Dual-drug chiral resolution: enantiospecific co-crystallization of (*S*)-Ibuprofen using Leviteracetam.

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Abstract

In this work we show the feasibility of resolving a racemic drug substance with a second chiral drug, through enantiospecific co-crystallization. Doing so, a dual-drug co-crystal is obtained. Such a method can be useful not only for chiral resolution but also for the parallel creation of dual drug formulations. Racemic Ibuprofen is resolved using Levetiracetam, through the formation of an enantiospecific co-crystal, effectively applying co-crystallization as a resolution tool for (in this case) (*S*)-Ibuprofen, the active enantiomer. Constructing appropriate ternary and quaternary phase diagrams, one can identify those process conditions under which the system can be resolved, which we have done successfully. Since these diagrams are governed by thermodynamics, the system is robust under scale-up conditions and is an interesting alternative to chiral chromatography or enantioselective synthesis for the pharmaceutical industry.

Introduction

For pharmaceutical compounds, chirality is of key importance. Where one enantiomer often has the envisioned effect, the opposite enantiomer might be inactive or in a worst case scenario, have an adverse or toxic effect.[1–3] Many examples can be found in history, with the most notorious one being Thalidomide.[4,5] Therefore, the marketing of pure enantiomer drugs is becoming commonplace.[6] The added benefit of marketing enantiopure drugs is the reduced complexity of the pharmacodynamics. Additionally, the absence of the unwanted enantiomer removes the undesired biological response.[7,8] From a synthetic point of view, different options exist to access enantiopure drugs. They can either be obtained synthetically starting from enantiopure materials (chiral pool) or by introducing asymmetric synthesis steps.[9–14] Alternatively, manufacturers can opt to synthesize a racemic mixture, and separate both enantiomers in a successive physical separation step. This is often the method of choice for financial reasons. The two most common physical separation approaches are the use of diastereomeric salts[15–17] or chiral chromatography.[18–20] Chiral chromatography is often found to be more expensive and used mainly when the compound of interest does not form a salt. Furthermore, the throughput is limited .[21] Resolution through diastereomeric salt formation is less costly, but requires the compound to readily form salts. When a salt is formed with a chiral base/acid, a set of diastereomers is created which can be separated as they show different physical properties. Recently, our group introduced an alternative to diastereomeric salt formation, showing how co-crystallization can also be used as a separation tool, in particular for those compounds that do not form salts. Co-crystals are alternative solid forms, [22] which can be of interest when the API solid form has solubility, bioavailability or stability issues.[23–25,26–28] In the context of this work, co-crystals are defined as a solid form which contains two neutral compounds that on their own are both also solid under ambient conditions. When both partners are chiral, two co-crystallizing components either form a diastereomeric co-crystal pair or behave enantiospecifically. [29] Both types of systems can be exploited to develop a chiral resolution process. In this study, we build upon the co-crystal resolution process we developed, taking the resolution to the next level, using a given drug compound to resolve another drug compound. Doing so, we develop a

dual drug resolution through co-crystallization. The advantage of such a process is that one not only obtains a chiral resolution through co-crystallization, but at the same time develops a process for a dual-drug formulation. (*RS*)-Ibuprofen has been chosen as the model compound to be resolved. (*S*)-Ibuprofen is the active enantiomer and inhibits cyclooxygenase, suppressing pain and inflammation, where (*R*)-Ibuprofen is inactive.[30] (*S*)-Ibuprofen was shown to co-crystallize enantiospecifically with Levetiracetam[31] (Fig. 1) (an anti-epileptic used to treat early onset seizures[32,33]). As illustrated in figure 1, no co-crystallization occurred when combining (*R*)-Ibuprofen with Levetiracetam. Resolving (RS)-Ibuprofen using Leviteracetam, we are not only able to directly resolve the former, but furthermore we obtain an end-product, which combines two APIs in a given solid form. Such a dual drug co-crystal has a tremendous potential in terms of pharmacokinetic properties, since it reduces the necessary active dosage up to 11 times and allows combining the beneficial effects of two distinct drugs.[34]

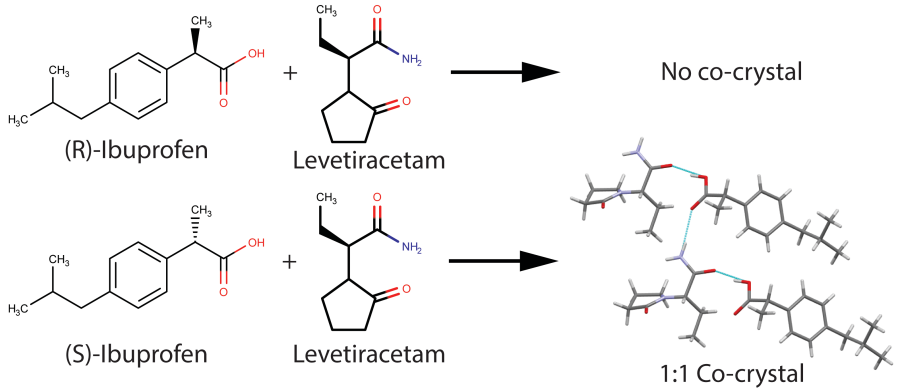


Figure 1: Enantiospecific co-crystal behavior between Ibuprofen enantiomers and Levetiracetam[31]

To show the feasibility of developing such a dual-drug resolution process, we start by showing the enantiospecificity of the system constructing binary melting phase diagrams. Then a solvent is introduced, and appropriate ternary and (pseudo)-ternary phase diagrams are constructed to identify those process conditions that lead to effective resolution. Finally, the feasibility of the resolution is illustrated through some dual drug co-crystallization resolution trials.

