Doctoral Thesis

Design of Crystallization Processes for Chiral Resolution

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Design of Crystallization Processes for Chiral Resolution

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Abstract

Enantiomers are molecules that are, like hands, non-superimposable mirror images of each other. Chirality is often encountered in the pharmaceutical industry as a large number of active pharmaceutical ingredients have at least one chiral centre. Due to the ability of living organisms to discriminate between enantiomers, several cases are known where the two enantiomers have a different therapeutic effect or differ in potency and toxicity. Hence, driven by the purity requirements enforced by the regulatory agencies, the demand for enantiopure substances has increased thus making chiral resolution an important step and challenge in the pharmaceutical industry.

Crystallization is a valuable and widely applied technique for the resolution of enantiomers. Spontaneous resolution from racemic solutions, i.e. solutions with an equimolar amount of two enantiomers, is not possible. Different techniques have been developed to overcome this limitation. One technique consists in the application of an alternative chiral separation technique upstream crystallization, e.g. continuous simulated moving bed chromatography, that enables selectively crystallizing the desired enantiomer from the enriched feed stream by exploiting solid-liquid equilibria involving enantiopure crystals and a liquid phase. The design of these crystallization processes, which is the focus of this thesis, is guided by the goal of maximizing the recovery of the target-enantiomer from the solution in as short time as possible. Hence, the crystallization process can be optimized based on an accurate knowledge of the thermodynamic properties of the system complemented by measurements of kinetic data.

Limitations in the choice of operating conditions are imposed by the occurrence of a liquid-liquid phase separation (LLPS). The occurrence of a LLPS during crystallization is a highly undesired phenomenon in industrial applications, as it slows down crystallization kinetics and yields highly agglomerated and impure crystals. Moreover, the process robustness is poor and the scale-up is difficult. The existence of a LLPS implies the presence of a liquid-liquid
domain in the phase diagram. The thermodynamic stability of the liquid-liquid equilibria is defined by the position of the liquid-liquid domain with respect to the solid-liquid domain. On the one hand the liquid-liquid domain might lie entirely in the solid-liquid domain thus resulting in a metastable LLPS. On the other hand, a portion of the liquid-liquid domain might lie above, i.e. at higher temperatures than the solid-liquid domain. In this case, the portion situated above the solid-liquid domain yields thermodynamically stable liquid-liquid equilibria, whereas the other portion lying inside the solid-liquid domain yields again metastable equilibria. The knowledge of the thermodynamic properties of the system enables finding operating conditions that allow circumventing the domain of liquid-liquid separation.

In this thesis the thermodynamic behavior of chiral systems with and without a LLPS are studied. The correctness of the proposed phase diagrams of ternary systems exhibiting a LLPS is successfully verified experimentally by determining the phase diagrams of the conglomerate forming system consisting of the two enantiomers of ethyl-2-ethoxy-3-(4-hydroxyphenyl)-propanoate and cyclohexane, and of the racemic compound forming system consisting of the two enantiomers of Ibuprofen and water.

Exploiting the knowledge on phase diagrams, a methodology is developed for the design of crystallization processes for chiral resolution from enriched solutions. The methodology is applicable to conglomerate forming systems and covers the entire temperature range of thermodynamic stability of solid-liquid equilibria. Applying this methodology, it can be demonstrated that chiral resolution is feasible even if the system exhibits a LLPS.

Finally, the effect of the counter-enantiomer on the growth kinetics of the target-enantiomer and on crystal purity is studied. In the case of $S$-mandelic acid grown from aqueous solutions, it is found that the presence of $R$-mandelic acid substantially lowers the growth kinetics of the $S$-mandelic acid and also decreases crystal purity.
Zusammenfassung


Eine Limitierung der Wahl der Betriebsbedingungen erfolgt durch das Auftreten von flüssig-flüssig Phasentrennungen (FFPT). In industriellen
Anwendungen ist das Auftreten von FFPT während eines Kristallisations-
prozesses in hohem Masse unerwünscht, da die Kristallisationskinetiken
verlangsamt werden und stark agglomerierte und unreine Partikel resultieren.
Zudem ist die Robustheit des Prozesses schlecht und der Scale-up schwierig.
Das Auftreten einer FFPT erfordert die Anwesenheit eines flüssig-flüssig
Phasengebietes im Phasendiagramm. Die thermodynamische Stabilität der
flüssig-flüssig Gleichgewichte ist durch die Position des flüssig-flüssig Phasen-
gebietes im Vergleich zur Position des flüssig-fest Phasengebietes bestimmt.
Einerseits kann das flüssig-flüssig Phasengebiet innerhalb des flüssig-fest
Phasengebietes liegen, was zu einer metastabilen FFPT führt. Andererseits
kann aber ein Teil des flüssig-flüssig Phasengebietes oberhalb des flüssig-fest
Phasengebietes liegen, d.h. bei höheren Temperaturen. In diesem Fall führt
der Teil des flüssig-flüssig Phasengebietes der oberhalb des flüssig-fest Gebietes
liegt zu stabilen Gleichgewichten, während der Teil der innerhalb liegt wieder
zu metastabilen Gleichgewichten führt. Mithilfe der thermodynamischen
Eigenschaften des Systems lassen sich Betriebsbedingungen bestimmen, die
das Umgehen des Gebiets der FFPT ermöglichen.

Diese Arbeit befasst sich mit der Studie des thermodynamischen Verhal-
tens chiraler Systeme sowohl in Abwesenheit als auch in Anwesenheit einer
FFPT. Die Richtigkeit der vorgeschlagenen Phasendiagramme wird erfolg-
reich durch die Bestimmung der Phasendiagramme des konglomeratbildenden
Systems bestehend aus den zwei Enantiomeren von Ethyl-2-Ethoxy-3-(4-
Hydroxyphenyl)-Propanat und Cyclohexan und des verbindungsbilden-
den Systems bestehend aus den Enantiomeren von Ibuprofen und Wasser
überprüft.

Das Wissen über Phasendiagramme erlaubt es eine Methodologie für das De-
sign von Kristallisationsprozessen für die Enantiomerentrennung aus partiell
angereicherten Lösungen zu entwickeln. Die Methodologie ist für konglome-
ratbildende Systeme anwendbar und deckt den ganzen Temperaturbereich ab,
in dem flüssig-fest Gleichgewichte thermodynamisch stabil sind. Durch die
Anwendung dieser Methodologie kann die Machbarkeit der Enantiomerentren-
nung auch in Anwesenheit einer flüssig-flüssig Phasentrennung gezeigt werden.
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Chapter 1

Introduction

Chirality refers to the geometric property that is responsible for the nonidentity of an object with its mirror-image.\(^1\) In chemistry, chirality can on the one hand be caused by the presence of a chiral centre, which is typically, but not exclusively a tetrahedral carbon atom bound to four different groups. On the other hand, a molecule can be chiral even without the presence of a chiral centre, as is the case for molecules that exhibit axial or planar chirality. Chiral molecules that are, like hands, non-superimposable mirror images of each other are called enantiomers. Pairs of enantiomers have practically all physicochemical properties in common, except for the direction in which they rotate polarized light and the interaction with chiral substrates.

Chirality is often encountered in the pharmaceutical industry as a large number of active pharmaceutical ingredients and their intermediates have at least one chiral center.\(^2\) Due to the different chemical behavior of enantiomers in a chiral environment, living organisms have the ability to
discriminate between them. As a consequence, the two enantiomers often
do not have the same pharmacological effect. Several cases are known
where the two enantiomers have a different therapeutic effect or differ in
potency and toxicity. Hence, driven by the strict purity requirements
of the regulatory agencies, the demand for enantiopure substances has
increased in the last years making chiral resolution an important step
and challenge in the pharmaceutical industry.

1.1 Chiral resolution through crystallization

Crystallization is the most important chiral resolution technique applied
on an industrial scale. Three classes of chiral substances exist based on
their crystallization behavior. Racemic compound forming substances
are the most common (90-95% of the known chiral substances) and
yield three different crystal forms, i.e. enantiopure crystals of the two
enantiomers and the racemic compound where the two enantiomers are
present in equal quantities and in a well ordered manner in the crystal
lattice. Racemic compound forming substances are followed by the con-
gglomerate forming substances (5-10%), which crystallize forming only
enantiopure crystals. The rarest type is the solid solution, where the two
enantiomers are present in an unordered manner in the crystal lattice
and hence yield solid phases of all possible enantiomeric compositions.

Independent of the nature of the chiral compound, due to the identical
thermodynamic properties of the two enantiomers no enrichment in
the solid phase can be obtained by recrystallizing the compound from
a racemic solution. Different techniques have been developed to over-
come this limitation. The formation of diastereomers through the addi-
tion of a chiral resolving agent introduces an asymmetry in the ternary phase diagram that enables the crystallization of the less soluble diastereomer from a racemic solution. In the case of conglomerate forming systems, preferential crystallization can be applied\(^7\) in which the desired species is crystallized by addition of seed crystals of the desired species to a racemic solution which is supersaturated and located inside the metastable zone for crystallization of both enantiomers. As far as the liquid phase is located inside the metastable zone of crystallization of the counter-enantiomer, only the target-enantiomer will crystallize. Such processes can be conducted in a semi-continuous manner by alternately crystallizing the two enantiomers and by adding racemate to the solution between the two crystallization steps.\(^8\) Alternatively, the target-enantiomer can be obtained by selectively crystallizing it from a partially enriched solution. A pre-enriched product stream can be achieved through, e.g. asymmetric synthesis\(^9\) or by an alternative separation technique upstream to crystallization such as simulated moving bed chromatography\(^{10-14}\) or pertraction.\(^{15}\) Given the enantiomeric excess exceeds the eutectic composition of the system, the desired enantiomer can be obtained by selectively crystallizing it by exploiting the equilibria involving enantiopure crystals and a less enriched liquid phase. In the case of racemic compound forming systems, a further option is to perform preferential crystallization in the solid-solid-liquid region, where a eutectic liquid phase is at equilibrium with crystals of the enantiomer in excess and the crystals of the racemic compound. In this particular case, the desired enantiomer and the racemic compound are alternately crystallized.\(^{16}\)
1.2 Design of cooling crystallization processes from partially enriched solutions

The focus of this thesis is the design of crystallization processes from partially enriched solutions, in which the target-enantiomer is crystallized exploiting the solid-liquid phase equilibria involving crystals of the target-enantiomer and a less enantiomerically enriched liquid phase. The view is thereby restricted to conglomerate and to racemic compound forming systems.

Supersaturation, which is the driving force for crystallization, can be created by cooling, i.e. crystallization starts from a saturated solution that is cooled to the final temperature where a favorable solid-liquid equilibrium can be exploited. The choice of the operating conditions, such as initial temperature, final temperature, cooling rate, etc., is guided by the goal of increasing the productivity without affecting the product quality. Operating conditions have to be chosen such that an equilibrium involving a liquid phase with the lowest possible enantiomeric enrichment and crystals of the target-enantiomer is reached. The optimal rate at which supersaturation is generated will result from a trade-off between product quality and process duration. As a consequence, the crystallization process can be optimized based on an accurate knowledge of the thermodynamic behavior of the ternary system involving the two enantiomers and the solvent from which the target-enantiomer is crystallized\textsuperscript{17}, complemented by measurements of kinetic data, e.g. nucleation and growth rates.

The design of crystallization processes always starts from the analysis of the phase diagram, which is a ternary diagram in the case of two enantiomers dissolved in the solvent. The analysis of phase diagrams reveals
1.2 Design of cooling crystallization processes from partially enriched solutions

that the lowest enrichment of a liquid phase which is at equilibrium with enantiopure crystals corresponds to the eutectic composition at the final crystallization temperature. In conglomerate forming systems, the least enriched eutectic liquid phase at equilibrium with homochiral crystals is of racemic composition, while in the case of racemic compound forming systems, the eutectic liquid phases are always more enriched. In ternary systems, solid-liquid equilibria involving a eutectic liquid phase are not limited to a single temperature and can be obtained by either fixing the temperature and adapting the composition of the feed solution or vice-versa. Hence, there are two ways to obtain the maximal recovery of the target enantiomer from the product stream delivered by the upstream process when we assume that the relative concentration of the two enantiomers, i.e. the enantiomeric excess, is fixed by the upstream process: either by leaving the composition of the feed stream unaltered and adapting the final operating temperature, or by choosing the final operating temperature and adapting the composition of the feed solution by addition or removal of solvent. Only few studies have addressed the determination of operating conditions that allow for chiral resolution over a wide temperature and composition range. Fung and Ng\textsuperscript{18} have identified compartments in the liquidus projections of the ternary phase diagrams that contain operating points that allow for chiral resolution. Using solid-liquid equilibrium data, Kaspereit\textsuperscript{19} determined operating conditions enabling the maximal recovery of the target-enantiomer, which could be represented as curves in the initial vs. final temperature plane for feed solutions of constant enantiomeric excess.

The analysis of the thermodynamic behavior of a ternary system yields a set of possible operating conditions that enable the maximal recovery of the target-enantiomer from the feed solution. The choice of optimal
operating conditions is made by considering the kinetic properties of the system. The goal is to obtain crystals of the target-enantiomer with a sufficient purity in as short time as possible. Recent studies have evidenced differences in the crystallization behavior between conglomerate and racemic compound forming systems. For the conglomerate forming Threonine grown from aqueous solutions, the presence of the counter-enantiomer is reported to have no effect on neither the growth kinetics of the target-enantiomer nor on the crystal purity.\textsuperscript{20} However when crystallizing racemic compound forming mandelic acid from aqueous solutions, the counter-enantiomer is found to lower both the growth kinetics of the target-enantiomer and the crystal purity.\textsuperscript{20,21}

The outcome of these studies evidences the importance of a thorough understanding of both the thermodynamic and the kinetic properties of chiral systems for the optimization of crystallization processes aimed at chiral resolution.

1.3 Liquid-liquid phase separations in crystallization processes

Limitations in the choice of operating conditions are imposed by the occurrence of a liquid-liquid phase separation (LLPS), in the practice of crystallization also termed as oiling out. LLPS is a well known phenomenon in the field of protein crystallization that is exhibited by several experimental systems.\textsuperscript{22–30} Relatively few studies have focused on LLPSs occurring in systems of small organic molecules, but the development of more potent and improved target specific active pharmaceutical ingredients leads to an increase in the number of less hydrophilic and less polar molecules.\textsuperscript{31} According to Derdour\textsuperscript{32}, these molecules do not easily self-
assemble in an organized manner and are thus more prone to undergo a liquid-liquid phase separation prior to crystallization. Cases of binary systems exhibiting LLPS have been studied by Svärd et al.\textsuperscript{33} and Groen and Roberts\textsuperscript{34}, whereas Bonnett et al.\textsuperscript{35}, Veesler et al.\textsuperscript{36}, Deneau and Steele\textsuperscript{37}, Lai et al.\textsuperscript{38}, Kiesow et al.\textsuperscript{39}, Duffy et al.\textsuperscript{40} and Lu et al.\textsuperscript{41} report LLPS occurring in systems involving solvent mixtures.

As one of the key purposes of crystallization of small organic molecules is their purification, LLPS prior to crystallization is unwanted, as the solute rich phase is typically a good solvent for impurities. The crystallization of the solute rich phase yields in fact impure crystals.\textsuperscript{37} Also, design and scale up of the process is difficult since the criterion of constant power gives emulsions consisting of smaller droplets.\textsuperscript{36,38} Furthermore, oiling out leads to the formation of droplets around the crystal surface, which slows down crystal growth and decreases crystal quality.\textsuperscript{38} Bonnett et al.\textsuperscript{35} and Lafferrère et al.\textsuperscript{42} report the formation of highly agglomerated quasi-spherical particles as crystallization occurred in the dense liquid droplets. In accordance with the Ostwald rule of stages, oiling out was found to slow down subsequent crystallization, as the first formed metastable liquid phase hinders primary and secondary nucleation.\textsuperscript{42,43} Thus, for purification purposes the aim is to avoid oiling out.

The existence of a LLPS implies the presence of a liquid-liquid domain in the phase diagram. The thermodynamic stability of the liquid-liquid equilibria is defined by the position of the liquid-liquid domain with respect to the solid-liquid domain. On the one hand the liquid-liquid domain might lie entirely in the solid-liquid domain thus resulting in metastable liquid-liquid phase equilibria.\textsuperscript{44} On the other hand, a portion of the liquid-liquid domain might lie above, i.e. at higher temperatures, the solid-liquid domain.\textsuperscript{33,40,41} In this case, the portion situated
above the solid-liquid domain yields thermodynamically stable liquid-liquid equilibria, whereas the other portion lying inside the solid-liquid domain yields again metastable equilibria.

Contrary to entirely metastable liquid-liquid equilibria, the occurrence of thermodynamically stable liquid-liquid equilibria restricts the number of operating points that are suitable for crystallization. In fact, in a well defined composition range, subcooling of a clear solution will lead to a stable liquid-liquid-equilibrium before obtaining the desired solid-liquid equilibrium, thus making the knowledge of the thermodynamic behavior of the system necessary for the choice of suitable operating points.

After determining suitable operating points, in both the metastable and the stable case the characterization of metastable liquid-liquid equilibria complemented by seeding strategies and an accurate control of supersaturation prevents the liquid phase from entering the liquid-liquid domain and thus from provoking an undesired phase separation.\textsuperscript{40,45}

### 1.4 Objectives and outline of the thesis

The design and the optimization of crystallization processes aimed at chiral resolution is influenced by the thermodynamic and the kinetic behavior of the system. The goal of this thesis is therefore on the one hand to develop a methodology based on a thorough understanding of the thermodynamic properties of chiral systems for the design of crystallization processes that is applicable to the entire temperature range where solid-liquid equilibria are thermodynamically stable. With this methodology, the feasibility of crystallization processes of systems exhibiting a thermodynamically stable LLPS is assessed. On the other hand, the effect of the counter-enantiomer on the growth kinetics of the target-
enantiomer and on crystal purity is investigated, which is accomplished by performing isothermal seeded batch experiments. To this aim, the applicability of a process monitoring protocol involving only ATR-FTIR spectroscopy, an in-situ monitoring tool which is not able to discriminate between the two enantiomers, is assessed.

In Chapter 2 and 3, the focus is set to the characterization of chiral ternary systems exhibiting a thermodynamically stable LLPS. In Chapter 2, the ternary phase diagram of conglomerate forming systems is derived and experimentally verified by determining the ternary phase diagram involving the conglomerate forming ethyl-2-ethoxy-3-(4-hydroxyphenyl)-propanoate (EEHP) and cyclohexane. The \( S \)-enantiomer of EEHP is an intermediate of Tezaglitazar\( \text{®} \), an active compound for the treatment of type II-diabetes.\(^{46}\) In Chapter 3, exploiting the consolidated knowledge on conglomerate forming systems presented in the previous chapter, the ternary phase diagram for racemic compound forming systems is derived and experimentally verified by characterizing the ternary system involving the two enantiomers of Ibuprofen and water. Ibuprofen is a nonsteroidal anti-inflammatory drug used as an analgesic and for the relief of symptoms of arthritis and fever. In Chapter 4, a methodology for the design of cooling crystallization processes for chiral resolution starting from partially enriched solutions is presented that is applicable to conglomerate forming systems. To this aim, the thermodynamic behavior of conglomerate forming systems is studied with the objective of deriving all possible generic polythermal phase diagrams both in the absence as well as in the presence of a thermodynamically stable LLPS. In Chapter 5, the effect of \( R \)-mandelic on the growth kinetics of \( S \)-mandelic acid and on crystal purity is studied. Mandelic acid is often applied as resolving agent and is an intermediate compound in the production of active
pharmaceutical ingredients. Isothermal seeded batch crystallization experiments at different temperature levels and at different concentrations of $R$-mandelic acid are conducted. The solute concentration during crystallization is monitored by in situ ATR-FTIR spectroscopy. The growth rate kinetics are estimated by simulating the concentration profile by solving population balance equations and by changing the parameters of a growth rate expression so as to minimize the residuum between the calculated and the measured concentration profiles. Finally, concluding remarks are given in Chapter 6.
Chapter 2

Conglomerate forming substance exhibiting oiling out*

In this chapter, the ternary phase diaigralm of the enantiomers of ethyl-2-ethoxy-3-(4-hydroxyphenyl)-propanoate (EEHP) (Figure 2.1) in cyclohexane is investigated. The enantiomers of EEHP form a conglomerate and both the pure enantiomer and the racemic mixture exhibit stable oiling out in cyclohexane. The analysis shows that the ternary phase diagram of such a system assumes a unique structural evolution around the onset temperature of oiling out, i.e., we found that the onset of oiling out strictly occurs through the emergence of a second liquid phase of racemic composition. Furthermore the further evolution of the ternary

2. Conglomerate forming substance exhibiting oiling out

![Figure 2.1: Ethyl-2-ethoxy-3-(4-hydroxyphenyl)-propanoate (EEHP) (the chiral center is on the carbon atom indicated with a star "*").](image)

phase diagram, i.e., above the onset temperature of oiling out, is dictated by the properties of the phase diagrams pure enantiomer/solvent and racemic mixture/solvent. Our theoretical considerations are in excellent agreement with experimental measurements of EEHP in cyclohexane.

2.1 Materials and Methods

2.1.1 Materials

Purified enantiomers of EEHP were supplied by AstraZeneca (Södertälje, Sweden). Cyclohexane of purity $\geq 99.9\%$, supplied by Sigma-Aldrich (Buchs, Switzerland), was used for all phase equilibrium measurements. The eluent for HPLC-analysis was a mixture of hexane with a purity of $\geq 98\%$ supplied by Merck (Darmstadt, Germany) and ethanol with a purity of $\geq 99.9\%$ supplied by Scharlau (Sentmenat, Spain).

2.1.2 Determination of the binary phase diagram

The liquidus and the solidus lines were determined using differential scanning calorimetry (DSC) (Mettler DSC822$^e$, Mettler Toledo GmbH,
2.1 Materials and Methods

Schwerzenbach, Switzerland). At first, powder mixtures of different compositions of the two enantiomers were ground in a mortar and analyzed by DSC. In a second phase, the measurements were confirmed by analyzing the solid phases obtained from the phase equilibrium experiments for the ternary system. A heating rate of 0.5 °C/min was chosen for all samples. The DSC-profiles were evaluated as follows: The temperature at the onset of the first peak corresponds to the solidus line, while the temperature at the second peak was attributed to the liquidus line. DSC-profiles with overlapping peaks were discarded. For this reason, part of the binary system could not be measured, and the solid phase behavior of the compound could not be determined based on the measured points of the liquidus line. To accomplish the latter, XRD-analysis of solid samples of pure and racemic EEHP was carried out. As the enantiomers were supplied separately, EEHP of racemic composition was recrystallized in cyclohexane.

2.1.3 Determination of the ternary phase diagram

For the determination of the ternary phase diagram two different measuring methods were adopted.

Direct measurements involved the equilibration of specified mixtures at constant temperature, and subsequent analysis of the liquid phases present by HPLC. Samples with total volume of 2 ml were prepared in small vials. The vials were placed in a thermostated bath and stirred with a magnetic bar for two days. After two days, the stirring device was turned off and the mixtures were allowed to settle. In cases where there was no LLPS the mixtures comprised a solid-liquid suspension where the solid was in the form of small white particles that rapidly settled down after turning off the stirrer. A portion of the liquid phase was then with-
2. Conglomerate forming substance exhibiting oiling out

drawn with a syringe, filtered (filter pore size 0.2 μm) and analyzed by HPLC. For the latter, an analytical chiral column, Chiralcel OJ (Diacel Chemical Industries, Osaka, Japan, 0.46 cm × 25 cm), was used. The eluent was a 9:1 (v:v) mixture of hexane and ethanol fed at 1 ml/min.

In cases were there was a LLPS the mixtures were liquid-liquid or liquid-liquid-solid suspensions. After turning off the stirrer the second liquid phase slowly formed large, highly viscous, yellowish droplets on the bottom of the vial, that could clearly be distinguished from the white solids. The solute lean liquid phase, i.e., the colorless liquid phase in the upper part of the vial, was sampled with a syringe. In order to sample and analyze by HPLC the solute rich liquid phase first the solute lean liquid phase was withdrawn completely. In cases where the mixtures were liquid-liquid-solid suspensions, the white solids particles settled to the bottom of the vial where they were covered by the solute rich liquid phase. In these cases, only the solute lean liquid phase was sampled as it was not possible to separate the solids from the solute rich liquid phase.

*Indirect measurements* involved the equilibration of specified mixtures at constant temperature without the analysis of the phases present. The point in the phase diagram corresponding to the overall composition of the mixture was assigned to a phase region by determining the number and type of phases present in the equilibrated mixture.

## 2.2 Phase behavior involving LLPS

### 2.2.1 The LLPS phenomenon

LLPS is caused by a non-ideal solution behavior of liquid mixtures of the species involved. In a binary liquid mixture, if the solution behaves
ideally, the Gibbs free energy of mixing has a single minimum at a 1:1 molar ratio and no LLPS occurs. If the solution is however non-ideal, a pressure and temperature range may exist where the Gibbs free energy of mixing has two local minima. Hence, depending on the overall composition two stable liquid phases may form. In the composition-temperature space, the resulting liquid-liquid region can be confined by either an upper or a lower consolution temperature whereas above (below) this upper (lower) consolution temperature the liquids are fully miscible; systems having both an upper and a lower consolution temperature exhibit a closed LLPS region.

LLPS is particularly interesting when interfering with a solid-liquid equilibrium, which is what hereafter we refer to as oiling out. There are two generic phase diagrams for oiling out.\(^{48}\) In the first case the LLPS is stable, i.e., part of it lies above the solubility line (Figure 2.2.a). In the second case the LLPS is metastable, i.e., it lies entirely below the solubility line (Figure 2.2.b).

Figure 2.2: Binary phase diagrams for systems admitting oiling out: (a) stable LLPS; (b) metastable LLPS.
An explanation of this rather general behavior could be established experimentally through the study of colloidal dispersions and theoretically through simulations of hard spheres with attractive interactions. Both these systems serve as model systems for molecular and macromolecular systems, in particular proteins, which, though exhibiting neither spherical shape nor isotropic interactions, show in most cases similar phase diagrams. It was found that a necessary condition for the existence of LLPS are attractive forces among the spheres, and that the topology of the phase diagram is determined by the range of attraction: for a sufficiently short range attraction the LLPS is metastable, whereas upon increasing the range of attraction the LLPS becomes stable.

So far a similar understanding for systems of small organic molecules could not be established, since the interactions in such systems are inherently anisotropic and depend on the molecular structure of the compounds involved and on their interactions with the solvent. The phase diagrams found by Bonnett et al. for the metastable LLPS and by Svärd et al. for the stable LLPS are consistent with the phase diagrams found for colloids. However, modeling the phase diagrams of such systems is rather challenging due to the complex interactions. Kiesow et al. predicted qualitatively the oiling-out in ternary systems containing solvent mixtures by using the PC-SAFT model; the existence of a miscibility gap was verified and validated through experiments. Fully quantitative predictions of phase diagrams involving LLPS, however, have not been reported yet.
2.2 Phase behavior involving LLPS

2.2.2 Ternary diagram of a conglomerate forming system exhibiting LLPS

In this section we study the ternary phase diagram of a conglomerate forming system where both the pure enantiomer and the racemic mixture admit a stable LLPS and we determine its generic evolution with temperature. For this, the knowledge of binary systems is exploited.\(^ {48}\)

The phase diagram shown in Figure 2.2.a applies to a binary system undergoing a stable LLPS. As shown, LLPS leads to the appearance of a two-phase region \(L_1 + L_{II}\). At the upper consolution temperature \(T_{uc}\) the two liquid phases have equal composition. Hence, \(T_{uc}\) is a critical temperature. With decreasing temperature, the difference in composition increases, one phase being solute lean (\(L_1\)), the other solute rich (\(L_{II}\)). The low temperature border of the LLPS region is at the binary monotectic temperature \(T_{mon,L-P}\). At this temperature the change from a liquid-liquid phase equilibrium to a liquid-solid phase equilibrium occurs via three phases at equilibrium, i.e. two liquid phases (points A and B) and a solid phase (point C). Below \(T_{mon,L-P}\) (but above \(T_{m,sol}\)) the thermodynamic stable condition is a solid-liquid phase equilibrium.

