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Purification of Partially Resolved Enantiomeric Mixtures with the Guidance of Ternary Phase Diagram

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Abstract:

The rationale and strategy for purification of partially resolved enantiomeric mixtures based on ternary phase diagrams are discussed. From the ternary phase diagram, one can deduce if a feasible process can be developed to upgrade the enantiomeric excess (ee) of a partially resolved enantiomeric mixture. When such a process is determined to be feasible, the optimal conditions can then be defined based on the ternary phase diagram to upgrade ee to a desirable value with maximum yield. Three ee upgrade examples of pharmaceutical processes are presented to demonstrate the importance and success of application of ternary phase diagrams in designing an optimal process.

Introduction

Enantiomers of active pharmaceutical ingredients (API) often have different biological activities.[1] It is estimated that more than half of all marketed drugs are chiral compounds,[2] making the isolation of optically pure compounds (greater than ~98% enantiomeric excess (ee)) of key importance.

Asymmetric synthesis[3,4] is frequently used to produce partially resolved mixtures of enantiomers in the pharmaceutical industry. Often these mixtures do not have high enough ee to meet clinical requirement, and process modifications are needed for further purification. A significant amount of work has been published on chiral resolution of racemate at a large scale using kinetic resolution by preferred crystallization,[5–8] enzymatic resolution,[9] and chromatographic methods.[10] However, the discussion of chiral resolution from partially resolved mixtures of enantiomers by crystallization or dissolution is rare.[11]

Jacques et al.[12] discussed the fundamentals of using a ternary phase diagram (TPD) to guide ee upgrade of partially resolved mixtures. Others have also reported work related to ee upgrade based on TPD;[13–16] however, the application of TPD in a rational design of ee upgrade by crystallization/dissolution has received surprisingly little attention in the pharmaceutical industry. Typically for ee upgrades of partially resolved mixtures, it is a common practice for different conditions to be randomly screened until a feasible process suffices. Thus, ee upgrade process development often requires a significant amount of time and material, and the resulting process may not be optimal or as robust as required.

This paper represents the first quantitative work on the application of TPD to the enrichment of desired enantiomer from partially resolved enantiomeric mixtures. First, the rationale and strategy of upgrading ee of partially resolved mixtures are systematically discussed. Second, equations to calculate the quantities of solvent needed in the process and product yield are derived. Based on the ee of starting material and composition of the eutectic point, these equations will both determine the optimal solvent/solid ratio and predict the maximum achievable yield. Finally, three ee upgrade examples of pharmaceutical processes representing three different scenarios are presented. The results from the three case studies clearly demonstrate the importance and success of TPD application in designing an optimal process to upgrade ee from partially resolved mixtures.

Rationale and Strategy of Upgrading ee of Partially Resolved Enantiomeric Mixtures Based on Ternary Phase Diagrams. There are three types of racemates (conglomerate, racemic compound, and solid solution), which display three types of symmetrical TPDs (Figure 1). The TPD of a chiral compound can be constructed by performing solubility measurements of either enantiomer mixtures or mixtures of racemate and one enantiomer in a solvent system. From the resulting TPD, the type of racemate that the two enantiomers form can then be conclusively determined.

Figure 1a represents a typical isothermal TPD of a conglomerate system. A′EA represents the saturated solution curve. Point E is the eutectic point with an ee equal to zero. Given the symmetry of the TPD, our discussion will only be focused

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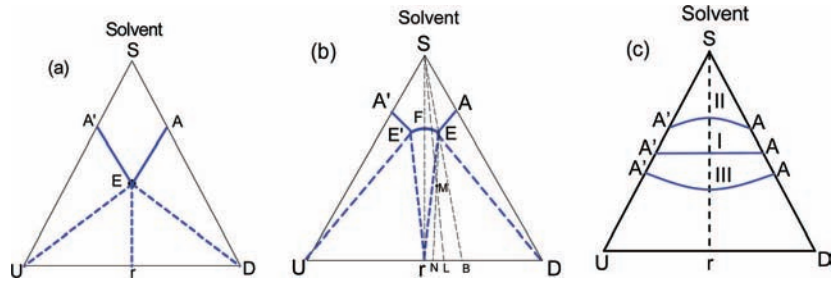

Figure 1. **Ternary phase diagrams of three types of racemates: (a) conglomerate, (b) racemic compound, and (c) solid solution.**

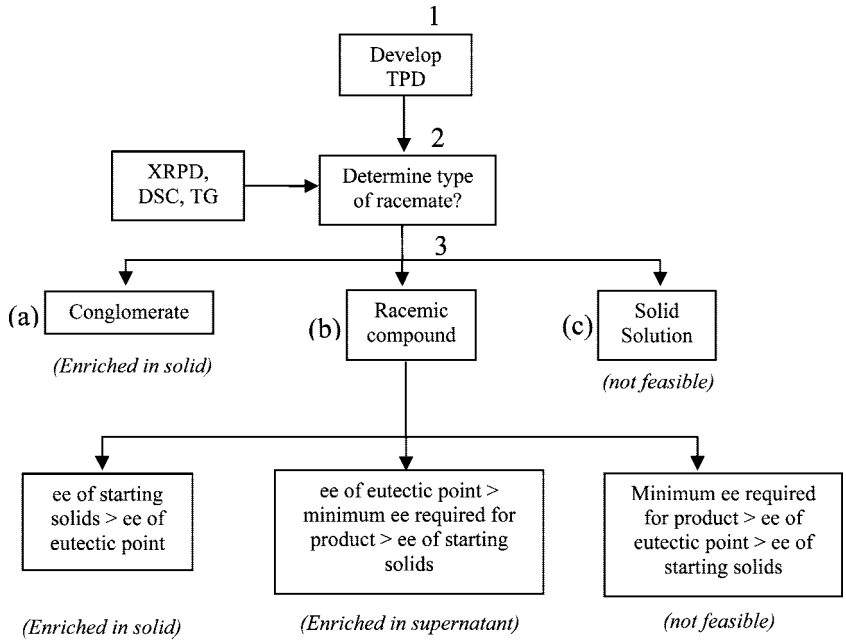

Figure 2. **Work flow of an optimal ee upgrade process development for partially resolved enantiomeric mixtures with the guidance of TPD.**

on the right half of the diagram with the bottom right vertex representing the desired enantiomer (D). In this paper, letter D is used to represent the desired enantiomer (the bottom left vertex, labeled as point U, represents the undesired enantiomer).

Two regions, ErD and AED, are of particular interest. Region ErD represents a system where, at equilibrium, both U and D exist in the solid phase. Therefore, based on the Gibbs phase rule, at constant pressure, there is only one variance. This means that at constant temperature, the composition of supernatant is fixed, independent of the total composition. As shown in Figure 1a, the supernatant composition is represented by eutectic point E. Region AED represents a system where, at equilibrium, U is completely dissolved in the liquid phase and only D exists in the solid phase. At constant pressure there are two variances. This means that at constant temperature, the composition of the supernatant changes with total system composition, moving along line EA. The solid will be pure D as represented by point D.

On the basis of the above discussion, for a partially resolved conglomerate system, pure solid D can be obtained as long as enough solvent is added so that the total composition reaches the region AED. It is apparent that when such an amount of solvent (V_{min}) is added that the total composition of the system is on line ED, a maximum yield (defined as the ratio of amount of D in the solid to the amount of D in the total system) will be achieved. As to be discussed in depth later, V_{min} and the corresponding maximum yield can be calculated based on the composition of eutectic point E and the ee of starting solid material.