Materials

S-2-(2-oxopyrrolidin-1-yl)butanamide ((*S*)-Etiracetam or Leviracetam) was purchased from Xiamen Top Health Biochem. Tech. Co., Ltd. (*R*)-Etiracetam was obtained via co-crystallisation followed by separation, as described elsewhere[29] (See Supplementary Information, section 1). (*RS*)-Ibuprofen was purchased from HoaHua Industry Co., Ltd. (*S*)-Ibuprofen was purchased from Thermofischer Acros Organics. Acetonitrile was purchased from VWR International S.A.S. Analytical standard 1,4-dinitrobenzene was obtained from Sigma Aldrich Co. LLC. All materials were used without further purification.

Methods

Powder X-Ray diffraction (XRPD) measurements were performed on a Siemens D5000 diffractometer equipped with a Cu X-ray source operating at 40kV and 40mA. A secondary monochromator allowed the

the selection of Kα radiation of Cu (λ = 1.5418 Å). A scanning range of 2Θ values from 2 to 72 at a scan rate of 0.6°/min was applied.

Differential Scanning Calorimetry (DSC) measurements were performed on a Mettler Toledo DSC821^e using 40µL aluminum crucibles, with a heating rate of 5°C/min from 25°C to 150°C. The crucibles were punctured to prevent variation in pressure.

Chiral High Performance Liquid Chromatography (Chiral HPLC) measurements were performed on a reverse phase Waters Alliance 2695 system, with a Photo Array Detector (Waters 2998) at 210nm. Samples were measured using a 1mL flow of 50/50 H_2O/MeCN with 0.1% formic acid added, on a Lux 5µm Amylose-1 250 x 4.6mm column from Phenomenex Inc.

Quantitative Nuclear Magnetic Resonance Spectroscopy (qNMR) measurements were performed on a 300MHz Bruker Avance, using 1,4-dinitrobenzene as an internal standard (see supplementary information section 3 for calculations) together with the compounds of interest, dissolved in DMSO-d6. The parameters were unchanged except for d1 of 60 seconds (to ensure full relaxation of all protons), a FID size of 32768 and 16 scans.

Sample Preparation & Phase diagram creation

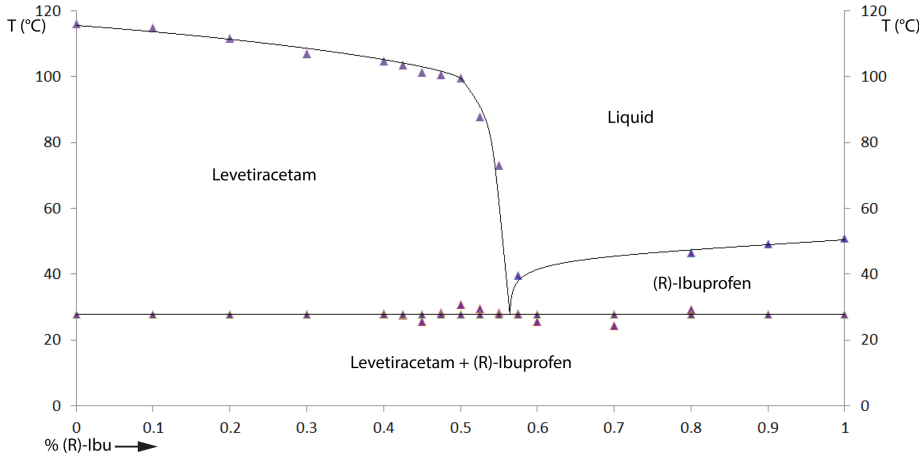
To create the binary melting phase diagrams, different stoichiometric ratios of both solids were added together and ball milled for 90 minutes at a frequency of 30Hz. The samples were then analyzed by DSC as described above. For the single component, pure co-crystal and eutectics, the onset of melting peaks were chosen as the melting temperature. For any other composition, the onset yields the eutectic melt, whereas the endset corresponds to the liquidus temperature. Isothermal ternary phase diagrams (including a solvent) were constructed through analysis of liquid and solid phases of samples corresponding to different positions within the ternary phase diagram. To achieve thermodynamically stable situations, initial suspensions were dissolved completely (heating was applied when needed). After cooling to the temperature at which the phase diagram is constructed, the samples were seeded with all possible solid state forms and the vials left to equilibrate. After one day, the vials were re-seeded with all forms to prevent the formation of kinetic or less stable products. After one week, the thermodynamic equilibrium was assumed and the crystals were separated from their mother liquor by drawing off the solution using a syringe with a needle. The crystals were not washed unless mentioned otherwise. Analysis on both the solid and liquid phase was performed as described in the methods section. The solid phases were analyzed with XRPD to verify which solid species were present, and cHPLC was used to determine the ratio between (*R*)- and (*S*)-Ibuprofen. From the liquid a fixed fraction (40µL) was taken and left to evaporate, after which a known amount of internal standard was added and the sample was analyzed. This allows a quantitative determination of the species present in solution. For all phase diagrams, the temperature was fixed to reduce the amount of variables. Full quaternary phase diagrams (body of figure 3) were not constructed, but rather some well-chosen planes within these diagrams (*pseudo*-ternary phase diagrams) by fixing the amount of solvent.[35]