The phase diagram of a ternary system can be represented by a triangular prism, as shown in Figure 2.3.b, where the temperature varies along the vertical axis; 2D diagrams are obtained as vertical sections cut through the prism, that pass through the vertex corresponding to the pure solvent. In Figure 2.3.b three such sections can be identified that are equivalent to the binary diagram of Figure 2.2.a: two cuts correspond to the pure enantiomers (drawn in grey in Figure 2.3.b and Figure 2.3.c), whereas one refers to an equimolar concentration of the two enantiomers, i.e. the vertical plane of symmetry of the ternary phase diagram (drawn in black in Figure 2.3.a and Figure 2.3.b). While the first two are
real binary systems, the third is not. However, due to symmetry every point on this plane has racemic composition. Therefore, since the solid of racemic composition is a 1:1 powder mixture of the R- and the S-enantiomer crystals, in the quasi-binary diagram shown in Figure 2.3.a the number of solid phases is increased by one, when compared with the real binary diagram shown in Figure 2.2.a. Hence, a point on the line DE, which in the binary case represents a solid-liquid equilibrium, becomes a solid-solid-liquid equilibrium in the ternary case. Similarly, the three phase equilibrium in the binary system (A, B and C in Figure 2.2.a) becomes a four phase equilibrium in the ternary system (A, B and C in Figure 2.3.a) where two liquid phases, a solute lean and a solute rich phase, are in equilibrium with two solid phases, $S_R$ and $S_S$.

The complete ternary diagram can be constructed combining the information from the quasi-binary diagram in Figure 2.3.a and the two binary diagrams in Figure 2.3.c. Due to symmetry the two binary diagrams consisting of the pure enantiomers and the solvent are identical and therefore only one of them, i.e. the binary system including the S-enantiomer, is discussed hereafter.

At low temperatures, that is at $T_{m,sol} < T < T_{mon,L-R-S}$, the system behaves like the well known conglomerate forming systems, as shown in Figure 2.4.a. Then, at $T = T_{mon,L-R-S}$, the onset of the LLPS occurs and manifests itself through the appearance of a single point within the three phase region $L + S_R + S_S$, which has the composition of a newly formed solute rich phase, $L_{II}$. Such new phase $L_{II}$ thereby leads to a ternary four-phase equilibrium (Figure 2.4.b), among phases $L_I$, $L_{II}$, $S_R$ and $S_S$. Increasing the temperature further the $L_{II}$-region grows from infinitesimally small to finite dimensions thus yielding a phase diagram with six new regions adjacent to it (Figure 2.4.c): these are three two-phase regions ($L_I + L_{II}$, $L_{II} + S_R$ and $L_{II} + S_S$) and three three-phase
2.2 Phase behavior involving LLPS

Figure 2.3: Ternary phase diagram of a conglomerate forming compound admitting stable oiling out: (a) vertical cut through the mirror plane of the polythermal ternary phase diagram; (b) polythermal ternary phase diagram; (c) binary phase diagram S-enantiomer/solvent.
regions ($L_I + L_{II} + S_R$, $L_I + L_{II} + S_S$ and $L_{II} + S_R + S_S$). The two liquid phases $L_I$ and $L_{II}$ do not exhibit any enantioselectivity. Therefore, after the appearance of the new liquid phase the ternary diagram maintains its symmetry with respect to the vertical axis in Figure 2.4 that passes through the solvent vertex, and the liquid phases that are at equilibrium have the same enantiomeric composition. This means that any tie-line of the $L_I + L_{II}$-phase region is on a straight line that passes through the vertex representing the pure solvent; and so are as a consequence also the phase region boundaries separating the $L_I + L_{II}$-phase region from both the $L_I + L_{II} + S_R$ and the $L_I + L_{II} + S_S$-phase regions.

The fact that the LLPS sets in along the symmetry plane of the ternary diagram, and not along the edges pure enantiomer/solvent, is a straightforward consequence of the phase rule. Assuming constant pressure, the phase rule states in fact that:

$$v = C - P + 1,$$  \hspace{1cm} (2.1)

where $v$ is the variance of the system, i.e. the number of degrees of freedom, $C$ is the number of components and $P$ is the number of phases that are at equilibrium (chemical reaction equilibria are excluded). If the liquid phase $L_{II}$ were to emerge along the edge of the phase triangle, the variance along the edge would be zero, i.e. $v = 2 - 3 + 1 = 0$, meaning that the three phases $L_I$, $L_{II}$ and $S_S$ would coexist only at that specific temperature. This would be in contradiction with the variance of the $L_I + L_{II} + S_S$-phase region, which at the onset of oiling out would be one, i.e. $v = 3 - 3 + 1 = 1$, meaning that the phase equilibrium consisting of the three phases $L_I$, $L_{II}$ and $S_S$ would not be limited to one single temperature.
2.2 Phase behavior involving LLPS

Figure 2.4: Generic evolution of the ternary phase diagram of a conglomerate forming system undergoing a stable LLPS: (a) phase diagram in the range \( T_m, \text{sol} < T < T_{\text{mon}}; \) (b) phase diagram at \( T = T_{\text{mon}}; \) (c) phase diagram right above \( T_{\text{mon}}. \)
With increasing temperature the ternary diagram will undergo further transitions, and, assuming that vapor-liquid equilibria exist only at higher temperatures, it eventually will evolve into a monophasic liquid phase. This occurs via the disappearance of the two- and three-phase regions, whereas the phase regions of $L_I$ and $L_{II}$ grow until they finally merge and cover the whole composition domain. The order of disappearance of the different phases is dictated by the properties of the two cuts shown in Figure 2.3.a and Figure 2.3.c, i.e. by the relative position of the eutectic temperature $T_{\text{eut},R-S}$, the monotectic temperature $T_{\text{mon},L-S}$, the melting point of the pure enantiomer $T_{m,S}$ and the upper consolution temperatures $T_{uc,S}$ and $T_{uc,R-S}$. To be consistent with the conglomerate forming character of the enantiomers, $T_{\text{eut},R-S}$ has to be lower than $T_{m,S}$. The possible orders of disappearance of the phase regions are restricted by this condition only. Therefore the structural evolution of the ternary diagram for $T > T_{\text{mon},L-R-S}$, is no more unique, but the knowledge of the two cuts shown in Figure 2.3.a and Figure 2.3.c allows for a qualitative drawing of the ternary diagram at any temperature.
2.3 Results and Discussion

2.3.1 Binary phase behavior of EEHP-enantiomers

The binary diagram of EEHP is shown in Figure 2.5. It shows the characteristic behavior of a conglomerate forming system. The pure enantiomers melt at 56.2°C, while the eutectic melting occurs at 35.2°C. Due to the overlap of the peaks, DSC-measurements with an enantiomeric excess lower than 36% could not be interpreted quantitatively and were discarded. The XRD-patterns of the pure enantiomers and of crystals of racemic composition are compared in the inset of Figure 2.5. No differences were detected in the measured range, thus confirming the conglomerate forming behavior.

Figure 2.5: Binary phase diagram of the EEHP-enantiomers. The XRD-patterns of the pure S-enantiomer (drawn in black) and of the racemic mixture (drawn in grey), respectively, are shown in the inset.
2. Conglomerate forming substance exhibiting oiling out

2.3.2 Ternary phase behavior of EEHP-enantiomers and cyclohexane

Phase behavior in cyclohexane

Figure 2.6.a shows the semi-quantitative phase diagram of the binary system S-EEHP/cyclohexane (gray lines) and the binary section racemic EEHP/cyclohexane (black lines). The two phase diagrams were constructed based on the eutectic, monotectic and melting temperatures of the two systems. Their determination relied on DSC data and on indirect measurements. $T_{\text{mon},L-R-S}$ was found to be between 24°C and 25°C, whereas $T_{\text{mon},L-S}$ is at a higher temperature, namely between 40°C and 45°C. The upper consolution temperatures were not determined in this study. However, indirect measurements showed that stable LLPS exists at $T > T_{\text{m},S} = 56.2^\circ$C for both the pure enantiomer and the racemic mixture.

Detailed measurements of the two phase diagrams in the proximity of $T_{\text{mon},L-R-S}$ are shown in Figure 2.6.b. The data points were determined through direct measurements except the two points on the right belonging to the solid-liquid equilibria of the binary section racemic EEHP/cyclohexane above 25°C, where we relied on indirect measurements. For this, mixtures of racemic composition at different solute mass fraction were equilibrated at a given temperature. If the equilibrated sample was monophasic, i.e. a clear liquid, the sample belonged to the one phase region. On the other hand, if the equilibrated sample contained solids, it belonged to the three phase region. The composition of the phase boundary was then determined by averaging the overall mass fraction of EEHP of the most concentrated liquid phase and of the lowest overall mass fraction of EEHP yielding a three-phase equilibrium.
Figure 2.6: Phase diagram of the systems S-EEHP/cyclohexane and racemic EEHP/cyclohexane: (a) schematic representation; (b) measurements in the range from 15°C to 30°C.
The binary section racemic EEHP/cyclohexane is in perfect agreement with the conceptual phase diagram shown in Figure 2.3.a. In fact, the solid-solid-liquid equilibrium at low temperatures evolves into a liquid-liquid and solid-solid-liquid equilibrium when crossing $T_{\text{mon},L-R-S}$. Clear indications of the existence of an upper consoluation temperature are given by the increasing and decreasing solute concentrations of the solute lean phase and of the solute rich phase, respectively. Also the two measured points of the phase boundary of the solid-solid-liquid phase region are in good agreement with the melting point of racemic EEHP. Furthermore, the relative position between the two phase diagrams shown in Figure 2.6 is in agreement with the proposed evolution of the ternary diagram and with the imposed physical constraint, i.e. $T_{\text{mon},L-R-S} < T_{\text{mon},L-S}$ is fulfilled. The scatter noted in the estimation of the concentration of the solute rich liquid phases is likely due to the high viscosity of this phase. Insufficient stirring could cause concentration gradients, and also, the high viscosity may hinder the removal of incorporated droplet of the solute lean phase.

**Evolution of the ternary phase diagram with temperature**

The results shown in Figure 2.6 allow us to draw the complete evolution of the ternary diagram. The latter is shown in Figure 2.7 where the temperature increases when going from panel (a) to panel (h). The first three panels are equivalent to those shown in Figure 2.4 as the evolution of the phase diagram is unique in this temperature range. Having crossed $T_{\text{mon},L-R-S}$ (Figure 2.7.c), one reaches next the eutectic melting temperature, $T_{\text{eut},R-S} = 35.2^\circ \text{C}$ (Figure 2.7.d). At this point, the region of the solute rich phase, $L_{II}$, touches the lower edge of the phase diagram. Increasing the temperature further (Figure 2.7.e), both the $L_{II}$- and the $L_{I}$-regions grow at the expenses of the two- and three-phase regions. At
2.3 Results and Discussion

Figure 2.7: Schematic of the evolution of the phase diagram of the ternary system consisting of the EEHP-enantiomers and cyclohexane.
$T_{\text{mon},L-S} \approx 40 - 45^\circ\text{C}$ (Figure 2.7.f), the $L_{\text{II}}$-region touches the side edges of the phase diagram, thus enabling the onset of LLPS in the binary system pure EEHP/cyclohexane. At this point, the phase diagram consists only of one- and two-phase regions. Increasing the temperature even further (Figure 2.7.g) leads the two one-phase regions ($L_1$ and $L_{\text{II}}$) to grow further until at $T_{m,S} = 56.2^\circ\text{C}$ the $L_{\text{II}}$-region has completely displaced the two-phase regions involving solids (Figure 2.7.h). The further evolution, i.e. the disappearance of the two-phase region $L_1 + L_{\text{II}}$, is governed by the relative position of the upper consolation temperature for pure and racemic EEHP, which are above $60^\circ\text{C}$ and which were not determined in the present study.
Ternary phase diagram below the onset of oiling out

To quantify the ternary phase diagram shown in Figure 2.7 detailed measurements of mixtures of non-racemic composition were performed. Below the onset-temperature of oiling out $T_{\text{mon}, L-R-S} \approx 24.5^\circ$, the system behaves like a typical conglomerate forming system (Figure 2.7.a). The complete set of measurements for the temperature range from 15°C to 24°C is shown in Table 2.1 and represented graphically in Figure 2.8.

Figure 2.8: Upper section of the ternary phase diagram for $T = 15^\circ$C - 24°C. The points element of the solubility curves are represented in mass fractions.

EEHP has a low solubility in cyclohexane. Moreover, the racemic mixture deviates from the Meyerhoffer double solubility rule,$^{52}$ as its solubility is more than double the solubility of one enantiomer in solution.
Ternary phase diagram above the onset of oiling out

The emergence of the second liquid phase, leading to the creation of six new regions (Figure 2.7.c) occurs at $T \approx 25^\circ C$. To verify the existence of the new phase equilibria, mixtures of different composition were equilibrated at $30^\circ C$. Figure 2.9 shows pictures of mixtures belonging to the new phase regions.

![Ternary Phase Diagram](image)

Figure 2.9: Pictures of different mixtures of the two enantiomers of EEHP and cyclohexane equilibrated at $30^\circ C$. The white bar appearing in the pictures is the magnetic stirring device.

The emerging liquid phase, shown in Figure 2.9.a, is a yellowish, highly viscous liquid. Figure 2.9.b shows a mixture having undergone a liquid-liquid phase separation. The solute lean phase is a colorless solution, while the solute rich phase is again yellowish. The solid object at the
bottom is the magnetic stirring bar. In the $L_1 + L_{II} + S_S$-phase region (Figure 2.9.c), two liquid phases, both enantiomerically enriched, are at equilibrium with the enantiomerically pure solid phase. Finally, Figure 2.9.d shows the liquid-solid-solid equilibrium involving the solute rich liquid phase and the two enantiomers. Crystals of the pure enantiomers are suspended in the liquid phase, being dark yellow due to the high solute concentration. The complete set of measurements of the ternary phase diagram above $T_{mon,L-R-S}$ is summarized in Table 2.1 and 2.2. Figure 2.10 shows the upper part of the diagram from $25^\circ C$ to $30^\circ C$.

![Figure 2.10: Upper part of the ternary phase diagram for $T = 25^\circ C$, 27.5$^\circ C$ and 30$^\circ C$, i.e. after the emergence of a new solute-rich liquid phase. The points element of the solubility curves are represented in mass fractions.](image)

The lines are guides to the eye and are defined by three points: the solute lean liquid phase of racemic composition, the solute lean phase of the $L_1 + L_{II} + S_S$-phase region, and the enantiomerically pure liquid phase.
At 25°C, the $L_I + L_{II}$-phase region is narrow. The growth of the $L_{II}$-phase region with increasing temperature leads to horizontal expansion of the $L_I + L_{II}$-phase region. This can be clearly seen by tracking the enantiomeric enrichment of the solute lean liquid phase in the $L_I + L_{II} + S_S$-phase region (point A in the inset). The lower part of the ternary diagram was measured at 27.5°C and 30°C and is shown in Figure 2.11.

![Figure 2.11: Lower part of the ternary phase diagram for the temperatures 27.5°C and 30°C. The points element of the solubility curves are represented in mass fractions.](image)

Here, only measurements of mixtures of racemic composition were conducted. The upper vertices of the $L_{II}$-phase region (point B in the inset) were constructed by taking the overall solute concentration of the racemic solute rich phase (point C) and the enantiomeric excess of the solute lean phase of the $L_I + L_{II} + S_S$-phase region (point A). The phase region border BC is expected to be curved, therefore the chosen solute concentration in B is only an approximation, however, the two liquid phases must have equal enantiomeric composition, as the solvent is not enantioselective. The result is in perfect agreement with the proposed
evolution, as the $L_{II}$-phase region is expected to expand in both vertical and horizontal direction with increasing temperature (see Figure 2.7).

Table 2.1: Measurements of the ternary phase diagram consisting of the EEHP-enantiomers and cyclohexane in the temperature range from 15°C to 30°C. The compositions of the liquid phases are given in mass fractions.

<table>
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<tr>
<th>$T$</th>
<th>$1000 \cdot w_{R-EEHP}$</th>
<th>$1000 \cdot w_{S-EEHP}$</th>
<th>phase</th>
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2.4 Conclusions

In this work, the phase diagram of the ternary system consisting of the enantiomers of EEHP and cyclohexane was determined in the temperature range from 15°C to 30°C. The chiral compound forms a conglomerate and shows a non-ideal behavior in the presence of the solvent: both the pure enantiomer and the racemic mixture exhibit in fact oiling out in cyclohexane. This behavior can be expected considering the low melting point of the solute, namely 56.2°C and 35.2°C for the pure enantiomer and the racemic mixture, respectively, and its low solubility in cyclohexane.

The generic evolution of the phase diagram for such systems, which has not been reported yet, is also derived in this work. The evolution is dictated by the properties of two vertical cuts through the ternary diagram, i.e. the binary system pure enantiomer/solvent and the binary section racemic mixture/solvent. The occurrence of a LLPS is related to the emergence of a new liquid phase at a specific temperature. At lower
temperatures the system behaves like a conglomerate forming system, whereas at higher temperature levels, LLPS creates new phase equilibria in the composition domain leading to substantial structural changes in the ternary diagram. Applying the phase rule, it can be shown that the emerging liquid phase leading to a LLPS can only be of racemic composition. From this it can be concluded that the changes in the ternary diagram caused by a LLPS are topologically unique.

The structure and the range of validity of the ternary diagrams derived theoretically showed perfect agreement with the experimental measurements.

The outcome of this study is particularly interesting for the design of industrial applications. In the presence of such a complex phase behavior, the practitioner has two alternatives. The first is that of substituting cyclohexane with a solvent that leads to a simpler phase diagram, i.e. without LLPS. The second possibility is that of using the phase diagram to design a suitable crystallization strategy from cyclohexane solutions, that allows obtaining the desired solid phase. As LLPS is not desirable, the temperature range where the system behaves like a conglomerate forming system is of interest. We have shown that the choice of such favorable operating conditions is simplified, as for it only the binary section racemic mixture/solvent has to be considered.
2.5 Nomenclature chapter 2

$L$ liquid phase
$L_I$ solute lean phase in liquid-liquid phase region
$L_{II}$ solute rich phase in liquid-liquid phase region
$S_P$ solid compound
$S_R$ solid $R$-enantiomer
$S_S$ solid $S$-enantiomer
$S_{sol}$ solid solvent
$T_{mon,L-P}$ temperature of the monotectic equilibrium

$L_{II} ⇋ L_I + S_P$

$T_{mon,L-R-S}$ temperature of the monotectic equilibrium

$L_{II} ⇋ L_I + S_R + S_S$

$T_{mon,L-S}$ temperature of the monotectic equilibrium

$L_{II} ⇋ L_I + S_S$

$T_{eut,R-S}$ temperature of the eutectic equilibrium $L ⇋ S_R + S_S$

$T_{eut,sol-P}$ temperature of the eutectic equilibrium $L ⇋ S_{sol} + P$

$T_{eut,sol-R-S}$ temperature of the eutectic equilibrium

$L ⇋ S_{sol} + S_R + S_S$

$T_{eut,sol-S}$ temperature of the eutectic equilibrium $L ⇋ S_{sol} + S_S$

$T_{m,S}$ melting temperature of the $S$-enantiomer

$T_{m,sol}$ melting temperature of the solvent

$T_{uc}$ upper consolution temperature

$T_{uc,R-S}$ upper consolution temperature of the racemic mixture/solvent system

$T_{uc,S}$ upper consolution temperature of the $S$-enantiomer/solvent phase system
Chapter 3

Racemic compound forming substance exhibiting oiling out*

In this chapter, the ternary phase behavior of the two enantiomers of Ibuprofen and water is investigated. The two enantiomers crystallize as a racemic compound and exhibit a thermodynamically stable liquid-liquid phase separation (LLPS), which extends over the entire enantiomeric composition range. First, the generic phase behavior of racemic compound forming systems exhibiting a stable LLPS is derived by exploiting the consolidated knowledge of conglomerate forming systems obtained in the previous chapter. Below the onset temperature of the LLPS, the system behaves like a typical racemic compound forming system. As

for the conglomerate forming system described in the previous chapter, the onset of the LLPS is found to occur through a ternary monotectic equilibrium, where a new, solute-rich liquid phase emerges inside each solid-solid-liquid phase region. Then, the ternary phase diagram of the Ibuprofen/water system in the temperature range from 40°C to 82°C is presented together with the outcome of a thorough experimental investigation. Our theoretical considerations are in excellent agreement with experimental results.

3.1 Materials and Methods

3.1.1 Materials

$S$-Ibuprofen with a chemical purity of $\geq 98\%$ and $RS$-Ibuprofen with a chemical purity of $\geq 98\%$ were purchased from TCI Europe (Eschborn, Germany) and used as delivered. All solubility experiments were conducted in deionized water that was filtered (pore size 0.22 $\mu$m) and purified (conductivity $< 18\text{m}\Omega$, total organic compounds $< 5\text{ppb}$) using a MilliQ Advantage A10 system (Millipore, Zug, Switzerland). The eluent for the HPLC analysis consisted of a mixture of methanol with a purity of $\geq 99.9\%$ (Merck, Darmstadt, Germany), deionized water and acetic acid with a purity of $\geq 99.5\%$ (Sigma Aldrich, Buchs, Switzerland).

3.1.2 Determination of the binary phase diagram $R$-$S$-Ibuprofen

Differential scanning calorimetry (DSC) measurements (Mettler DSC822e, Mettler Toledo, Schwerzenbach, Switzerland) were performed for the determination of the melting temperature and the
melting enthalpy of the racemic compound and of the S-enantiomer. The samples were heated at a rate of 2.5°C/min. The peak temperature was considered to be the melting temperature.

3.1.3 Determination of the ternary phase diagram

Two different methods were applied for the determination of points of the ternary phase diagram. In both methods, ternary mixtures were prepared in 10 ml vials, whose content was stirred with a magnetic bar and kept at constant temperature for equilibration using the EasyMax 102 device (Mettler Toledo, Schwerzenbach, Switzerland). In direct measurements on the one hand, the samples were equilibrated overnight. After equilibration stirring was stopped for at least two hours to allow the phases to separate. In the case of an equilibrium involving a single liquid phase, the liquid phase was sampled with a pre-heated syringe and filtered using a pre-heated polytetrafluoroethylene HPLC-filter with a pore size of 0.2 μm. In the case of an equilibrium involving two liquid phases, the solute-lean phase was sampled with a pre-heated syringe and not filtered afterwards. In both cases, the composition of the liquid phase was determined by HPLC-analysis, using Chiralcel-OJ-3R (Daicel Chemical Industries, Osaka, Japan) as stationary phase and a mobile phase consisting of a 72:27.9:0.1 (v/v/v) methanol-water-acetic acid mixture, and applying a flow rate of 0.9 ml/min.

In indirect measurements on the other hand, the equilibration time of the ternary mixture was reduced to two hours. No sampling of any phase occurred, but the number and the nature of the phases involved in the equilibrium were determined visually, thus allowing for the attribution of the operating point to a specific domain in the ternary phase diagram.
3.2 Phase diagram of systems involving racemic compound forming chiral substances and a solvent

3.2.1 Ternary phase diagram without LLPS

The racemate of a conglomerate forming chiral compound crystallizes as a mixture of enantiopure crystals. Therefore, assuming the presence of neither polymorphs nor solvates, only three solid phases, each constituted of one of the pure components, can be obtained from any ternary mixture consisting of the two enantiomers and the solvent. On the contrary, the racemate of a racemic compound forming chiral species yields crystals, in which the two enantiomers are present in equimolar amounts in a regularly arranged crystal lattice. Hence, four solid phases can be obtained in principle from ternary mixtures of the two enantiomers and the solvent, namely the racemic compound and three phases, each composed of one of the three pure components.

In the temperature range where solid-liquid equilibria are thermodynamically stable, the ternary phase diagram of a conglomerate forming system features three liquidus surfaces each attaining maximum temperature at a pure component vertex (Figure 3.1(a)), i.e. the melting points of the pure components. In the case of a racemic compound forming system however, an additional liquidus surface (orange surface in Figure 3.1(b)) is present, attaining maximum temperature at the point corresponding to the melting point of the racemic compound (In Figure 3.1(b) this is chosen to be higher than the melting point of the pure enantiomers, but also the opposite is possible).

In both cases, equilibria involving two or more solid phases arise from
Figure 3.1: Schematic representation of a conglomerate forming system (a) and of a racemic compound forming systems (b) excluding polymorphs and solvates. The yellow surfaces describe the liquidus surfaces of the pure enantiomers. The green surfaces describe the liquidus surfaces of the solvent. The orange surface in (b) describes the liquidus surface of the racemic compound.
3. Racemic compound forming substance exhibiting oiling out

intersections of liquidus surfaces. The intersection between two liquidus surfaces yields an monovariant solid-solid-liquid-equilibrium as the liquid phase at the point of intersection is at equilibrium with two solid phases. Intersections among three liquidus surfaces yield an invariant ternary eutectic equilibrium, where a liquid phase is at equilibrium with three solid phases.

Ternary eutectic equilibria correspond to the lowest temperature of thermodynamic stability of all equilibria involving liquid phases. Conglomerate forming systems feature a single ternary eutectic equilibrium, whose liquid phase lies on the symmetry plane of the ternary phase diagram (Figure 3.1(a)). On the contrary, as the liquidus surface of the racemic compound is located between the liquidus surfaces of the two enantiomers, racemic compound forming systems exhibit two ternary eutectic equilibria (see Figure 3.1(b)); these arise from the intersection of the liquidus surfaces of one enantiomer, of the racemic compound and of the solvent. Due to chiral symmetry, the temperature of the two ternary eutectic equilibria is the same and the liquid phases involved have identical enantiomeric excess and solute concentration.

The ternary phase diagram of racemic compound forming systems can therefore be divided in two subsystems that are mirror images of each other. These subsystems consist of the liquidus surfaces of one enantiomer and half of each of the liquidus surfaces of the solvent and of the racemic compound. As each subsystem is of eutectic nature, it exhibits identical geometric features as those of conglomerate forming systems, i.e. same number and types of phase equilibria, but it is not symmetric anymore as none of its constituents exhibits identical behavior.
3.2 Phase diagram of systems involving racemic compound forming chiral substances and a solvent

3.2.2 Ternary phase diagram with LLPS

Based on the considerations above, one can exploit the knowledge of conglomerate forming systems presented in the previous chapter for the derivation of the generic ternary phase diagram of racemic compound forming systems exhibiting a thermodynamically stable LLPS.

The occurrence of a thermodynamically stable LLPS manifests itself through the emergence of a new surface consisting of liquid-liquid equilibrium states, which might interfere with the liquidus surfaces already described above.