Figure 1b represents a typical isothermal TPD of a racemic compound-forming system. For this system, there are two symmetric eutectic points, with E′ in the left half and E in the right half. A′E′EA represents the saturated solution curve. The ee of eutectic point E is between 0 and 100. Again, given the symmetry of the TPD, our discussion will only be focused on the right half of the diagram. Region FrE represents a system where only racemic compound exists in the solid phase. Based on the Gibbs phase rule, there are two variances under constant pressure. At constant temperature, the composition of supernatant varies as a function of total composition, along FE. The solid phase is represented by point r. Region ErD represents a system where, at equilibrium, both racemic compound and D exist in the solid phase. Therefore the system has only one variance at fixed pressure. This means that at constant temperature, the composition of supernatant is fixed, represented by eutectic point E. Region AED represents a system where, at equilibrium, only D exists in the solid phase, resulting in two variances for the system at fixed pressure. Therefore, at constant temperature, the supernatant composition varies along line EA as a function of total composition.

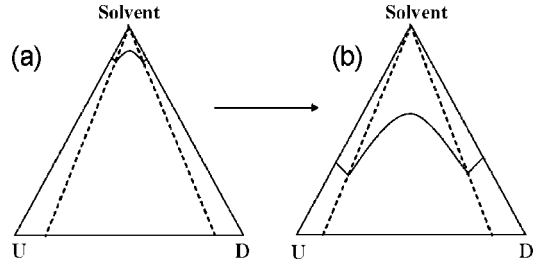

Figure 3. **Ternary phase diagrams plotted using (a) same unit for each component and (b) different units for solvent and solid.**

Depending on the relationship of the ee of starting solids and the ee of eutectic point, two different strategies should be applied in upgrading ee of partially resolved mixtures of two enantiomers that form a racemic compound. When the starting solids have an ee greater than that of the eutectic point (starting composition is between B and D), the system is similar to a conglomerate system in the sense that the U (or r) can be totally dissolved, and thus the same strategy as that for the conglomerate system should be used. In other words, enough solvent should be added to the solids until the total composition reaches the region AED. Then upon equilibrium, the solids will be pure D with 100% ee.

When a starting solid, e.g., point L, has an ee lower than that of eutectic point (starting composition is between r and B), a different strategy should be considered. In this case, by adding solvent, the system composition will move from region ErB to FrE. In region ErB, e.g., point M, upon equilibrium, the composition of the supernatant will be represented by eutectic point E and the remaining solids will be a mixture of racemic compound and D with an ee lower than that of starting solids, point N. In region FrE, D will completely dissolve, the remaining solids will be pure racemic compound, and the supernatant will have an ee lower than that of the eutectic point. It is clear that the ee of the liquid phase will always be greater than the ee of the starting solid at the expense of lower ee of the solid phase. Therefore, when the ee of starting solids is lower than that of the eutectic point, the system can be purified in filtrate and the highest ee achievable is the ee of the eutectic point. To achieve this, the total composition after addition of solvent has to be within region ErB. Within this region, as more solvent is added, the yield will increase. The maximum yield will be achieved when an amount of solvent, V_{max}, is added so that the total composition is on the line Er. When the starting ee is the same as the eutectic ee, no ee upgrade can be achieved in either solid or liquid phase.

Figure 1c represents isothermal TPDs of three types of solid solutions. A′A represents the saturated solution curves. In the case of type I, no ee upgrade can be achieved in solid phase or in solution, and in the cases of type II and type III, only a slight ee upgrade could be achieved in solution and solid phase, respectively. Therefore, methods other than dissolution or crystallization should be considered for systems that form solid solution.

It should be noted that the TPDs in Figure 1 represent systems where neither enantiomer nor racemic compound forms a solvate. In cases where these assumptions do not apply, the isothermal TPDs can be easily adjusted.[12]

From the above discussion, it is clear that TPD is essential in designing an optimal process to upgrade ee of partially resolved mixture. Primarily, the strategy of upgrading ee is dependent on the type of racemate that two enantiomers form and the relationship between the starting ee and eutectic ee in the case of racemic compound-forming systems. Second, by using TPD, the optimal solvent/solid ratio can be predefined and the corresponding maximum yield can be predicted.

The development of an optimal ee upgrade process based on TPD can be summarized into the following steps (Figure 2):

1. Develop the TPD by performing solubility measurements of mixtures of two enantiomers or mixtures of racemate and one enantiomer in the chosen solvent system.

2. Determine the type of racemate that the two enantiomers form.

3. (a) If it is a conglomerate system, then ee can be upgraded to 100% with a maximum yield by adding V_{min} amount of solvent. (b) If it is a racemic compound system when the ee of starting solid is greater than that of eutectic point, ee can be upgraded to 100% in the solid phase with a maximum yield by adding V_{min} amount of solvent; when the ee of starting solid is lower than that of eutectic point and the eutectic ee is greater than the minimum ee required for the product, the ee can be upgraded to the same as that of the eutectic point in the supernatant and the maximum yield can be achieved by adding V_{max} amount of solvent; when the ee of starting solid is lower than that of eutectic point and the eutectic ee is lower than the minimum ee required for the product, no feasible process can be developed to upgrade ee of the partially resolved mixtures directly to meet the minimum ee requirement. (c) If it is a solid solution system, a slight ee upgrade can be achieved in the cases of type II and type III by dissolution or crystallization, and no ee upgrade can be achieved in the case of type I.

Plot of TPD. In most literature references, TPDs were plotted by using same unit for solids and solvent in an attempt to make each point represent mole fraction or weight fraction. In this paper, we introduce a more practical way to plot the TPDs by using different units for solids and solvent. This approach makes TPDs easier to read and easier to apply for an industrial setting. Figure 3a represents an example where the TPD is plotted by using the same unit for solids and solvent, and the saturated solution curves are too close to the apex of the triangle to be read. By adjusting the units, the saturated solution curve in Figure 3a can always be moved down and shown in an area suitable for reading, as shown in Figure 3b. It is apparent that, by using different units for solids and solvent, the symmetry of the TPD remains unchanged as two enantiomers still use the same unit and the TPD only moves up and down vertically. This concept of using different units for enantiomers and solvent in plotting the TPD is especially useful when dealing with a cosolvent system or a solvent system with various types of impurities as to be illustrated in our case studies.