Results & Discussion

Binary Phase Diagrams

(*S*)-Ibuprofen was found to co-crystallize enantiospecifically with Levetiracetam as illustrated in Fig. 1. Liquid assisted grinding of Levetiracetam with (*R*)- and (*S*)-Ibuprofen leads to respectively a physical mixture of the two components, or formation of a co-crystal. To confirm this finding, binary phase

125 diagrams were constructed. Binary phase diagrams can be obtained from DSC measurements on pure samples and samples with varying ratios of both components. The diagrams are shown in figure 2a and b for the combination of (*R*)-Ibuprofen/Levetiracetam and (*S*)-Ibuprofen/Levetiracetam systems, respectively. All DSC data is given in the supporting information.



130 **Figure 2a: Binary phase diagram of Levetiracetam and (*R*)-Ibuprofen. Lines are a guide to the eye.**

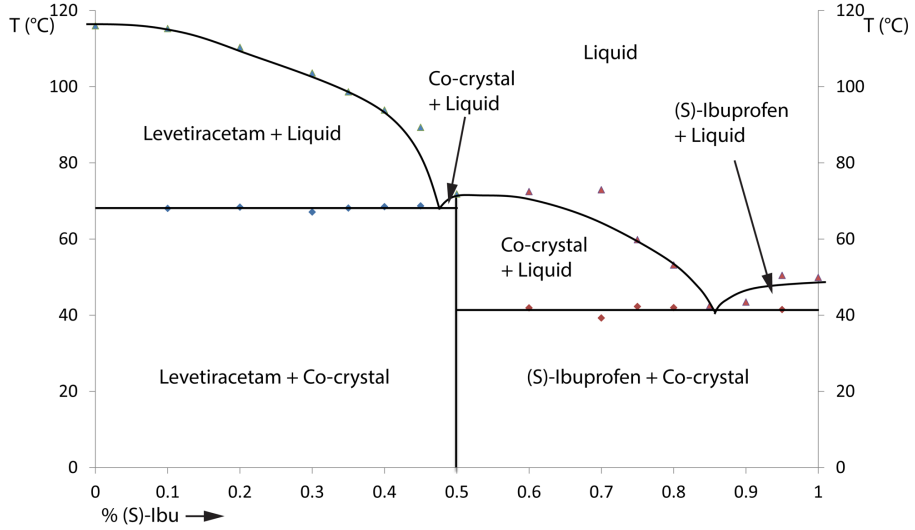


Figure 2b: Binary phase diagram of Levetiracetam and (S)-Ibuprofen. Lines are guide to the eye

In case of a binary phase diagram, the melting points of the pure phases are observed at both extremes (as illustrated in Figure 2a showing a melting point of 116°C for Levetiracetam, and 50°C for (*R*)-Ibuprofen, in agreement with literature[36–38]). The co-crystal in figure 2b has a melting point of 72°C.

When the two crystalline phases are mixed in different ratios, the melting behavior differs. Upon heating, melting starts at the eutectic temperature. The melt that forms at this temperature has the eutectic composition. Therefore, when the overall sample has the eutectic composition, the entire sample melts at this temperature, with a single melting peak showing in the DSC analysis. For any other sample, the temperature needs to be increased further to fully melt the sample up to the liquidus temperature. The binary diagram between (*R*)-Ibuprofen and Levetiracetam in figure 2a, confirms the absence of co-crystal formation between these two partners. These two components form a physical mixture of two crystalline phases, as illustrated by the single eutectic temperature. The diagram in Figure 2a shows a single eutectic composition at 58% of (*R*)-Ibuprofen and a eutectic melting temperature of 28°C, which, as expected, is lower than the melting temperature of both components. For the co-crystal forming (*S*)-Ibuprofen:Levetiracetam system (Figure 2b) the situation is different. The binary diagram now shows three different crystalline phases. The diagram is therefore also characterized by two different eutectics. A first eutectic which occurs between Levetiracetam and the co-crystal is found for a (overall) ratio of 47% (*S*)-Ibuprofen and is characterized by a eutectic melting temperature of 68°C, which lies just below the melting temperature of the pure co-crystal phase. A second eutectic is found between the co-crystal and (S)-Ibuprofen characterized by 86% of (S)-Ibuprofen, and shows a eutectic melting temperature of 41°C.