Figure 3.2(a) shows the ternary phase diagram of a conglomerate forming system exhibiting a thermodynamically stable LLPS. For the sake of simplicity the formation of polymorphs and of solvates is excluded. Furthermore, it is assumed first that the new surface does not interfere with the liquidus surface of the solvent, and secondly that it extends over the entire enantiomeric composition range. The ternary phase diagram consists of two liquidus surfaces for each enantiomer (yellow), a liquidus surface of the solvent (green), and the surface associated to the liquid-liquid phase equilibria (blue). Starting close to the ternary eutectic temperature and moving upwards along the temperature axis, the onset of the LLPS occurs through a ternary monotectic equilibrium, where two racemic liquid phases are at equilibrium with crystals of the two enantiomers. This equilibrium is caused by the concomitant intersection of the new (blue) surface with the two lower and with the two upper (yellow) liquidus surfaces of the two enantiomers. As the surface describing liquid-liquid phase equilibria expands over the complete enantiomeric composition range, the two binary systems consisting of one enantiomer and the solvent, both located on the lateral planes of the ternary prism, feature a binary monotectic equilibrium.
3. Racemic compound forming substance exhibiting oiling out

Figure 3.2: Schematic representation of a conglomerate forming system (a) and of a racemic compound forming system (b) both exhibiting thermodynamically stable LLS, excluding polymorphs and solvates. The yellow surfaces describe the liquidus surfaces of the pure enantiomers. The green surfaces describe the liquidus surfaces of the solvent. The orange surface in (b) describes the liquidus surface of the racemic compound. The blue surfaces describe liquid-liquid phase equilibria. For reasons of clarity, in (b) only equilibria of the subsystem consisting of the racemic compound, the R-enantiomer and the solvent are labeled.
3.2 Phase diagram of systems involving racemic compound forming chiral substances and a solvent

This is further illustrated in Figures 3.3(a) to 3.3(c). Below the onset temperature of the LLPS, the system behaves like a typical conglomerate forming system (Figure 3.3(a)), i.e. it has two solid-liquid phase regions separated by a solid-solid-liquid phase region. At the onset temperature of the LLPS (Figure 3.3(b)), a new solute-rich liquid phase emerges within the three phase region \( L + S_R + S_S \), thus leading to a solid-solid-liquid-liquid equilibrium. Increasing the temperature, the domain of the liquid phase \( L_{II} \) increases its size, thus leading to the emergence of six new phase equilibria (Figure 3.3(c)).

Now, let us consider compound forming systems. Following the principle of geometrical equivalence, we consider the phase diagram in Figure 3.2(a) to be a subsystem of the complete ternary phase diagram of Figure 3.2(b). It follows that each of the subsystems that constitutes the ternary phase diagram of a racemic compound forming system exhibiting a LLPS features a surface describing liquid-liquid equilibria, a lower and an upper liquidus surface for the pure enantiomer and for the racemic compound, respectively, and the liquidus surface of the solvent. As for conglomerate forming systems, the onset of the LLPS occurs through a ternary monotectic equilibrium. Moreover, the two binary systems pure enantiomer/solvent and racemic compound/solvent exhibit one binary monotectic equilibrium each. The surface describing the liquid-liquid phase equilibria is assumed to have either one maximum located on the symmetry plane of the ternary prism, i.e. the case shown in Figure 3.2(b), or two maxima located either on the lateral planes of the prism or in between the lateral planes and the symmetry plane (not shown here).

The emergence of the LLPS is further illustrated in Figures 3.3(d) to 3.3(f). At temperatures below the onset temperature of the LLPS (Figure 3.3(d)), the isothermal ternary phase diagram exhibits two solid-
Figure 3.3: (a)-(c) Isothermal ternary phase diagrams of a conglomerate forming system exhibiting a thermodynamically stable LLPS given that $T_{m,solv} < T_{mon,L-R-S}$. (a) $T < T_{mon,L-R-S}$, (b) $T = T_{mon,L-R-S}$, (c) $T > T_{mon,L-R-S}$. (d)-(f) Isothermal ternary phase diagrams of a racemic compound forming system exhibiting a thermodynamically stable LLPS given that $T_{m,solv} < T_{mon,L-RS-S}$. (d) $T < T_{mon,L-RS-S}$, (e) $T = T_{mon,L-RS-S}$, (f) $T > T_{mon,L-RS-S}$. 


solid-liquid equilibria, whose phase regions are bounded by three solid-liquid phase equilibria. At the onset temperature of the LLPS (Figure 3.3(e)), two solute-rich liquid phases emerge inside the $L + S_{RS} + S_R$ and the $L + S_{RS} + S_S$-phase region, respectively, leading to two ternary monotectic equilibria. Since the solvent is not enantioselective and the enantiomers are symmetric, the four liquid phases involved in these equilibria have the same enantiomeric excess. As for conglomerate forming systems, in each subsystem the domain of the new liquid phase $L_{II}$ increases in size when the temperature is increased, thus leading to the creation of six new phase equilibria adjacent to it (Figure 3.3(f)).

After identifying the equilibrium causing the emergence of a LLPS, all possible phase equilibria together with their lower and upper temperature of thermodynamic stability for one subsystem can be determined (Table 3.1). The order of these temperatures along the temperature axis defines the topological evolution of the ternary phase diagram with increasing temperature. As the order of these temperatures is not unique but system-dependent, different topological evolutions can be obtained from racemic compound forming systems exhibiting a LLPS.
Table 3.1: Lower $T_{lb}$ and upper temperature $T_{ub}$ of thermodynamic stability of all possible phase equilibria of a racemic compound forming system exhibiting a LLPS. Due to symmetry, only the phase equilibria of the subsystem involving the racemic compound, the $S$-enantiomer and the solvent are considered.

<table>
<thead>
<tr>
<th>Equilibria</th>
<th>$T_{lb}$</th>
<th>$T_{ub}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L+S_S$</td>
<td>$T_{\text{eut,solv}-RS-S}$</td>
<td>$T_{\text{mon},L-S}$</td>
</tr>
<tr>
<td>$L_{II}+S_S$</td>
<td>$T_{\text{mon},L-RS-S}$</td>
<td>$T_{m,S}$</td>
</tr>
<tr>
<td>$L+S_RS$</td>
<td>$T_{\text{eut,solv}-RS-S}$</td>
<td>$T_{\text{mon},L-RS-S}$</td>
</tr>
<tr>
<td>$L_{II}+S_RS$</td>
<td>$T_{\text{mon},L-RS-S}$</td>
<td>$T_{m,RS}$</td>
</tr>
<tr>
<td>$L+S_{solv}$</td>
<td>$T_{\text{eut,solv}-RS-S}$</td>
<td>$T_{m,\text{solv}}$</td>
</tr>
<tr>
<td>$L_1+L_{II}$</td>
<td>$T_{\text{mon},L-RS-S}$</td>
<td>$\max(T_{uc,RS};T_{uc,S};T_{uc,RS-S})$</td>
</tr>
<tr>
<td>$L+S_RS+S_S$</td>
<td>$T_{\text{eut,solv}-RS-S}$</td>
<td>$T_{\text{mon},L-RS-S}$</td>
</tr>
<tr>
<td>$L_{II}+S_RS+S_S$</td>
<td>$T_{\text{mon},L-RS-S}$</td>
<td>$T_{\text{eut,RS-S}}$</td>
</tr>
<tr>
<td>$L+S_S+S_{solv}$</td>
<td>$T_{\text{eut,solv}-RS-S}$</td>
<td>$T_{\text{eut,solv}-S}$</td>
</tr>
<tr>
<td>$L+S_RS+S_{solv}$</td>
<td>$T_{\text{eut,solv}-RS-S}$</td>
<td>$T_{\text{eut,solv}-RS}$</td>
</tr>
<tr>
<td>$L_1+L_{II}+S_S$</td>
<td>$T_{\text{mon},L-RS-S}$</td>
<td>$T_{\text{mon},L-S}$</td>
</tr>
<tr>
<td>$L_1+L_{II}+S_RS$</td>
<td>$T_{\text{mon},L-RS-S}$</td>
<td>$T_{\text{mon},L-RS}$</td>
</tr>
<tr>
<td>$L+S_RS+S_S+S_{solv}$</td>
<td>$T_{\text{eut,solv}-RS-S}$</td>
<td>$T_{\text{eut,solv}-RS-S}$</td>
</tr>
<tr>
<td>$L_1+L_{II}+S_RS+S_S$</td>
<td>$T_{\text{mon},L-RS-S}$</td>
<td>$T_{\text{mon},L-RS-S}$</td>
</tr>
</tbody>
</table>
3.3 Results and discussion

3.3.1 Binary phase behavior of the two Ibuprofen enantiomers

The racemate of Ibuprofen crystallizes as a racemic compound.\textsuperscript{53,54} The racemic compound was often reported to be isomorphic,\textsuperscript{55,56} however a metastable form with a melting point at 17°C has recently been discovered and reported.\textsuperscript{57} So far, only one form of the pure enantiomer has been identified.\textsuperscript{58} Burger et al.\textsuperscript{59} noticed the formation of an unstable solid phase upon recrystallizing partially enriched mixtures from the melt. However, this unstable solid phase, melting between 40°C and 43°C, could not be isolated and characterized by XRPD. In this study, exclusively the stable form of the racemic compound and the known form of the S-enantiomer were obtained from solubility experiments.

The binary phase diagram of the two enantiomers of Ibuprofen has been subject of three studies. Dwivedi et al.\textsuperscript{60} measured melting points of 71°C and 46°C for the racemic compound and for the pure enantiomers, respectively. After measuring the melting enthalpies of the racemic compound and of the pure enantiomers (26.9 kJ/mol and 19.9 kJ/mol, respectively), a eutectic temperature of 37°C and enantiomeric excess of the liquid phase of 64%ee was obtained by describing the liquidus curves of the pure enantiomer and of the racemic compound by the Schroeder-Van-Laar- and the Prigogine-Defay-equations in their ideal form, respectively. The outcome of this work is however in strong disagreement with the works of Romero and Rhodes\textsuperscript{61} and Burger et al.\textsuperscript{59}, who found similar melting temperatures for the racemic compound (75.8°C and 75.5°C, respectively) and for the pure enantiomer (53.8°C and 52.3°C, respectively) and comparable melting enthalpies for the racemic compound
3. Racemic compound forming substance exhibiting oiling out

(25.5 kJ/mol and 25.7 kJ/mol, respectively) and for the pure enantiomer (17.9 kJ/mol and 18.7 kJ/mol, respectively). Romero and Rhodes obtained a eutectic temperature of 50.4°C and an enantiomeric enrichment of the liquid phase of 87%ee, while Burger et al. considering also the specific heat capacities (342 kJ/molK for the racemic compound and 376 kJ/molK for the pure enantiomer and a heat capacity of the liquid of 398 kJ/molK) obtained a eutectic temperature of 49.6°C and an enantiomeric excess of the eutectic liquid phase of 88%ee.

DSC measurements were performed in this work for the determination of the properties of the racemic compound and of the S-enantiomer. The melting enthalpy of the racemic compound is in good agreement with the value of Burger et al. (25.48 ± 0.08 kJ/mol), while its melting temperature is found to be slightly higher, namely 77.07 ± 0.12°C. The analysis of crystals of the S-enantiomer, whose optical purity was of 98%ee, yielded a melting enthalpy (18.46 ± 0.07 kJ/mol) and a melting temperature (52.79 ± 0.10°C) that are comparable to the values in Burger et al. Summarizing, the binary phase diagram proposed by Burger et al., reproduced in Figure 3.4, is used in the following for the characterization of the ternary phase diagram.

3.3.2 Ternary phase behavior

Qualitative evolution of the ternary phase diagram

As discussed in Section 3.2.2, the topological evolution of a racemic compound forming system exhibiting a LLPS is not unique. Hence, the temperatures of Table 3.1 have to be estimated in order to determine the temperature ranges of thermodynamic stability of the single phase equilibria and then to derive the qualitative ternary phase behavior.
3.3 Results and discussion

The values of $T_{m,S}$, $T_{m,RS}$ and $T_{eut,RS-S}$ are obtained from the binary phase diagram discussed in the previous section. The three monotectic temperatures $T_{mon,L-RS-S}$, $T_{mon,L-RS}$ and $T_{mon,L-S}$ are determined through indirect measurements. A change in the phase equilibrium induced by a change in temperature can be visually determined, as the different phases can easily be distinguished from each other. Liquid-liquid equilibria yield two transparent phases, which separate quickly after stopping the stirring device. In the case of solid-liquid-liquid equilibria, crystals of Ibuprofen gather in the solute-rich liquid phase; due to the hydrophobic nature of Ibuprofen after stirring is stopped a white phase forms, which consists of the Ibuprofen-rich liquid phase and of crystals and floats above the aqueous phase. This is exploited to measure the binary monotectic temperatures. A racemic and an enantiopure mixture turn from solid-liquid to liquid-liquid when increasing the temperature from below to above $T_{mon,L-RS}$ and $T_{mon,L-S}$, respectively. Hence, the monotectic temperature is in the temperature range spanned by the highest temperature yielding a solid-liquid-equilibrium and the lowest temperature yielding a liquid-liquid equilibrium.
The ternary monotectic temperature is estimated in a similar manner. The enantiomeric excess of the two invariant monotectic liquid phases is expected to be similar to the one of the eutectic liquid phase of the binary system involving the two enantiomers, namely 88%$ee$. A ternary mixture with the enantiomeric excess of the two invariant monotectic liquid phases at $T_{\text{mon},L-\text{RS}-S}$ turns from solid-solid-liquid to liquid-liquid when increasing the temperature from below to above $T_{\text{mon},L-\text{RS}-S}$. Since it is clearly not possible to exactly set the enantiomeric excess of the two invariant monotectic liquid phases, the ternary mixtures probed transform from a solid-solid-liquid to a solid-liquid-liquid equilibrium when crossing $T_{\text{mon},L-\text{RS}-S}$ and yield a liquid-liquid equilibrium at higher temperatures, i.e. at the temperature where the liquid-liquid domain reaches the enantiomeric excess of the ternary mixture. Hence, the monotectic temperature is in the temperature range spanned by the highest temperature yielding a solid-solid-liquid equilibrium and the lowest temperature yielding an equilibrium involving two liquid phases, i.e. either a liquid-liquid or a solid-liquid-liquid equilibrium.

In this way the ternary monotectic temperature $T_{\text{mon},L-\text{RS}-S}$ is found to be between 43°C and 45°C, while the two binary monotectic temperatures are found at a higher temperature: $T_{\text{mon},L-S}$ between 47°C and 48°C, $T_{\text{mon},L-\text{RS}}$ between 69°C and 72°C.

The temperatures of the eutectic equilibria are always lower than the melting temperature of the involved components. Therefore, $T_{\text{eut},\text{solv}-\text{R-\text{RS}}}$, $T_{\text{eut},\text{solv}-\text{S}}$ and $T_{\text{eut},\text{solv}-\text{RS}}$ are lower than the melting temperature of water. As $T_{\text{mon},L-\text{RS}-S}$ is higher than $T_{m,\text{solv}}$, the order of the three temperatures is not determined, as it does not define the topology of the ternary phase diagram in the temperature range where liquid-liquid phase equilibria are thermodynamically stable.

The final step consists in the investigation of the thermodynamic sta-
bility of liquid-liquid equilibria at different enantiomeric excesses; this is also accomplished by indirect measurements. For all enantiomeric excesses probed, a liquid-liquid phase equilibrium can be established at a temperature above the melting point of the racemic compound. From this it can be concluded that the upper consolution temperatures are the highest temperatures of relevance for the qualitative evolution of the ternary phase diagram.

The outcome of the indirect measurement complemented by the information of the binary diagram of the two enantiomers is presented in Table 3.2.

Table 3.2: Temperatures defining the qualitative evolution of the phase diagram of the ternary phase diagram consisting of the two enantiomers of Ibuprofen and water

<table>
<thead>
<tr>
<th>Temperature</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{eut, solv} - RS - S}, T_{\text{eut, solv} - S}, T_{\text{eut, solv} - RS}$</td>
<td>$&lt; 0^\circ\text{C}$</td>
</tr>
<tr>
<td>$T_{\text{m, solv}}$</td>
<td>$0^\circ\text{C}$</td>
</tr>
<tr>
<td>$T_{\text{mon, L - RS - S}}$</td>
<td>43-45$^\circ\text{C}$</td>
</tr>
<tr>
<td>$T_{\text{mon, L - S}}$</td>
<td>47-48$^\circ\text{C}$</td>
</tr>
<tr>
<td>$T_{\text{eut, RS - S}}$</td>
<td>49.6$^\circ\text{C}$</td>
</tr>
<tr>
<td>$T_{\text{m, S}}$</td>
<td>52.3$^\circ\text{C}$</td>
</tr>
<tr>
<td>$T_{\text{mon, L - RS}}$</td>
<td>69-72$^\circ\text{C}$</td>
</tr>
<tr>
<td>$T_{\text{m, RS}}$</td>
<td>75.5$^\circ\text{C}$</td>
</tr>
<tr>
<td>$T_{\text{uc, S}}, T_{\text{uc, RS}}, T_{\text{uc, RS - S}}$</td>
<td>$&gt; 75.5^\circ\text{C}$</td>
</tr>
</tbody>
</table>

This information enables the construction of the qualitative ternary phase diagram at any temperature ranging from the melting temperature of the solvent to a temperature slightly above the melting temperature of the racemic compound. Figures 3.5 and 3.6 show the complete phase diagram constructed from the data in Table 3.2 given in terms of isothermal phase diagrams at temperatures where they exhibit differ-
3. Racemic compound forming substance exhibiting oiling out
tendent topological features. Due to chiral symmetry, the two subsystems
including one enantiomer, the solvent and the racemic compound are
identical, thus only the subsystem involving $S$-Ibuprofen, $RS$-Ibuprofen
and water is considered in the following.

The topological evolution of the ternary phase diagram in the temper-
ature range from $T_{m,solv}$ to slightly above $T_{mon,L−RS−S}$ (Figures 3.5(a)
to 3.5(c)) corresponds to the evolution discussed in Section 3.2.2. Above
$T_{mon,L−RS−S}$, the single phase regions $L_1$ and $L_{II}$ increase in size with
increasing temperature at the expenses of the other phase domains, thus
leading to their disappearance.

At $T_{mon,L−S}$ (Figure 3.5(d)), the upper right vertex of the phase region
$L_{II}$ reaches the side of the triangle leading to the concomitant disappear-
ance of the $L_1 + S_S$- and of the $L_1 + L_{II} + S_S$-phase region. Increasing the
temperature even further, passing through the intermediate state shown
in Figure 3.5(e), the lower vertex of the $L_{II}$-phase region reaches the
lower side of the triangle at $T_{eut,RS−S}$, thus leading to the disappear-
ance of the $L_{II} + S_{RS} + S_S$-phase region (Figure 3.5(f)). Increasing the
temperature from below (Figure 3.6(a)) to above $T_{m,S}$ (Figure 3.6(b))
leads to the disappearance of the $L_{II} + S_S$-phase region. The $L_1 + S_{RS}$-
and the $L_1 + L_{II} + S_{RS}$-phase region disappear when the upper left vertex
of the $L_{II}$-phase region reaches the symmetry line of the phase triangle
(Figure 3.6(c)). Above $T_{mon,L−RS}$, the two $L_{II}$-phase regions merge and
separate the $L_{II} + S_{RS}$-phase region from the $L_1 + L_{II}$-phase region (Fig-
ure 3.6(d)). As the melting point of the racemic compound is lower
than the upper consolution temperature, the $L_{II} + S_{RS}$-phase region
disappears at a lower temperature than the liquid-liquid phase region
(Figure 3.6(e)). It is worth emphasizing that the temperature evolution
of phase diagrams shown in Figure 3.5 has entirely been obtained from
thermodynamic considerations and indirect measurements.
Figure 3.5: Structural evolution of the ternary phase diagram involving the two enantiomers of Ibuprofen and water from above $T_m,solv$ to $T_{eut,RS-S}$ as constructed from the data in Table 3.2.
3. Racemic compound forming substance exhibiting oiling out

Figure 3.6: (g) to (k) Structural evolution of the ternary phase diagram involving the two enantiomers of Ibuprofen and water from above $T_{eut,R S-S}$ to slightly above $T_{m,R S}$ as constructed from the data in Table 3.2. (l) Polythermal projection of the ternary phase diagram.
3.3 Results and discussion

Selected isothermal ternary phase diagrams

As the temperatures of the invariant equilibria reported in Table 3.1 define the temperature ranges of thermodynamic stability of specific phase equilibria, pairs of successive temperatures define the lower and the upper bound of temperature intervals, in which the number and the type of stable phase equilibria remain unaltered. The temperatures of the invariant equilibria of the Ibuprofen/water system reported in Table 3.2 define seven different temperatures intervals above the melting temperature of the solvent. The correctness of the ternary phase diagram is experimentally verified by characterizing the ternary phase diagrams at different temperature levels, whereby each of the selected temperatures lies inside one of the seven temperature intervals. Figures 3.7 to 3.14 show the experimentally determined isothermal ternary phase diagrams. Figures 3.15 and 3.16 show the polythermal projection of the ternary phase diagram. The states used to construct the isothermal ternary phase diagrams and the polythermal projection are reported in Table 3.3 in terms of temperature and composition.

Upper section of ternary phase triangle  The composition of liquid phases that are part of of the lower liquidus surfaces, as well as that of solute-lean liquid phases involved in liquid-liquid equilibria were determined through direct measurements using HPLC. The measurements were repeated at least thrice. Errors in the direct measurements estimated from the standard deviation of repeated measurements are given in Table 3.3.
At 40°C (Figure 3.7), i.e. below the onset temperature of the LLPS, the ternary phase diagram features three solid-liquid phase regions, which due to the low solubility appear as lines in the complete ternary phase diagram (Figure 3.7(a)). The solid-liquid phase regions are separated by two solid-solid-liquid phase regions, which in turn cover almost the complete composition domain. The eutectic liquid phase has an enantiomeric excess of 88.8% which is comparable to the enantiomeric excess of the eutectic liquid phase of the binary system of the two enantiomers (88% Burger et al. [59]).

The emergence of a LLPS leads to a substantial change in the topology of the ternary phase diagram. According to indirect measurements, liquid-liquid phase regions are expected to emerge above 45°C between the symmetry plane and the lateral planes of the ternary prism. In fact, at 46°C (Figure 3.8), partially enriched mixtures yield equilibria involving two liquid phases, while solid-liquid equilibria are obtained from racemic and enantiopure mixtures. Two different monovariant monotectic equilibria
3.3 Results and discussion

Figure 3.8: Upper section of the isothermal ternary phase diagram at 46°C, a temperature between $T_{\text{mon}, L-RS-S}$ and $T_{\text{mon}, L-S}$.

are obtained at 46°C, whose solute-lean liquid phases were characterized through direct measurements (insert of Figure 3.8). The more enriched monotectic liquid phase belongs to the $L_1 + L_{II} + S_S$-phase region. The less enriched liquid phase in turn is attributed to the $L_1 + L_{II} + S_{RS}$ phase region. At this temperature, which is only slightly above $T_{\text{mon}, L-RS-S}$, the $L_1 + L_{II}$-phase region is rather narrow, as confirmed by the small difference in enantiomeric excess of the two monotectic liquid phases at 46°C (86.8%ee and 91.1%ee). Ternary mixtures located between the two monotectic liquid phases yield a liquid-liquid equilibrium. The point in the insert of Figure 3.8 between the two monotectic liquid phases with an enrichment of 87.3%ee corresponds to the solute-lean liquid phase of a liquid-liquid phase equilibrium.

The $L_1 + L_{II}$-phase regions expand in the horizontal direction and reach the lateral planes only a few degrees above the onset temperature of the LLPS, i.e. between 47°C and 48°C, thus leading to the disappearance of the $L_1 + L_{II} + S_{R}$-, the $L_1 + L_{II} + S_{S}$-, the $L_1 + S_{R}$- and the $L_1 + S_{S}$-
3. Racemic compound forming substance exhibiting oiling out

Figure 3.9: Isothermal ternary phase diagram at 48°C, a temperature between \( T_{\text{mon}} \) and \( T_{\text{eut}} \). The green squares represent solute-rich liquid phases of liquid-liquid phase equilibria. The red squares represent points of the upper liquidus surfaces of the racemic compound and the of the \( S \)-enantiomer. The two orange diamonds represent the solute-rich monotectic liquid phase and the eutectic liquid phase and were determined by linear extrapolation.

Phase regions (Figure 3.5(d)). This is confirmed by measuring the phase equilibria of enantiopure mixtures at temperatures equal to and above 48°C (Figures 3.9 to 3.14). At these temperatures, the binary system \( S \)-Ibuprofen/water exhibits a LLPS which means that the \( L_1 + L_{\text{II}} \)-phase regions expand to the lateral planes of the ternary phase diagram.

On the contrary, the \( L_1 + L_{\text{II}} \)-phase regions reach the symmetry plane of the ternary prism at a much higher temperature, i.e. above 69°C. In fact, solid-liquid-liquid equilibria were obtained up to a temperature of 66°C (Figures 3.8 to 3.12). The enantiomeric excess of the solute-lean liquid phases decreases with increasing temperature, e.g. from 85.7%ee at 48°C to 81.0%ee at 52°C and to 47.2%ee at 66°C, thus proving the horizontal expansion of the liquid-liquid phase region with increasing temperature. At 75°C (Figure 3.13), i.e. above \( T_{\text{mon}, L-RS} \), racemic mixtures yield
3.3 Results and discussion

Figure 3.10: Isothermal ternary phase diagram at 52°C, a temperature between $T_{\text{eut.}, RS-S}$ and $T_{\text{m}, S}$. The magenta and the green squares represent direct and indirect measurements, respectively, performed in this work. The blue circles were calculated applying the Prigogine-Defay equation with the parameters proposed by Burger et al. $^{59}$ The orange diamond represents the solute-rich monotectic liquid phase and was determined by linear extrapolation. A second point on the upper liquidus surface of the pure enantiomer was not determined as the enantiomer excess of the least enriched point on the curve exceeded the excess of the crystals of the S-enantiomer used in this work.

Lower section of the ternary phase triangle Due to their high solute concentration, the solute-rich liquid phases involved in liquid-liquid phase equilibria were characterized by indirect measurements, which were performed only once. The indirect measurements carried out here were started from an operating point yielding a liquid-liquid equilibrium. Adding a solid mixture with the same enantiomeric excess of the initial
mixture, the operating point moves in the direction of the lower side of the triangle along a straight line connecting the operating point with the vertex of the pure solvent. After stepwise addition of crystals and equilibration of the sample, the liquid-liquid equilibrium is expected to turn into a single liquid phase when the composition of the solute-rich liquid phase is crossed. This enables the determination of the composition range in which the composition of solute-rich liquid phases is located. The composition of the solute-rich liquid phase involved in liquid-liquid equilibria is approximated by calculating the average of the cumulative solute concentrations of the two points lying closest to the phase region boundary, i.e. the most concentrated operating point yielding a liquid-liquid equilibrium and the least concentrated operating point yielding a single liquid phase. The measurement uncertainty reported in Table 3.3 corresponds to one half of the difference in the solute concentration of the two points. With this method, solute-rich liquid phases were successfully characterized in the temperature range from 48°C to 82°C.
3.3 Results and discussion

For any enantiomeric excess, the solute-lean and the solute-rich liquid phase involved in liquid-liquid equilibria reach equal composition at their upper consolusion temperature. Hence, with increasing temperature the concentration of the solute-lean liquid phase is expected to decrease, while that of the solute-rich liquid phase is expected to increase, which is in perfect agreement with the experimental outcome. At 82°C (Figure 3.14), the difference in composition between the two liquid phases is still considerable, thus indicating that the upper consolusion temperatures might exceed the boiling point of water.

The experimental verification of the proposed ternary phase diagram was completed by the investigation of the upper liquidus surfaces of the racemic compound and of the pure enantiomer. The latter is present at temperatures between \( T_{mon,L-RS-S} \) and \( T_{mon,L-RS} \) (Figures 3.5(b) to 3.5(d)). Two points on the upper liquidus surface of the pure enantiomer were determined at 48°C. To this aim, mixtures that fall in the

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Figure 3.12: Isothermal ternary phase diagram at 66°C, a temperature between \( T_{m,S} \) and \( T_{mon,L-RS} \). The symbols have the same meaning as in Figure 3.10.
3. Racemic compound forming substance exhibiting oiling out

Figure 3.13: Isothermal ternary phase diagram at 75°C, a temperature between $T_{\text{mon}, L-RS}$ and $T_{\text{m}, RS}$. The symbols have the same meaning as in Figure 3.10.

$L_{II}$-region were prepared. As the enantiomeric excess of the mixtures exceeded the one of the binary eutectic liquid phase, it was assumed that the mixtures would cross the solubility isotherm of the $L_{II} + S_{S}$-phase region upon addition of a sufficient amount of crystals with the same enantiomeric excess of the initial mixture. In fact, in both cases a composition was reached, at which the added crystals did not dissolve anymore. The average of the highest solute concentration yielding a single liquid phase and the lowest concentration yielding a solid-liquid-equilibrium was taken as the composition of the solubility isotherm. The measurement uncertainty declared in Table 3.3 was calculated by applying the same method as for the characterization of the solute-rich liquid phases involved in liquid-liquid equilibria. The results are shown with red symbols in Figure 3.9(a).