Exploration of the TPD. The coordinate of any point in the TPD can be represented by (X, Y, Z), where X, Y, Z represent the percentage of desired enantiomer (D), undesired enantiomer (U), and the solvent, respectively. The sum of X, Y, and Z is 100. Given that solubility is often reported as milligrams of

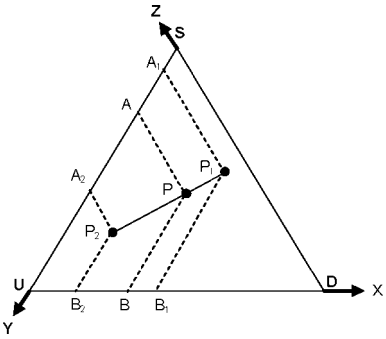

Figure 4. **Ternary phase diagram.**

solids per milliliters of solvent, in this paper, milligram is used as the unit for D and U and milliliter is used as the unit for solvent unless otherwise specified. This means that for a system represented by point (*X*, Y, Z), it consists of *X* (mg) of D, *Y* (mg) of U for every *Z* (mL) of solvent. For example, if a system consists of 12.0 mg of D, 7.0 mg of U, and 1.0 mL of solvent, its coordinate can be determined as:

$$X = 12.0/(12.0 + 7.0 + 1.0) * 100 = 60.0$$

$$Y = 7.0/(12.0 + 7.0 + 1.0) * 100 = 35.0$$

$$Z = 1.0/(12.0 + 7.0 + 1.0) * 100 = 5.0$$

As shown in Figure 4, P_1 (X_1, Y_1, Z_1) and P_2 (X_2, Y_2, Z_2) represent any two points in the TPD. Based on the geometry, for any point P on the line P_1P_2 with coordinate (*X*, *Y*, *Z*), the *X* and *Y* can be respectively defined by eqs 1 and 2:

$$\frac{X - X_1}{X_2 - X_1} = \frac{BB_1}{B_2B_1} = \frac{PP_1}{P_2P_1} \tag{1}$$

$$\frac{Y - Y_1}{Y_2 - Y_1} = \frac{AA_1}{A_2A_1} = \frac{PP_1}{P_2P_1} \tag{2}$$

Combining eqs 1 and 2 will give

$$Y = \frac{(Y_2 - Y_1)(X - X_1)}{(X_2 - X_1)} + Y_1 \tag{3}$$

For a given TPD, as shown in Figure 1, the coordinate of point r is (50, 50, 0) and that of point D is (100, 0, 0). The coordinate of the eutectic point E is expressed in (X_0, Y_0, Z_0) in this work. Based on eq 3, the *X* and *Y* of any point (*X*, *Y*, *Z*) on the line Er can be calculated from the coordinates of points E and r:

$$Y = \frac{(50 - Y_0)(X - X_0)}{(50 - X_0)} + Y_0 \tag{4}$$

Similarly, the coordinate of any point (*X*, *Y*, *Z*) on line ED can be calculated from the coordinates of points E and D:

$$Y = \frac{(0 - Y_0)(X - X_0)}{(100 - X_0)} + Y_0 = \frac{-XY_0 + 100Y_0}{100 - X_0} \tag{5}$$

Racemic Compound System. In this work, ee_0 is used to represent the ee of starting solid mixture of enantiomers (or total system), e.g., for the starting solid with 94% ee, ee_0 is 0.94. *V* represents the milliliters of solvent that is added to every milligram of starting solid, and V_m represents the milliliters of solvent that needs to be added to every milligram of starting solid so that the total composition reaches the border of two regions (line ED in Figure 1a and line Er or ED in Figure 1b).

For a racemic compound system with the starting solid ee lower than that of eutectic, V_m is the maximum milliliters of solvent that can be added to every mg of starting solid while still upgrading ee to that of eutectic in the supernatant. Therefore, $V_m = V_{max}$.

By adding V_{max} mL of solvent to a starting solid with composition represented by point P_1 as shown in Figure 5, the system will have a composition represented by O (the intersection of line SP_1 and line Er). Given 1 mg of starting solid, the weight of D is given by $(0.5 + 0.5ee_0)$ mg and U by $(0.5–0.5ee_0)$ mg, so the system represented by point O consists of $(0.5 + 0.5ee_0)$ mg of D, $(0.5–0.5ee_0)$ mg of U, and V_{max} (mL) solvent. Therefore the *X* and *Y* of the coordinate of point O will be

$$X = \frac{(0.5 + 0.5ee_0) * 100}{(1 + V_{max})} \tag{6}$$

$$Y = \frac{(0.5 - 0.5ee_0) * 100}{(1 + V_{max})} \tag{7}$$

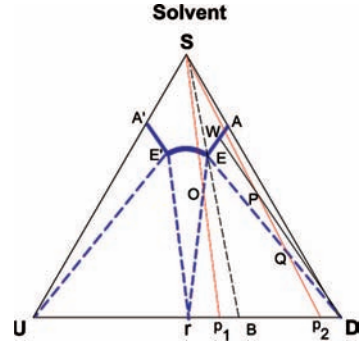

Figure 5. **TPD of a racemic compound system.**

Since the intersection is on line Er, it will satisfy eq 4, and hence

$$\frac{(0.5 - 0.5ee_0) * 100}{(1 + V_{max})} = \frac{(50 - Y_0)}{(50 - X_0)}\left[\frac{(0.5 + 0.5ee_0) * 100}{(1 + V_{max})} - X_0\right] + Y_0 \tag{8}$$

By solving eq 8, we get

$$V_{max} = \frac{Z_0}{(X_0 - Y_0)} \cdot ee_0 = \frac{ee_0}{[D]_{eu} - [U]_{eu}} \tag{9}$$

where $[D]_{eu}$ and $[U]_{eu}$ represent the concentration of D and U (mg solids/mL solvent) at the eutectic point, respectively.

At $V \le V_{max}$, the yield, defined as the ratio of amount of D in the supernatant to the amount of D in the total system, can be calculated by

$$\text{yield} = \frac{V \times \dfrac{X_0}{Z_0}}{0.5 + 0.5\text{ee}_0} = \frac{[\text{D}]_{eu}}{0.5 + 0.5\text{ee}_0} \cdot V \qquad (10)$$

On the basis of eq 10, it is apparent that for a starting solid with a constant ee of ee_0, the yield increases as more solvents are added and finally reaches a maximum when V reaches V_{max}, the maximum amount of solvent (in mL) that can be added to upgrade the ee to the same as that of eutectic point E. Letting ee_{eu} represent the ee of eutectic point E, we have

$$\frac{Y_0}{X_0} = \frac{1 - \text{ee}_{eu}}{1 + \text{ee}_{eu}} \qquad (11)$$

According to eqs 10 and 11, at $V_{max} = [Z_0/(X_0 - Y_0)] \cdot ee_0$, the yield reaches the maximum, which is

$$\text{yield}_{(max)} = \frac{\dfrac{Z_0}{(X_0 - Y_0)} \cdot \text{ee}_0 \cdot \dfrac{X_0}{Z_0}}{0.5 + 0.5\text{ee}_0} = \frac{\text{ee}_0}{(0.5 + 0.5\text{ee}_0)\left(1 - \dfrac{Y_0}{X_0}\right)} = \frac{\text{ee}_0(1 + \text{ee}_{eu})}{(1 + \text{ee}_0)\text{ee}_{eu}} \qquad (12)$$

For a racemic compound system with the starting solid ee greater than that of eutectic, V_m is the minimum milliliters of solvent that needs to be added to every milligram of starting solid in order to upgrade ee to 100% in the solid phase. Therefore, $V_m = V_{min}$.