The thermodynamic binary phase diagrams shown in figures 2a and 2b, confirm that under the temperature range studied, only the combination of (*S*)-Ibuprofen and Levetiracetam leads to co-crystal formation, whereas the combination with (*R*)-Ibuprofen does not. The systems thus behaves enantiospecifically.

Ternary and quaternary phase diagrams

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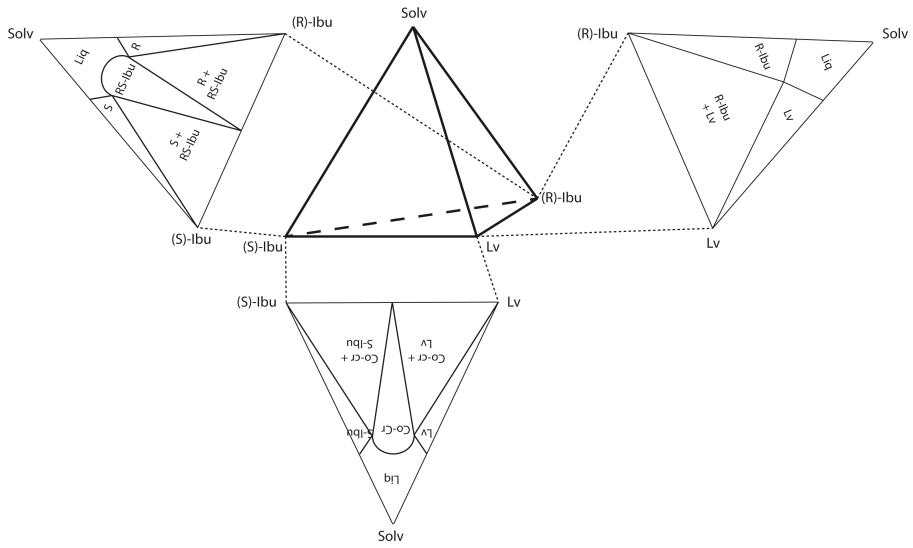

Figure 3: Graphical representation of quaternary (center) and three ternary phase diagrams. (*R*)- and (*S*)-Ibuprofen are related enantiomerically and crystallize as a racemic compound. (*S*)-Ibuprofen and Levetiracetam co-crystallize together as the target API-API co-crystal. Diagrams are shown as an illustration and are not true experimental diagrams.

Our final goal is to resolve (*S*)-Ibuprofen from a racemic mixture, using Levetiracetam as a resolving agent. To do so, a solvent needs to be introduced. Acetonitrile was chosen for its aprotic nature (minimize hydrogen bonding competition with respect to both components) and because both compounds show good solubility in this solvent. At 25°C, Ibuprofen has a solubility of 199 mg/mL and Levetiracetam of 53mg/mL. Following variables need to be considered when describing the system thermodynamically:

1. The amount of *S*-enantiomer of the target API
2. The amount of *R*-enantiomer of the target API
3. The amount of chiral co-former
4. The amount of Solvent
5. Temperature
6. Pressure

A description of a system with six variables is difficult to represent in a concise graphical manner. For this reason, reducing the number of variables is desirable. In most crystallization processes the pressure is kept constant, and we therefore decided to fix the pressure to ambient pressure. Any small fluctuations in pressure have a negligeable effect on a crystallization process, as there is almost no change in system volume. We then decided to work isothermally, removing temperature as a variable. If need be, the phase diagrams can be constructed at different temperatures and overlain to show the temperature effect. This leaves four final variables, leading to a quaternary phase diagram representation, as shown in Figure 3. In this figure, the three components (*S*)-Ibuprofen, (*R*)-Ibuprofen and Levetiracetam make up the base of the tetrahedron. The tip of the tetrahedron represents the solvent. The faces represent ternary phase diagrams, corresponding to a system of two different

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components and the solvent. For an enantiospecific system, one typically observes a ternary diagram of a racemic compound forming system, a ternary diagram of a co-crystal forming system, and a ternary diagram of two components that do not form a co-crystal. Figure 3 is a theoretical representation given for the purpose of clarity. All the ternary phase diagrams represented from hereon are based on experimental data and therefore true experimental thermodynamic diagrams. The three relevant ternary phase diagrams are expressed in molar percentages. The experimental data used to construct the ternary phase diagrams can be found in the supplementary information (Section 3).