As the $L_{II} + S_{RS}$-phase region is found to be very narrow at 48°C, its solubility isotherm is described by two points, both obtained by linear
3.3 Results and discussion

Figure 3.14: Isothermal ternary phase diagram at 82°C, a temperature above $T_{m,RS}$.

regression. The liquid phase of the $L_{II} + S_{RS} + S_{S}$-phase region was obtained by approximating the solubility isotherm of the $L_{II} + S_{S}$-phase region (described by the red squares Figure 3.9(a)) by a straight line and by taking the point on the line with the same enantiomeric excess as the binary eutectic liquid phase. The point determined in this way is shown by the lower orange diamond in Figure 3.9(a). The solute-rich liquid phase of the monotectic equilibrium $L_{I} + L_{II} + S_{RS}$ was calculated in a similar way, i.e. by estimating the solubility isotherm (described by the green symbols in Figure 3.9(a)) using a straight line. As the two liquid phases involved in the monotectic equilibrium have the same enantiomeric excess, the point on the line with the enantiomeric excess of the solute-lean monotectic liquid phase was taken as the solute-rich monotectic liquid phase. The upper orange diamond in Figure 3.9(a) corresponds to the point determined in this way. The point on the upper liquidus surfaces of the racemic compound, obtained through indirect measurements (least enriched red square in the insert of Figure 3.9(a)) is in reasonable agreement with the obtained solubility isotherm.
3. Racemic compound forming substance exhibiting oiling out

Figure 3.15: Upper part of the ternary diagram representing the polythermal projection of the ternary system Ibuprofen/water. The solid curves connect monovariant liquid phases, while the dashed curves are an extrapolation of the polythermal projection and are consistent with the solubility data presented in Table 3.3.

Figure 3.16: Bottom part of the ternary diagram representing the polythermal projection of the ternary system Ibuprofen/water. The solid curves connect monovariant liquid phases, while the dashed curves are an extrapolation of the polythermal projection and are consistent with the solubility data presented in Table 3.3.
3.3 Results and discussion

Above $T_{\text{ut,RS-S}}$, the upper liquidus surface of the racemic compound belongs to the lower side of the phase triangle (Figures 3.5(f) to 3.6(d)). Hence, in the temperature range from 52°C to 66°C, its solubility isotherm could be determined by calculating the composition of the liquid phase of the binary system of the two enantiomers (circles in Figures 3.10(a) to 3.12(a)) and by calculating the solute-rich monotectic liquid phase (diamonds in Figures 3.10(a) to 3.12(a)) as described above for 48°C. In all cases, the solute-rich monotectic liquid phase was found inside the phase triangle. Moreover, the enantiomeric excess was found to be lower than the liquid phase of the binary system of the two enantiomer, which is in perfect agreement with the expectations.

At $T_{\text{mon, L-RS}}$ (Figure 3.6(c)), the two $L_{\text{II}} + S_{\text{RS}}$-phase regions merge. Above this temperature, the $L_1 + L_{\text{II}}$-phase region is decoupled from the $L_{\text{II}} + S_{\text{RS}}$-phase region (Figure 3.6(d)). This was confirmed by indirect measurements with racemic mixtures. At 75°C (Figure 3.13(a)), a liquid-liquid phase turned into a single liquid phase and then into a solid-liquid-equilibrium upon addition of crystals of the racemic compound, i.e. by moving the operating point in the direction of the lower side of the ternary triangle along a straight line through points of racemic composition.
Table 3.3: Points of ternary phase diagram in the temperature range from 40°C to 62°C. The points are given in mass fractions and were determined according to four different methods: 1 = direct measurements; 2 = calculated using the parameters proposed by Burger et al. 59; 3 = indirect measurements; 4 = linear extrapolations

<table>
<thead>
<tr>
<th>T °C</th>
<th>w_R</th>
<th>w_S</th>
<th>phase</th>
<th>method</th>
</tr>
</thead>
<tbody>
<tr>
<td>40°C</td>
<td>(3.09 ± 0.13) · 10⁻⁵</td>
<td>(1.29 ± 0.04) · 10⁻⁴</td>
<td>L of L + S RS</td>
<td>1</td>
</tr>
<tr>
<td>40°C</td>
<td>(2.05 ± 0.38) · 10⁻⁶</td>
<td>(1.28 ± 0.02) · 10⁻⁴</td>
<td>L of L + L + S RS</td>
<td>1</td>
</tr>
<tr>
<td>46°C</td>
<td>(4.18 ± 0.06) · 10⁻⁵</td>
<td>(2.03 ± 0.02) · 10⁻⁴</td>
<td>L of L + S RS</td>
<td>1</td>
</tr>
<tr>
<td>46°C</td>
<td>(1.34 ± 0.02) · 10⁻⁵</td>
<td>(1.97 ± 0.05) · 10⁻⁴</td>
<td>L₁ of L₁ + L₂</td>
<td>1</td>
</tr>
<tr>
<td>46°C</td>
<td>(9.36 ± 0.75) · 10⁻⁶</td>
<td>(2.02 ± 0.001) · 10⁻⁴</td>
<td>L₁ of L₁ + L₂ + S RS</td>
<td>1</td>
</tr>
<tr>
<td>46°C</td>
<td>(2.07 ± 0.31) · 10⁻⁶</td>
<td>(1.53 ± 0.02) · 10⁻⁴</td>
<td>L₁ of L₁ + S RS</td>
<td>1</td>
</tr>
<tr>
<td>48°C</td>
<td>(5.49 ± 0.64) · 10⁻⁵</td>
<td>(5.61 ± 0.64) · 10⁻⁵</td>
<td>L₁ of L₁ + S RS</td>
<td>1</td>
</tr>
<tr>
<td>48°C</td>
<td>(1.59 ± 0.007) · 10⁻⁵</td>
<td>(2.06 ± 0.008) · 10⁻⁴</td>
<td>L₁ of L₁ + L₂ + S RS</td>
<td>1</td>
</tr>
<tr>
<td>48°C</td>
<td>(6.52 ± 10⁻²) · 10⁻²</td>
<td>0.901</td>
<td>L₁ of L₁ + L₂ + S RS</td>
<td>1</td>
</tr>
<tr>
<td>48°C</td>
<td>(2.29 ± 0.02) · 10⁻⁶</td>
<td>(2.17 ± 0.008) · 10⁻⁴</td>
<td>L₁ of L₁ + L₂ + S RS</td>
<td>1</td>
</tr>
<tr>
<td>48°C</td>
<td>(9.90 ± 0.02) · 10⁻²</td>
<td>0.952 ± 0.001</td>
<td>L₁ of L₁ + L₂ + S RS</td>
<td>1</td>
</tr>
<tr>
<td>48°C</td>
<td>(4.82 ± 0.006) · 10⁻²</td>
<td>0.916 ± 0.001</td>
<td>L₁ of L₁ + L₂ + S RS</td>
<td>1</td>
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<tr>
<td>52°C</td>
<td>(6.81 ± 0.005) · 10⁻²</td>
<td>0.904 ± 0.0007</td>
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<tr>
<td>52°C</td>
<td>(9.98 ± 0.01) · 10⁻²</td>
<td>0.959 ± 0.001</td>
<td>L₁ of L₁ + L₂ + S RS</td>
<td>1</td>
</tr>
<tr>
<td>52°C</td>
<td>(4.87 ± 0.003) · 10⁻²</td>
<td>0.925 ± 0.0007</td>
<td>L₁ of L₁ + L₂ + S RS</td>
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</tr>
<tr>
<td>52°C</td>
<td>(6.84 ± 0.004) · 10⁻²</td>
<td>0.909 ± 0.0004</td>
<td>L₁ of L₁ + L₂ + S RS</td>
<td>1</td>
</tr>
<tr>
<td>52°C</td>
<td>5.85 · 10⁻²</td>
<td>0.916</td>
<td>L₁ of L₁ + L₂ + S RS</td>
<td>1</td>
</tr>
<tr>
<td>52°C</td>
<td>(6.14 ± 0.48) · 10⁻⁵</td>
<td>(2.12 ± 0.003) · 10⁻⁴</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>52°C</td>
<td>(2.42 ± 0.04) · 10⁻⁶</td>
<td>(2.31 ± 0.008) · 10⁻⁴</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>52°C</td>
<td>(9.83 ± 0.02) · 10⁻³</td>
<td>0.945 ± 0.002</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>52°C</td>
<td>(4.79 ± 0.009) · 10⁻²</td>
<td>0.910 ± 0.002</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>52°C</td>
<td>(6.79 ± 0.006) · 10⁻²</td>
<td>0.903 ± 0.0008</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>52°C</td>
<td>7.64 · 10⁻²</td>
<td>0.924</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>52°C</td>
<td>6.40 · 10⁻³</td>
<td>0.994</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>62°C</td>
<td>(9.45 ± 0.75) · 10⁻⁵</td>
<td>(2.53 ± 0.02) · 10⁻⁴</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>62°C</td>
<td>(5.48 ± 0.14) · 10⁻⁵</td>
<td>0.803</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>62°C</td>
<td>(3.04 ± 0.11) · 10⁻⁶</td>
<td>(2.83 ± 0.03) · 10⁻⁴</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>62°C</td>
<td>(9.73 ± 0.03) · 10⁻⁵</td>
<td>0.935 ± 0.003</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
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<tr>
<td>62°C</td>
<td>(4.77 ± 0.01) · 10⁻²</td>
<td>0.907 ± 0.002</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>62°C</td>
<td>1.17 ± 0.03</td>
<td>0.856</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>62°C</td>
<td>(8.22 ± 0.38) · 10⁻⁵</td>
<td>(2.29 ± 0.002) · 10⁻⁴</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>62°C</td>
<td>0.261</td>
<td>0.729</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>62°C</td>
<td>(3.19 ± 0.05) · 10⁻⁶</td>
<td>(3.03 ± 0.08) · 10⁻⁴</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>62°C</td>
<td>(9.67 ± 0.04) · 10⁻³</td>
<td>0.929 ± 0.004</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>62°C</td>
<td>(4.75 ± 0.01) · 10⁻²</td>
<td>0.903 ± 0.002</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>62°C</td>
<td>0.115 · 0002</td>
<td>0.845 ± 0.001</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
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<td>62°C</td>
<td>0.188</td>
<td>0.812</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>75°C</td>
<td>(1.88 ± 0.04) · 10⁻⁴</td>
<td>(1.89 ± 0.05) · 10⁻⁴</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>75°C</td>
<td>0.490 ± 0.0003</td>
<td>0.490 ± 0.0003</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>75°C</td>
<td>(3.91 ± 0.09) · 10⁻⁶</td>
<td>(3.74 ± 0.06) · 10⁻⁴</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>75°C</td>
<td>(9.67 ± 0.04) · 10⁻³</td>
<td>0.929 ± 0.004</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>75°C</td>
<td>0.495 ± 0.0002</td>
<td>0.495 ± 0.0002</td>
<td>L₃ of L₃ + L₁</td>
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</tr>
<tr>
<td>75°C</td>
<td>0.421</td>
<td>0.579</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>82°C</td>
<td>(2.22 ± 0.12) · 10⁻⁴</td>
<td>(2.23 ± 0.11) · 10⁻⁴</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>82°C</td>
<td>0.487 ± 0.001</td>
<td>0.487 ± 0.001</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>82°C</td>
<td>(4.47 ± 0.24) · 10⁻⁶</td>
<td>(4.30 ± 0.08) · 10⁻⁴</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
<tr>
<td>82°C</td>
<td>(9.58 ± 0.05) · 10⁻³</td>
<td>0.920 ± 0.005</td>
<td>L₃ of L₃ + L₁</td>
<td>1</td>
</tr>
</tbody>
</table>
3.4 Conclusions

In this chapter, the ternary phase diagram of the system consisting of the two enantiomers of Ibuprofen and water was determined in the temperature range from 40°C to 82°C. The system exhibits a thermodynamically stable LLPS which extends over the entire enantiomeric composition range. The generic phase diagram of such systems, which has not been reported before, is derived by exploiting the consolidated knowledge of the phase behavior of conglomerate forming systems. The two subsystems consisting of one enantiomer, the racemic compound and the solvent are found to exhibit the same topological properties of conglomerate forming systems exhibiting a thermodynamically stable LLPS. In fact, also in the case of racemic compound forming systems, the onset of oiling out occurs through a ternary monotectic equilibrium, where a solute-rich liquid phase emerges inside the solid-solid-liquid-phase region creating a four phase equilibrium involving two liquid phases with the same enantiomeric excess and two solid phases.

Despite the occurrence of a LLPS, the presence of thermodynamically stable solid-liquid equilibria involving crystals of the pure enantiomer demonstrate that operating conditions exist enabling chiral resolution processes through crystallization from partially enriched solutions.

In this particular case however, the high enantiomeric excess of the eutectic liquid phases and the low solubility of Ibuprofen in water results in low yields and high losses of the target-enantiomer in the mother liquor, thus making the ternary system unsuitable for chiral resolution processes through crystallization. The knowledge of the phase behavior gained in this work and the characterization protocols devised in this study can however be exploited to identify suitable operating conditions for crystallization processes aimed at chiral resolution for other systems.
3. Racemic compound forming substance exhibiting oiling out

that exhibit a LLPS, i.e. exhibit the same qualitative features, but have more favorable properties.
3.5 Nomenclature of chapter 3

ee enantiomeric excess
L liquid phase
L$_I$ solute-lean liquid phase in liquid-liquid phase region
L$_{II}$ solute-rich liquid phase in liquid-liquid phase region
S$_{solv}$ crystals of the solvent
S$_R$ crystals of the R-enantiomer
S$_{RS}$ crystals of the racemic compound
S$_S$ crystals of the S-enantiomer
T$_{eut,RS-S}$ temperature of the eutectic equilibrium $L \rightleftharpoons S_{RS} + S_S$
T$_{eut,solv-\text{RS-S}}$ temperature of the eutectic equilibrium
$L \rightleftharpoons S_{solv} + S_{RS} + S_S$
T$_{eut,solv-\text{RS}}$ temperature of the eutectic equilibrium $L \rightleftharpoons S_{solv} + S_{RS}$
T$_{eut,solv-\text{S}}$ temperature of the eutectic equilibrium $L \rightleftharpoons S_{solv} + S_S$
T$_{m,RS}$ melting temperature of the racemic compound
T$_{m,S}$ melting temperature of the S-enantiomer
T$_{m,solv}$ melting temperature of the solvent
T$_{mon,L-\text{RS}}$ temperature of the monotectic equilibrium $L_{II} \rightleftharpoons L_I + S_{RS}$
T$_{mon,L-\text{RS-S}}$ temperature of the monotectic equilibrium $L_{II} \rightleftharpoons L_I + S_{RS} + S_S$
T$_{mon,L-\text{S}}$ temperature of the monotectic equilibrium $L_{II} \rightleftharpoons L_I + S_S$
T$_{uc,RS}$ upper consolution temperature of the racemic compound/solvent system
T$_{uc,RS-S}$ upper consolution temperature of a partially enriched ternary mixture
T$_{uc,S}$ upper consolution temperature of the S-enantiomer/solvent system
3. Racemic compound forming substance exhibiting oiling out
A methodology for the design of cooling crystallization processes for chiral resolution from non racemic initial solutions is presented. Such processes are encountered when chiral resolution is attained by hybrid processes, where the crystallization step is preceded by a pre-enrichment

4. Design of crystallization processes for conglomerate forming systems

step accomplished by either asymmetric synthesis or another separation technique. The work focuses on substances, which crystallize as conglomerates, and accounts for the occurrence of oiling out, i.e. an undesired liquid-liquid phase separation during crystallization. The generic ternary phase diagrams for conglomerate forming systems with and without oiling out are derived. This knowledge is then applied to identify suitable operating conditions for chiral resolution. As crystallization is started from saturated solutions, the crystallization process is characterized by three parameters: the initial enantiomeric excess and the initial temperature, which together implicitly define the position of the operating point in the phase diagram, and the final operating temperature, which defines the composition and the amount of the phases present at the end of crystallization. For any initial enantiomeric excess, the methodology yields distinct areas in the initial vs. final temperature plane containing pairs of operating temperatures that are suitable for chiral resolution. Such operating map bears great potential in improving the design and optimization of chiral resolution processes by crystallization.

4.1 Generic phase diagrams

4.1.1 Conglomerate forming systems

Thermodynamically stable multiphase equilibria

The phase diagram of a ternary system can be represented at constant pressure by a triangular prism with temperature as vertical axis. Assuming complete immiscibility in the solid phase and excluding the formation of polymorphs, only three solid phases, each composed of one of the three components, can be obtained from any ternary mixture. In
4.1 Generic phase diagrams

Figure 4.1: Schematic representation of the three liquidus surfaces of a ternary system forming conglomerates under the assumption of complete immiscibility in the solid phase and no formation of polymorphs. The yellow surfaces represent the solid-liquid equilibria comprising enantiopure solids, while the green surface describes the solid-liquid equilibria involving the solid solvent.

The temperature range where solid-liquid equilibria are thermodynamically stable, the equilibria among the individual solid phases and a liquid phase are represented by three liquidus surfaces that attain maximum temperature at the pure component vertex (Figure 4.1). Where two liquidus surfaces intersect, a single liquid phase is at equilibrium with two different solid phases, thus forming a three phase equilibrium, while the intersection of three liquidus surfaces leads to an equilibrium among four phases. Hence, beside the three solid-liquid equilibria, the three liq-
uidus surfaces yield three solid-solid-liquid equilibria, one involving the two enantiopure solids, the other two involving the solid solvent and the solid $R$- or $S$-enantiomer, respectively, and a unique four-phase equilibrium comprising one liquid phase and the three pure components in the solid phase.

**Temperature range of thermodynamic stability of the multiphase equilibria**

When increasing the temperature the first liquid phase from a three phase solid-solid-solid system is formed through the ternary eutectic equilibrium $L \rightleftharpoons S_{solv} + S_R + S_S$ corresponding to the intersection of the three liquidus surfaces. As the two liquidus surfaces of the two enantiomers are mirror images of each other, the emerging liquid phase $L$ is of racemic composition. This is proven by demonstrating that the first liquid phase cannot be of non-racemic composition. If a non-racemic liquid phase were formed, system symmetry would require the concomitant appearance of another liquid phase equally enriched with the other enantiomer, thus forming an equilibrium comprising five phases, namely two liquid and three solid phases, which would not comply with Gibbs phase rule applied to a three component system at constant pressure.

Since the emerging liquid phase is at equilibrium with all solid phases, the temperature of the ternary eutectic equilibrium is the lowest temperature of thermodynamic stability among all possible multiphase equilibria. For all solid-liquid equilibria the corresponding highest temperatures are the melting points of the pure components. For the solid-solid-liquid equilibrium involving the two enantiopure solids, the highest temperature corresponds to the temperature of the binary eutectic equilibrium $L \rightleftharpoons S_R + S_S$. For the solid-solid-liquid equilibria involv-
ing the solid solvent and one enantiopure solid, the highest temperature coincides with the temperatures of the two binary eutectic equilibria $L \rightleftharpoons S_{solv} + S_R$ and $L \rightleftharpoons S_{solv} + S_S$, which are identical due to symmetry. These two eutectic equilibria and the melting points of the solvent and of the pure enantiomers are found on the two polythermal cuts of the ternary phase diagram corresponding to the binary phase diagrams pure enantiomer/solvent. Due to symmetry, the two polythermal cuts are identical, thus only one will be considered in the following. Furthermore, the liquid phases of the two eutectic equilibria $L \rightleftharpoons S_R + S_S$ and $L \rightleftharpoons S_{solv} + S_R + S_S$ are found on the polythermal cut characterized by an equimolar concentration of the two enantiomers (racemic composition). These two polythermal cuts, providing the temperatures of all eutectic equilibria and melting points, contain enough information to derive the temperature range of thermodynamic stability of all multiphase equilibria. In this particular case, the two polythermals cuts are two mono-eutectic systems and are shown in Figure 4.2.

**Generic phase diagrams**

The knowledge of the temperature ranges of thermodynamic stability of all multiphase equilibria leads to a qualitative picture of the ternary phase diagram at any temperature. After identifying particular states and conditions on the polythermal ternary phase diagram that allow determining the temperature range of thermodynamic stability of all multiphase equilibria, constraining the position of these states by applying standard thermodynamic rules enables the determination of all possible types of ternary phase diagrams that fulfill the assumptions.

The conglomerate forming behavior requires the melting temperature of the pure enantiomer $T_{m,R}$ to be larger than the temperature of the
4. Design of crystallization processes for conglomerate forming systems

Figure 4.2: Eutectic and melting temperatures determining the topological evolution of the phase diagram of a ternary system forming conglomerates. The three polythermal cuts are turned down. The red one includes the \( R \)-enantiomer and the solvent; the blue one includes the racemic solid mixture and the solvent; the green phase diagram corresponds to a part of the binary phase diagram of the two enantiomers and is only added for the better understanding of the figure, as all the information it carries are comprised in the first two polythermal cuts.

eutectic equilibrium \( L \rightleftharpoons S_R + S_S; T_{\text{eut},R-S} \). Due to the eutectic character of the polythermal cuts, the temperature of the ternary eutectic equilibrium \( L \rightleftharpoons S_{\text{solv}} + S_R + S_S; T_{\text{eut},\text{solv}-R-S} \), has to be lower than both the eutectic temperature \( T_{\text{eut},R-S} \) and the melting point of the solvent, \( T_{\text{m,solv}} \). The same applies to the temperature of the binary eutectic equilibrium \( L \rightleftharpoons S_{\text{solv}} + S_R; T_{\text{eut},\text{solv}-R} \), which has to be lower
4.1 Generic phase diagrams

than the melting temperature of the pure enantiomer $T_{m,R}$ and of the pure solvent $T_{m,solv}$. The constraint $T_{\text{eut},solv−R−S} < T_{\text{eut},solv−R}$ follows from the fact that the first liquid phase emerging from a three phase solid-solid-solid system is of racemic composition. The complete set of constraints is summarized in Table 4.1.

Table 4.1: Constraints applicable to eutectic and melting temperatures of simple conglomerate forming systems

<p>| | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>$T_{m,R} &gt; T_{\text{eut},R−S}$</td>
</tr>
<tr>
<td>(2)</td>
<td>$T_{\text{eut},R−S} &gt; T_{\text{eut},solv−R−S}$</td>
</tr>
<tr>
<td>(3)</td>
<td>$T_{m,solv} &gt; T_{\text{eut},solv−R−S}$</td>
</tr>
<tr>
<td>(4)</td>
<td>$T_{m,R} &gt; T_{\text{eut},solv−R}$</td>
</tr>
<tr>
<td>(5)</td>
<td>$T_{m,solv} &gt; T_{\text{eut},solv−R}$</td>
</tr>
<tr>
<td>(6)</td>
<td>$T_{\text{eut},solv−R} &gt; T_{\text{eut},solv−R−S}$</td>
</tr>
</tbody>
</table>

The number of generic ternary phase diagrams is finally obtained by permuting the order of the two eutectic and of the three melting temperatures while accounting for the constraints mentioned above. The permutation yields five types of phase diagram, whose sequences of eutectic and melting temperatures are reported in Table 4.2.
Table 4.2: Types of conglomerate forming systems categorized by the sequence of eutectic and melting temperatures. The temperature increases from left to right.

<table>
<thead>
<tr>
<th>Type</th>
<th>$T_{eut,solv-R}$</th>
<th>$T_{eut,R-S}$</th>
<th>$T_{m,solv}$</th>
<th>$T_{m,R}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>$T_{eut,solv-R}$</td>
<td>$T_{eut,R-S}$</td>
<td>$T_{m,solv}$</td>
<td>$T_{m,R}$</td>
</tr>
<tr>
<td>Type II</td>
<td>$T_{eut,solv-R}$</td>
<td>$T_{eut,R-S}$</td>
<td>$T_{m,solv}$</td>
<td>$T_{m,R}$</td>
</tr>
<tr>
<td>Type III</td>
<td>$T_{eut,R-S}$</td>
<td>$T_{eut,solv-R}$</td>
<td>$T_{m,solv}$</td>
<td>$T_{m,R}$</td>
</tr>
<tr>
<td>Type IV</td>
<td>$T_{eut,R-S}$</td>
<td>$T_{eut,solv-R}$</td>
<td>$T_{m,solv}$</td>
<td>$T_{m,R}$</td>
</tr>
<tr>
<td>Type V</td>
<td>$T_{eut,R-S}$</td>
<td>$T_{eut,solv-R}$</td>
<td>$T_{m,solv}$</td>
<td>$T_{m,R}$</td>
</tr>
</tbody>
</table>

Table 4.3: Main groups of conglomerate forming systems exhibiting thermodynamically stable oiling out categorized by the sequence of monotectic, eutectic and melting temperatures. The temperature increases from left to right. Due to their elevated number, the generic phase diagrams have been distributed into five main groups that do not account for the position of three key events $T_{m,solv}$, $T_{uc,R-S}$ and $T_{uc,R}$, which have no impact on the solid-liquid equilibria involving the enantiopure solids and consequently on process design.

<table>
<thead>
<tr>
<th>Type</th>
<th>$T_{eut,solv-R}$</th>
<th>$T_{mon,L-R-S}$</th>
<th>$T_{m,R}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>$T_{eut,solv-R}$</td>
<td>$T_{mon,L-R-S}$</td>
<td>$T_{m,R}$</td>
</tr>
<tr>
<td>Type II</td>
<td>$T_{eut,solv-R}$</td>
<td>$T_{mon,L-R-S}$</td>
<td>$T_{m,R}$</td>
</tr>
<tr>
<td>Type III</td>
<td>$T_{mon,L-R-S}$</td>
<td>$T_{mon,L-R-S}$</td>
<td>$T_{m,R}$</td>
</tr>
<tr>
<td>Type IV</td>
<td>$T_{mon,L-R-S}$</td>
<td>$T_{mon,L-R-S}$</td>
<td>$T_{m,R}$</td>
</tr>
<tr>
<td>Type V</td>
<td>$T_{mon,L-R-S}$</td>
<td>$T_{mon,L-R-S}$</td>
<td>$T_{m,R}$</td>
</tr>
</tbody>
</table>
Construction of the qualitative ternary phase diagrams from eutectic and melting temperatures

The construction of the ternary phase diagram using a specific sequence of eutectic and melting temperatures is exemplarily demonstrated for a system of type I. For this purpose, the ternary phase diagram of a system of this type was modeled using the ideal Schroeder-Van Laar-equation:

\[
\ln x_i = \frac{\Delta H_m(T_{m,i})}{R} \left( \frac{1}{T_{m,i}} - \frac{1}{T} \right),
\]

where \(x_i\) is the mole fraction of component \(i\) in solution, \(T_{m,i}\) and \(\Delta H_m(T_{m,i})\) are its melting temperature and melting enthalpy, respectively.\(^6\) A selection of isothermal ternary phase diagrams at increasing temperature is shown in Figure 4.3. The six parameters used in the model to calculate the diagrams are listed in the figure caption.

