (seeded suspension crystallizations). The initial liquid phase purity was varied between $PU_P^{C0} = 0.6$ and 0.99, while the final liquid phase compositions were between $PU_P^C = 0.5$ and 0.99. The effect of crystallization temperature was studied between $T^C = -12$ and 21°C. The operating modes considered were cooling, evaporation and drowning out crystallization (Mersmann, 1995). The compositions of the liquid phase and the obtained solid product were analyzed by HPLC and DSC methods.

3.3. Adsorption Studies

Adsorption isotherms of the isomers (*P, SP*) were measured using single component frontal analysis of consecutive breakthrough curves (Lisec et al., 2001) with a 0.46 × 25 cm column packed with the same batch of adsorbent (Kromasil SIL, 16 μm, 100 Å, Eka

Chemicals, Sweden) subsequently used for SMB experiments. A $65/35_{v/v}$ ethyl acetate/heptane mixture was used as mobile phase. The initial slopes of the adsorption isotherms were calculated from retention times of the smallest sample amounts detectable. The experimental setup consisted of a Waters (U.S.A.) 600 E quaternary solvent delivery system together with a UV detector (Knauer, Germany).

SMB experiments were done with a Novasep (France) SMB unit (5 pump configuration) with 2 columns in each zone of the system. 8 columns were used (Merck, Germany) with an inner diameter of 2.5 cm (see Table 1 for details). The system was controlled with the Licosep-Lab software (Novasep).

4. Results

4.1. Solid Liquid Equilibria Studies

A simple eutectic system was determined from the binary *P-SP* melting point diagram. The eutectic composition with respect to P was between 0. 36–0.40 g_P/g_{isomers}. This value corresponds with measurements of the solubility of both isomers in a number of solvents. The ratio of the solubility of the product P and side product *SP* is about 1:1.8. This ratio is almost independent of the solvent and temperature.

4.2. Crystallization Studies

The conditions of the crystallization experiments were set based on the results of the solid liquid equilibria studies (SLE). On the basis of the determined eutectic composition it appeared to be possible to crystallize pure P out of mixtures with a purity PU_P down to about 0.4. However, the performed crystallization study revealed the following two facts (Fig. 2):

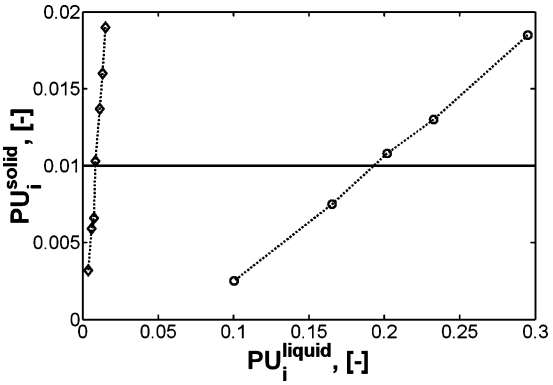

Figure 2. Amount PU_i^{solid} of the side product ($i = \text{SP}$, circles) and the impurity ($i = I$, diamonds) in the crystallized product P depending on the final liquid phase composition PU_i^C in the crystallizer.

1. The side product is not fully separated from the solid P by crystallization. High purity requirements of the solid product ($PU_P \geq 0.99$) can only be met if the final crystallizer liquid phase purity exceeds 0.8, i.e. $PU_P^C > 0.8$ ($\equiv PU_{\text{SP}}^C < 0.2$).
2. The amount of the impurity cannot be decreased during crystallization, i.e. I has to be removed by SMB chromatography.

These results define the requirements for the chromatographic enrichment and demonstrate the importance of such preliminary crystallization experiments. An explanation for the observed discrepancy between the SLE and results of the crystallization studies might be partial miscibility of the isomers. This hypothesis is currently under investigation.

4.3. Adsorption Studies

The experimentally determined loadings of the two isomers are shown in Fig. 3. A modified Langmuir competitive isotherm model (Nicoud et al., 1993) was found

Table 1. Conditions of the SMB experiments.

$c_{\text{total}}^{\text{feed}}$ (g/l)	Column bed length (cm)	Column overall porosity (-)	NTP (−)	$Q_{\max}^*$ (ml/min)	Feed composition P:SP:I	Solubility,** (g/l)	V_{extra}^{***} (ml)
10	20.3	0.752	1100	59.1			
20	20.3	0.752	1100	63.2	49:49:2	25	80
10	9.83	0.741	650	120.3			

*Maximal flow rate in zone 1 of the SMB resulting in a pressure drop over the system of appr. 60 bars.
**Solubility of the isomeric mixture in the mobile phase at the feed composition and 25°C.
***Tubing, recycling pump and valve volume of the SMB system.