(*R*)- and (*S*)-Ibuprofen ternary diagram (racemic Ibuprofen)

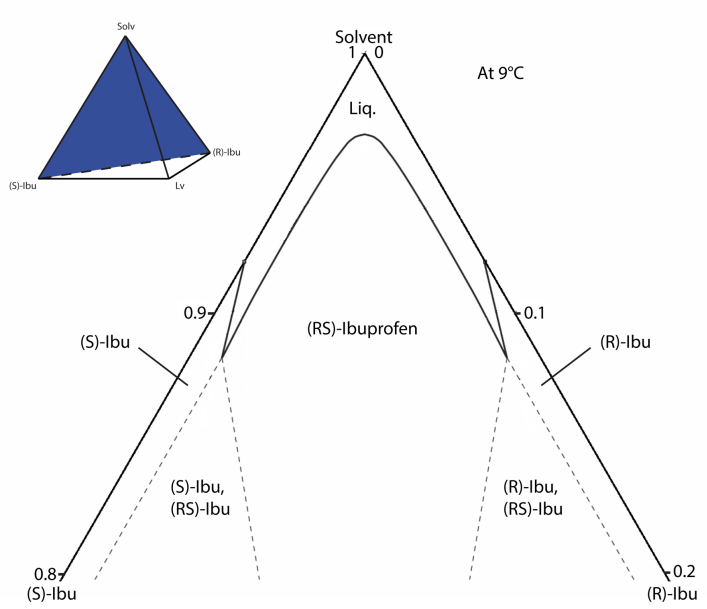

Figure 4: Ternary phase diagram of (R)- and (S)-Ibuprofen. Constructed at 9°C

Figure 4 shows the ternary phase diagram of (R)- and (S)-Ibuprofen in acetonitrile at 9°C. As expected, the diagram is symmetrical and corresponds to the diagram of a racemic compound forming system. On the left axis, one finds the solubility of (*S*)-Ibuprofen (348 mg/mL at 9°C) and on the right axis that for (*R*)-Ibuprofen. The solubility of (*RS*)-Ibuprofen can be found at a 50:50 ratio and is 86 mg/mL at 9°C. At this temperature, the racemic compound is therefore about 4 times less soluble compared to the enantiopure material. The solid lines are the liquidus (or solubility 'curves') and represent the change in solubility of respectively (S)-ibuprofen, and (RS)-Ibuprofen under varying compositions (enantiomeric ratios differing from the pure phases). Where the two liquidus lines meet, a eutectic occurs. This eutectic corresponds to the composition of the solution in equilibrium with both phases : (S)-Ibuprofen, and (RS)-Ibuprofen The eutectic composition lies at a ratio (*S*)-Ibuprofen:(*R*)-Ibuprofen of 88:12 (and *vice versa*), as expected considering the higher solubility of the enantiopure component. At the eutectic, an overall composition is found of 485 mg/mL (*S*)-Ibuprofen and 54 mg/mL (*R*)-Ibuprofen. Addition of small

amounts of (*R*)-Ibuprofen allows increasing the solubility of (*S*)-Ibuprofen, which implies an interaction of both enantiomers in solution. Since the diagram is symmetrical, these values are reversed for the other eutectic.

(*R*)-Ibuprofen and Levetiracetam

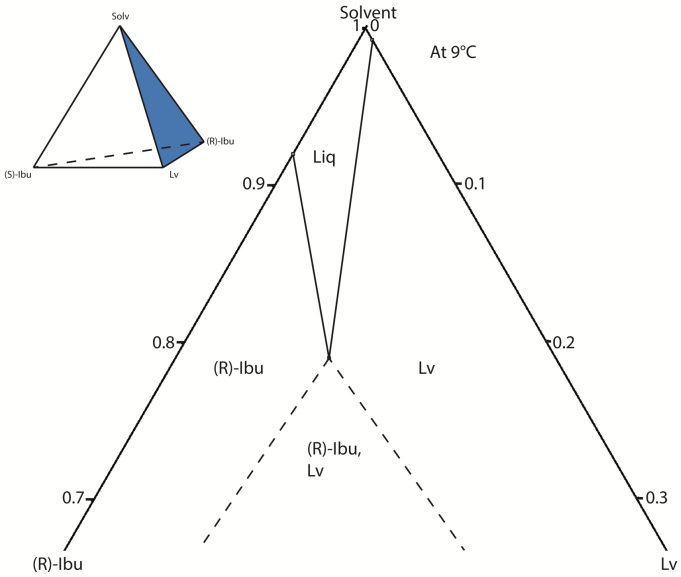

Figure 5: Ternary phase diagram of (*R*)-Ibuprofen with Levetiracetam. Constructed at 9°C.

Figure 5 shows the ternary phase diagram between (*R*)-Ibuprofen and Levetiracetam. Again, the solubilities for both compounds (348mg/mL for (*R*)-Ibuprofen, 27 mg/mL for Levetiracetam) can be seen on the left and right axes. This difference in solubility between the two compounds causes the diagram to be asymmetrical. The diagram corresponds to a non co-crystal forming system, as would be expected based on the data of the binary phase diagram (figure 2a) . The eutectic composition lies at a ratio of 59:41 ((*R*)-Ibu:Lv, resp.), which is in agreement with the ratio found in the binary phase diagram (figure 2a). This implies that in this case, the solvent (acetonitrile) does no significantly impact the eutectic composition. This is likely due to acetonitrile's aprotic character, since there is no competitive hydrogen bonding interaction from the solvent with the two compounds. The compounds do interact in solution, as shown by the dramatic increase in solubility of one compound, when the other is added. At the eutectic composition, the solubilities of (*R*)-Ibuprofen and Levetiracetam, are respectively 626 mg/mL and 359 mg/mL. This implies that addition of Levetiracetam can almost double the solubility of (*R*)-Ibuprofen, whilst a 13-fold solubility can be achieved for Levetiracetam. This important increase in solubility of both compounds, highlights the strong amide-acid intermolecular interaction occurring in solution. This result shows, that the even if no co-crystal is formed, the solution interactions between the 'mismatched' enantiomers, are still of importance and can strongly impact solution behavior.