By adding V_{min} mL of solvent to every milligram of starting solid with composition represented by point P_2 as shown in Figure 5, the system will have composition represented by Q, the intersection of line SP_2 and line ED. Given 1 mg of starting solid, then the system at Q will contain $(0.5 + 0.5ee_0)$ mg of D, $(0.5 - 0.5ee_0)$ mg of U, and V_{min} mL of solvent. Therefore the X and Y of the coordinate of point Q will be

$$X = \frac{(0.5 + 0.5\text{ee}_0) \cdot 100}{(1 + V_{min})} \qquad (13)$$

$$Y = \frac{(0.5 - 0.5\text{ee}_0) \cdot 100}{(1 + V_{min})} \qquad (14)$$

Since the intersection is on line ED, it will satisfy the eq 5, and hence

$$\frac{(0.5 - 0.5\text{ee}_0) \cdot 100}{(1 + V_{min})} = \frac{-\left(\dfrac{0.5 + 0.5\text{ee}_0}{1 + V_{min}}\right) \cdot 100 \cdot Y_0 + 100Y_0}{(100 - X_0)} \qquad (15)$$

By solving eq 15, we get

$$V_{min} = \frac{Z_0}{2Y_0} \cdot (1 - \text{ee}_0) = \frac{1}{2[\text{U}]_{eu}}(1 - \text{ee}_0) \qquad (16)$$

On the basis of the above discussion for this system, a minimum of V_{min} mL of solvent needs to be added to the starting solid in order to achieve 100% ee in the solid phase at equilibrium. Therefore, it is useful to calculate the yield when V_{min} or more solvent is added to the solid so that the total composition reaches the region AED.

Now let point P (X_p, Y_p, Z_p) represent the total composition of the system and point W (X_w, Y_w, Z_w) represent the composition of the supernatant at equilibrium when V mL of solvent is added to 1 mg of starting solid so that the total composition reaches the region AED. Since at $V \ge V_{min}$, the racemic compound is completely dissolved in supernatant and the amount of U in supernatant is equal to the amount of U present in the total system $(0.5–0.5ee_0)$; therefore we have

$$Z_w = \frac{Y_w V}{(0.5 - 0.5\text{ee}_0)} \qquad (17)$$

When the total composition is at point P, the amount of D in supernatant can be calculated by $(X_w/Z_w)V$. The yield, defined as the ratio of amount of D in the solid phase to the amount of D in the total system, can therefore be calculated by

$$\text{yield} = 1 - \frac{\dfrac{X_w}{Z_w}V}{0.5 + 0.5\text{ee}_0} = 1 - \frac{\dfrac{X_w}{\left(\dfrac{Y_w V}{0.5 - 0.5\text{ee}_0}\right)}V}{0.5 + 0.5\text{ee}_0} = 1 - \frac{\dfrac{X_w}{Y_w} \cdot (1 - \text{ee}_0)}{(1 + \text{ee}_0)} \qquad (18)$$

Assuming the point A, which represents the saturated solution of pure D, has coordinate $(X_d, 0, Z_d)$, then on the basis of eq 3, the X and Y of any point (X, Y, Z) on line AE will satisfy the following equation:

$$Y = \frac{(0 - Y_0)(X - X_0)}{(X_d - X_0)} + Y_0 = \frac{Y_0(X_d - X)}{(X_d - X_0)} \qquad (19)$$

Also, given point P (X_p, Y_p, Z_p), we have

$$X_p = \frac{(0.5 + 0.5\text{ee}_0) \times 100}{(1 + V)} \qquad (20)$$

$$Y_p = \frac{(0.5 - 0.5\text{ee}_0) \times 100}{(1 + V)} \qquad (21)$$

Therefore, based on the coordinate of point P and point D (100, 0, 0), the X and Y of any point (X, Y, Z) on line PD will satisfy the following equation:

$$Y = \frac{\left(\frac{(0.5 - 0.5\mathrm{ee}_0)\times 100}{(1+\upsilon)} - 0\right)(X - 100)}{\frac{(0.5 + 0.5\mathrm{ee}_0)\times 100}{(1+\upsilon)} - 100} + 0 = \frac{(1-\mathrm{ee}_0)(100 - X)}{1 + 2\upsilon - \mathrm{ee}_0} \quad (22)$$

Given that point w (X_w, Y_w, Z_w) is on both lines AE and PD, X_w and Y_w should satisfy both eqs 19 and 22; therefore, we have

$$Y_w = \frac{Y_0(X_d - X_w)}{(X_d - X_0)} \quad (23)$$

$$Y_w = \frac{(1-\mathrm{ee}_0)(100 - X_w)}{1 + 2\upsilon - \mathrm{ee}_0} \quad (24)$$

Now let $k = X_w/Y_w$, then

$$X_w = kY_w \quad (25)$$

Substituting eq 25 into both eqs 23 and 24, we have

$$k = \left(\frac{X_d}{Z_d}\right)\cdot\left(1 + \frac{2V}{1-\mathrm{ee}_0} - 100\cdot\frac{(X_d - X_0)}{X_d Y_0}\right) \quad (26)$$

Substituting eq 26 into eq 18, we have

$$\mathrm{yield}_{(\mathrm{at}\ V \geq V_{\min})} = 1 - \left(\frac{X_d}{Z_d}\right)\left(\frac{1-\mathrm{ee}_0}{1+\mathrm{ee}_0}\right)\left(1 + \frac{2V}{1-\mathrm{ee}_0} - 100\cdot\frac{(X_d - X_0)}{X_d Y_0}\right) = 1 - \left(2V\cdot[\mathrm{D}]_{\mathrm{pure}} + \frac{[\mathrm{D}]_{\mathrm{eu}} - [D]_{\mathrm{pure}}}{[\mathrm{U}]_{\mathrm{eu}}}\cdot(1-\mathrm{ee}_0)\right)\cdot\left(\frac{1}{1+\mathrm{ee}_0}\right) \quad (27)$$

where $[\mathrm{D}]_{\mathrm{pure}}$ represents the solubility of pure D at mg solid/mL solvent.

At $V = V_{\min,}$ the above equation can be simplified to

$$\mathrm{yield}_{\max} = 1 - \frac{(1-\mathrm{ee}_0)(1+\mathrm{ee}_{\mathrm{eu}})}{(1+\mathrm{ee}_0)(1-\mathrm{ee}_{\mathrm{eu}})} \quad (28)$$

Conglomerate System. For a conglomerate system, V_m is the minimum milliliters of solvent that needs to be added to every milligram of starting solid in order to upgrade ee to 100% in the solid phase. It can be treated as a special case of racemic compound with the starting ee greater than the eutectic ee, which is 0. So eqs 16, 27, and 28 also apply to the conglomerate system:

$$V_{\min} = \frac{1}{2[\mathrm{U}]_{\mathrm{eu}}}(1 - \mathrm{ee}_0) \quad (29)$$

$$\mathrm{yield}_{(\mathrm{at}\ V \geq V_{\min})} = 1 - \left(2V\cdot[\mathrm{D}]_{\mathrm{pure}} + \frac{[\mathrm{D}]_{\mathrm{eu}} - [\mathrm{D}]_{\mathrm{pure}}}{[\mathrm{U}]_{\mathrm{eu}}}\cdot(1-\mathrm{ee}_0)\right)\cdot\left(\frac{1}{1+\mathrm{ee}_0}\right) \quad (30)$$

$$\text{and at } V = V_{\min}, \mathrm{yield}_{\max} = \frac{2\mathrm{ee}_0}{1+\mathrm{ee}_0} \quad (31)$$

Results and Discussion

Case Study One: Racemic Compound. (Starting material has an ee lower than the eutectic ee, which is greater than the required ee for the product.) Compound I (taranabant, Figure 6), *N*-[(1*S*,2*S*)-3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2[[5-(trifluoromethyl)pyridin-2-yl]oxy] propanamide, is a potent CB-1R inverse agonist developed for the treatment of obesity.[17]

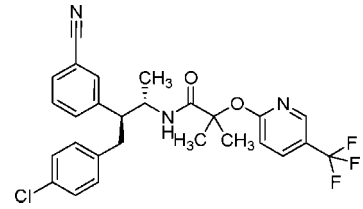

Figure 6. **Molecular structure of compound I.**

Compound I was first obtained as an MTBE solvate (form A) with ee ranging from 94% to 96% through asymmetric synthesis and subsequent crystallization. A purification process is required to upgrade the ee as well as to generate the desired anhydrous crystalline form (Form B).