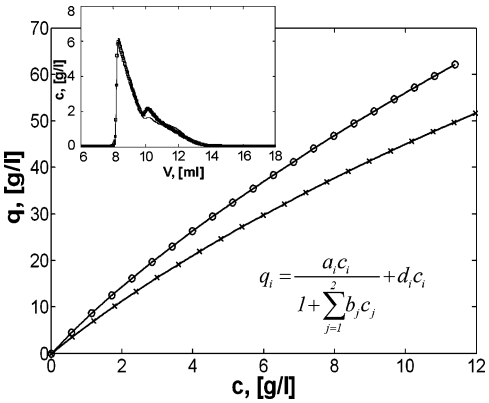

Figure 3. Experimental loadings of P (crosses) and SP (circles), Isotherm Parameters: P: $a_P = 4.877$; $b_P = 0.0513$; $d_P = 1.289$; SP:$a_{SP} = 6.986$; $b_{SP} = 0.0647$; $d_{SP} = 1.289$; small picture: comparison of an experimental (symbols) and a simulated (line) elution profile, $NTP = 1600$; $V_{inj} = 1$ ml; $c_{P,inj} = 6.97$ $c_{SP,inj} = 2.98$ $C_{I,ing} = 0.21$ g/l.

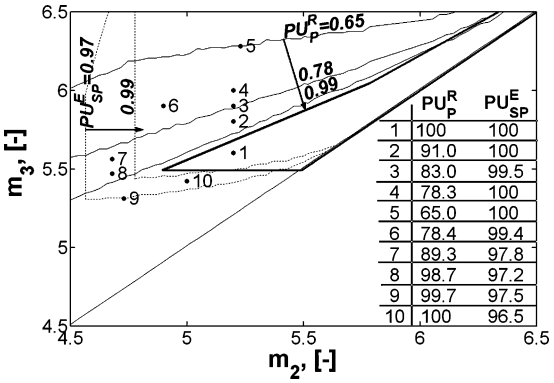

Figure 4. SMB-experiments (Table 1, 3rd row), symbols: experimental steady state conditions, thick line: region of complete separation (Mazzotti et al., 1997) with modified initial slopes and modified isotherm parameters: $a_P = 5.49$, $a_{SP} = 7.27$, $b =$ see Fig. 3, $d_P = d_{SP} = 0$; thin lines: simulated purity contours of the SMB outlets.

to be sufficient to describe the adsorption behavior. The impact of the impurity could only be estimated based on pulse experiments (initial slope of I : $a_I + d_I = 9.84$).

4.3.1. Simulation Results. With the measured isotherms a simulation study of the SMB process using the equilibrium dispersive model (Ruthven and Ching, 1989; Golshan-Shirazi and Guiochon, 1994) was performed disregarding the impurity I. The flow rates in the solid phase regeneration zone (zone 1) were kept at the Q_{max}-values given in Table 1. The operating parameters of the regeneration zones (1 & 4) were kept at safe values (Mazzotti et al., 1997). A productivity PRS based on the mass flow of product P out of the raffinate port of the SMB per unit stationary phase and time is used as the performance parameter (Eq. (1)). Note that similar trends were obtained for other objective functions, e.g. for the specific eluent consumption.

$$PRS = \frac{Q^R c_P^R}{n(1-\varepsilon)V_{Column}} \tag{1}$$

An example of PRS as a function of the raffinate purity is given in Fig. 5. Product should not be lost through the extract of the SMB in this particular case. Therefore, the purity requirement of the extract was set to $PU_{SP}^E = 0.99$. For this extract purity an increase of the objective function is possible by a factor of about 2.6 for $PU_P^R = 0.6$ compared to $PU_P^R = 0.99$. For high purity requirements on the extract stream, the operation points of reduced raffinate purity requirements are quite close which makes those points sensitive to changes in the system parameters (see simulated purity contours in Fig. 4).