(*S*)-Ibuprofen and Levetiracetam

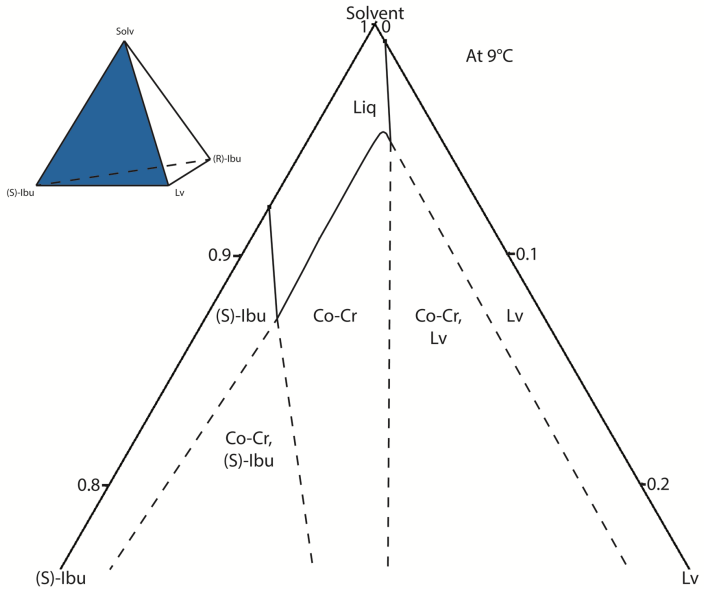

Figure 6: Ternary phase diagram of (S)-Ibuprofen with Leviteracetam showing the co-crystal forming zone. Diagram was constructed at 9°C.

The final face of the quaternary diagram, is given by the ternary phase diagram shown in figure 6 and corresponds to the co-crystal forming (*S*)-Ibuprofen and Levetiracetam system. This result is in agreement with the binary phase diagram of figure 2b. The solubilities for (*S*)-Ibuprofen and Levetiracetam at 9°C are 348mg/mL and 27mg/mL, respectively. The system is now more complex, as the co-crystal can also be formed in solution. Due to the difference in solubilities, the ternary diagram is skewed towards the (*S*)-Ibuprofen side. Nevertheless, the diagram remains congruent, which implies that if the co-crystal phase is introduced in suspension it remains stable in suspension. This makes it possible to determine the solubility of the co-crystal from the ternary phase diagram. The solubility for the co-crystal is 379 mg/mL (see supplementary information section 3). When comparing the eutectics of the ternary phase diagram, the first one (left) is found at 87:13, with a solubility of 514mg/mL for (*S*)-Ibuprofen and 63mg/mL for Levetiracetam and in agreement with the binary phase diagram (figure 2b). The second eutectic (right) is at 31:69 and has a solubility of 44mg/mL for (*S*)-Ibuprofen and 142mg/mL for Levetiracetam. This eutectic is different from the eutectic found in the binary diagram. Since only one eutectic is different, it is highly unlikely that the shift is caused by solvent interactions as this would likely impact both eutectics. A plausible hypothesis is a stronger impact of the addition of carboxylic acid groups to the amide-amide interaction, explaining why only the eutectic on the Levetiracetam-rich part of the diagram is impacted. However, a detailed investigation of these interactions lies outside the

scope of this article. The solubility difference between Ibuprofen and Levetiracetam also causes a strong difference in the overall solid/solvent ratio between the two eutectics.

Pseudo-ternary phase diagram for (*RS*)-Ibuprofen and Levetiracetam at a given amount of solvent

When developing a resolution process, one starts with a racemic amount of Ibuprofen and adds Leviteracetam. For the resolution to be effective, conditions need to be identified for which either only the co-crystal, or the co-crystal with an excess amount of co-former come out of solution.

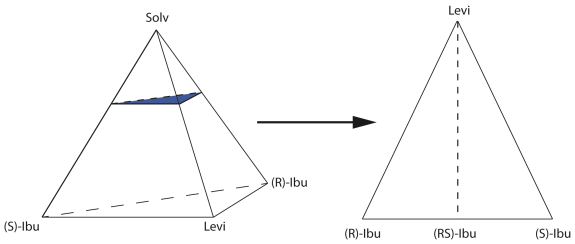

Figure 7: Taking a cut of the quaternary diagram to form a (pseudo)ternary diagram.

