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Selective crystallisation of a chiral compound-forming system—Solvent screening, SLE determination and process design

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ABSTRACT

A newly developed crystallisation scheme produces single enantiomers from asymmetric mixtures of stereoisomers. The process was modified, adapted and evaluated on bicalutamide, the active pharmaceutical ingredient of the drug Casodex™. A comprehensive solvent/antisolvent screening was carried out based on the COSMO-SAC model and a solvent database of 1432 compounds. Ternary and quaternary phase diagrams of the enantiomers and promising solvent candidates were derived and compared to experimental data. Solid–liquid equilibrium (SLE) model based chiral separation of bicalutamide enantiomers was conducted and the process performance was evaluated in terms of yield and product purity. A concept for internal recycling of process streams enhances the overall yield.

1. Introduction

The number of chiral compounds used in agrochemicals, flavours, fragrances and pharmaceuticals has been growing rapidly over the last years and analogously the demand for asymmetric synthesis and efficient chiral separation techniques has increased. One promising pathway towards optically pure enantiomers from a racemic mixture consists of coupling a chiral pre-enrichment step using chromatographic columns with a subsequent selective crystallisation step [1,2]. For the latter several techniques have been presented [3,4]. Crystallisation techniques have in common that they require a comprehensive knowledge of the underlying solid–liquid phase equilibria (SLE) of the chiral, in most cases compound-forming systems in solution.

While the determination of thermodynamic properties is often a tedious and time consuming task, the use of g^E-models with predictive capabilities is considered to be useful to shorten laboratory time and can provide the necessary theoretical framework to design coupled processes. In addition, the identification of solvents with favourable properties for a particular crystallisation scheme can be accelerated through theoretical screening methods.

A more recent approach to quantify solvent/solute interactions is based on quantum chemistry calculations. The Conductor-like Screening MOdel with the Segment Activity Coefficient approach (COSMO-SAC) accounts for specific solute/solvent interactions by calculation of the contributions of the electrostatic Gibbs energy and the van der Waals Gibbs energy to the Gibbs energy of solvation. Once a histogram of the distribution of surface polarization charge densities (so-called "*sigma profile*") is obtained from quantum mechanical COSMO computations, both for the solvent and for the solute, the chemical potential and therefore the activity coefficients of both components can be computed *a priori*. However, for most cases one has to account for the formation of (racemic) compounds in the crystalline phase and the (refined) COSMO-SAC model [5] cannot treat those correctly. For this reason the Non-Random Two Liquid model (NRTL), which is capable of considering racemic compounds, was used here in addition. The NRTL model parameterisation was carried out making use of the predicted COSMO-SAC activity coefficients. This allows the ternary phase diagram to be determined for a pair of enantiomers in an arbitrary solvent without recourse to measured solubility data. The heats of fusion and the melting points of the considered compounds need to be provided only.

Within this study the chiral active pharmaceutical ingredient bicalutamide was investigated. The compound is manufactured at a scale of several metric tons *per annum* and is used as a racemate for the treatment of prostate cancer. The sales value (sales figures are

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for 2008) is approximately 210 million US dollars. During a development program within AstraZeneca targeting manufacture of the pure (R)-enantiomer of bicalutamide, the manufacturing method developed utilized SMB-HPLC for essentially full enantioseparation of the racemic material. Here, an alternative separation route based on the selective crystallisation of asymmetric mixtures of bicalutamide enantiomers is evaluated. Therefore, binary, ternary and quaternary SLE were derived using the methodology described above and compared to experimental data generated in-house. A separation scheme developed previously for the methionine enantiomers [6,7] was modified, adapted, balanced and evaluated. The scheme is based on the change of a characteristic property within the ternary SLE, the eutectic composition, and aims to produce the pure target enantiomer with an acceptable yield using a two-step crystallisation process.

2. Process design

Systems of enantiomers can be categorized into three main classes according to the solid phases formed. The majority (>90% [8]) of all known pairs of enantiomers form a racemic compound, which crystallizes with a distinct crystal structure when compared to that adopted by the single enantiomers. Calorimetric properties of the racemic compound, such as the melting point and the heat of fusion, are generally different than those of the pure enantiomers and the same applies to their solubility. The region within which the racemic compound is crystallised from a solution often spans a large domain, which is always centred around the racemic composition within a ternary, solid–liquid phase diagram (see Fig. 1, shaded areas). Within this region, only crystals of the racemic compound can be harvested. In contrast to the class of conglomerate forming systems, where the enantiomers are mutually immiscible in the solid state and the racemate comprises distinct crystals containing only one type of enantiomer, no direct access to the target enantiomer is possible from racemic solutions or melts through crystallisation techniques. In general, a pre-enrichment with the target enantiomer is required in order to leave the domain of the racemic compound and to allow selective crystallisation and harvesting of the desired enantiomer. Often the eutectic composition