In order to define the type of racemate (conglomerate, racemic compound, or solid solution) and to construct the TPD, a racemate was synthesized, crystallized, and then analyzed by thermogravimetric analysis (TG), differential scanning calorimetry (DSC), and X-ray powder diffraction (XRPD). TG showed no residual solvent, indicating the racemate is anhydrous. XRPD displayed a different pattern from that of form B of the enantiomer. DSC showed a higher melting point than form B of the enantiomer. These data indicate that the racemate is either a conglomerate with a crystalline form different from that of the anhydrous form B or a racemic compound. To find out if the racemate is a conlomerate of a new polymorph of the enantiomers or a racemic compound, conversion experiments were performed. In these experiments, mixtures of the racemate and form B of the enantiomer were slurried in several solvents for 24 h and the solid phases were analyzed by XRPD for possible phase changes. The XRPD patterns showed still

(17) Lin, L. S.; Lanza, T. J.; Jewell, J. P.; Liu, P.; Shah, S. K.; Qi, H; Tong, X.; Wang, J.; Xu, S. S.; Fong, T. M.; Shen, C.; Lao, J.; Xiao, J.; Shearman, L. P.; Stribling, D. S.; Rosko, K.; Strack, A.; Marsh, D. J.; Feng, Y.; Kumar, S.; Samuel, K.; Yin, W.; Van der Ploeg, L. H. T.; Goulet, M. T.; Hagmann, W. K. *J. Med. Chem.* **2006**, *49* (26), 7584–7587.

Table 1. **Composition of the total system and the supernatant in solubility measurements in 2:3 (v:v) IPAC/heptane solvent at 25.0 °C**

	total composition				composition of supernatant at equilibrium				
tube	*S* (mg)	*R* (mg)	solvent (mL)	ee (%)	*S* (mg)	*R* (mg)	solvent (mL)	ee (%)	XRPD of residual wet cakes
1	11.20	10.85	1.0	1.52	7.4	7.0	1.0	3.16	racemate
2	17.2	9.30	1.0	29.81	12.5	4.5	1.0	46.90	racemate
3	322.78	4.97	1.0	96.97	298.84	1.86	1.0	98.76	mixture of racemate and form B
4	342.83	5.27	1.0	96.97	297.69	1.68	1.0	98.88	mixture of racemate and form B
5	320.47	4.93	1.0	96.97	296.25	1.83	1.0	98.77	mixture of racemate and form B

mixtures of two starting materials, suggesting no form changes and that the racemate is likely a racemic compound.

To confirm the type of racemate, the TPD was developed in 2:3 (v:v) IPAC/heptane cosolvent, the solvent system to be used to isolate the desired crystal form (form B) in the down stream. Several mixtures of the racemate and the desired enantiomer (form B) covering the 0−100% ee range were used for solubility measurements. Table 1 lists the system composition used for this study and the resulting solution compositions. The remaining solids were analyzed by XRPD, and the results are also included in Table 1.

On the basis of the magnitude of the concentration, 1 mg and 0.1 mL are chosen as units for the enantiomers and the solvent, respectively, to display the saturated solution curve in a readable region of TPD (Figure 7). The TPD clearly indicates that the racemate is a racemic compound. Although the solubility of pure racemic compound is not directly available from Table 1, we can calculate from the solubility data of tube 1 based on the following equation:[16]

$$[\mathrm{r}]_{\mathrm{pure}} = 2\sqrt{[S]\cdot[R]} \tag{32}$$

where $[\mathrm{r}]_{\mathrm{pure}}$ represents the solubility of pure racemic compound and $[S]$ and $[R]$ are the concentrations of *S* and *R* in the supernatant of tube 1, respectively. This approach is very accurate in our case where the ee of the supernatant of tube 1 is so close to 0. From the above discussion, the solubility of pure racemic compound can therefore be determined to be 7.2 mg of *R* and 7.2 mg of *S* per milliliter of solvent. In addition, based on the average of solubility data of tubes 3, 4, and 5, the solubility of desired enantiomer (1*S*,2*S*) and undesired enantiomer (1*R*,2*R*) at the eutectic point can be determined to be 297.6 and 1.79 mg/mL of solvent, respectively. Given the high eutectic point ee (98.80%), the solubility of pure enantiomer will be very close to that of desired enantiomer at the eutectic point (∼297.6 mg/mL). Clearly, the extremely high ee of the eutectic point is due to the low solubility ratio of racemic compound to enantiomer.

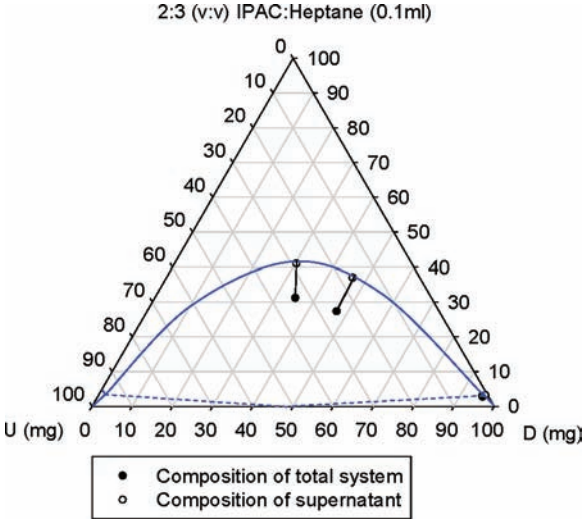

Figure 7. **Ternary phase diagram of compound I in 2:3 (v:v) IPAC/heptane solvent system at 25.0 °C.**

From the TPD, the ee of the eutectic point (98.80%) is greater than that of starting solids (∼94−96%). Therefore, according to Figure 2, the ee can be upgraded to a maximum value of 98.80% in the supernatant by dissolution.

Based on eqs 9 and 12, $V_{\max}$ and $\mathrm{yield}_{(\max)}$ can be calculated as follows:

$$V_{\max} = \left(\frac{\mathrm{ee}_0}{[\mathrm{D}]_{\mathrm{eu}} - [\mathrm{U}]_{\mathrm{eu}}}\right) = 0.00338\mathrm{ee}_0$$

$$\mathrm{yield}_{(\max)} = \frac{\mathrm{ee}_0(1+\mathrm{ee}_{\mathrm{eu}})}{(1+\mathrm{ee}_0)\mathrm{ee}_{\mathrm{eu}}} = \frac{2.012\mathrm{ee}_0}{(1+\mathrm{ee}_0)}$$

Given a starting mixture with ee of 94%, we can easily determine $V_{\max}$ to be 0.00318 and the maximum yield to be 97.6% at $V=V_{\max}$. This means by adding 0.00318 mL of 2:3 (v:v) IPAC/heptane solvent to every milligram of starting solid with 94% ee at 25.0 °C, at equilibrium, the ee will be upgraded to 98.80% in the supernatant with a yield of 97.6%.