Ideally, the development of a resolution process would benefit from the construction of a full quaternary phase diagram. However, doing so would be very time-consuming. In our previous work[35], we proposed to limit the quaternary phase diagrams to some well-chosen cut-planes, which contain the necessary phases and show the feasibility of chiral resolution. As illustrated in figure 7, one such cut-plane, can be achieved by fixing the amount of solvent, which translates to a horizontal slice of the quaternary phase diagram, leading to a pseudo-ternary phase diagram. The slice is taken perpendicularly to the base of the tetrahedron. Within this plane we analyze which solid phase is stable in suspension for a given proportion of components. The composition of the supernatant solution corresponds to a point on the solubility surface which lies within the tetrahedron, but outside of this cut-plane. We therefore decided not to represent this solution composition to prevent confusion.

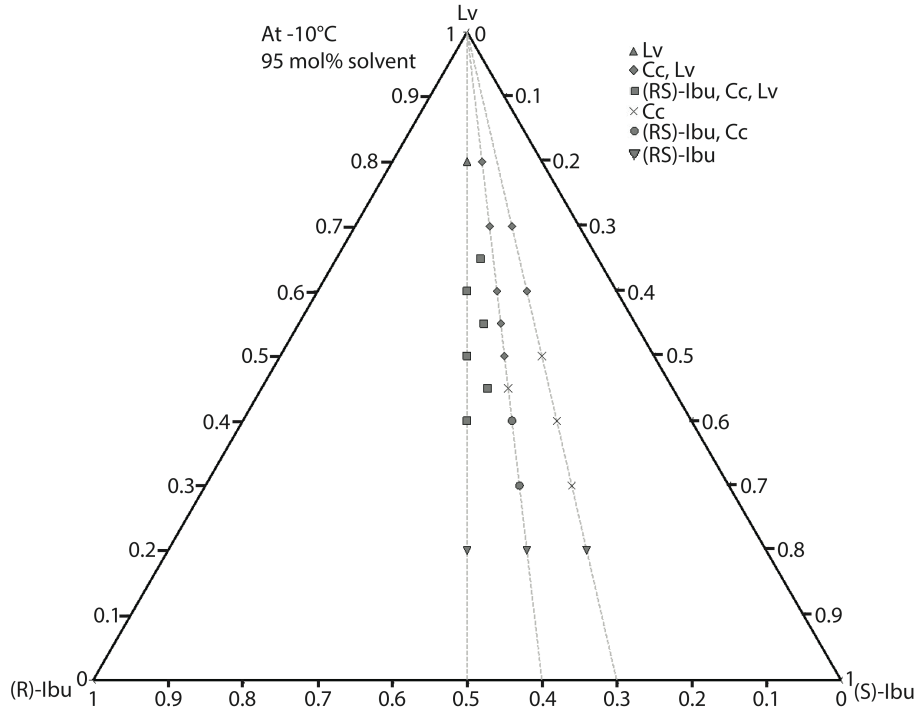

Figure 8: (pseudo)Ternary phase diagram obtained through analysis of the solid phases at -10°C and for 95 mol% of solvent.

To achieve resolution or enantio-enrichement through co-crystallization starting from a racemic mixture, we need to identify an area within this cutplane in which the enantiospecific co-crystal is formed. Furthermore, the racemic composition line (dashed 50:50 line) needs to cross a zone in which such a co-crystal is formed. In our case, the cut-plane was analyzed at 9°C and -10°C. At 9°C the 1:1 stoichiometric line does not cross a zone that contains the co-crystal phase. Springuel *et al.*[29] noted that when the temperature is lowered, the whole diagram can shift substantially due to the asymmetric changes in solubility (changes in solubility of both components are not linearly related to each other). This was also the case in our system where at -10°C the racemic line, now crosses zones where the co-crystal is formed. As can be seen in Figure 8, all possible combinations of solid forms occur except for (*RS*)-Ibuprofen with Levetiracetam. Figure 8 focuses on three sample sets: one along the racemic Ibuprofen line (50:50 dashed line), one along the 60:40 and one along the 70:30 (R:S) line. By varying the amount of Levetiracetam one moves from the base to the top of the diagram. The apexes of the triangle correspond to 5% pure component in 95% acetonitrile.

Evaluating the data points along the racemic line going from the bottom to the top, one first crosses a zone where (*RS*)-Ibuprofen is stable in suspension. For this zone, according to Gibbs' phase rule, two degrees of freedom remain, meaning that two components can be varied independently without

changing the number of phases. When the amount of Levetiracetam is increased, a zone is identified for which three solid phases are stable in suspension: both starting compounds as well as the co-crystal. Here, no degrees of freedom remain, meaning that a singular variable is enough to determine the whole system at this point. This also means that we have a eutectic composition of the liquid phase, as confirmed by the experimental data. The composition of the eutectic point lies at a 96.6:3.4 ratio for the solvent:solids and consists of 96.6 mol% acetonitrile, 1.8 mol% Ibuprofen and 1.6 mol% Levetiracetam (see supporting information section XX). Moving further along the 50:50 ratio to a more Levetiracetam enriched composition, Levetiracetam seems to be the only stable form in suspension.