According to Table 4.2, the first liquid phase emerges at the temperature of the ternary eutectic equilibrium \(T_{eut,solv-R-S}\) (Figure 4.3(a)). The new liquid phase yields new phase equilibria with the pure solid phases, leading to three solid-solid-liquid equilibria and three solid-liquid equilibria right above \(T_{eut,solv-R-S}\) (Figure 4.3(b)). Once the temperature of the first binary eutectic equilibrium \(T_{eut,solv-R}\) is reached, a liquid phase will emerge along the binary diagram consisting of the pure enantiomer and the solvent. This corresponds to the temperature where the liquid region \(L\) reaches the sides of the phase triangle (Figure 4.3(c)); the two three-phase regions involving the solid solvent disappear at this temperature. After going through an intermediate situation shown in Figure 4.3(d), at the melting temperature of the solvent, \(T_{m,solv}\), the solid-liquid phase region \(L+S_{solv}\) disappears (Figure 4.3(e)). Increasing the temperature, the solubility isotherms of the two remaining solid-liquid equilibria
Figure 4.3: Evolution of the phase diagram of an ideal conglomerate forming system of type I. Properties of the two enantiomers: $\Delta H_{m,R} = 29.6\text{kJ/mol}$, $T_{m,R} = 56^\circ\text{C}$; Properties of the solvent: $\Delta H_{m,solv} = 2.6\text{kJ/mol}$, $T_{m,solv} = 7^\circ\text{C}$; Key temperatures obtained from model: $T_{\text{eut, solv} - R - S} = -15.9^\circ\text{C}$, $T_{\text{eut, solv} - R} = -9.3^\circ\text{C}$, $T_{\text{eut, R} - S} = 36.2^\circ\text{C}$. 
will move towards higher concentrations and at $T_{eut,R-S}$, the intersection of the two solubility isotherms will reach the base of the triangle, thus leading to the disappearance of the solid-solid-liquid phase region $L + S_R + S_S$ (Figure 4.3(f)). Above these temperatures, the area of the two remaining solid-liquid phase regions (Figure 4.3(g)) will become smaller and smaller, until they disappear at the melting temperature of the pure enantiomers $T_{m,R}$.

In all five types of systems, the first liquid phase will emerge at $T_{eut,solv-R-S}$ and will lead to a phase diagram with the same number of phase regions as the one presented in Figure 4.3(b). Increasing temperature causes the disappearance of the multiphase equilibria until reaching a ternary phase diagram consisting of one single liquid phase above the highest melting temperature of the system. The sequence of disappearance of the single phase regions is unequivocally defined by the sequence of the other eutectic temperatures and of the three melting temperatures.

### 4.1.2 Conglomerate forming systems exhibiting oiling out

**Thermodynamically stable multiphase equilibria**

Following the same approach, consider conglomerate forming systems exhibiting thermodynamically stable oiling out, under the assumptions of complete immiscibility in the solid phase and of lack of polymorphs. Regarding oiling out, we assume that the region of liquid-liquid phase separation extends over the entire range of enantiomeric compositions and we restrict our discussion to cases where oiling out affects only solid-liquid equilibria involving crystals of the pure enantiomers.
In the ternary phase diagram, schematically represented in Figure 4.4, oiling out manifests itself in the appearance of a new (blue) surface describing the liquid-liquid equilibria, which completely separates the lower (yellow) from the upper (orange) liquidus surfaces describing the solid-liquid equilibria involving crystals of the pure enantiomers.

![Figure 4.4: Schematic representation of the surfaces describing solid-liquid and liquid-liquid equilibria of a ternary system forming conglomerates exhibiting oiling out. The yellow and the orange surfaces represent the liquidus surfaces of the enantiopure solids, while the green surface describes the liquidus surface of the solvent. The blue surface represents the liquid-liquid equilibria.](image)

The six surfaces indicate the presence of different six two-phase equilibria, namely five solid-liquid equilibria and one liquid-liquid equilibrium. Three solid-solid-liquid equilibria are generated by the pairwise intersec-
4.1 Generic phase diagrams

...tions among the two lower liquidus surfaces of the pure enantiomers and the liquidus (green) surface of the solvent. Moreover, the concomitant (at the same temperature) intersections of the lower and the upper liquidus surfaces of each enantiomer with the solute lean and the solute rich part of the liquid-liquid equilibrium surface, respectively, generate two different solid-liquid-liquid equilibria. Finally, the intersection between the two upper liquidus surfaces creates another solid-solid-liquid equilibrium involving the two enantiopure solids. As for simple conglomerate forming systems, the intersection of three liquidus surfaces, i.e. the lower liquidus surfaces of the two enantiomers and the liquidus surface of the solvent, creates a ternary eutectic equilibrium \( L \rightleftharpoons S_{solv} + S_R + S_S \).

The concomitant intersection of the solute lean part of the liquid-liquid equilibrium surface with the two lower liquidus surfaces and of the solute rich part with the two upper liquidus surfaces yields a ternary monotectic equilibrium \( L_{II} \rightleftharpoons L_I + S_R + S_S \).

**Thermodynamic stability of the multiphase equilibria**

After having identified the possible multiphase equilibria, their range of thermodynamic stability has to be determined. The temperature of the ternary eutectic equilibria \( T_{eut,solv−R−S} \) corresponds to the lowest temperature of thermodynamic stability among all multiphase equilibria arising from intersections among the lower liquidus surfaces of the pure enantiomers and the liquidus surfaces of the solvent. We refer to Section 4.1.1 for the highest temperature of thermodynamic stability of the solid-liquid and of the solid-solid-liquid equilibria involving the solid solvent.

In Chapter 2, it was demonstrated that a second liquid phase can only emerge as temperature increases through the ternary monotectic equilibrium \( L_{II} \rightleftharpoons L_I + S_R + S_S \). First, the temperature of the monotectic
equilibrium represents the highest temperature of thermodynamic stability of the solid-solid-liquid equilibrium created by the intersection of the two lower liquidus surfaces of the pure enantiomers. Secondly, the same temperature is also the lowest temperature of thermodynamic stability of six multiphase equilibria, namely the two solid-liquid equilibria and the solid-solid-liquid equilibrium stemming from the two upper liquidus surfaces of the pure enantiomers, as well as the liquid-liquid equilibrium and the two solid-liquid-liquid equilibria, where the solid is one of the two enantiomers.

The highest temperature of thermodynamic stability of the two solid-liquid equilibria associated to the lower liquidus surfaces and the highest temperature of the two solid-liquid-liquid equilibria are the temperatures of the binary monotectic equilibria \( L_{II} \rightleftharpoons L_1 + S_R \) and \( L_{II} \rightleftharpoons L_1 + S_S \), which are equal due to symmetry of chiral compounds. The eutectic temperature \( T_{eut,R-S} \) corresponds to the highest temperature of thermodynamic stability of the solid-solid-liquid equilibrium created by the intersection of the two upper liquidus surfaces of the two enantiomers, while the highest temperature for the solid-liquid equilibria associated to the same liquidus surfaces corresponds to the melting point of the pure enantiomer \( T_{m,R} \). Finally, the highest temperature of thermodynamic stability of the liquid-liquid equilibria corresponds to the upper consolution temperature. As a discussion on possible shapes of the liquid-liquid equilibrium surface is beyond the scope of this work, we assume the surface to have either one maximum along the symmetry plane of the ternary phase diagram or two maxima on the lateral planes of the ternary phase diagram.

The two binary monotectic equilibria \( L_{II} \rightleftharpoons L_1 + S_R \) and \( L_{II} \rightleftharpoons L_1 + S_S \) are both located on the polythermal cuts referring to the binary systems solvent/pure enantiomer and as they are identical, the analysis of
only one of them suffices. The two liquid phases of the ternary monotectic equilibrium $L_{II} \rightleftharpoons L_1 + S_R + S_S$ are both racemic and are thus located on the polythermal cut corresponding to the symmetry plane of the ternary phase diagram. Having forced the liquid-liquid equilibrium surface to have its maximum either along the symmetry plane or along the lateral planes of the ternary phase diagram, all relevant states for the determination of the range of thermodynamic stability of all multiphase equilibria are found on two polythermal cuts, one referring to the binary system pure enantiomer/solvent, the other representing the symmetry line of the ternary phase diagram.

The two polythermal cuts are schematically represented in Figure 4.5. As the liquid-liquid equilibrium covers the whole range of enantiomeric compositions, both polythermal cuts exhibit a eutectic and a monotectic equilibrium. The upper boundaries of the liquid-liquid phase regions are denoted by the upper consolution temperatures $T_{uc,R-S}$ and $T_{uc,R}$.

**Generic phase diagrams**

In order to derive the number of generic phase diagrams, the relative position of the two eutectic equilibria, of the two monotectic equilibria, of the three melting points and of the two upper consolution temperatures along the temperature axis has to be considered. The conglomerate forming behavior of the two enantiomers and the constraints applicable to equilibria created by the liquidus surface of the solvent and its intersections with the lower liquidus surfaces of the two enantiomers remain unaltered, therefore the conditions (1), (3), (5) and (6) of Figure 4.1 can be applied also to systems exhibiting oiling out. As liquid-liquid equilibria affect only the solid-liquid equilibria involving the enantiopure solids, the temperature of the ternary monotectic equilibrium $L_{II} \rightleftharpoons L_1 + S_R + S_S$,
Figure 4.5: Eutectic, monotectic, melting and upper consolution temperatures defining the topological evolution of the phase diagram of ternary systems forming conglomerates and exhibiting thermodynamically stable oiling out. The three polythermal cuts are turned down. The red one includes the R-enantiomer and the solvent; the blue one includes the racemic solid mixture and the solvent; the green phase diagram corresponds to a part of the binary phase diagram of the two enantiomers and is only added for the better understanding of the figure, as all the information it carries are comprised in the first two polythermal cuts.

$T_{\text{mon}, L-R-S}$, has to be larger than the temperature of the ternary eutectic equilibrium $T_{\text{eut,solv}-R-S}$. The same applies also for the other polythermal cut, where the temperature of the binary monotectic equilibrium $L_{II} \leftrightarrow L_{I} + S_{R}$, $T_{\text{mon}, L-R}$, has to be larger than $T_{\text{eut,solv}-R}$. Given that the onset of oiling out occurs at the ternary monotectic equi-
4.1 Generic phase diagrams

Table 4.4: Constraints for monotectic, eutectic, melting and upper consolution temperatures applicable to conglomerate forming systems exhibiting thermo-
dynamically stable oiling out.

<table>
<thead>
<tr>
<th></th>
<th>Constraint</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>( T_{m,R} &gt; T_{\text{eut,R-S}} )</td>
</tr>
<tr>
<td>2</td>
<td>( T_{m,\text{solv}} &gt; T_{\text{eut,solv-R-S}} )</td>
</tr>
<tr>
<td>3</td>
<td>( T_{m,\text{solv}} &gt; T_{\text{eut,solv-R}} )</td>
</tr>
<tr>
<td>4</td>
<td>( T_{\text{eut,solv-R}} &gt; T_{\text{eut,solv-R-S}} )</td>
</tr>
<tr>
<td>5</td>
<td>( T_{\text{mon,L-R-S}} &gt; T_{\text{eut,solv-R-S}} )</td>
</tr>
<tr>
<td>6</td>
<td>( T_{\text{mon,L-R}} &gt; T_{\text{eut,solv-R}} )</td>
</tr>
<tr>
<td>7</td>
<td>( T_{\text{mon,L-R}} &gt; T_{\text{mon,L-R-S}} )</td>
</tr>
<tr>
<td>8</td>
<td>( T_{\text{uc,R-S}} &gt; T_{\text{mon,L-R-S}} )</td>
</tr>
<tr>
<td>9</td>
<td>( T_{\text{uc,R}} &gt; T_{\text{mon,L-R}} )</td>
</tr>
<tr>
<td>10</td>
<td>( T_{\text{eut,R-S}} &gt; T_{\text{mon,L-R-S}} )</td>
</tr>
<tr>
<td>11</td>
<td>( T_{m,R} &gt; T_{\text{mon,L-R}} )</td>
</tr>
</tbody>
</table>

Equilibrium, \( T_{\text{mon,L-R-S}} \) has to be lower than \( T_{\text{mon,L-R}} \). Finally, the ternary and the binary monotectic equilibria stemming from the occurrence of oiling out require the upper consolution temperatures \( T_{\text{uc,R-S}} \) and \( T_{\text{uc,R}} \) to be larger than \( T_{\text{mon,L-R-S}} \) and \( T_{\text{mon,L-R}} \), respectively. The same applies to the eutectic temperature \( T_{\text{eut,R-S}} \) and to the melting point of the pure enantiomer \( T_{m,R} \), which have to be larger than \( T_{\text{mon,L-R-S}} \) and \( T_{\text{mon,L-R}} \), respectively. The complete set of constraints is summarized in Table 4.4.

Permutation of the nine temperatures in compliance with the above-
mentioned constraints yields 406 possible ternary phase diagrams, i.e. a very large number. The purpose of this work is to develop generic design strategies for chiral resolution, hence it is essential to obtain exhaustive information on solid-liquid phase equilibria involving the enantiopure solids. In this regard, the two upper consolution temperatures \( T_{\text{uc,R-S}} \) and \( T_{\text{uc,R}} \) as well as the melting point of the solvent \( T_{m,\text{solv}} \) are irrelevant.
as these temperatures do not represent any boundary for the temperature ranges of thermodynamic stability of the multiphase equilibria involving the enantiopure solids. As a consequence, the 406 generic phase diagrams can be grouped in five main classes that do not account for these three temperatures. The order of the monotectic, the eutectic and the melting temperatures of these five classes are shown in Table 4.3. The sequence of the six temperatures is not sufficient to unambiguously define the evolution of the ternary phase diagram, but it provides unambiguous information about the temperature range of thermodynamic stability of the solid-liquid equilibria involving enantiopure solids.

**Construction of the qualitative ternary phase diagram from eutectic, monotectic, melting and upper consoluition temperatures**

The construction of the ternary phase diagram of a system exhibiting oiling out is exemplarily demonstrated by considering a ternary phase diagram of type I, whereby it is assumed that $T_{\text{eut,solv}} < T_{\text{m,solv}} < T_{\text{mon,L-R-S}}$ and that both upper consoluition temperatures are larger than the melting temperature of the pure enantiomer. A selection of isothermal ternary phase diagrams at increasing temperatures, in this case drawn only qualitatively, is shown in Figure 4.6. The first liquid phase $L$ emerging from a three phase solid-solid-solid system at $T_{\text{eut,solv-R-S}}$ leads to three solid-liquid- and three solid-solid-liquid equilibria slightly above $T_{\text{eut,solv-R-S}}$ (Figure 4.6(a)). At the temperature of the binary eutectic $T_{\text{eut,solv-R}}$, the single liquid phase region will reach the sides of the triangle, thus leading to the disappearance of the two solid-solid-liquid phase regions $L+S_{\text{solv}}+S_R$ and $L+S_{\text{solv}}+S_S$. Increasing the temperature from below (Figure 4.6(b)) to above $T_{\text{m,solv}}$ (Figure 4.6(c)) will lead to the disappearance of the phase region $L+S_{\text{solv}}$. At
Figure 4.6: (a)-(j) Schematic evolution of the phase diagram of an ideal conglomerate forming system exhibiting oiling out of type I. The conditions $T_{\text{eut,solv}} - R < T_{\text{m,solv}} < T_{\text{mon}, L - R - S}$ and $T_{\text{uc}, R - S}, T_{\text{uc}, R} > T_{\text{m}, R}$ unambiguously define the evolution of the ternary phase diagram in the temperature range where solid-liquid equilibria are thermodynamically stable. (k) Polythermal projection of the ternary phase diagram.
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A new liquid phase $L_{II}$ will emerge within the $L + S_R + S_S$-phase region (Figure 4.6(d)). The phase regions of the six new phase equilibria that arise from the emergence of $L_{II}$ are shown in Figure 4.6(e). Increasing the temperature, the phase region $L_{II}$ will increase in size and reach the base of the triangle at $T_{eut,R-S}$ (Figure 4.6(f)). Passing through an intermediate situation shown in Figure 4.6(g), at $T_{mon,L-R}$, the liquid-liquid phase equilibrium becomes thermodynamically stable for the entire range of enantiomeric excesses, thus leading to the concomitant disappearance of the solid-liquid phase regions $L_1 + S_R$ and $L_1 + S_S$ and of the solid-liquid-liquid phase regions $L_1 + L_{II} + S_R$ and $L_1 + L_{II} + S_S$ (Figure 4.6(h)). Above this temperature, the liquid-liquid phase region $L_1 + L_{II}$ separates the two single phase regions $L_1$ and $L_{II}$. The two remaining solid-liquid phase regions $L_{II} + S_R$ and $L_{II} + S_S$ are confined to the vicinity of the vertices of the pure enantiomers (Figure 4.6(i)) and will disappear at their melting temperature (Figure 4.6(j)).

Independent of the type of system, the ternary eutectic equilibrium $L \rightleftharpoons S_{solv} + S_R + S_S$ yields a ternary phase diagram with the same number of phase equilibria as the phase diagram shown in Figure 4.6(a). For systems of type I and II, oiling out occurs at temperatures above the binary eutectic temperature $T_{eut,solv-R}$, i.e the two phase regions $L + S_R + S_{solv}$ and $L + S_S + S_{solv}$ are not present at $T_{mon,L-R-S}$. Regarding systems of type III to V, the second liquid phase emerges within the three phase region of the diagram shown in Figure 4.6(a). Hence, immediately above $T_{mon,L-R-S}$, the isothermal ternary phase diagram will feature all possible multiphase equilibria. In all types of systems, all multiphase equilibria that are thermodynamically stable immediately above $T_{mon,L-R-S}$ will disappear with increasing temperature according to the sequence of the eutectic, the monotectic, the melting and the upper consolution temperatures of the ternary system.
4.2 Crystallization process design

In this and the next section we aim at using the phase diagram demonstrated above to design optimal crystallization processes for the formation of crystals of a single enantiomer, i.e. the target-enantiomer.

Upstream of crystallization we assume that there is a process step that yields a partially enriched solution with an enantiomeric excess $e_{e_0}$. Several cases are possible: $e_{e_0} = 0\%$ if the upstream step is for instance symmetric synthesis; $e_{e_0} = 100\%$ if there is an infinitely selective upstream step (e.g. highly selective preparative chromatography); $e_{e_0}$ between 0% and 100% if crystallization is preceded by (partially) enantioselective synthesis or (partial) deracemization, e.g. by chiral chromatography.

The solute concentration is adjusted by addition or removal of solvent so as the solution can be assumed to be a saturated liquid at the initial temperature for crystallization, $T_{\text{initial}}$. Cooling down the solution to the final process temperature, $T_{\text{final}}$, a supersaturation is created that is depleted by the formation and growth of new crystals. The design of the crystallization process consists in the choice of an appropriate pair of $T_{\text{initial}}$ and $T_{\text{final}}$ that allows exploiting the solid-liquid equilibria involving the enantiopure crystals with the aim of selectively crystallizing the target-enantiomer, i.e. the one in excess in the feed solution.

Figure 4.7(a) and Figure 4.7(b) show the isothermal ternary phase diagrams at the operating temperatures, i.e. at $T_{\text{initial}}$ and $T_{\text{final}}$, of two crystallization processes starting from the same initial temperature and initial enantiomeric excess but ending at different final temperatures.

The state at $T_{\text{initial}}$ is described by a single point, i.e. the operating point (blue point in each figure), as the crystallization process is started from a saturated solution. The operating point is at the intersection of the
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Figure 4.7: Isothermal ternary phase diagrams at $T_{\text{initial}}$ and $T_{\text{final}}$ for two crystallization processes starting from the same initial temperature and initial enantiomeric excess but ending at two different final temperatures. The phases that are at equilibrium are denoted by circles. (a) at $T_{\text{final}}$, the operating point lies within the solid-liquid phase region involving the crystals of the target-enantiomer; (b) at $T_{\text{final}}$, the operating point lies within the solid-solid-liquid equilibrium involving the crystals of the two enantiomers.

The solubility curve at $T_{\text{initial}}$ with the straight line at constant enantiomeric excess $\text{ee}_0$, which defines the set of operating points that can be obtained through addition or removal of solvent from the feed solution.

If a final temperature is chosen so as the operating point lies within the solid-liquid-phase region (Figure 4.7(a)), only crystals of the target-enantiomer will precipitate and grow until equilibrium is reached. The state at $T_{\text{final}}$ is represented by two points corresponding to the solid and the liquid phase at equilibrium (magenta points); the solid phase is on the vertex corresponding to the pure target-enantiomer. The path the liquid phase follows during the removal of the target-enantiomer is defined by the operating line, i.e. a straight line that connects the vertex corresponding to the pure target-enantiomer. The intersection
4.3 Feasible and optimal design: criteria and operating diagrams

of the operating line with the solubility curve at $T_{\text{final}}$ defines the final composition of the liquid phase.

If a final temperature is chosen so as the operating point lies within the solid-solid-liquid phase region, besides the target-enantiomer also the counter-enantiomer precipitates and grows (Figure 4.7(b)). The state at $T_{\text{final}}$ is then represented by three points associated to the two solid phases and the liquid phase (magenta points). The solid phases lie on the vertices corresponding to the pure enantiomers. The liquid phase is of racemic composition and, as both enantiomers crystallize, it does not belong to the operating line.

The crystallization process shown in Figure 4.7(b) is not suitable for chiral resolution as crystals of the counter-enantiomer are formed. The knowledge of the ternary phase diagram is essential for the design of crystallization processes that are not only suitable for chiral resolution but also optimal in the sense defined in the next section.

4.3 Feasible and optimal design: criteria and operating diagrams

4.3.1 Conglomerate forming systems

Determination of operating points for crystallization

Crystallization processes for chiral resolution are carried out at temperatures where solid-liquid-equilibria involving the enantiopure crystals of the target-enantiomer are thermodynamically stable. The liquid phases involved in these equilibria lie on the liquidus surface of the target-enantiomer and as crystallization processes start from a saturated solu-
tion, also the operating points lie on the same liquidus surface at $T_{\text{initial}}$. Hence, the portion of the liquidus surface of the target-enantiomer that is thermodynamically stable defines the set of operating points that are suitable for crystallization.

Independent of the type of system, the liquidus surface of the target-enantiomer is delimited by its intersection with the liquidus surfaces of the counter-enantiomer and of the solvent. The points of intersection between liquidus surfaces lie on monovariant curves connecting the liquid phases involved in the binary eutectic equilibria on the lateral planes of the ternary prism with the liquid phase involved in the ternary eutectic equilibrium located on the symmetry plane of the prism. Having three thermodynamically stable liquidus surfaces in any conglomerate forming system, the ternary phase diagram always exhibits three monovariant curves, which meet at the point corresponding to the liquid phase of the ternary eutectic equilibrium.\textsuperscript{7}

The liquidus projection, where the projections of the monovariant curves onto the base of the ternary prism are plotted, allows determining the operating points that are feasible for chiral resolution by crystallization. The pink region in the liquidus projection shown in Figure 4.8 shows the set of possible operating points in the case where the $R$-enantiomer is the target enantiomer.

**Determination of operating temperatures for crystallization**

The temperatures that are required to saturate ternary mixtures of different composition decrease with decreasing $\text{ee}_0$ and solute concentration. Independent of the type of system $T_{m,R}$, i.e. the temperature corresponding to the point on the liquidus surface with the highest solute concentration and enantiomeric enrichment, is larger than both $T_{\text{eut,solv}−R}$,
corresponding to the point with the same enantiomeric enrichment but with the lowest solute concentration, and $T_{\text{eut},R-S}$, corresponding to the point with the same solute concentration but of racemic composition. Furthermore, $T_{\text{eut},\text{solv}-R}$ and $T_{\text{eut},R-S}$ are larger than $T_{\text{eut},\text{solv}-R-S}$, i.e. the temperature corresponding to the point of racemic composition with the lowest solute concentration.

The highest $T_{\text{initial}}$-value for a set of operating points with constant ee$_0$ required to liquefy a binary mixture of the two enantiomers, decreases
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from $T_{m,R}$ to $T_{eut,R-S}$ when dropping $ee_0$ from 100% to 0%. Its lowest $T_{\text{initial}}$-value, which is required to liquefy a ternary mixture corresponding to the most diluted operating point, also decreases when decreasing $ee_0$ from 100% to 0%, namely it goes from $T_{eut,solv-R}$ to $T_{eut,solv-R-S}$.

For each operating point, the highest final temperature is its saturation temperature, i.e. $T_{\text{initial}}$, whereas the lowest final temperature is always the temperature of the ternary eutectic equilibrium $T_{eut,solv-R-S}$, because below this temperature only solid phases can be obtained.

**Determination of feasible operating temperatures for chiral resolution**

For any operating point that is suitable for crystallization, only one temperature out of the set of possible final temperatures allows crystallizing the target-enantiomer selectively and maximizing the yield, i.e. the ratio between the mass of final crystals of the target-enantiomer and the mass of target-enantiomer in the feed solution. The yield $Y$ can be calculated from the concentration of the target-enantiomer in the liquid phase at the initial and at the final process temperature as follows:

$$Y = \frac{c_{R,\text{initial}} - c_{R,\text{final}}}{c_{R,\text{initial}}}$$ (4.2)

The enantiomeric excess $ee$ (in percentage) can be calculated using the following equation:

$$ee = 100 \cdot \frac{c_R - c_S}{c_R + c_S},$$ (4.3)

where $c_R$ and $c_S$ are the concentrations of the $R$- and the $S$-enantiomer in the liquid phase, respectively. The concentrations in equations (4.2) and (4.3) are expressed in mass of solute per mass of solvent.
Considering that in chiral resolution processes the concentration of the counter-enantiomer remains constant throughout the process, i.e. \( c_{S,\text{initial}} = c_{S,\text{final}} \), the yield can be expressed as a function of the initial and the final enantiomeric excess only:

\[
Y = 1 - \frac{(1 - ee_0)(1 + ee_{\text{final}})}{(1 + ee_0)(1 - ee_{\text{final}})}
\]  

(4.4)

The yield is increased by decreasing \( ee_{\text{final}} \), which reaches its minimum when the liquid phase at equilibrium at \( T_{\text{final}} \) has eutectic composition, i.e. it lies on a monovariant curve. In this case the position of the operating line at \( T_{\text{final}} \) coincides with the line separating the solid-liquid from the solid-solid-liquid phase region. Intersections between the liquidus surfaces of the two enantiomers yield monovariant eutectic equilibria involving racemic liquid phases, whereas intersections between the liquidus surfaces of one enantiomer and of the solvent yield monovariant eutectic equilibria involving liquid phases varying from racemic to enantiopure composition. For conglomerate forming systems, the eutectic liquid phase with the lowest enantiomeric excess has racemic composition. Therefore, the operating points whose operating line crosses the monovariant curve at a point of racemic composition, i.e. where \( ee_{\text{final}} = 0 \), allow obtaining the global maximal yield, which corresponds to:

\[
Y_{\text{global,max}} = \frac{2ee_0}{(1 + ee_0)}
\]  

(4.5)

The maximal yield of all the other operating points decreases from \( Y_{\text{global,max}} \) to 0 depending on the enantiomeric excess of the eutectic liquid phase at \( T_{\text{final}} \) and corresponds only to a local maximum. The set of operating points can therefore be divided in two classes depending on the maximal yield possible. Therefore the operating line passing through the liquid phase of the ternary eutectic equilibrium separates
the two classes of operating points (Figure 4.9). Operating points on or below this line (green region in the same figure) allow for chiral resolution processes attaining the global maximal yield.

For a specific operating point, any final temperature between $T_{\text{initial}}$ and the optimal final temperature yields an equilibrium involving crystals of the target-enantiomer and a liquid phase an enantiomeric excess larger than zero. Hence, for these final temperatures chiral resolution is feasible but the yield is not maximal. In case final temperatures below the optimal final temperature are chosen, the operating point lies in a three phase region where crystals of either the counter-enantiomer
or the solvent become thermodynamically stable and might crystallize, thus leading to a loss of performance of the chiral resolution process. Thus, for any value of $T_{\text{initial}}$, the final temperature that maximizes the yield represents always the lowest final temperature that allows for chiral resolution.

**Design criteria for an ideal conglomerate forming system of type I**

For the system of type I discussed in Section 4.1.1, Figure 4.10(a) and Figure 4.10(b) show the isothermal ternary phase diagrams at two operating temperatures for two chiral resolutions both starting from a feed solution with $\text{ee}_0 = 50\%$ and leading to maximal yield.