When $V_{\max}$ amount of solvent is added, the solid phase at equilibrium is pure racemic compound and the supernatant has composition E. With addition of any extra amount of solvents, more racemic compound will dissolve into the supernatant, resulting in a decrease of supernatant ee. This suggests that if the minimum ee required for the final product is lower than the eutectic ee (98.80%), more than $V_{\max}$ amount of solvent can be added to the solids so that the ee of supernatant is between 98.80% and the minimum required ee and a yield slightly greater than 97.6% can be achieved.

Once supernatant with 98.80% ee is produced, it can be isolated by filtration, and then the solids can be crystallized by charging an antisolvent, cooling, or evaporation. In our case, we chose to crystallize the solids by adding heptane. Preliminary studies indicated 1:35 (v:v) IPAC/heptane was a suitable final solvent composition in terms of affording minimal yield loss while charging suitable volume of antisolvent. Therefore, to ensure an optimal ee can be obtained in the solid at the end of

Table 2. **Composition of the total system and the supernatant at equilibrium for solubility measurements in 1:35 (v:v) IPAC/heptane solvent at 25.0 °C**

	total composition				composition of supernatant at equilibrium			
tube	*S* (mg)	*R* (mg)	solvent (mL)	ee (%)	*S* (mg)	*R* (mg)	solvent (mL)	ee (%)
1	8.75	8.45	1.0	1.52	0.15	0.109	1.0	15.96
2	13.05	12.7	1.0	1.52	0.18	0.118	1.0	20.28
3	28.55	13.6	1.0	35.44	1.57	0.020	1.0	97.44
4	38.3	6.0	1.0	72.86	1.56	0.015	1.0	98.12
5	23.55	7.1	1.0	53.58	1.70	0.016	1.0	98.14
6	50.15	1.7	1.0	93.43	1.61	0.015	1.0	98.18
7	14.85	0.05	1.0	99.52	1.55	0.007	1.0	99.10

crystallization, the TPD of two enantiomers in 1: 35 (v:v) IPAC/heptane solvent at 25.0 °C is further developed.

The composition of the total system and the saturated solution at equilibrium for each tube is summarized in Table 2. The TPD is shown in Figure 8 after appropriately adjusting the scale. The solubility of racemic compound is about 0.13 mg of *S* and 0.13 mg of *R* per milliliter of solvent. The ee of the eutectic point is 98.15%, which is slightly lower than that of eutectic of the TPD in 2:3 IPAC/heptane solvent system. The solubility at eutectic point is 1.63 mg/mL of *S* and 0.015 mg/mL of *R*.

As shown in Figure 8, E_2 represents the eutectic point in the right part of the TPD, and it has ee equal to 98.15% and very low solubility.

The total system after adding antisolvent can be considered a mixture of solids with 98.80% ee and 1: 35 IPAC/heptane solvent. Such a system can be represented by E_1 in the TPD in Figure 8.

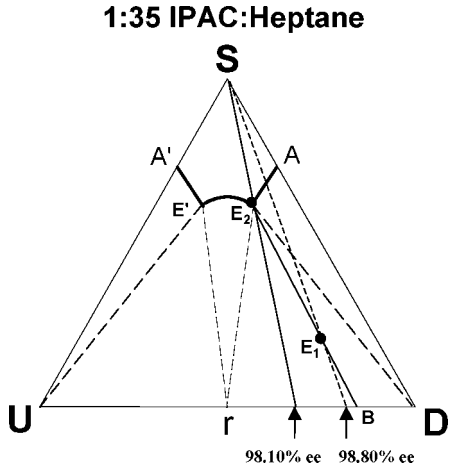

Figure 8. **Adjusted TPD of two enantiomers of compound I in 1: 35 (v:v) IPAC/heptane solvent at 25.0 °C.**

Given that most solids will be crystallized, the E_1 point will be far below the saturated solution curve. Since E_1 is within the E_2rD region, at equilibrium the new supernatant will have a composition as represented by the eutectic point E_2 and the crystallized solids will have a composition as represented by point B, which is the intersection of UD and extrapolated E_2E_1. As shown in Figure 8, point E_2 has ee of 98.10% and point B has ee slightly greater than 98.80%. This means that by adding antisolvent to the supernatant with 98.80% ee, the crystallized solids, as represented by point B, will have ee slightly greater than 98.80%.

With the guidance of ternary phase diagram, ee upgrade was then performed on different batches at pilot scale (~18 kg) in heptane/IPAC solvent system at 20–25 °C. In all batches, ee was successfully upgraded to ~99.0% from ~93% with a yield of ~91%. The yield was slightly lower than predicted; however, this was expected given some yield loss during filtration in the real process.

Case Two: Racemic Compound. (Starting material has an ee greater than the eutectic ee.) Compound II (Figure 9), [(3*R*)-4-(4-chlorophenyl)methyl-7-fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl]acetic acid, is a DP1-receptor antagonist developed for the treatment of niacin-induced flushing.[18]

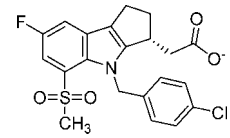

Figure 9. **Molecular structure of compound II.**

Compound II with 92−96% ee can be produced through asymmetric synthesis. Initial studies showed that by forming a salt with diisopropylamine (DIPA), the compound II DIPA salt could be crystallized in ethanol as the anhydrous form with ee of ~100%. Initial XRPD, TG, and DSC analysis of the racemate indicates it is a racemic compound. To further conclusively determine the type of racemate in EtOH solvent system and use the TPD to guide the ee upgrade process, the TPD of compound II DIPA salt in EtOH at 25.0 °C was developed. The composition of the total systems and corresponding saturated solutions at equilibrium are summarized in Table 3, and the TPD is shown in Figure 10. The TPD confirms the racemate is a racemic compound.

Based on Table 3, the solubility of the pure desired enantiomer is 4.76 mg/mL of solvent. The solubilities of desired enantiomer (*R*) and undesired enantiomer (*S*) at the eutectic point are, respectively, 4.27 and 2.28 mg/mL of solvent, resulting in the eutectic point ee being 30.3%.

The ee of eutectic point, 30.3%, is lower than that of starting solids, 92−96% ee. Therefore, according to Figure 2, the ee of the starting enantiomeric mixture can be upgraded to 100% in the solid phase by adding V_{min} or greater amounts of solvents to the solids.

(18) Cheng, K.; Wu, T.; Wu, K. K.; Sturino, C.; Metters, K.; Gottesdiener, K.; Wright, S. D.; Wang, Z.; O'Neil, G.; Lai, E.; Waters, M. G *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 6682–6687.