4.3.2. Experimental Results. The SMB operating parameters (flow rates and switch time) were determined based on the simulation results. In order to drain the impurity through the extract port the flow rate ratio m_1 was adjusted to the initial slope of the impurity (Mazzotti et al., 1997). Starting from a point of complete separation (e.g. point 1 in Fig. 4) the parameters were changed to decrease the purity at the raffinate port while keeping the extract port clean. During the course of experimentation the adsorption capacity seemed to vary gradually. To account for that, the initial slopes of the isotherms were measured again with pulse experiments directly at the SMB system and the operating conditions were modified to meet the actual initial slopes. Therefore the initially measured adsorption isotherms and the used SMB model were able to describe the experiments qualitatively but not quantitatively. Nevertheless, a satisfactory agreement has been observed between the simulation results and experiments (Fig. 4).

The impurity was always separated from the product even for reduced raffinate purity (as required due to the results of the crystallization studies). Since the size of the separation region decreased considerably for increased total feed concentrations of 20 g/l, a stable SMB operation could not be guarantied for further increased feed concentrations.

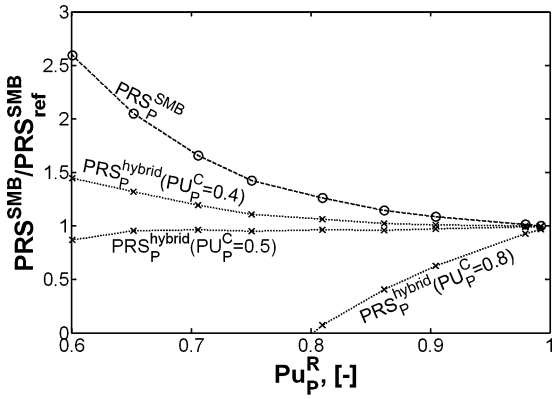

Figure 5. Increase of the productivity of a hybrid separation compared to the stand-alone SMB separation of the diastereomers; circles: simulated productivity PRS^{SMB}; crosses: resulting productivity PRS^{hybrid} for 3 compositions in the crystallizer; simulation parameters see Fig. 4; $PRS^{\mathrm{SMB}}_{\mathrm{ref}}$ at $PU^R_P = 0.99$; $PU^E_{\mathrm{NP}} = 0.99$, $c^F = 10$ g/l.

5. Coupled Process

Decreasing the purity requirements for the SMB process increases the productivity PRS^{SMB} (Fig. 5). However, a subsequent crystallization step partly consumes this increase and thus reduces the overall productivity of the hybrid process. The yield of the crystallization process can be defined as:

$$Y^C = \frac{\textit{mass of solid } P}{\textit{initial mass of dissolved } P} \tag{2}$$

This can be expressed as:

$$Y^C = \frac{PU_P^{C0} - PU_P^C}{PU_P^{C0}\left(1 - PU_P^C\right)} \tag{3}$$

where PU_P^{C0} and PU_P^C are the purity in the liquid phase at the beginning and at the end of the crystallization process. The purity of the liquid phase at the beginning obviously corresponds here to the one of the raffinate port of the SMB PU_P^R. The productivity of the hybrid process, PRS^{hybrid}, can now be calculated as:

$$PRS^{\mathrm{hybrid}} = PRS^{\mathrm{SMB}}\, Y^C \tag{4}$$

Figure 5 shows that for the studied SMB separation the hybrid process would only be more productive than the single SMB operation if the crystallizer purity holds: $PU_P^C < 0.5$. Thus, with the eutectic composition of about 0.4 in principle the hybrid process could be more productive. However, according to the crystallization experiments described above a final crystallizer composition of $PU_P^C < 0.8$ does not yield in product meeting the purity requirements. As a consequence for the system studied in this work the hybrid approach does not outperform the stand-alone SMB process.

Table 2. Maximal shift of the SMB feed compositions of the hybrid process (complete recycling of mother liquor, $PU_P^{FO} = 0.5$).

PU_P^R	0.60	0.70	0.80	0.85	0.90	0.95
PU_P^F for:						
$PU_P^C = 0.4$	0.45	0.47	0.48	0.49	0.49	0.50
$PU_P^C = 0.8$	–	–	–	0.68	0.60	0.54

In order to reach high yields of such hybrid processes of course a recycle of mother liquor has to be established. This was not considered up to now (since it does not affect PRS^{SMB} directly). However, such a reflux shifts the composition of the SMB feed towards the mother liquor purity. This shift influences PRS^{SMB}. For several combinations of the raffinate and crystallizer purity the shift of the SMB feed composition is listed in Table 2. This effect is rather small and may be neglected in a first and quick evaluation of the potential of the hybrid process.