The operating point shown in Figure 4.10(a) has a higher solute concentration than the one shown in Figure 4.10(b). As crystallization is started from a saturated solution, both operating points lie on the (blue) solubility isotherms at the initial temperature of crystallization. If a clear solution, whose composition corresponds to the operating point of Figure 4.10(a), is cooled down to the temperature represented by the green solubility isotherms, an equilibrium is obtained between crystals of the target-enantiomer and a racemic liquid phase (green dot in the same figure), which has the lowest possible enrichment. This operating point therefore allows reaching the global maximal yield. If reported in the liquidus projection of Figure 4.9, the operating point would lie inside the green region and its operating line would cross the monovariant curve through racemic liquid phases.
Figure 4.10: Isothermal ternary phase diagrams at $T_{\text{initial}}$ and $T_{\text{final}}$ for two chiral resolution processes starting from the same ee$_0$-value for the ideal conglomerate forming system of type I presented in Section 4.1.1: (a) case where the global maximal yield is obtained; (b) case where only the local maximal yield is obtained. The ternary phase diagram in sub-Figure (b) refers only to the upper part of the complete ternary phase diagram (see insert). The blue lines define the isothermal ternary phase diagram at $T_{\text{initial}}$, while the green lines the one at $T_{\text{final}}$. The circles indicate the composition of the liquid phases at equilibrium at the two operating temperatures. The light-blue lines within the triangle represent the operating lines, the yellow lines represent the lines at constant ee$_0$. 
For the operating point of Figure 4.10(b) however, no final temperature exists, which allows reaching an equilibrium involving a racemic liquid phase. The eutectic liquid phase (green dot in the same figure), which maximizes the yield arises from the intersection between the liquidus surfaces of the target-enantiomer and of the solvent. The operating point of Figure 4.10(b) therefore allows reaching the local maximal yield only. In the liquidus projection of Figure 4.9, the operating point is part of the magenta region and its operating line crosses the monovariant curve through non-racemic liquid phases.

The determination of optimal $T_{\text{initial}}$- and $T_{\text{final}}$-values can be repeated for all operating points at constant $\text{ee}_0$ resulting in a set of pairs of optimal operating temperatures. This set can be split in two subsets, i.e. those operating points reaching the global maximal yield and the others. Plotting the points with optimal operating temperatures as coordinates in the $T_{\text{final}}$ vs. $T_{\text{initial}}$-plane, that will be called operating plane in the following, two curves are obtained as shown in Figure 4.10(a): the solid line represents operating temperatures yielding the global maximal yield, whereas the yield of points with operating temperatures on the dashed line correspond only to the local maximum. At the lowest initial temperature, the operating point is of eutectic composition. In this case $T_{\text{initial}}$ and $T_{\text{final}}$ are equal and define a point on the diagonal of the operating plane.

Along the solid line in the operating plane, the yield is constant but the solvent mass fraction increases with decreasing initial and final temperatures, as the saturation temperature decreases with increasing solvent mass fraction. Along the dashed line, the yield decreases while the solvent mass fraction increases with decreasing $T_{\text{initial}}$. The two monovariant curves in the liquidus projection consisting of the liquid phases that are at equilibrium at the optimal final temperatures meet at the
point corresponding to the liquid phase of the ternary eutectic equilibrium. Hence, the two curves in the operating plane containing optimal operating temperatures have a common point at the final temperature corresponding to the ternary eutectic temperature $T_{\text{eut},\text{solv} - R - S}$, which is the lowest possible final temperature for crystallization.

The pairs of $T_{\text{initial}}$- and $T_{\text{final}}$-values for a specific $ee_0$ span an area in the operating plane where crystallization is feasible. The colored areas in Figure 4.11 indicate the area spanned by the sets of suitable operating temperatures for an initial enantiomeric excess of 50%. The solid and the dashed lines correspond to the curves of optimal operating temperatures shown in Figure 4.10(a). As $T_{\text{final}}$-values above the optimal final temperature lead to solid-liquid-equilibria involving crystals of the target-enantiomer only, the points within the blue region are also suitable for chiral resolution, but the larger the horizontal distance from the solid and the dashed line, the smaller the yield. On the other hand, final temperatures below the optimal value are unsuitable for chiral resolution. The solid line separates the region suitable for chiral resolution from the unsuitable region where crystals of the counter-enantiomer form (yellow region), while the dashed line separates it from a second unsuitable region where crystals of the solvent form (red region).

The determination of the optimal operating conditions and, consequently, of the different regions in the operating plane can be repeated for all $ee_0$-values. Figure 4.9 indicates that the classification of operating points based on the maximal possible yield is independent of $ee_0$. Considering operating points on the same operating line, i.e. operating points with the same optimal $T_{\text{final}}$-value but with different $ee_0$, the higher $ee_0$, the higher the solute concentration hence also the initial temperature. Therefore the optimal operating curves defined by the pairs of operating temperatures giving the global and the local maximal
4.3 Feasible and optimal design: criteria and operating diagrams

Figure 4.11: $T_{\text{final}}$ vs. $T_{\text{initial}}$-diagram for the ideal conglomerate forming system of type I of Section 4.1.1 for an initial enantiomeric excess of 50%. The three colored areas correspond to the area spanned by the sets of $T_{\text{final}}$ and $T_{\text{initial}}$ that allow for crystallization. The solid line contains pairs of operating temperature that allow obtaining the global maximal yield, whereas the dashed line contains pairs of operating temperatures that allow obtaining the local maximal yield only.

Yield shift to higher initial temperatures with increasing $\text{ee}_0$. The two curves of optimal operating temperatures for different $\text{ee}_0$-values are shown in Figure 4.12. The range of final temperatures that leads to the global maximal yield coincides with the range of thermodynamic stability of the solid-solid-liquid equilibrium involving the two enantiopure crystals, i.e. from $T_{\text{eut,solv}} - R - S$ to $T_{\text{eut},R - S}$, and is independent of $\text{ee}_0$. Moreover, for any $\text{ee}_0$-value the two optimal operating curves divide the area of suitable operating conditions for crystallization (colored areas in
Figure 4.11) in three different regions, namely one that is suitable for chiral resolution and two that are not.

The operating diagrams for different $\text{ee}_0$-values shown in Figure 4.12 have to be interpreted as completed by their information about operating regions as shown in Figure 4.11 for one specific $\text{ee}_0$-value. Thus, Figure 4.12 provides a complete picture about feasible and optimal conditions for chiral resolution, which are based on the phase diagram.

Figure 4.12: Curves representing pairs of optimal operating temperatures for the ideal conglomerate forming system of type I presented in Section 4.1.1 for different initial enantiomeric enrichments. The solid lines contain pairs of operating temperatures that allow obtaining the global maximal yield, whereas the dashed lines contain pairs of operating temperatures that allow obtaining the local maximal yield only. For each $\text{ee}_0$, the region delimited by the bisecting line, the solid, the dashed and the dotted lines contain pairs of operating temperatures that are suitable for chiral resolution.
4.3 Feasible and optimal design: criteria and operating diagrams

4.3.2 Conglomerate forming systems exhibiting oiling out

Determination of operating points for crystallization

In the ternary phase diagrams of conglomerate forming systems exhibiting oiling out (see Section 4.1.2 and Figure 4.13), for each enantiomer two liquidus surfaces are present, which are separated from each other by the surface corresponding to the liquid-liquid phase equilibria. As crystallization processes are started from saturated solutions, the portions of the two liquidus surfaces belonging to the target-enantiomer that are thermodynamically stable define the set of operating points that are suitable for crystallization. The upper liquidus surface is in all cases delimited by its intersections with the solute rich part of the liquid-liquid equilibrium surface and by the upper liquidus surface of the counter-enantiomer, while the lower liquidus surface is delimited by its intersection with the solute lean part of the liquid-liquid equilibrium surface, the liquidus surface of the solvent and the lower liquidus surface of the counter-enantiomer.

The liquidus projection of these systems, schematically represented in Figure 4.13, contains eight monovariant curves. The four blue curves describe the compositions of the liquid phases involved in monovariant eutectic equilibria, while the four green curves describe the compositions of the two liquid phases involved in monovariant monotectic equilibria. Due to the lack of enantioselectivity of the solvent, points lying on the monovariant monotectic curves having equal enantiomeric excess are at equilibrium, i.e. they are connected by straight tie-lines that go through the solvent vertex. The three monovariant eutectic curves on the border the lower liquidus surfaces connect the liquid phases of the two binary eutectic equilibria involving the solvent and the solute lean liquid
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Figure 4.13: Schematical liquidus projection of a conglomerate forming system exhibiting oiling out as discussed in Section 4.1.2. The four blue curves represent monovariant eutectic curves. The four green curves represent monovariant monotectic curves. The pink areas show the set of operating points that are suitable for crystallization.

Phase of the ternary monotectic equilibrium with the liquid phase of the ternary eutectic equilibrium. The four monovariant monotectic curves connect the two liquid phases of the two binary monotectic equilibria with the liquid phases of the ternary monotectic equilibrium. Finally, the monovariant eutectic curve separating the two upper liquidus surfaces connects the liquid phase of the binary eutectic equilibrium with the solute rich liquid phase of the ternary monotectic equilibrium.

The two pink regions in the liquidus projection shown in Figure 4.13
represent the operating points that are feasible for crystallization in the case where the $R$-enantiomer is the target enantiomer.

**Determination of operating temperatures for crystallization**

Also for systems exhibiting oiling out, the temperatures required to saturate ternary mixtures decrease with decreasing initial enantiomeric excess and solute concentration. This can be demonstrated by comparing the temperatures at the four corners of the two liquidus surfaces of the target-enantiomer. On the upper liquidus surface, $T_{m,R}$ is larger than both $T_{eut,R−S}$ and $T_{mon,L−R}$, whereas the latter two temperatures are larger than $T_{mon,L−R−S}$. On the lower liquidus surface, $T_{mon,L−R}$ is larger than both $T_{mon,L−R−S}$ and $T_{eut,solv−R}$, which are in turn larger than $T_{eut,solv−R−S}$.

The highest $T_{initial}$-value for a set of operating points at constant initial enantiomeric excess $ee_0$ decreases from $T_{m,R}$ to $T_{eut,R−S}$ when decreasing $ee_0$ from 100% to 0%. For any $ee_0$-value, the most diluted operating point on the upper liquidus surface and the most concentrated operating point on the lower liquidus surface also belong to the surface corresponding to the liquid-liquid equilibria. As the tie-lines describing liquid-liquid equilibria connect liquid phases with the same enantiomeric excess, the two liquid phases are part of the same liquid-liquid equilibrium. Hence, the lowest $T_{initial}$-value for operating points lying on the upper liquidus surface is equal to the highest $T_{initial}$-value for operating points lying on the lower liquidus surface and varies from $T_{mon,L−R}$ at $ee_0 = 100\%$ to $T_{mon,L−R−S}$ at $ee_0 = 0\%$. Finally, the lowest $T_{initial}$-value, required to saturate a mixture corresponding to the most diluted operating point with a given $ee_0$, decreases when decreasing $ee_0$ from 100% to 0%, namely from $T_{eut,solv−R}$ to $T_{eut,solv−R−S}$.
The set of possible final temperatures for each operating point ranges from its saturation temperature, i.e. $T_{\text{initial}}$, to the temperature of the ternary eutectic equilibrium $T_{\text{eut},\text{solv}-R-S}$.

**Determination of feasible operating temperatures for chiral resolution**

After determining the set of operating points, the final temperature that maximizes the yield for each of them can be determined. In processes with operating points lying on the upper liquidus surface at $T_{\text{initial}}$, the liquid phases at equilibrium at the optimal final temperatures can have either eutectic or monotectic composition. Liquid phases of eutectic composition are racemic, as they arise from intersections between the two upper liquidus surfaces of the pure enantiomers. The liquid phases of monotectic composition vary from racemic to enantiopure composition, as they are at the intersection between the solute rich part of the liquid-liquid equilibrium surface and the upper liquidus surface of the target-enantiomer.

The liquid phases that can be obtained at the optimal final temperatures for operating points lying on the lower liquidus surface at $T_{\text{initial}}$ depend on the steepness and on the curvature of the monovariant monotectic curve delimiting the lower liquidus surface. Figure 4.14(a) shows the case where no monotectic liquid phase exists that maximizes the yield of any operating point.

Thus, the possible liquid phases are of eutectic composition and are racemic if the liquid phases belong to a monovariant eutectic equilibrium involving the two enantiopure crystals, whereas they vary between racemic and enantiopure composition when the liquid phase is part of a monovariant equilibrium involving crystals of the target-enantiomer.
Figure 4.14: Liquidus projections of the ternary phase diagram of two conglomerate forming systems exhibiting oiling out as discussed in Section 4.1.2. (a) no monotectic liquid phase maximizes the yield of any operating points lying on the lower liquidus surface at $T_{\text{initial}}$. (b) monotectic liquid phases maximize the yield for a limited number of operating points lying on the lower liquidus surface at $T_{\text{initial}}$. In both figures, operating points in the green regions allow obtaining the global maximal yield, while the ones in the magenta regions allow obtaining the local maximal yield only. $ee^*$ is the largest initial enantiomeric excess that allows obtaining the global maximal yield independent on which liquidus surfaces the operating point lies at $T_{\text{initial}}$. $ee'$ is the enantiomeric excess of the monotectic liquid phase with the highest enantiomeric excess that maximizes the yield.

and of the solvent. Figure 4.14(b) shows the case where for a limited number of operating points the yield is maximized when an equilibrium involving a monotectic liquid phase is obtained. In this case the liquid phases at the optimal final temperatures can be either eutectic or monotectic, whereby the monotectic liquid phases vary from $ee'$ to 0% ($ee'$ is
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the enantiomeric excess of the intersection point between the monotectic curve and the operating line passing through the solute-lean liquid phase of the ternary monotectic equilibrium).

Hence, operating points on both the upper and the lower liquidus surface exist that allow obtaining the global maximal yield. From this it follows that the set of operating points of each liquidus surface can be divided into two classes based on the maximal yield possible, namely whether it corresponds to the global maximum (green regions in Figure 4.14(a) and Figure 4.14(b) including the lines delimiting them) or to the local maximum (magenta regions).

The operating line passing through the solute-rich liquid phase of the ternary monotectic equilibrium divides the set of operating points lying on the upper liquidus surface at any $T_{\text{initial}}$-level in two parts. In the liquidus projection shown in Figure 4.14(a), the operating line passing through the liquid phase of the ternary eutectic equilibrium divides the set of operating points lying on the lower liquidus surface at any $T_{\text{initial}}$-value also in two parts. In the liquidus projection of Figure 4.14(b), the two operating lines passing through the liquid phase of the ternary eutectic equilibrium and through the solute lean liquid phase of the ternary monotectic equilibrium, respectively, divide the two classes of operating points lying on the lower liquidus surface.

For initial enantiomeric excesses lower than $ee^*$, the global maximal yield can be reached independently of which liquidus surface the operating point lies at $T_{\text{initial}}$, whereas for initial enantiomeric excesses larger than $ee^*$, the global maximal yield can only be reached for operating points lying on the upper liquidus surface.

Independent of the composition of the operating points, a final temperature comprised in the range between $T_{\text{initial}}$ and the optimal final
temperature allows for chiral resolution, since in this case an equilibrium is reached involving enantiopure crystals of the target-enantiomer and a liquid phase with an enantiomeric excess larger than the corresponding eutectic or monotectic composition. At any final temperature below the optimal final temperature, the operating points lie in a three-phase equilibrium where either a second liquid phase or crystals of either the counter-enantiomer or of the solvent become thermodynamically stable and might crystallize, thus leading to a loss of performance of the chiral resolution process. As in the case of simple conglomerate forming systems, for all operating points the lowest final temperature possible for chiral resolution corresponds to their optimal final temperature.

**Design criteria for a conglomerate forming system exhibiting oiling out of type I**

We are considering a conglomerate forming system of type I, more specifically one whose liquidus projection corresponds to that shown in Figure 4.14(a). Let us consider operating points, whose enantiomeric excesses are equal and smaller than $ee^*$. According to 4.14(a), the set of possible operating points can be split in four different subsets, based on which liquidus surface the operating point at $T_{\text{initial}}$ lies and based on whether it allows reaching the global maximal yield or not. In Figure 4.15(a) to Figure 4.16(b) one operating point out of each subset is considered. The two operating points in Figure 4.15(a) and Figure 4.15(b) lie on the lower liquidus surface at $T_{\text{initial}}$ (right yellow liquidus surface in Figure 4.13). The operating point in Figure 4.15(a) allows reaching the global maximal yield and is therefore element of the upper green surface in the liquidus projection shown in Figure 4.14(a), while the one in Figure 4.15(b) allows reaching the local maximal yield only and thus belongs to the upper magenta surface in Figure 4.14(a).
Figure 4.15: Isothermal ternary phase diagrams at $T_{\text{initial}}$ (blue lines) and $T_{\text{final}}$ (green lines) for two chiral resolution processes at constant $\text{ee}_0$ for a hypothetical conglomerate forming system exhibiting oiling out of type I, where $T_{\text{eut,solv}-\text{R}} < T_{\text{mon,L-R-S}}$ and $T_{\text{uc,R-S}}, T_{\text{uc,R}} > T_{\text{m,R}}$. $\text{ee}_0$ is the same for all operating points and is larger than $\text{ee}^*$. Furthermore, no monotectic liquid phase is obtained at any optimal final temperature of operating points lying on the lower liquidus surface. The operating points in case (a) and (b) lie on the lower liquidus surface at $T_{\text{initial}}$ at $T_{\text{initial}}$. In case (a), the global maximal yield is reached. The circles indicate the composition of the liquid phase at equilibrium at the two operating temperatures. The ternary phase diagram in sub-Figure (b) refers only to the upper part of the complete ternary phase diagram (see insert). The light-blue lines within the triangle represent the operating lines, the yellow lines represent the lines at constant $\text{ee}_0$. 

\[ T_{\text{initial}} \]

\[ T_{\text{final}} \]
4.3 Feasible and optimal design: criteria and operating diagrams

Figure 4.16: Isothermal ternary phase diagrams at \( T_{\text{initial}} \) (blue lines) and \( T_{\text{final}} \) (green lines) for two chiral resolution processes at constant ee\(_0\) for a hypothetical conglomerate forming system exhibiting oiling out of type I, where \( T_{\text{eut,solv}} < T_{\text{mon,L-R-S}} < T_{\text{uc,R-S}} \). Furthermore, no monotectic liquid phase is obtained at any optimal final temperature of operating points lying on the lower liquidus surface. The circles indicate the composition of the liquid phase at equilibrium at the two operating temperatures. The light-blue lines within the triangle represent the operating lines, the yellow lines represent the lines at constant ee\(_0\).
The two operating points shown in Figure 4.16(a) and Figure 4.16(b) lie on the upper liquidus surfaces at $T_{\text{initial}}$ (right orange surface in Figure 4.13). Only the operating point in Figure 4.16(a) allows reaching the global maximal yield and is element of the lower green surface in Figure 4.14(a), while the one in Figure 4.16(a) belongs to the lower magenta region of the same figure. The optimal pairs of $T_{\text{initial}}$- and $T_{\text{final}}$-values for each operating point at constant ee$_0$ can be determined, yielding four subsets of pairs of optimal operating temperatures.

In the operating plane, the four subsets of pairs of $T_{\text{final}}$- and $T_{\text{initial}}$-values maximizing the yield define points belonging to four curves. The two solid curves represent the pairs of operating temperatures giving the global maximal yield, whereas the two dashed curves represent pairs of operating temperatures leading to the local maximal yield. The most diluted operating points on the upper and on the lower liquidus surfaces have monotectic and eutectic composition, respectively. Hence, the optimal temperatures of these two operating points are equal and lie on the diagonal of the operating plane.

As the two monovariant eutectic curves delimiting the lower liquidus surface meet at the point corresponding to the liquid phase of the ternary eutectic equilibrium, the two curves of operating points lying on the lower liquidus surface at $T_{\text{initial}}$ have one common point at $T_{\text{eut,solv}−R−S}$. The other two curves of optimal operating temperatures have a common point at $T_{\text{mon,L−R−S}}$, as the monovariant monotectic and eutectic curves delimiting the upper liquidus surface meet at the point corresponding to the solute-rich liquid phase of the ternary monotectic equilibrium. The temperatures $T_{\text{eut,solv}−R−S}$ and $T_{\text{mon,L−R−S}}$ correspond to the lowest optimal final temperatures for operating points lying on the lower and on the upper liquidus surface, respectively.

The colored domains in Figure 4.17 show the area spanned by pairs of
4.3 Feasible and optimal design: criteria and operating diagrams

Figure 4.17: $T_{\text{final}}$ vs. $T_{\text{initial}}$-plane for an hypothetical conglomerate forming system exhibiting oiling out of type I. The liquidus projection qualitatively corresponds to the one shown in Figure 4.14(a) and $\text{ee}_0$ is smaller than $\text{ee}^*$, thus the diagram exhibits four curves containing optimal operating temperatures. The solid lines pass through pairs of operating temperatures giving the global maximal yield, the dashed line contain operating temperature that allow obtaining the local maximal yield only. The five colored areas correspond to the area spanned by the sets of operating temperatures that allow for crystallization.

$T_{\text{final}}$- and $T_{\text{initial}}$-values that allow for crystallization for a specific $\text{ee}_0$. The solid and the dotted lines represent the pairs of operating temperatures maximizing the yield already shown in Figure 4.16. As any final temperature equal or above the optimal value allows selectively crystallizing the target-enantiomer, the two blue regions including the lines delimiting them contain operating temperatures that are suitable for chiral resolution. Pairs of operating temperatures within the other
three regions are unsuitable for chiral resolution as a third undesired phase becomes thermodynamically stable and might crystallize. If operating temperatures within the green region are chosen, the crystals of the target-enantiomer are at equilibrium with two liquid phases at $T_{\text{final}}$. Operating temperatures within the yellow and the red region yield solid-solid-liquid equilibria involving crystals of the counter-enantiomer and of the solvent, respectively, as the second solid phase.

The two yellow regions in Figure 4.17 are separated by the blue vertical line at the final temperature equal to the ternary monotectic temperature, $T_{\text{mon},L-R-S}$. At any final temperatures above $T_{\text{mon},L-R-S}$, the liquid phase, which is at equilibrium with crystals of the two enantiomers, is racemic and is part of the two upper liquidus surfaces of the two enantiomers. On the blue vertical line, a ternary monotectic equilibrium consisting of two racemic liquid phases and crystals of the two enantiomers is obtained (Figure 4.6(d)). At final temperatures below $T_{\text{mon},L-R-S}$, the racemic liquid phase, which is at equilibrium with crystals of the two enantiomers, is part of the two lower liquidus surfaces of the two enantiomers. The green region in Figure 4.17 is delimited by the blue vertical line representing the ternary monotectic equilibrium. Any operating point leading to a liquid-liquid-solid equilibrium above $T_{\text{mon},L-R-S}$, will yield a liquid-solid-solid equilibrium involving crystals of the two enantiomers at temperatures below $T_{\text{mon},L-R-S}$. The transition from a liquid-liquid-solid equilibrium to a liquid-solid-solid equilibrium induced by lowering the temperature occurs through a ternary monotectic reaction.

The determination of the five regions in the operating plane can be repeated for all ee$_0$-values. Figure 4.18 shows the curves bounding these regions for different ee$_0$-values. Analogous to simple conglomerate forming systems, the curves corresponding to optimal temperatures are shifted
to higher initial temperatures when increasing the initial enantiomeric excess. For all $ee_0$, two regions that are suitable for chiral resolution are obtained.

![Curves representing pairs of optimal temperatures for an hypothetical conglomerate forming system exhibiting oiling out of type I for different initial enantiomeric excesses. No equilibria involving a monotectic liquid phase exist that maximize the yield of operating points lying on the lower liquidus surface. The solid lines represent pairs of operating temperature that allow obtaining the global maximal yield. The dashed lines contains pairs of operating temperatures that allow obtaining the local maximal yield. For each $ee_0$, the two regions delimited by the bisecting line, the solid, the dashed and the dotted lines contain operating temperatures that are suitable for chiral resolution.](image)

**Figure 4.18:** Curves representing pairs of optimal temperatures for an hypothetical conglomerate forming system exhibiting oiling out of type I for different initial enantiomeric excesses. No equilibria involving a monotectic liquid phase exist that maximize the yield of operating points lying on the lower liquidus surface. The solid lines represent pairs of operating temperature that allow obtaining the global maximal yield. The dashed lines contains pairs of operating temperatures that allow obtaining the local maximal yield. For each $ee_0$, the two regions delimited by the bisecting line, the solid, the dashed and the dotted lines contain operating temperatures that are suitable for chiral resolution.

At least one operating point for each $ee_0$-value lying on the upper liquidus surface at $T_{\text{initial}}$ allows obtaining the global maximal yield. Hence, the curve containing operating temperatures giving the global maximal yield
is present for all $ee_0$-values. On the other hand, for operating points on the lower liquidus surface the global maximal yield can only be reached for operating points with an initial enantiomeric excess below $ee^*$. The highest initial enantiomeric excess considered in Figure 4.18 is larger than $ee^*$, therefore no curve of operating temperatures giving the global maximal yield exists for an operating point lying on the lower liquidus surface at $T_{\text{initial}}$.

Once again Figure 4.18 provides a complete characterization of feasible and optimal operating temperatures to achieve chiral resolution through crystallization, whatever the initial enantiomeric excess.

### 4.4 Discussion and conclusions

#### 4.4.1 Process design and generalization

The outcome of the process design for the two systems discussed in Section 4.3.1 and Section 4.3.2 can be generalized to all types of conglomerate forming systems.

For simple conglomerate forming systems, the possible operating points lie on the single liquidus surface associated to the target-enantiomer, hence, they belong to a single connected region in the liquidus projection (pink region in Figure 4.8). Independent of the type of system, the region is delimited by a monovariant eutectic curve featuring racemic liquid phases, which arises from the intersection among the two liquidus surfaces associated to the two enantiomers. The operating points, whose operating line crosses this curve, lead to the global maximal yield. Consequently, the area of operating points in the liquidus projection can be divided into two adjoining areas by the operating line passing through
the liquid phase belonging to the ternary eutectic equilibrium, i.e. the most diluted eutectic liquid phase of racemic composition (Figure 4.9). Any operating point on or below this line leads to the global maximal yield, whereas the ones above this line allow only for the local maximal yield. Hence, for a fixed $ee_0$, the optimal operating temperatures of the two classes of operating points yield two curves in the operating plane. As the two areas of operating points are adjacent, the two curves have a common point with coordinates corresponding to the optimal temperatures of the point located on the operating line dividing the two areas. The optimal final temperature of this point is always $T_{\text{eut,solv}} - R - S$ and corresponds to the lowest final temperature possible, whereas its optimal initial temperature is dependent of $ee_0$.

When considering conglomerate forming systems exhibiting oiling out, the possible operating points lie on the two liquidus surfaces that are associated to the target-enantiomer. In contrast to single conglomerate forming systems, the liquidus projection features two regions consisting of possible operating points (pink areas in Figure 4.13). Independent of the type of system, each area is delimited by a monovariant eutectic curve through racemic liquid phases. The two curves stem from the intersections among the two upper and the two lower liquid surfaces of the two enantiomers, respectively. Accordingly, each liquidus surface of the target-enantiomer exhibits operating points that lead to the global maximal yield. The complete set of operating points of each liquidus surface can therefore be divided into two classes based on the maximal yield (Figure 4.14(a) and Figure 4.14(b)).

The set of operating points on the upper liquidus surface is divided into two adjacent areas by the operating line through the solute rich liquid phase of the ternary monotectic equilibrium, which is the most diluted racemic liquid phase, and is located on the upper liquidus surface. Op-
erating points on or below this line lead to the global maximal yield, whereas the others lead to the local maximal yield. The optimal operating temperatures for a specific $ee_0$-value are therefore represented by two curves in the operating plane. Again the two regions of operating points are adjacent, thus the two curves have one common point corresponding to the optimal operating temperatures of the operating point lying on the operating line dividing the two areas. The optimal final temperature of this point is always $T_{\text{mon},L-R-S}$, whereas its optimal initial temperature depends on $ee_0$.

The area representing the set of operating points located on the lower liquidus surface is divided either into two or into three adjoining areas depending on the shape of the monovariant monotectic curve confining it.