Once the system is in a zone where the co-crystal phase appears, resolution is occurring, as the solution enriches in (*R*)-Ibuprofen and the solid in (*S*)-Ibuprofen. This therefore occurs along the 50:50 line for the compositions where all three solid forms (including the co-crystal) are formed.

When the starting ratio is 40:60 (*R*:*S*), two new zones emerge. Starting at the bottom, initially only (*RS*)-Ibuprofen is stable in suspension. Increasing the amount of Levetiracetam, a zone appears where both both (*RS*)-Ibuprofen and the co-crystal are stable in suspension. A further increase in Levetiracetam leads to a small zone where only the co-crystal is stable in suspension. Finally, a zone where the co-crystal and Levetiracetam are stable in suspension emerges. Along this line, the zone where Levetiracetam co-crystallizes with (*S*)-Ibuprofen is of particular interest, as within this zone, the solid material in suspension only contains (*S*)-Ibuprofen. Filtration at this stage could lead to enantiopure Ibuprofen, whereas the initial starting solid material had a 40:60 (*R*:*S*) composition.

The third dataset at a ratio of 30:70 (*R*:*S*) shows a similar trend. Initially in the Ibuprofen rich zone, only (*RS*)-Ibuprofen crystallizes. The next zone contains the co-crystal only, but is large in comparison to the zone we encountered for the 40:60 line. Increasing the amount of Levetiracetam even further, leads to a mixture of Levetiracetam and co-crystal in suspension. The areas where the co-crystal is the only stable phase in suspension or where it is stable in suspension together with Levetiracetam, are the zones where the solid phase only contains the *S*-enantiomer of Ibuprofen, and which after filtration can lead to enantiopure material.

Preliminary scale up experiments

To test the possibility of full resolution, some successive crystallization experiments were performed based on the thermodynamic data shown above. All experiments were performed at least twice to show the repeatability. The results are shown in table 1.

In a first cycle, the starting point was chosen in the center of the pseudo-ternary diagram shown in Figure 8: 2.5:2.5 mol% ratio ((*RS*)-Ibuprofen:Levetiracetam) and 95 mol% solvent. The mixture of Ibuprofen and Levetiracetam was dissolved in 95 mol% acetonitrile and cooled to -10°C. For exact amounts used, see supplementary information section XX. The solution was seeded immediately upon reaching -10°C with all possible solid forms and seeded once more on the following day, to ensure the formation of the thermodynamically most stable form. The solution was left at -10°C for a week, after which the solid phase was filtered. The solids were then analyzed via chiral HPLC to determine the enantiomeric excess in Ibuprofen (and thus confirming resolution is taking place). Table 1 shows that resolution takes place. A first step, therefore leads to a solid phase with a *ee* of +/- 46%. We considered the outcome of the first step, as our starting point for the second step. In this step, we started from a 30:70 (*R*:*S*) composition (corresponding to the outcome of step 1) and followed the same experimental procedure as described above implying a 2.5:2.5 ratio Ibuprofen/Leviteracetam and a 95 mol% solvent. This should lead to the formation of the co-crystal phase only. Surprisingly, the recovered solid showed a 94% amount of S-Ibuprofen vs the R-enantiomer. To verify where the presence of R-Ibuprofen came from, additional experimetns from step 2 were performed with a washing step added assuring the presence of the R-enantiomer is due to the solid phase and not to remaining mother liquor. As shown by

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Table 1, washing does not significantly impact the *e.e.* (for enantiopurity determination via HPLC, see supplementary information section 3). This implies that the co-crystal most likely forms as a solid-solution. As Ibuprofen does not form a solid solution on its own, the remaining R-enantiomer can be removed upon successive co-crystal dislocation which will be described elsewhere.

	% (*R*)-Ibuprofen	% (*S*)-Ibuprofen	*e.e.*
Step 1: 2.5:2.5 at 50:50 No wash	26.8%	73.2%	46.4%
Step 2: 2.5:2.5 at 30:70 No wash	6.1%	93.9%	87.8%
Step 2: 2.5:2.5 at 30:70 Wash	6.2%	93.8%	87.6%

Table 1: Scaled up steps. Average value of experiments given. The table shows the amount of R vs S enantiomer of Ibuprofen in the resulting solid phase.

Conclusion

In this contribution, we developed a dual-drug chiral resolution process, focusing on the Ibuprofen/Levetiracetam system. Binary and ternary phase diagrams of both Ibuprofen enantiomers with Levetiracetam ((*S*)-Etiracetam) have been constructed confirming the existence of an enantiospecific co-crystal between (*S*)-Ibuprofen and Levetiracetam. We then introduced a solvent into the system, showing how the use of appropriate phase diagrams, can lead to enantio-enrichement and ultimately resolution of a targeted enantiomer of a given drug using a second drug as chiral resolution agent. This way a dual drug co-crystal resolution process is developed. Such a process can have strong potential impact for pharmaceutical industry as one not only opens novel possibilities for chiral resolution, but one furthermore obtains new dual- drug formulations.

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