# The Role of Diastereomer Impurity in Oiling-Out during the Resolution of trans-4-Methyl-2-piperidine Carboxylic Ethyl Ester **Enantiomers by Crystallization**

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ABSTRACT: Isolating enantiomers by crystallization via diastereomer salt formation is widely used in the pharmaceutical industry. Unfortunately, we found that, when some diastereomer impurity exists, oiling-out will take place and significantly decrease the resolution efficiency. To identify the role of impurities in oiling-out, three series of chiral resolution of trans-4methyl-2-piperidine carboxylic ethyl ester (trans-4MPE) with different levels of diastereomer impurity were performed. Using process analytical technologies (PAT) technologies, the demixing region was identified by measuring  $T_{L-L}$  curves and supersolubility curves for different series. It was found that a series with a higher level of impurity has a higher  $T_{\rm L-L}$  point and a wider demixing region. Besides, it seems that the resolution efficiency through oiling-out, as well as the crystallization kinetics, was significantly decreased. Here we initially put forward this particular diastereomer purification problem, where the impurity has a positive effect on oiling-out. To reduce or eliminate oiling-out, an efficient prepurification strategy must be ensured.

## 1. INTRODUCTION

Crystallization must surely rank as the oldest and most commonly used unit operation in chemical processing. It can not only provide crystalline products with the desired particle size, particle distribution, and even special polymorphs with high purity but also directly affect the extent of chiral separation. However, in less than 8% of cases, enantiomer mixtures could be separated by direct and preferential crystallization, where each enantiomer could crystallize separately, known as a conglomerate. In other chiral separation processes, direct crystallization would give rise to a racemic crystal structure and separation cannot be achieved, and then we need to bring about diastereomeric crystallization. Diastereomeric crystallization is based on the reaction of racemic mixture with a single isomer resolving agent to give two diastereomeric derivatives, which are salts or complexes. By taking advantage of the differences in their solubility, enantiomer mixtures can be separated indirectly. A recent study of market drugs shows that more than 65% are manufactured by methods involving diastereomer crystallization.<sup>1,2</sup>

A large number of factors, such as supersaturation, agitation intensity, crystallization temperature, and so forth, need to be controlled to separate enantiomer mixtures with a high resolution efficiency. The difficulty in chiral resolution is further exacerbated when a second liquid phase is formed upon cooling, where one phase contains the solvent(s) and the other phase is mainly made up by the solute in the form of a very heavy viscous oil-like phase. This phenomenon is frequently termed oiling-out or liquid-liquid phase separation (LLPS).<sup>3,4</sup> It is a commonly recognized issue in organic crystallization as

well as in protein and polymer systems.<sup>5-8</sup> Usually, LLPS is unexpected, as products obtained from oil droplets are usually of low purity and poor crystal properties, and scale-up of such systems will be problematic.

(2*R*,4*R*)-4MPE (4-methyl-2-piperidine carboxylic ethyl ester) is a synthesis intermediate of an active pharmaceutical ingredient that is used for cardiovascular diseases. It is usually separated from its racemic mixture by a diastereomeric salt formation method, as raw 4MPE supplied is usually a mixture of (2R,4R)-4MPE, (2S,4S)-4MPE, and their diastereomers, (2R,4S)-4MPE and (2S,4R)-4MPE. A brief resolution process for (2R,4R)-4MPE is shown in Figure 1. Distillation here is meant to remove the cis-isomer. Then the trans-4MPE is treated with L-(+)-tartaric acid (LTA) in the acetone/water solvent mixture, where LTA works as a resolving agent. The resulting salt form of (2R,4R)-4MPE is selectively isolated from solution by crystallization.<sup>9</sup> In this system the ratios of solvent mixture  $V_1/V_2$  cannot be identified here for commercial interests.

What we need to point out here is that the boiling points of trans-4MPE and cis-4MPE are so close that they are difficult to be totally separated from each other without very delicate distillation technology. Besides, a certain degree of racemization will occur during distillation. Thus, the presence of cis-4MPE before salt formation becomes inevitable, and the ratio of cis-4MPE remained after distillation may vary from 5% to 30% in different batches. In that case, it is reasonable for us to regard the undesirable *cis*-diastereomers as impurities for chiral

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Figure 2. Structures of trans-4MIPE and cis-4MIPE.

resolution. The structures of main components are given in Figure 2.