A detailed description of a more general approach to evaluate the potential of hybrid separation processes is in preparation.

6. Conclusions

For a mixture of two diastereomers a hybrid separation process was studied using simulated moving bed chromatography as an enrichment step followed by a subsequent crystallization. Initially, based on the specific eutectic composition of 0.4 (with respect to the target isomer) the hybrid approach appeared to be promising. Increases of the productivity by a factor of about 1.5 could have been achieved theoretically (for $PU_P^R = 0.6$, $PU^E_{\mathrm{SP}} = 0.99$, $PU_P^C = 0.4$). However, crystallization experiments revealed that the minimum acceptable liquid phase composition PU_P^C within a crystallization unit should be above 0.8 (not 0.4) to assure the required product purity. Under these conditions the single chromatographic process is superior compared to the coupled processes.

The authors recommend for similar studies of other systems to determine the minimal crystallizer liquid

phase composition from solid liquid equilibria and crystallization experiments. Chromatographic simulations based on adsorption isotherms can be used to test with the methodology given above (for one product component) whether the hybrid approach has the potential to outperform the exclusive chromatographic separation. If promising results are obtained one should subsequently collect the data necessary (e.g. crystallization kinetics) for a detailed design and performance optimization of all processes in the hybrid scheme.

Nomenclature

Arabic

c	Concentration in the liquid phase, (g/l)
m_i	Flow rate ratio of zone i, with $i = 1$–4 (Mazzotti et al., 1997) (-)
NTP	Number of theoretical plates of a column (-)
PRS	Productivity related to the amount of stationary phase (g/l/h)
PU_i	Purity or composition with respect to i defined as $\text{mass}_i/(\Sigma\text{mass}_{\text{solutes}})$; $solutes = P, SP, I$ (g/g)
q	Concentration in the solid phase (g/l)
Q	Volumetric flow rate (l/h)
T	Temperature (K)
V	Volume (l)
Y	Yield (g/g)

Greek

ε	Total porosity of a column

Subscripts

I	Impurity
P	Product
SP	Side product

Superscripts

0	Initial
C	Crystallizer
E	Extract port of the SMB
F	Feed into the SMB unit
$F0$	Feed into the hybrid process
R	Raffinate port of the SMB

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References

Crosby, J., in *Chirality in Industry II*, A.N. Collins, G.N. Sheldrake, and J. Crosby (Eds.), pp. 1–10, John Wiley & Sons, Chichester, 1997.

Golshan-Shirazi, S. and G. Guiochon, *J. Chromatogr. A*, **658**, 149–171 (1994).

Heuer, C., H. Kniep, T. Falk, and A. Seidel-Morgenstern, *Chem. Eng. Technol.*, **21**, 469–477 (1998).

Jacques, J., A. Collet, and S.H. Wilen, *Enantiomers, Racemates and Resolutions*, Krieger, Malabar, 1994.

Kaspereit, M., P. Jandera, M. Skavrada, and A. Seidel-Morgenstern, *J. Chromatogr. A*, **944**, 249–262 (2002).

Lim, B.G., C.B. Ching, R.B.H. Tan, and S.C. Ng, *Chem. Eng. Sci.*, **50**, 2289–2298 (1995).

Lisec, O., P. Hugo, and Seidel-Morgenstern, *J. Chromatogr. A*, **908**, 19–34 (2001).

Lorenz, H., P. Sheehan, and A. Seidel-Morgenstern, *J. Chromatogr. A*, **908**, 201–214 (2001).

Mazzotti, M., G. Storti, and M. Morbidelli, *J. Chromatogr. A*, **769**, 3–24 (1997).

Mersmann, A., *Crystallization Technology Handbook*, A. Mersmann (Ed.), pp. 1–78, Marcel Dekker, New York, 1995.

Nicoud, R.M., G. Fuchs, P. Adam, M. Bailly, E. Küsters, F.D. Antia, R. Reuille, and E. Schmid, *Chirality*, **5**, 267–271 (1993).

Ruthven, D.M. and C.B. Ching, *Chem. Eng. Sci.*, **44**, 1011–1038 (1989).

Schulte, M. and J. Strube, *J. Chromatogr. A*, **906**, 399–416 (2001).