In the case where no monotectic liquid phase allows maximizing the yield (Figure 4.14(a)), the two classes of operating points belong to two adjacent regions divided by the operating line passing through the liquid phase of the ternary eutectic equilibrium. As the area of operating points leading to the global maximal yield does not extend over the whole range of enantiomeric excesses, the global maximal yield is only obtained through operating points with an enantiomeric excess lower than $ee^*$ ($ee^*$ is defined as the enantiomeric excess of the intersection point among the operating line dividing the two regions and the projection of the monovariant monotectic curve confining the lower liquidus surface). Consequently, for $ee_0$-values below $ee^*$, the operating points of the lower liquidus surface yield two curves of optimal operating temperatures in the operating plane, which have one common point. However for $ee_0$-values above $ee^*$, no operating point located on the lower liquidus surface leads to the global maximal yield, thus the operating plane features only one curve, which represents the optimal operating temperatures leading to the local maximal yield.
In the case where monotectic liquid phases allow maximizing the yield, three different regions of operating points are obtained (Figure 4.14(b)). The region of operating points leading to the global maximal yield is adjacent to two areas representing operating points leading to the local maximal yield. Two operating lines divide the three regions, one passing through the liquid phase of the ternary eutectic equilibrium, the other through the solute lean liquid phase belonging to the ternary monotectic equilibrium. The yield of operating points, which are more diluted than those leading to the global maximal yield, is maximized by obtaining equilibria involving eutectic liquid phases, whereas the yield of those which are more concentrated is maximized obtaining equilibria involving monotectic liquid phases. For any ee₀-value below ee′, operating points at constant initial enantiomeric enrichment yield three curves in the operating plane, two of them leading to the local maximal yield (ee′ is defined as the enantiomeric excess of the point of intersection between the operating line through the solute lean liquid phase of the ternary monotectic curve and the projection of the monovariant monotectic curve confining the lower liquidus surface). The curve of operating temperatures leading to the global maximal yield has one point in common with each curve representing operating temperatures leading to the local maximal yield. Increasing the ee₀-value between ee′ and ee*, the operating points yield two curves, one curve through pairs of operating temperatures leading to the global maximal yield, the other through pairs of operating temperatures leading to the local maximum. Finally, for ee₀-values above ee*, the operating points yield only one curve in the operating plane representing optimal operating temperatures leading to the local maximal yield.

Independent of the type of system, the optimal final temperature for each operating point corresponds to the lowest final temperature that
allows for the selective crystallization of the target-enantiomer. Any final temperature below the optimal value will lead to the formation of an undesired phase. Therefore, the curves of optimal temperatures always delimit the region feasible for resolution from the unfeasible region.

The same methodology can also be applied to substances, which crystal- lize as a racemic compound. As the number of solid phases is increased by one, a new liquidus surface is introduced in the ternary phase dia- gram. The new liquidus surface intersects with the liquidus surfaces of the solvent and of the two enantiomers, and in the case of oiling out, also with the surface describing liquid-liquid phase equilibria. As temperatures exist, where solid-liquid equilibria involving crystals of a pure enantiomer are thermodynamically stable, the selective crystallization of the desired enantiomer from enriched solutions is possible. Analogous to the conglomerate forming systems, suitable operating points together with their pair of optimal operating temperatures can be determined. As the eutectic liquid phases maximizing the yield arise from the inter- section between the liquidus surface of the racemic compound and of the target-enantiomer, they are non-racemic and their enantiomeric excesses are generally dependent on temperature. Therefore, only one operating point out of the set of possible operating points at constant ee₀ will lead to the global maximal yield, whereas the others lead to a local maximal yield only.

4.4.2 Concluding remarks about practical imple- mentation

The design methodology presented here and based on the knowledge of the ternary phase diagram of the two enantiomers and the solvent allows determining for each initial enantiomeric excess a map of the operating
regions in the plane having as coordinates the initial and the final crystallization temperature. Such a map contains one or more (in the case of oiling out) regions where chiral resolution of the target-enantiomer can be achieved, and regions that are unfeasible in that respect.

Every region of chiral resolution is delimited by four lines, one of which consists of points when maximum yield is achieved. Each point along this optimal line corresponds to different initial and final temperature levels, hence different viscosity of the solution, different nucleation and growth rates, etc. High viscosity might make the post-processing difficult. High growth rates might facilitate the formation of agglomerates, hence of inclusions of the wrong enantiomer into crystals of the target-enantiomer. Temperature levels have of course also an impact not only on process costs, but also on possible thermal degradation of the chiral compound. As a consequence, the choice of the operating temperatures along the optimal line shall be based on a careful trade-off between process costs and product quality.

On the other hand, there are reasons to choose an operating point not exactly on the optimal line, but close to it within the region of chiral resolution. The optimal line depends on the phase diagram and on the initial enantiomeric excess. Any uncertainty on the phase diagram causes an uncertainty in the exact position of the optimal line in the operating plane. Unexpected changes in the performance of the upstream process might yield changes of the initial enantiomeric excess and as consequence a perturbation in the position of the optimal line. Accordingly any fluctuation in the operating temperatures might drive the operating point out of the optimal line even when this is known with the highest precision. In other words, operating points on the optimal line give the maximum yield at the cost of the minimum possible robustness, which is defined as the capacity of the system to withstand perturbations or un-
certainties. Robustness can be improved by moving the operating point from the optimal line to a location within the region of chiral resolution. In practice this can be obtained by choosing a specific initial temperature and then by cooling the suspension to a temperature a few degrees above the optimal final temperature.

Thus concluding, the design of a crystallization process to obtain pure crystals of the target-enantiomer from an enriched solution requires that an optimal trade-off between yield and robustness be found. The knowledge of the phase diagram allows for the determination of the operating regions in the operating plane spanned by initial and final temperature, both in the case where no oiling out occurs and in that when it does.
Chapter 5

Growth kinetics of 
S-mandelic acid in 
aqueous solutions in the 
presence of R-mandelic 
acid*

In this work, the effect of R-mandelic acid on the growth kinetics of 
S-mandelic acid in aqueous solutions is investigated. Isothermal seeded 
batch experiments are conducted inside the two phase region where crys-
tals of the S-enantiomer are at equilibrium with an enantiomerically en-

5. Growth kinetics of S-mandelic acid in aqueous solutions

Riched liquid phase. Crystal growth of S-mandelic acid is studied at three different temperature levels, i.e. at 15°C, 20°C and 25°C, and at three different levels of concentration of the R-enantiomer, i.e. at 0 g/g water, 0.0231 g/g water and 0.0393 g/g water. Perlberg et al. report a very narrow metastable zone width (MSZW) for secondary nucleation. The MSZW for secondary nucleation is however found to be dependent on the suspension density and on particle size. By decreasing the average particle size and by increasing the mass of seed crystal, the MSZW for secondary nucleation could be increased thus enabling the exploration of a wider range of supersaturations. The concentration profile during the batch experiment is monitored by ATR-FTIR, the growth parameters are estimated by solving a population balance model. R-mandelic acid is found to substantially lower the growth rate of S-mandelic acid. Using a semi-empirical, size-independent growth rate expression, the measured concentration profiles can be satisfactorily described by three parameters, two that are independent of the concentration of R-mandelic acid in solution and one which implicitly describes the change in the growth rate due to presence of R-mandelic acid. Moreover, the presence of the R-enantiomer is also found to have a negative impact on crystal purity.

5.1 Materials and Methods

5.1.1 Materials

Racemic mandelic acid and S-mandelic acid, both with a chemical purity of > 99%, were purchased from TCI Europe (Eschborn, Germany) and used as delivered. S-mandelic acid, the only solid species crystallized in this work, is reported to be isomorphic. The batch experiments were conducted in deionized water filtered (pore size 0.22 μm) and purified.
5.1 Materials and Methods

(conductivity $<$18 mΩ, total organic compounds $<$5 ppb) using a MilliQ Advantage A10 system (Millipore, Zug, Switzerland). The eluent for the HPLC analysis consisted of a ternary mixture of heptane with a purity of $>$ 99% (Sigma-Aldrich, Buchs, Switzerland), isopropanol with a purity of $>$ 99.8% (Scharlau, Sentmenat, Spain) and trifluoroacetic acid with a purity of $>$ 99.8% (Acros Organics, Geel, Belgium).

5.1.2 Characterization techniques

ATR-FTIR spectroscopy has been used to monitor in situ the cumulative concentration of the two enantiomers of mandelic acid in the course of the crystallization experiments. Due to the low penetration depth of the infrared beam, the ATR technique enables to exclusively measure the composition of the liquid phase even in the presence of crystals. Spectra were collected using a ReactIR 45m system (Mettler Toledo, Schwerzenbach, Switzerland) equipped with a 9.5mm x 1.5 m AgX Fiber Conduit DiComp immersion probe and a diamond ATR crystal. Spectra were recorded over a time interval of 30 s in the range 650-2800 cm$^{-1}$ with a resolution of 4 cm$^{-1}$ and were averaged over 128 scans.

A laboratory scale focused beam reflectance measurement device FBRM 600L from Lasentec (Redmond, WA, USA) is used to detect nucleation during a batch experiment, that manifests itself through a steep increase in the signal of the small chord lengths (1-12 μm).

The composition of the liquid phases sampled from solubility experiments as well as the crystal purity were determined by HPLC using Chiralcel AD-H (Daicel Chemical Industries, Osaka, Japan) as stationary phase and a mobile phase consisting of a 92:7.9:0.1 (v/v/v) heptane-isopropanol-trifluoroacetic acid mixture applying a flow rate of 1 ml/min.
Particle size distributions (PSD) were measured using a Multisizer 3 (Beckman Coulter, Nyon, Switzerland). Using the Coulter principle, the device measures the particle size in the range of 60-1000 µm. An aqueous solution saturated with S-mandelic acid was used as quench solution in the measurements.

Optical microscopy using a Axioplan microscope (Zeiss, Feldbach, Switzerland) was applied to characterize the produced crystals.

5.1.3 Solubility of the mandelic acid enantiomers in water

Specified, properly chosen ternary mixtures were prepared and equilibrated for at least 8 hours at constant temperature. After equilibration, the liquid phase was sampled with a syringe and filtered using a polytetrafluoroethylene HPLC-filter with a pore size of 0.2 µm. The composition of the liquid phase was determined by HPLC using the protocol described in the previous section.

5.1.4 Preparation of seed crystals

An aqueous solution with a concentration of 0.1 g/g water of S-mandelic acid was prepared in a 100 ml temperature controlled reactor equipped with an overhead stirrer (EasyMax, Mettler Toledo, Schwerzenbach, Switzerland) and kept at 45°C for at least 30 minutes to ensure complete dissolution of the crystals. Thereafter, nucleation was induced by setting the jacket temperature at 0°C. When a temperature of 2°C was reached inside the reactor, the suspension was filtered. The filter cake was washed with around 100 ml of ice-cold deionized water. Two populations of seed crystals were obtained by sieving the dried crystals in
the size range between 63 and 180 \(\mu m\) and in the size range between 355 and 500 \(\mu m\).

5.1.5 Experimental protocol for isothermal seeded batch experiments

All isothermal seeded batch experiments were performed in a jacketed 250 ml glass reactor equipped with a four-blade Teflon impeller with 45° inclined blades. Temperature control was guaranteed by a Ministat cc3 thermostat (Huber, Switzerland) and a Pt 100 temperature sensor. The stirring speed was set to 200 rpm in all experiments. The reactor was equipped with a FBRM probe when secondary nucleation during the crystallization process was studied, while it was equipped with an ATR-FTIR probe when experiments for the estimation of growth kinetics were carried out.

The solutions used in batch experiments consisted of a mixture of \(S\)-mandelic acid, \(RS\)-mandelic acid and deionized water that was prepared in a 250 ml bottle heated up to a temperature above 40°C and stirred for at least 30 minutes to ensure complete dissolution of the solid. The clear solution was poured in the reactor and cooled down to the operating temperature. The seed crystals were fed right above the liquid level with a paper funnel in order to ensure that all crystals entered the solution. At the end of the experiment, the suspension was filtered. The filter cake was washed with approximately 100 ml of ice-cold water. Prior to the purity analysis, the crystals were dried overnight.
5.1.6 ATR-FTIR calibration

A calibration model was built through a multivariate regression at each temperature level investigated. The calibration set was obtained by measuring spectra of aqueous mandelic acid solutions maintained at constant temperature. The solute concentrations were chosen so as to cover the entire concentration domain reached during the batch experiments carried out at the temperature level of the calibration model. In order to record spectra at undersaturated conditions or at only slightly supersaturated conditions, the solutions were prepared either using racemic mandelic acid, whose solubility exceeds the one of S-mandelic acid, or a mixture of the two enantiomers corresponding to the eutectic composition of the binary system (38%ee\textsuperscript{71}). The solutions were prepared as described in Section 5.1.5. After reaching the desired temperature, 24 spectra were recorded, whose averaged value served as input for the calibration model. In order to eliminate signal shifts, the first derivatives of the averaged spectra are taken using the Savitzky-Golay method,\textsuperscript{72} which calculates the first derivative at a point in the spectrum by taking the first derivative of an individual polynomial function fitted to a user-defined window width around the point. For the measured spectra, a polynomial of order two and a window width of three points is chosen.

The calibration model was built by a multivariate partial least squares regression with three latent variables using the fingerprint region from 1037 cm\textsuperscript{-1} to 1239 cm\textsuperscript{-1}, resulting in 55 variables. The average root-mean-square error of cross validation of the calibration models corresponded to 0.74% of the mean value of the solute concentrations.
ATR-FTIR spectroscopy is not able to discriminate between two enantiomers in solution. Hence, the recorded spectra yield the cumulative solute concentration of the two enantiomers of mandelic acid during the experiments. As all experiments are conducted in the two-phase region \( L + S_S \) (green region in Figure 5.1), where only crystals of the \( S \)-enantiomer are thermodynamically stable, the decrease in the cumulative concentration is only attributed to the crystallization of the \( S \)-enantiomer, i.e. the enantiomer that is in excess. The concentration profile of the \( S \)-enantiomer used for the estimation of the growth rate parameters is therefore obtained under the assumption that \( R \)-mandelic acid remains in solution by subtracting the concentration of the \( R \)-enantiomer at \( t = 0 \) from the concentration profile obtained from IR-spectroscopy (see Section 5.4.3 for a discussion of this point).

Figure 5.1: Schematic representation of an isothermal ternary phase diagram of a racemic compound forming system. The batch experiments are carried out in the green region, where crystal of the \( S \)-enantiomer are at equilibrium with a liquid phase.
5. Growth kinetics of $S$-mandelic acid in aqueous solutions

5.2 Population balance modeling

For a well-mixed batch reactor containing particles with a characteristic length $L$ the population balance equation (PBE) can be written as

$$\frac{\partial n}{\partial t} + \frac{\partial (Gn)}{\partial L} = B - D$$

(5.1)

where $n$ is the particle number density, $t$ is the time, $G$ is the growth rate, $B$ and $D$ are the birth and death term, respectively, which include nucleation, agglomeration and breakage. The experiments carried out in this work are designed such that nucleation, agglomeration and breakage occur at a negligible level, thus $B = D = 0$.

The concentration of the $S$-enantiomer in solution, $c_S$, can be obtained by solving together with the PBE also the material balance:

$$\frac{dc_S}{dt} = -\frac{3k_v \rho_S G}{m_{\text{water}}} \int_0^{\infty} L^2 ndL$$

(5.2)

where $k_v$ is the shape factor and $\rho_S$ is the density of crystals of $S$-mandelic acid. In this work, spheres have been assumed, i.e. $k_v = \pi/6$. The density of $S$-mandelic acid is $1.349 g/cm^3$. The initial and boundary conditions for the PBE are

$$c_S(0) = c_{S,0}$$

(5.3)

$$n(0, L) = n_0$$

(5.4)

$$n(t, 0) = 0$$

(5.5)

The mass balance and the population balance equation are simultaneously solved using the method of moments.\textsuperscript{73}
5.3 Growth rate expression

In this work, semi-empirical, size-independent growth rate functions are used to express the growth kinetics of $S$-mandelic in aqueous solutions. In a first stage, the concentration profile of each experiment is fitted individually using the temperature independent growth rate function that can be written as

$$G = k_1(S - 1)^k_2$$

(5.6)

with $k_1$ and $k_2$ as parameters. Then the concentration profiles of experiments carried out at different temperature levels are simultaneously fitted using the growth rate function

$$G = k_3\exp\left(-\frac{k_4}{T}\right)(S - 1)^k_5$$

(5.7)

with $k_3$, $k_4$ and $k_5$ as parameters. Using this expression, a change in the growth rate due to the presence of the counter-enantiomer is implicitly described by a change in the three model parameters.

The supersaturation $S$ in Equation 5.6 and 5.7 is defined as the ratio between the concentration of $S$-mandelic acid and its solubility, $c_{S,\text{sat}}$, which is not only dependent on temperature but also on the concentration of the counter-enantiomer in solution

$$S = \frac{c_S}{c_{S,\text{sat}}(T,c_R)}.$$  

(5.8)
5.4 Results and discussion

5.4.1 Solubility measurements

Isothermal seeded desupersaturation experiments were conducted at three different temperature levels, i.e. at 15°C, 20°C and 25°C, and at three different levels of concentration of the counter-enantiomer, i.e. at 0 g/g water, 0.0231 g/g water and 0.0393 g/g water. The nine required solubilities are shown in Table 5.1 and are compared with the literature data. As below 35°C the solubility isotherm can be approximated by straight lines, the missing solubility data from Lorenz et al. were obtained by linear interpolation.

The obtained solubilities agree well with the data from literature. Besides the least enriched point at 15°C, the deviation from the literature data is always below 5%. The solubility values obtained in this work are used in the following for the estimation of the growth kinetics.

5.4.2 Operating conditions without secondary nucleation

For the system mandelic acid/water, Perlberg et al. determined the metastable zone width (MSZW) for both primary and secondary nucleation. The MSZW for secondary nucleation, determined by applying the polythermal method proposed by Nyvlt et al. to suspensions containing a small number of large particles (>1 mm in size), was found to be very narrow. In isothermal experiments carried out in enantiopure solutions, the highest supersaturation possible is approximately 1.15. This outcome severely restricts the range of supersaturations that can be investigated, as the experiments have to be designed such that nucleation
5.4 Results and discussion

Table 5.1: Solubilities of the mandelic acid enantiomers in aqueous solutions required for the estimation of the growth kinetics. The second and the third column show the solubility obtained in this work, the last two columns refer to the solubility data of Lorenz et al.\textsuperscript{71}. The concentration are given in g/g water.

<table>
<thead>
<tr>
<th>$T$</th>
<th>$c_{R-MA}$</th>
<th>$c_{S-MA}$</th>
<th>$c_{R-MA}^{71}$</th>
<th>$c_{S-MA}^{71}$</th>
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<td>0.0799</td>
</tr>
<tr>
<td></td>
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</tr>
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<td>20$^\circ$C</td>
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<td>0.0917</td>
<td>0</td>
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</tr>
<tr>
<td></td>
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<td>0.0393</td>
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</tr>
<tr>
<td>25$^\circ$C</td>
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<td>0.1102</td>
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<tr>
<td></td>
<td>0.0230</td>
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</tr>
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<td>0.0399</td>
<td>0.1431</td>
<td>0.0393</td>
<td>0.1488</td>
</tr>
</tbody>
</table>

occurs at a negligible level. However, Kubota et al.\textsuperscript{67} found that the event of secondary nucleation is dependent on the size of the seed population and on the seed loading, defined as the ratio between the seed mass and the mass of grown crystals at the end of the experiment. In cooling crystallization experiments carried out applying a cubic cooling profile, for each average particle size of the seed population a critical seed loading exists above which secondary nucleation occurs at a negligible level. This is demonstrated by comparing the average size of the particles at the end of the experiment with the theoretical average particle size that would be obtained when supersaturation were depleted by growth only. Equal average particle sizes indicate that secondary nucleation occurred at a negligible level. The critical seed loading is found to decrease with decreasing particle size. The MSZW for secondary nucleation reported by Perlberg et al.\textsuperscript{66} accounts for the dependence of neither particle size nor seed loading; since the measurements are carried out at favourable
conditions for secondary nucleation, i.e. using large particles and low seed loadings, the measurements yield a rather conservative domain of supersaturation where no secondary nucleation occurs, i.e. a narrow MSZW.

In this work, we aimed on the one hand at experimentally verifying the effect of particle size and seed loading on the occurrence of secondary nucleation and on the other hand at finding an average particle size and a seed loading that enables conducting seeded isothermal batch experiments in a wide range of supersaturations under conditions where secondary nucleation occurs at a negligible level. This is accomplished by conducting seeded isothermal batch experiments with two different seed populations and with different seed loadings. The intention is thereby to investigate only one operating condition, where secondary nucleation is deemed to be more likely to occur and to assume that the outcome is valid for all other operating conditions investigated. The occurrence of secondary nucleation is verified by monitoring the evolution of the FBRM-signal at small chord lengths and by characterizing the crystals at the end of the experiments by light microscopy. As the MSZW for secondary nucleation is found to be the narrowest when the solution is enantiopure, experiments were started from an enantiopure solution at 20°C with a supersaturation of 1.22, which according to Perlberg et al. is located outside the MSZ for secondary, but inside the MSZ for primary nucleation.

When using seed crystals in the sieve range from 355 μm to 500 μm (Figure 5.2.a), secondary nucleation occurs at seed loadings equal to or below 20 wt% of the expected yield. This can be demonstrated by the large increase of the FBRM-signal at small chord lengths (red and blue profiles in Figure 5.3.a) and by the presence of small particles in the light microscope pictures (Figure 5.4.a and 5.4.b). In accordance to Kubota
5.4 Results and discussion

et al.\textsuperscript{67} secondary nucleation can be suppressed by increasing the seed loading. In fact, with a seed loading of 40 wt\% of the expected yield, secondary nucleation is found to not occur at a significant extent, as the FBRM signal stabilizes at a low level (green profile in Figure 5.3.a) and no small particles can be identified in the light microscope pictures (Figure 5.4.c).

Figure 5.2: Seed crystals used in the batch experiments carried out to detect operating condition where no secondary nucleation occurs. (a) seed crystals in the sieve fraction from 355 μm to 500 μm. (b) seed crystals in the sieve fraction from 63 μm to 180 μm. The black bar correspond to 200 μm.

When using seed crystals in the sieve range from 63 μm to 180 μm (Figure 5.2.b), the critical seed loading is expected to decrease. In fact, a seed loading of 10 wt\% is enough to suppress secondary nucleation, as demonstrated by the constant FBRM signal (red and green profiles in Figure 5.3.b) and by the lack of small particles in the light microscope pictures (Figure 5.4.e and 5.4.f). Vigorous secondary nucleation is however encountered when the seed loading is lowered to 1 wt\% of the expected yield, as demonstrated by a high number of counts in the small chord lengths of the FBRM signal (blue profile in Figure 5.3.b) and by the presence of small particles in the light microscope pictures (Figure 5.4.d).
5. Growth kinetics of S-mandelic acid in aqueous solutions

Figure 5.3: FBRM-signals in the range of chord lengths from 1 to 12 μm. In Figure (a), secondary nucleation occurs at the two lowest seed loadings, while in Figure (b), secondary nucleation occurs only at the lowest seed loading.

This result on the one hand confirms the occurrence of secondary nucleation when crystallizing S-mandelic acid from aqueous solutions and on the other hand demonstrates that secondary nucleation can be suppressed by an appropriate choice of seed particle size and seed loading. When seed crystals in the sieve fraction between 63 μm and 180 μm are used, any seed loading above 10 wt% enables suppressing the occurrence of secondary nucleation.
5.4 Results and discussion

(a) large sieve fraction; seed mass: ~5 wt% of exp.yield

(b) large sieve fraction; seed mass: ~20 wt% of exp.yield

(c) large sieve fraction; seed mass: ~40 wt% of exp.yield

(d) small sieve fraction; seed mass: ~1 wt% of exp.yield

(e) small sieve fraction; seed mass: ~10 wt% of exp.yield

(f) small sieve fraction; seed mass: ~20 wt% of exp.yield

Figure 5.4: Light microscope pictures of crystals obtained in experiments carried out to detect operating condition where no secondary nucleation occurs. Substantial secondary nucleation occurred using large seeds when using a seed loading equal to or below 20 wt% of the expected yield (a) and (b) and with small seeds when using a seed loading of 1 wt% of the expected yield (d). No secondary nucleation is observed with large seeds when the seed loading is 40 wt% (c) and with small seeds when the seed loading is equal to or above 10 wt% of the expected yield (e) and (f). The black bar in the four pictures corresponds to 200 μm.
5.4.3 Estimation of growth parameters

Characterization of the seed crystals

Five different batches of seed crystals were produced in this work. Figure 5.5 shows their normalized volume weighted particle size distributions. The small deviations among the batches evidence the good reproducibility of the experimental protocol for the production of seed crystals. The moments of the depicted particle size distributions were used as initial conditions of the population balance equation model.

![Figure 5.5: Normalized volume weighted particle size distributions of the five batches used in the seeded isothermal batch experiments for the estimation of growth rates](image)

Estimation of growth rate parameters

Table 5.2 gives an overview of the 25 isothermal seeded desupersaturation experiments carried out in this work. Prior to the addition of seed
Table 5.2: Overview of the experiments used for the estimation of the growth rates. Second last column: coefficients of determination obtained when all three parameters of Equation 5.7 are assumed to be dependent on the concentration of \( R \)-mandelic acid. Last column: coefficients of determination obtained when only the \( k_5 \)-value in Equation 5.7 is assumed to depend on the concentration of \( R \)-mandelic acid.

<table>
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<tr>
<th>( c_{R-MA} ) [g/g water]</th>
<th>( T ) [°C]</th>
<th>( S_0 ) [-]</th>
<th>( c_{end} ) [g/g water]</th>
<th>( m_{seeds/m_{yield,th.}} )</th>
<th>( m_{water} ) [g]</th>
<th>( R^2 ) (9 param.) [-]</th>
<th>( R^2 ) (5 param.) [-]</th>
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<td>0.14</td>
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<td>0.875</td>
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<td>0.519</td>
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<td>139.1</td>
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<td>0.17</td>
<td>150.0</td>
<td>0.991</td>
<td>0.961</td>
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crystals spectra of the clear solution at the operating temperature were collected for a duration of four minutes. The average deviation of the measured concentration from the weighted mass amounts to 0.45%. The largest deviation corresponds to 1.94%. The amount of seed crystals added to the solution ranged between 13 and 28% of the expected yield, which according to Section 5.4.2 should guarantee that no secondary nucleation occurs during the experiment. The difference between the concentration at the end of the experiment (averaged over the last 20 experimental points) and the measured solubilities never exceeded 1.3% of the solubility value, thus indicating that all experiments were stopped close to solubility.

In experiments carried out in the solid-liquid region, the composition of the liquid phase moves from the operating point, i.e. the point corresponding to the supersaturated solution at $t = 0$ (squares in Figure 5.6), towards the solubility line following the tie-line, which crosses the operating point and connects the vertex of the pure enantiomer which is in excess with the liquid phase which is at equilibrium (dots in Figure 5.6). The tie-line coincides with a straight line through points with a constant concentration of the counter-enantiomer (Figure 5.6).