Table 3. **Composition of the total system and the supernatant at equilibrium for solubility measurements in ethanol at 25.0 °C**

	total composition				composition of supernatant at equilibrium				
tube	*R* (mg)	*S* (mg)	solvent (mL)	ee (%)	*R* (mg)	*S* (mg)	solvent (mL)	ee (%)	XRPD of residual wet cakes
1	42.8	13.5	1.0	52.0	4.26	2.27	1.0	30.4	mixture of enantiomer and racemate
2	47.9	10.4	1.0	64.3	4.28	2.27	1.0	30.6	mixture of enantiomer and racemate
3	25.15	3.75	1.0	74.0	4.26	2.30	1.0	29.8	mixture of enantiomer and racemate
4	52.35	4.85	1.0	83.0	4.27	2.28	1.0	30.4	mixture of enantiomer and racemate
5	43.0	0	1.0	100	4.76	0.00	1.0	99.8	enantiomer

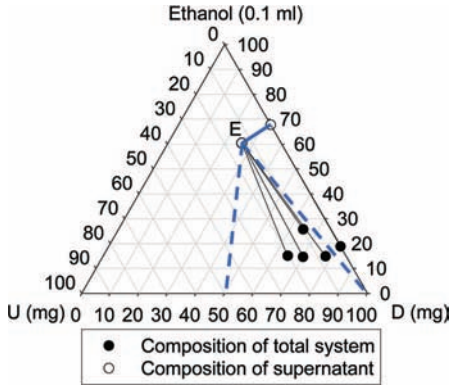

Figure 10. **Ternary phase diagram of compound II DIPA salt in ethanol at 25.0 °C.**

Therefore, based on eqs 16 and 28, V_{min} and the maximum yield at $V = V_{min}$ can be calculated as follows:

$$V_{min} = 0.219(1 - ee_0)$$

$$\text{yield}_{max} = 1 - 1.869\frac{(1 - ee_0)}{(1 + ee_0)}$$

Given a starting enantiomeric mixture with 94% ee, V_{min} can be determined to be 0.0132 and the maximum yield is 91.6% at $V = V_{min}$.

To apply TPD to the real system, more experiments were performed to understand the effect of temperature and impurities on the eutectic composition. With these results, a robust process was developed to crystallize the pure enantiomer of compound II DIPA salt directly from the postasymmetric synthesis solution by adding DIPA and some other chemical agents in ethanol with the final solvent/solid ratio within optimal range according to the TPD. At pilot scale (>10 kg), DIPA salt with >99.0% ee has been consistently produced.

Case Three: Conglomerate. Compound III (Figure 11), (2*R*)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-A]pyrazin-7(8*H*)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, is a DPP-IV inhibitor developed for type 2 diabetes.[19]

Similar to compounds I and II, compound III with 92–96% ee can be produced by asymmetric synthesis. Therefore, a further ee upgrade step is required. A racemate was made by mixing an equimolar mixture of enantiomers and then swishing in different solvents. The racemate thus obtained was then analyzed by XRPD, DSC and TG. TG indicated no residual solvent. XRPD showed the same pattern as the pure enantiomer and DSC showed a lower melting point than that of pureenantiomer. These data suggested the racemate is a conglomerate.

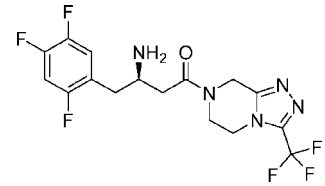

Figure 11. **Molecular structure of compound III.**

Initial crystallization experiments showed that isopropyl alcohol (IPA)/heptane cosolvent system with IPA as solvent and heptane as antisolvent is an ideal solvent system to crystallize compound I with ~100% ee. Therefore, the TPD was developed in 1:3 (v:v) IPA/heptane at 25.0 and 45.0 °C, respectively. The composition of the total system and the saturated solution at equilibrium for each tube at 25 and 45.0 °C are summarized in Tables 4 and 5, respectively, and the TPD at 25 and 45.0 °C are respectively shown in Figure 12a and b. The TPDs confirmed the racemate is a conglomerate.

According to Figure 2, the ee of stating solid mixture can be upgraded to 100% in the solid phase by adding V_{min} or more solvents to the solid. Based on the TPD at 25.0 °C, the solubility

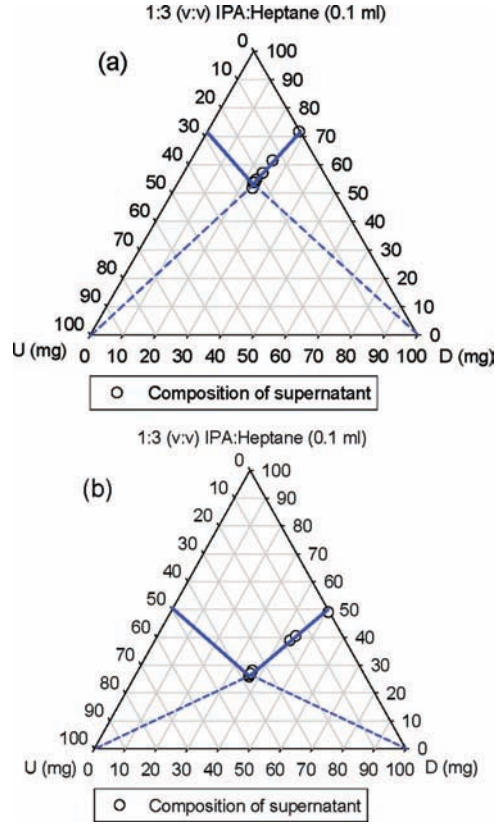

Figure 12. **Ternary phase diagrams of compound III in 1:3 IPA/heptane at (a) 25.0 and (b) 45.0 °C.**

Table 4. **Composition of the total system and the supernatant at equilibrium for solubility measurements in 1:3 (v:v) IPA/heptane at 25.0 °C**

	total composition				composition of supernatant at equilibrium				XRPD of residual
tube	*R* (mg)	*S* (mg)	solvent (mL)	ee (%)	*R* (mg)	*S* (mg)	solvent (mL)	ee (%)	wet cakes
1	27.8	27.3	1.0	0.91	4.62	4.74	1.0	−1.20	same as pure enantiomer
2	12.0	12.5	1.0	−2.05	4.29	4.34	1.0	−0.59	same as pure enantiomer
3	20.4	9.5	1.0	36.45	4.39	4.24	1.0	1.72	same as pure enantiomer
4	18.9	6.1	1.0	51.10	4.31	3.99	1.0	3.86	same as pure enantiomer
5	21.1	2.0	1.0	82.68	4.09	2.20	1.0	30.06	same as pure enantiomer
6	26.3	2.9	1.0	80.14	4.26	3.28	1.0	13.06	same as pure enantiomer
7	31.7	0.0	1.0	100.00	3.94	0.04	1.0	98.21	same as pure enantiomer

Table 5. **Composition of the total system and the supernatant at equilibrium for solubility measurements in 1:3 (v:v) IPA/heptane at 45.0 °C**

	total composition				composition of supernatant at equilibrium				XRPD of residual
tube	*R* (mg)	*S* (mg)	solvent (mL)	ee (%)	*R* (mg)	*S* (mg)	solvent (mL)	ee (%)	wet cakes
1	33.6	33.6	1.0	0.00	14.30	14.53	1.0	−0.80	same as pure enantiomer
2	26.0	26.0	1.0	0.00	13.88	14.05	1.0	−0.60	same as pure enantiomer
3	33.5	11.6	1.0	48.56	13.13	12.57	1.0	2.18	same as pure enantiomer
4	37.1	19.8	1.0	30.40	13.71	13.52	1.0	0.69	same as pure enantiomer
5	21.9	4.0	1.0	69.38	11.21	4.57	1.0	42.07	same as pure enantiomer
6	20.6	3.3	1.0	72.69	11.04	3.73	1.0	49.53	same as pure enantiomer
7	44.6	0.0	1.0	100.00	10.37	0.07	1.0	98.60	same as pure enantiomer

of pure conglomerate is 4.44 mg of *R* and 4.44 mg of *S* per milliliter of solvent and that of pure enantiomer *R* is 3.94 mg/mL of solvent. Therefore, according to eqs 29 and 31, we have

$$V_{\min} = 0.113(1 - \mathrm{ee}_0)$$

$$\mathrm{yield}_{\max} = \frac{2\mathrm{ee}_0}{1 + \mathrm{ee}_0}$$

Given a starting solid mixture with 94% ee, $V_{\min}$ can be determined to be 0.00678 and the maximum yield is 96.9% at $V = V_{\min}$. This means by adding 0.00678 mL of 1:3 (v:v) IPA/heptane to every milligram of starting solid with 94% ee at 25.0 °C, at equilibrium, the ee of desired enantiomer can be upgraded to 100% in the solid phase with 96.9% yield.