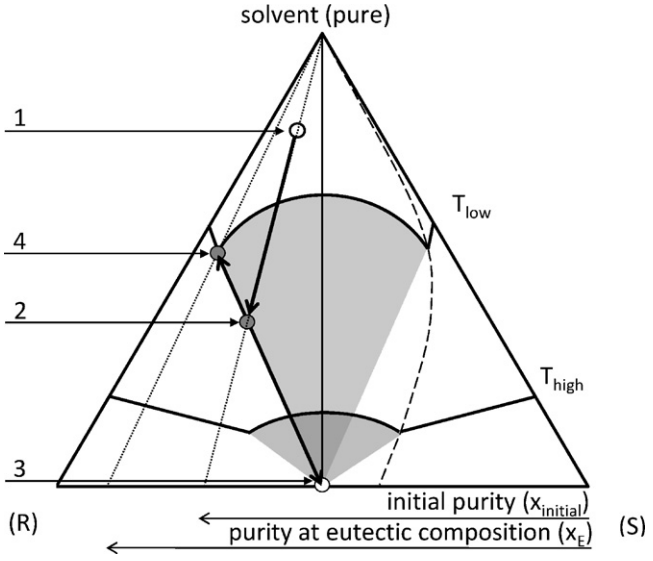

Fig. 1. 1st process step: schematic ternary phase diagram of (R)- and (S)-enantiomers in solution. Shown are two solubility isotherms at T_{low} and T_{high} (solid lines). Dashed line: shift of the eutectic composition for different temperatures. Shaded areas: two-phase regions. Circles and numbers: 1, initial composition; 2, composition after partial solvent evaporation; 3, crystalline solid phase after equilibration; 4, liquid phase composition after equilibration.

(Fig. 1, x_E) of a system of enantiomers in solution is the lower limit for crystallisation of a single enantiomer [1,9]. This composition is a substance specific property and is known to be close to unity for a number of substances. This is unfavourable for the pre-enrichment step, since the throughput of physical separation methods drops with increasing purity requirements.

Here, a modified separation scheme is exploited, which was applied earlier for the separation of methionine [6,7,10]. This scheme requires no substance specific enrichment. The principle is illustrated in Figs. 1 and 2 and consists of a two-step process. Starting from an asymmetric mixture of enantiomers (Fig. 1, point 1, $x_{initial}$) originating either from partial selective synthesis, partial chromatographic separation or use of a chiral membrane (with a certain slip), for example, a further enrichment in the target enantiomer can be achieved through simple solvent removal and equilibration at a low temperature T_{low}. Thus, the composition approaches point 2 in Fig. 1 at the phase boundary between the inner two-phase region (Fig. 1, shaded) and the three-phase region and separates into a solid phase (Fig. 1, point 3) and a liquid phase of eutectic composition (Fig. 1, point 4). The latter composition x_E is already enriched by the target enantiomer compared to the initial composition $x_{initial}$ at point 1.

It is known that the eutectic point is of invariant type for constant temperature and pressure. However, shifts are thermodynamically possible upon changes in solution temperature and were first described by Wang et al. [11]. We found, that such a shift can also be expected for certain systems under isothermal conditions in different solvents [10]. The possible impact of a pronounced change in the eutectic composition on the shape of two solubility isotherms (corresponding to T_{low} and T_{high}) and accordingly on the size and location of the two- and three-phase regions is shown by the dashed line in Fig. 1. The shaded region shrinks not only due to the temperature change but also because the intersection of the two parts of the solubility isotherm moves at T_{high} closer to the mirror axis of the phase diagram. This feature can be exploited in order to crystallize single enantiomers. The liquid phase contains enantiomers at the eutectic composition in the 1st process step and is re-used after separation from the solid phase (Fig. 1, point 3; pure racemic compound). Point 4 in Fig. 2 represents, as a starting state for a 2nd process step, the re-used liquid phase and the corresponding composition in a ternary phase diagram at elevated temperature T_{high} in the same solvent as in the 1st process step. The solubility isotherm at T_{high} ('pure solvent') corresponds to this state. It should be noted, that the eutectic composition in the diagram is lower than the eutectic composition shown in Fig. 1 for the lower temperature T_{low}. There are two options for shifting point 4 into the outer two-phase region (shaded in Fig. 2), in which selective crystallisation of the target enantiomer can take place. Either more solvent is evaporated in order to concentrate the solution up to the phase boundary towards the three-phase region (Fig. 2, point 4′), or, alternatively, the solubility isotherm can be shifted upwards by controlled injection of an antisolvent (two antisolvent 'injection steps' are shown in Fig. 2, dashed arrows). The applicability of the first option depends strongly on the solubility of the compound considered. It is possible, that almost the complete solvent needs to be evaporated to achieve the maximum yield. According to the Lever-rule the amount of the solid phase exceeds by far the fraction of the liquid phase for the example given by Fig. 2 [12]. Heavy slurries are generally undesired since SLE can hardly be controlled. Therefore, in particular the use of an antisolvent was investigated, since it appears to be better applicable in general. Upon reaching the outer two-phase region the supersaturated solution will separate into a solid phase containing the crystalline target enantiomer (Fig. 2, point 6) and the corresponding equilibrated liquid phase (Fig. 2, point 5). The latter is still richer in the target enantiomer than the initial composition $x_{initial}$. An optimum amount of antisolvent places point 4 onto