Hence, independent of temperature, the liquid phases of experiments carried out at a fixed concentration of the counter-enantiomer move all along the same line. As a consequence, crystals grown at a fixed concentration of the counter-enantiomer are assumed to exhibit the same growth behavior, i.e. their growth can be described by the same growth rate expression. To verify this, first it has to be shown that experiments carried out at a fixed temperature level and at a fixed concentration of $R$-mandelic acid yield equal growth rates. This is accomplished by fitting the concentration profile of each experiment individually by applying the growth rate function of Equation 5.6 (the obtained growth
5.4 Results and discussion

Figure 5.6: Schematic representation of the trajectory of the liquid phase in two isothermal batch experiments carried out at the same level of concentration of the counter-enantiomer. The squares represent the operating points, the circles represent liquid phase at equilibrium with crystals of the target-enantiomer.

parameters are not reported here). The two parameters $k_1$ and $k_2$ in Equation 5.6 provide enough flexibility to represent the data points of a single desupersaturation profile in an almost perfect manner. The initial concentration required to solve the population balance equation corresponds to the average solute concentration over four minutes obtained from IR spectroscopy prior to seed addition. The concentration profiles are cut at the point where the liquid phase reaches a concentration level that is 1% larger than the saturation concentration. The parameter fitting is performed using a nonlinear optimization algorithm that minimizes the sum of the squared residuals, $SSR$, of the relative error between the measured and the experimental concentration of $S$-mandelic...
acid in solution:

\[ SSR = \sum_{i=1}^{N^D} \left( \frac{c_{S,\text{exp},i} - c_{S,\text{sim},i}}{c_{S,\text{exp},i}} \right)^2 \]  \hspace{1cm} (5.9)

where \( N^D \) is the number of data points of the single experiment. Figure 5.7(a) to 5.7(c) show the obtained growth rates as function of supersaturation at the three temperature levels investigated. The growth rates expressions fitted on experiments with the same concentration of \( R \)-mandelic acid are similar, thus justifying the assumption of equal growth behavior at constant concentration of \( R \)-mandelic acid in solution. Moreover, the decrease in the growth rate due to presence of \( R \)-mandelic acid in the solution is substantial and visible at all temperature levels.

In Figure 5.7(d) to 5.7(f) the same growth rate functions are represented at fixed concentration of the counter-enantiomer. Compared to the effect of the counter-enantiomer, the effect of temperature is less pronounced. Only at 0.0231 g/g water and 0.0393 g/g water, the increase in the growth rate due to an increase in temperature becomes appreciable.

After having assured the similar behavior of experiments carried out at the same level of concentration of the counter-enantiomer, the parameter estimation is now repeated by simultaneously fitting the concentration profiles of the experiments at constant concentration of \( R \)-mandelic using the temperature dependent growth rate expression shown in Equation 5.7. Due to the different durations of the experiment and the different number of experiments carried out at different temperature levels, the residuals are weighted according to: \(^{75}\)

\[ SSR = \sum_{i=1}^{N^T} \sum_{j=1}^{N^E} \sum_{k=1}^{N^D} \frac{1}{N^E N^D_{i,j}} \left( \frac{c_{S,\text{exp},i,j,k} - c_{S,\text{sim},i,j,k}}{c_{S,\text{exp},i,j,k}} \right)^2 \]  \hspace{1cm} (5.10)
Figure 5.7: Growth rates obtained by individually fitting the 25 batch experiments using the growth rates expression in Equation 5.6. The dashed lines refers to the experiments carried out at the lowest initial supersaturation and with the highest seed loading.
Table 5.3: Three sets of growth parameters of Equation 5.7 estimated by fitting the PBE model to the experimental data assuming that all parameters are dependent on the concentration of \( R \)-mandelic acid.

<table>
<thead>
<tr>
<th></th>
<th>( c_R = 0 \text{ g/g} )</th>
<th>( c_R = 0.0231 \text{ g/g} )</th>
<th>( c_R = 0.0393 \text{ g/g} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k_3 ) [m/s]</td>
<td>((1.81 \pm 2.04) \cdot 10^{-2})</td>
<td>(41.8 \pm 40.7)</td>
<td>((3.38 \pm 1.72) \cdot 10^8)</td>
</tr>
<tr>
<td>( k_4 ) [K]</td>
<td>(2260 \pm 320)</td>
<td>(4550 \pm 280)</td>
<td>(9180 \pm 150)</td>
</tr>
<tr>
<td>( k_5 ) [-]</td>
<td>(1.55 \pm 0.03)</td>
<td>(1.75 \pm 0.03)</td>
<td>(2.08 \pm 0.02)</td>
</tr>
</tbody>
</table>

where \( N^T \) is the number of temperature levels investigated at a fixed concentration of \( R \)-mandelic acid, \( N_i^E \) the number of experiments carried out at a temperature level and \( N^D \) the number of data points of the single experiment. In Table 5.3 the three sets of parameters \( k_3 \), \( k_4 \) and \( k_5 \) together with their confidence intervals are reported. Figures 5.8 to 5.10 give an overview of the experimental and the simulated concentration profiles, while the growth rates as a function of temperature and supersaturation are represented in Figure 5.11. In line with the results obtained from the individual fits, the growth rates are found to be substantially decreased when the concentration of the counter-enantiomer is increased. The three estimated parameter sets describe the performed experiments very well, yielding an overall coefficient of determination of 0.95. The experiments with the lowest initial supersaturation are described less accurately than those with a high initial supersaturation. Nonetheless, the parameter estimation demonstrates that experiments carried out at a fixed concentration of \( R \)-mandelic acid can be described using the same set of parameters hence that crystals grown at a fixed concentration of \( R \)-mandelic acid exhibit the same growth behavior.
5.4 Results and discussion

$c_r = 0 \text{ g/g; } T = 15^\circ\text{C}$

$c_r = 0.0231 \text{ g/g; } T = 15^\circ\text{C}$

$c_r = 0.0393 \text{ g/g; } T = 15^\circ\text{C}$

Figure 5.8: Concentration profiles of $S$-mandelic acid in the course of the isothermal seeded batch experiments at $15^\circ\text{C}$. The inserts refer to experiments carried out at the lowest supersaturation levels but with a higher seed loading. The dots correspond to experimental values. Only the values used for the parameter estimation are reported. The lines correspond to the simulated concentration profiles using the parameters shown in Table 5.3.
Figure 5.9: Concentration profiles of S-mandelic acid in the course of the isothermal seeded batch experiments at 20°C. The inserts refer to experiments carried out at the lowest supersaturation levels but with a higher seed loading. The dots correspond to experimental values. Only the values used for the parameter estimation are reported. The lines correspond to the simulated concentration profiles using the parameters shown in Table 5.3.
5.4 Results and discussion

Figure 5.10: Concentration profiles of S-mandelic acid in the course of the isothermal seeded batch experiments at 25°C. The dots correspond to experimental values. Only the values used for the parameter estimation are reported. The lines correspond to the simulated concentration profiles using the parameters shown in Table 5.3.
Despite the fact that the concentration profiles of the experiments are described very well by the three sets of parameters, the parameter estimation is not satisfactory. On the one hand, the estimated $k_3$-values range over 11 orders of magnitudes which is not a physically meaningful result. On the other hand, the $k_{3}$-values are affected by a large confidence interval. This indicates a possible collinearity of two model parameters which is confirmed by the covariance matrices (Table 5.4), which in all three cases indicate a large collinearity between the parameters $k_3$ and $k_4$.

Due to the large collinearity, the parameter estimation was repeated by keeping two parameters independent of the concentration of the counter-enantiomer and by fitting all experiments simultaneously. The sum of
Table 5.4: Covariance matrices of the three sets of parameters listed in Table 5.3.

<table>
<thead>
<tr>
<th>g/g</th>
<th>$k_3$</th>
<th>$k_4$</th>
<th>$k_5$</th>
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<td>0</td>
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<td>0.998</td>
<td>0.328</td>
</tr>
<tr>
<td>0.0231</td>
<td>1</td>
<td>0.998</td>
<td>0.394</td>
</tr>
<tr>
<td>0.0393</td>
<td>1</td>
<td>0.997</td>
<td>0.395</td>
</tr>
</tbody>
</table>

The squared residuals is then redefined as:

$$SSR = \sum_{i=1}^{N_C} \sum_{j=1}^{N_T} \sum_{i,j,k,l=1}^{N_E} \sum_{i,j,k,l}^{N_D} \frac{1}{N_{i,j}^E N_{i,j,k}^D} \left( \frac{c_{S,exp,i,j,k,l} - c_{S,sim,i,j,k,l}}{c_{S,exp,i,j,k,l}} \right)^2$$

where $N_C$ is the number of concentration levels of $R$-mandelic acid investigated. Not surprisingly, by far the best result is obtained by keeping the $k_3$- and the $k_4$-value independent of the concentration of $R$-mandelic acid, i.e. the two highly collinear parameters in the previous parameter estimation, and letting only $k_5$ vary with concentration of $R$-mandelic acid. Despite a penalty in the overall coefficient of determination, which drops from 0.95 to 0.91, the five parameters shown in Table 5.5 describe the experimental concentration profiles in a satisfactory manner (Figures 5.12 to 5.14). Moreover, the confidence intervals could be significantly decreased.
Table 5.5: Set of growth parameters of Equation 5.7 estimated by fitting the PBE model to the experimental data assuming that only $k_5$ is dependent on the concentration of $R$-mandelic acid.

<table>
<thead>
<tr>
<th></th>
<th>$c_R = 0$ g/g</th>
<th>$c_R = 0.0231$ g/g</th>
<th>$c_R = 0.0393$ g/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_3$ [m/s]</td>
<td></td>
<td>9.09 ± 4.53</td>
<td></td>
</tr>
<tr>
<td>$k_4$ [K]</td>
<td></td>
<td>4080 ± 140</td>
<td></td>
</tr>
<tr>
<td>$k_5$ [-]</td>
<td>1.56 ± 0.01</td>
<td>1.79 ± 0.02</td>
<td>2.02 ± 0.02</td>
</tr>
</tbody>
</table>

The largest penalty in the coefficient of determination arises from the experiments starting from a low initial supersaturation at $c_R = 0.0393$ g/g water, whose growth kinetics are largely overestimated. Similarly to the growth parameters shown in Table 5.3, the parameters in Table 5.5 evidence a net decrease in the growth rate of $S$-mandelic with increasing concentration of $R$-mandelic acid (Figure 5.15). The results from the last parameter estimation indicate that the slowdown of growth caused by the presence of the counter-enantiomer increases with decreasing supersaturation, an effect which can be visualized best by representing the relative growth rate between experiments carried in partially enriched solutions and the ones carried out in enantiopure solutions. As the $k_4$-value is independent of the concentration of the $R$-mandelic acid, the calculated relative growth rates are independent of temperature (Figure 5.16).

This result can be explained by the fact that the ratio between the concentrations of $R$-mandelic acid, i.e. the species that slows down growth and of $S$-mandelic acid, i.e. the species that crystallizes is not constant but increases throughout the experiment. In fact, the concentration of $R$-mandelic acid remains constant, while the concentration of the $S$-enantiomer in solution decreases. The parameter $k_5$ in the semi-empirical growth rate of Equation 5.7 is the only parameter that can account for a varying degree of slowdown of growth during the experiment.
Figure 5.12: Concentration profiles of S-mandelic acid in the course of the isothermal seeded batch experiments at 15°C. The inserts refer to experiments carried out at the lowest supersaturation levels and with the highest seed loading. The dots correspond to experimental values. Only the values used for the parameter estimation are reported. The lines correspond to the simulated concentration profiles using the parameters shown in Table 5.5.
5. Growth kinetics of \(S\)-mandelic acid in aqueous solutions

Figure 5.13: Concentration profiles of \(S\)-mandelic acid in the course of the isothermal seeded batch experiments at 20\(^\circ\)C. The insets refer to experiments carried out at the lowest supersaturation levels and with the highest seed loading. The dots correspond to experimental values. Only the values used for the parameter estimation are reported. The lines correspond to the simulated concentration profiles using the parameters shown in Table 5.5.
Figure 5.14: Concentration profiles of S-mandelic acid in the course of the isothermal seeded batch experiments at 25°C. The dots correspond to experimental values. Only the values used for the parameter estimation are reported. The lines correspond to the simulated concentration profiles using the parameters shown in Table 5.5.
5. Growth kinetics of \( S \)-mandelic acid in aqueous solutions

Figure 5.15: Fitted growth rates of \( S \)-mandelic acid in dependence of supersaturation and temperature for concentrations of 0, 0.0231 and 0.0393 g \( R \)-mandelic acid/g of water. The growth rate parameters are listed in Table 5.5.

Figure 5.16: Relative growth rates of \( S \)-mandelic acid grown from partially enriched aqueous solutions, defined as the ratio between the growth rates of \( S \)-mandelic acid from enriched solutions and the growth rates obtained when growing the crystals from an enantiopure solution. As the \( k_4 \)-value in Equation 5.7 is assumed to be independent on the concentration of \( R \)-mandelic acid, the relative growth rates are independent of temperature.
5.4 Results and discussion

It has however to be mentioned, that an increase in the $k_5$-values leads to a decrease in the growth only when supersaturation is below 2. An alternative growth rate expression should be used when system with large metastable zone widths are investigated.

Crystal purity

All experiments have been carried out inside the two phase region where only crystals of the $S$-enantiomer are thermodynamically stable. Nonetheless, $R$-mandelic acid was detected in the crystals grown from partially enriched solutions. Figure 5.17 shows the purity of the grown crystal masses.

Incorporation of $R$-mandelic acid leads to a decrease of the enantiomer in the solution and hence in a change in the solubility. However, the largest change in the solubility did not exceed 0.3% of the solubility value, which is in the order of magnitude of the measurement uncertainty of the IR-spectroscope. Hence, the assumption of constant concentration of $R$-mandelic acid can still assumed to be valid.

$R$-mandelic acid is contained in all crystals grown from a partially enriched solution and demonstrates that crystallization in the solid-liquid phase region does not guarantee enantiopure crystals. Crystal purity is affected by the initial supersaturation and by the operating temperature, whereby the latter has a higher influence. At constant concentration of $R$-mandelic acid, the observed decrease of crystal purity when decreasing operating temperature is accordance with the outcome of the study carried out by Perlberg\textsuperscript{20}.

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5. Growth kinetics of $S$-mandelic acid in aqueous solutions

Figure 5.17: Purity of the grown crystal masses obtained from the batch experiments with partially enriched solutions. The diamonds refer to experiments carried out at higher seed loadings.
Analogous to crystal growth, also crystal purity appears to be dependent on the ratio between the concentrations of $R$- and $S$-mandelic acid. As for a fixed concentration of $R$-mandelic acid, the ratio increases with decreasing operating temperature (compare the two processes schematically represented in Figure 5.6), the level of concentration of the $S$-enantiomer decreases with decreasing temperature, and the higher the ratio, the lower is crystal purity. The effect of the seed loading on the crystal purity is found to be minor, as no significant change in the crystal purity was observed when seed loading was increased.

5.5 Conclusions

The effect of $R$-mandelic acid on the growth kinetics of $S$-mandelic acid is investigated through isothermal seeded batch experiments carried out at different temperature levels and at different concentrations of $R$-mandelic acid. Secondary nucleation is likely to occur during crystallization, however, through an appropriate choice of a seed population and a seed loading, the MSZW for secondary nucleation can be increased, thus enabling the exploration of a wider range of supersaturations. The maximal supersaturation that guarantees that secondary nucleation occurs at a negligible level could be increased from approximately 1.15 to a value far above 1.2. Using a semi-empirical, size independent growth rate function, the growth of $S$-mandelic acid in aqueous solutions over a wide range of temperature and concentration of $R$-mandelic acid can be accurately described by three parameters: two parameters that are independent on the concentration of $R$-mandelic acid and one parameter that implicitly accounts for a change in the concentration of $R$-mandelic acid. The estimation of the growth parameters confirm a slowdown of the growth rates caused by the presence of the counter-enantiomer in
the solution, that was also observed in previous studies.\textsuperscript{20,66} However on the contrary to these previous studies, the slowdown of the growth rate when compared with the growth rate obtained when crystallizing in enantiopure solutions is found to be dependent on supersaturation. The lower the supersaturation the higher the slowdown of growth. This effect can be explained by an increase in the ratio between the concentration of $R$-mandelic acid, i.e. the growth retarding species, and of $S$-mandelic acid, i.e. the crystallizing species, throughout the experiment.

The crystallization in the solid-liquid phase region where only crystal of the $S$-enantiomer are thermodynamically stable does not always guarantee the production of enantiopure crystals. $R$-mandelic acid was detected in all experiments carried out in partially enriched solutions. Analogous to the slowdown of crystal growth, crystal purity is also found to decrease when increasing the ratio between the concentrations of $R$-mandelic acid and of $S$-mandelic acid. Hence, for a fixed concentration of $R$-mandelic acid, the lower the operating temperature, the lower the solubility of $S$-mandelic acid and so the lower the crystal purity.

Finally, this study demonstrates that ATR-FTIR spectroscopy is a valuable process analytical technique for the monitoring of crystallization processes carried out in the solid-liquid phase region. The cumulative concentration profile during the crystallization process can be obtained through a multivariate calibration model. The concentration of the target-enantiomer required for the estimation of the growth kinetics is obtained by simply subtracting the concentration of the counter-enantiomer at the beginning of the experiment from the complete concentration. For the system investigated, the change in the solubility caused by the unexpected incorporation of the counter-enantiomer in the crystals is in the size range of the measurement uncertainty of the ATR-FTIR spectroscope. Finally, as no sampling loop is required, the
volume required to carry out kinetic experiments can be sensibly reduced
thus making the use of this experimental protocol very attractive also at
a very early stage of process development.

### 5.6 Nomenclature of Chapter 5

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$B$</td>
<td>birth term in the PBE [m$^{-1}$ s$^{-1}$]</td>
</tr>
<tr>
<td>$c_R$</td>
<td>concentration of $R$-mandelic acid [g g$^{-1}$ water]</td>
</tr>
<tr>
<td>$c_S$</td>
<td>concentration of $S$-mandelic acid [g g$^{-1}$ water]</td>
</tr>
<tr>
<td>$D$</td>
<td>death term in the PBE [m$^{-1}$ s$^{-1}$]</td>
</tr>
<tr>
<td>$G$</td>
<td>growth rate [m s$^{-1}$]</td>
</tr>
<tr>
<td>$k_j$</td>
<td>parameters in the crystal growth rate ($j=1,2,3,4,5$)</td>
</tr>
<tr>
<td>$k_v$</td>
<td>volume shape factor</td>
</tr>
<tr>
<td>$L$</td>
<td>characteristic particle length [m]</td>
</tr>
<tr>
<td>$n$</td>
<td>particle size distribution [m$^{-1}$]</td>
</tr>
<tr>
<td>$R^2$</td>
<td>coefficient of determination</td>
</tr>
<tr>
<td>$S$</td>
<td>supersaturation [-]</td>
</tr>
<tr>
<td>$T$</td>
<td>temperature [$^\circ$C]</td>
</tr>
<tr>
<td>$t$</td>
<td>time [s]</td>
</tr>
<tr>
<td>$\rho_S$</td>
<td>density of $S$-mandelic acid crystals [g cm$^{-3}$]</td>
</tr>
</tbody>
</table>
5. Growth kinetics of S-mandelic acid in aqueous solutions
Chapter 6

Conclusions

Crystallization is a valuable and widely applied technique to obtain product of high chiral purity. The symmetric behavior of two enantiomers does not allow a chiral resolution from racemic solutions which is driven by thermodynamics. Enantiopure crystals can however be obtained from partially enriched solutions when exploiting solid-liquid equilibria involving crystals of the target-enantiomer and a less enriched liquid phase. The design of such crystallization processes is guided by the aim of maximizing the recovery of the target-enantiomer from the feed solution in as short time as possible without admitting a penalty in the quality of the product. A rigorous optimization by design of the crystallization process can therefore only be accomplished by considering both the thermodynamic and the kinetic properties of the system. The possible occurrence of thermodynamically stable liquid-liquid phase separation (LLPS) limits the choice of possible operating conditions. In this thesis the thermodynamic behavior of chiral systems with and without a LLPS was studied. The correctness of the proposed phase diagram of ternary
6. Conclusions

systems exhibiting a LLPS was verified experimentally. Exploiting the knowledge of the thermodynamic properties, a methodology is developed for the design of crystallization processes from partially enriched solutions that is applicable to conglomerate forming systems. Finally, the effect of the counter-enantiomer on the growth kinetic of the target-enantiomer and on crystal purity was studied for a racemic compound forming system through isothermal seeded batch experiments.

6.1 Process design based on thermodynamic properties

In Chapter 2 and 3, the generic ternary phase diagram of conglomerate and of racemic compound forming exhibiting a thermodynamically stable LLPS has been derived and successfully experimentally verified. In both cases the onset of the LLPS occurs through a ternary monotectic equilibrium, where two liquid phases with the same enantiomeric excess are at equilibrium with two solid phases. Both compounds investigated have comparably low melting temperatures (below 100°C) and are only poorly soluble in the solvent in which they exhibit a LLPS. The combination of these two properties appears to be a good indicator for the occurrence of a LLPS.

A thorough understanding of the thermodynamic behavior of chiral systems enables developing a methodology for the design of cooling crystallization processes from partially enriched solutions, which is presented in Chapter 4. In the developed methodology, the crystallization process can unequivocally be described by three parameters, i.e. the initial enantiomeric excess, the initial and the final process temperature. The methodology allows dividing the possible crystallization processes
in three different classes: one class comprising feasible processes leading to the global maximal yield, one class of feasible but not optimal processes and one class of unfeasible processes as they lead to the formation of an undesired phase, e.g. crystals of the counter-enantiomer or of the solvent or a second liquid phase. These three classes of processes yield distinct areas in the operating plane with initial and final temperatures as coordinates. The methodology is also applicable to systems exhibiting a stable LLPS and demonstrates that chiral resolution can be carried out even if the system exhibits a LLPS. The methodology has only been applied to conglomerate forming systems, but due to the eutectic nature of racemic compound forming systems, the methodology could be extended to these systems. Two differences in the operating plane arise when changing from a conglomerate forming system to a racemic compound forming system. On the one hand, the undesired species that might crystallize at high initial temperatures are not crystals of the counter-enantiomer anymore but crystals of the racemic compound. On the other hand, the composition of the eutectic liquid phase is generally dependent on temperature. Hence, for a fixed initial enrichment only one process, the one yielding the least enriched eutectic liquid phase at the final temperature, leads to the global maximal yield. The remaining processes yielding a eutectic liquid phase at the final temperature only lead to the local maximal yield.

The outcome from Chapter 2 to 4 offers an additional option to the practitioner who encounters a system exhibiting a LLPS. Added to the option of repeating a possibly time-consuming solvent screening in order to find a solvent in which the compound does not exhibit a LLPS, the practitioner can apply the knowledge gained in this work to identify operating conditions that enable circumventing the region of the LLPS. It is worthwhile to mention that notwithstanding the fact that the ternary
phase diagram of a system exhibiting a LLPS increases in complexity, the amount of experimental work to determine the relevant portion of the ternary phase diagram, i.e. the solid-liquid phase region involving crystals of the desired enantiomer, required for the design of crystallization can be kept at a reasonable level. It is thereby crucial to determine at a very early stage the number of possible phase equilibria together with their range of thermodynamic stability. This is accomplished by determining the qualitative ternary phase diagram of the system, i.e. a polythermal ternary phase diagram with the same number and type of phase equilibria. It is defined by the relative position of the invariant equilibria along the temperature axis and can be estimated with a sufficient precision by coupling differential scanning calorimetry measurements with indirect measurements, i.e. by equilibrating well defined mixtures at different temperatures and determining only the number and the nature of the phases at equilibrium. Neither technique is time-consuming and they both enable the determination of the ternary phase within a few days at maximum. Once the qualitative ternary phase diagram is known, the experimental work required to obtain information on the solubility of the two enantiomers corresponds to the one of a system without a LLPS. In fact, assuming that the solubility curves can be approximated by lines, the minimum amount of information to characterize the relevant portion of the ternary phase diagram at a fixed temperature is the composition of the monovariant eutectic liquid phase and the solubility of the pure enantiomer. In the case the system exhibits a LLPS, the required information are the solubility of the pure enantiomer together with the composition of the monovariant eutectic liquid phase if the temperature is lower than the ternary monotectic temperature or together with the composition of the monovariant monotectic liquid phase when the temperature is above the ternary monotectic equilibrium.
6.2 Impact of crystallization kinetics on process design

In Chapter 5, the effect of $R$-mandelic acid (the distomer) on the growth kinetics of $S$-mandelic acid (the eutomer) and on crystal purity is presented. Isothermal seeded batch experiments were carried out at different temperature levels and at different levels of concentration of $R$-mandelic acid. The presence of the counter-enantiomer is found to substantially slow down growth of the target-enantiomer. The slow down is thereby found to increase with decreasing supersaturation. This outcome indicates that the penalty in the productivity caused by the presence of the counter-enantiomer is expected be striking when the experiment is carried out at low supersaturations, i.e. by applying low cooling rates. Moreover, the choice of the optimal crystallization process out of the set of processes leading to the maximal recovery of the solute requires an optimal trade-off between the volume productivity of the process, i.e. mass of crystals per volume of solution, and the process duration time. Moving towards lower temperatures lowers the volume productivity. However, the productivity might nevertheless be increased in the case the growth kinetics are more strongly dependent on the concentration of the counter-enantiomer, which decreases when the temperatures are lowered, than on temperature. On the other hand, moving towards higher temperatures increases the volume productivity. Productivity is increased only in the case the growth kinetics are only weakly dependent on the concentration of the counter-enantiomer. The presence of the counter-enantiomer is also found to have an effect on crystal purity. A decrease in crystal purity is found with increasing the ratio between the concentration of the counter-enantiomer and the concentration of the target-enantiomer is increased. This effect leads to a reduction in the
number of feasible crystallization processes obtained by thermodynamic considerations and make the size of the feasible domain dependent on the purity specifications. According to the outcome of this study, product purity can be increased by either carrying out the crystallization at lower solute concentrations, i.e. by lowering the initial and the final process temperature, or by increasing the final temperature however admitting a penalty in the yield.

Finally, the study of growth kinetics presented in Chapter 5, demonstrates that ATR-FTIR spectroscopy is a valuable process analytical technique for the monitoring of crystallization processes carried out in the solid-liquid phase region. The cumulative concentration profile during the crystallization process can be obtained through a multivariate calibration model. The concentration of the target-enantiomer required for the estimation of the growth kinetics is obtained by simply subtracting the concentration of the counter-enantiomer at the beginning of the experiment from the complete concentration. For the system investigated, the change in the solubility caused by the unexpected incorporation of the counter-enantiomer in the crystals is in the size range of the measurement uncertainty of the ATR-FTIR spectroscope. Finally, as no sampling loop is required, the volume required to carry out kinetic experiments can be sensibly reduced thus making the use of this experimental protocol very attractive also at a very early stage of process development.

6.3 Outlook

After having determined the generic phase diagrams of chiral systems exhibiting a thermodynamically stable LLPS, the next step could consist
in the identification of suitable models for the activity coefficients that enables modeling the ternary phase diagram, which will in turn facilitate the construction of the operating diagram for the design of crystallization processes.

In the mandelic acid/water system, the presence of the distomer in solution is found to slow down crystal growth of the eutomer and to decrease crystal purity. Further work in this area is required to establish general rules that allow quantifying the effect of the distomer on the growth kinetics of the eutomer. This is accomplished by developing experimental protocols that enable characterizing the mechanisms of inhibition of crystal growth and of incorporation of the distomer in the crystal. The established general rules can then be applied to extend the methodology for process design developed in this thesis by complementing it with kinetic information. This step will improve process design as on the one hand it allows sorting out crystallization processes that are feasible based on thermodynamic considerations but lead to an insufficient crystal purity due to the incorporation of the distomer during crystallization, on the other hand it enables identifying the most efficient process out of the set of feasible crystallization processes.

When the eutomer is crystallized from a system that exhibits a LLPS, the distomer present is not the only cause for a penalty in crystal quality and process productivity. Metastable liquid-liquid phase equilibria, that are present below the thermodynamically stable liquid-liquid domain, are also expected to have an effect on the outcome of the crystallization process. Hence, the application of experimental protocols for the determination of liquid-liquid phase separations will allow establishing additional general rules that in a later stage can be incorporated in the methodology for process design.
6. Conclusions

The improved methodology can then be applied for a rigorous optimization of hybrid processes combining continuous simulated moving bed chromatography with crystallization. Moreover, the methodology can also find an application outside the field of chiral resolution. The concept of identifying optimal operating conditions through a generalization of the phase diagram can be applied to any ternary separation which includes a crystallization step from a ternary mixture. After identifying possible areas of application, the effectiveness of the methodology should be assessed experimentally.
Bibliography


Bibliography


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