On the basis of the TPD at 45.0 °C, the solubility of pure conglomerate is 14.0 mg of *R* and 14.0 mg of *S* per milliliter of solvent and that of pure enantiomer *R* is 10.4 mg/mL solvent. Therefore, similar $V_{\min}$ and the maximum yield at $V = V_{\min}$ can be determined on the basis of eqs 29 and 31.

With the guidance of the ternary phase diagram, a robust process was then developed to crystallize the pure enantiomer of compound III from the IPA/heptane solvent system with the final solvent/solid ratio within optimal range according to the TPD at both pilot and commercial scale. Compound III with >99.0% ee has been consistently produced in all batches.

Thermodynamic Equilibrium versus Kinetic Behavior. The ternary phase diagram describes the thermodynamic equilibrium of an enantiomeric system in a given solvent system. As demonstrated in all three cases above, when a process reaches thermodynamic equilibrium, the optimal ee upgrade conditions can be designed on the basis of the ternary phase diagram and the ee upgrade outcome can be predicted. In most industrial settings, it is preferable to design an ee upgrade process under thermodynamic rather than kinetic control. However, it is not uncommon that a real process does not reach thermodynamic equilibrium within the process time frame due to slow kinetics. For example, in some cases, the desired enantiomer is supersaturated in solution at the end of crystallization due to slow release of supersaturation. This supersaturation will result in a lower yield than theoretically predicted when ee is upgraded in the solid phase. Also commonly observed is that the undesired enantiomer is not completely rejected although enough solvent is present to dissolve all undesired enantiomer under thermodynamic equilibrium because the undesired enantiomer is occluded or physically adsorbed on the crystals of desired enantiomer. This inefficient rejection of undesired enantiomer results in a lower ee of the product when ee is upgraded in the solid phase.

The kinetic behavior of an enantiomeric system is of very importance since it can result in a failure of an ee upgrade process which would otherwise succeed under thermodynamic equilibrium. We suggest the readers to deal with the kinetic factors separately from thermodynamic equilibrium. The ternary phase diagram is the key to understanding and predicting the thermodynamic equilibrium of an enantiomeric system; while in real processes, the kinetic behavior should be seriously taken into account. If appropriately utilized, kinetic behavior can be purposely employed to our advantages, such as kinetic resolution by preferential crystallization. In cases where kinetic behaviors exert an adverse effect on the product quality, efforts to optimize the crystallization condition to minimize the effect of the kinetic behavior should be made. Such efforts generally

(19) Herman, G. A.; Stevens, C.; Van Dyck, K.; Bergman, A.; Yi BDe Smet, M.; Snyder, K.; Hilliard, D.; Tanen, M.; Tanaka, W.; Wang, A. Q.; Chen, L; Zeng, W.; Musson, D.; Laethem, M; Zhou, Y. Y.; Winchell, G.; Davies, M. J.; Ramael, S; Gottesdiener, K. M.; Wagner, J. A. *Clin. Pharm. Ther.* **2005**, *78*, 675–688.

include, but are not limited to, varying temperature, changing solvent composition, decreasing rate of antisolvent addition, and increasing the amount of seeds. As the present paper focuses on ternary phase diagram under thermodynamic equilibrium, extensive investigation of the kinetic behavior of an enantiomeric system will be discussed elsewhere.

Conclusion

In summary, the rationale and strategy for purification of partially resolved enantiomeric mixtures with the guidance of TBD were discussed. Equations to both calculate the optimal ratio of solvent/solid that should be used in ee upgrade process to achieve desirable ee and determine the corresponding yield were derived. Finally, development of optimal ee upgrade processes for three pharmaceutical examples with the guidance of TPD were presented. Each example represents a unique scenario where a different strategy was applied and a different process was developed to upgrade the ee. The results from all three examples showed that with the guidance of TPD and the derived equations, the optimal process conditions can be predefined and the yield can be predicted. More importantly, all three examples demonstrated that the ee upgrade processes developed with the guidance of TPD are robust with great reproducibility and scalability. Our results clearly demonstrated the benefit and the importance of using TPD to guide ee upgrade process development, especially in the context of pharmaceutical development.

Experimental Section

Materials. Compounds I, II, and III were all prepared at Merck Research Laboratories, Rahway, NJ, U.S.A. Isopropyl acetate (99%), heptane (≥99%), and isopropyl alcohol ((≥99.5%) were purchased from Aldrich. Ethanol (200 proof) was purchased from Fisher Scientific.

XRPD. The data were generated on a Philips Analytical X'Pert PRO X-ray diffraction system with a PW3040/60 console. A PW3373/00 ceramic Cu LEF X-ray tube Kα radiation was used as the source with an average wavelength of 1.54178 Å. The applied voltage and current were 45 kV and 40 mA, respectively. The powder samples were loaded onto a low-background silicon support plate and spread uniformly so that the sample surface was flat with the rim of the sample holder, which held the silicon support plate. The experiments were run at ambient condition.

TGA. Thermogravimetric analyses were conducted using a Perkin-Elmer TGA 7 or Pyris 1 thermogravimetric analyzer. A heating rate of 10 °C/min was employed, and a nitrogen purge was used. The balance was calibrated using a standard weight, and the sample temperature was calibrated using Curie-point standards.

DSC. DSC curves were acquired using a TA Instrument Q1000 differential scanning calorimeter. The experiments were run in a crimped pan with nitrogen flow at a heating rate of 10 °C/min. Calibration of the temperature and cell constants were performed with indium under the same condition.

Solubility Measurement. A solid sample was suspended in solvent in a glass tube and then sealed with flame. The glass tube was then agitated in a temperature-controlled water bath for at least 24 h. After the equilibration, the solid was allowed to settle by rapid centrifugation, the glass tube was then opened, and the supernatant was filtered through a 0.2 μm filter into a volumetric flask and then diluted. The concentration of each enantiomer in the solution was determined by HPLC. The remaining solids from each tube were analyzed by XRPD.

Construction of Ternary Phase Diagram. Ternary phase diagrams were plotted using software SigmaPlot 10.0 based on the data from solubility measurements.

Note Added after ASAP: In the version published on the Web February 19, 2008, the column heads for Table 3 for the desired and undesired enantiomers were incorrect. They are correct for the version published February 22, 2008, and for the print version.

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