During our resolution, the phenomenon that levels of impurity have a dramatic impact on the miscible region has aroused our great interest. While most of the researches have focused their study on the levels of saturation, the selection of solvents, cooling rate, seeding or not, etc.,  $^{10-12}$  we believe that without some discussion of impurities, no discussion of oiling-out would be complete. Oiling-out in chiral resolution is no exception. Since neither process could guarantee a product with an enantiomeric excess meeting regulatory requirements, but instead provide a chiral mixture enriched with the desired enantiomer. In this paper, with a series of experiments we designed, the aims of the investigations discussed here are to (i) use a range of process analytical technologies (PAT) to track the generation and evolution of oiling-out and subsequent crystallization in different experiments; (ii) explore the role of diastereomer impurity in oiling-out during chiral resolution.

#### 2. EXPERIMENTAL SECTION

**2.1. Materials.** Salt forms of *trans*-4MPE with a purity of 97.8% and (2R,4R)-4MPE-LTA and (2S,4S)-4MPE-LTA with a purity of 99% were supplied respectively by Tianjin Hengbida Chemical Synthesis Co., Ltd. Raw 4MPE with different ratios of *cis*-4MPE (liquid state), 24%, 16%, and 8%, was obtained from different manufacturing batches operated by Hengbida, the rest of which are (2R,4R)-4MPE and (2S,4S)-4MPE in equimolar. They were used in the chiral separation experiments without further purification. L-(+)-LTA was purchased from Qingdao Shengke Biological Technology Co. Ltd. of China. Acetone, analytical reagent-grade was obtained from Tianjin KeWei Chemical Co. Ltd. of China, and deionized water was generated from a Millipore filter unit.

**2.2. Equipment and Technique.** A cryo-compact circulator of the high-tech series CF41 from JULABO Labortechnik GmbH was used to control temperature throughout the experiment, and its temperature stability is  $\pm 0.02$  °C with a PID temperature control technology. ATR-FTIR (ReactIR 15 reaction analysis system coupled with iC IR 4.2 software) was supplied by Mettler-Toledo, and in our work

it was used to make sure the salt-forming reaction was complete and monitor the solute concentration during oiling-out and subsequent crystallization.

FBRM (model M400LF) system coupled with iC FBRM software from Mettler-Toledo was introduced to detect both droplets and particle dimensions during oiling-out and subsequent crystallization processes with a 10 s duration. A Lasentec PVM (probe model V819) with an update rate of 1 image per 30 s was employed to visualize the formation of the oil phase and subsequent dispersion into the solution in situ.<sup>13,14</sup>

An optical microscope (Eclipse E200, Nikon) was used for the examination of oil droplets and final products. Highperformance liquid chromatography (HPLC), with an Eslipse Plus C18 Agilent column (5  $\mu$ m, 4.6 × 250 mm) and acetyl glucosamine isothiocyanate (GITC) working as precolumn derivatization reagent, was performed on samples quickly removed from the bottom layer to determine the concentration of 4MPE-LTA in the oil phase.

2.3. Measurement of the Solubility of the LTA Salts of **4MPE.** As indicators of relative solubility and the propensity to separate, the solubility of the two individual diastereomer salts of the R,R-form and S,S-form, namely (2R,4R)-4MPE-LTA and (2S,4S)-4MPE-LTA, and their equimolar mixture—a typical raw salt—was measured gravimetrically in  $v_1/v_2$  acetone/water using the isothermal method. Since the boiling point of acetone is about 56.5 °C, the temperature range was about from 15 to 45 °C. Excess solid was added to the solvent and kept at a particular temperature with agitation for 24 h to reach solidliquid equilibrium. A portion of 10 mL of liquid samples was extracted from each vial for three times using a preheated filtered syringe, and then the samples were weighed and stored in a drying chamber to reach constant weight, which was used to determine the solubility. Each experiment was performed three times, and the average value was taken as the final solubility data. The average relative error was less than 2.1%.

2.4. Methodology Used To Determine Oiling-Out Curves and Crystallization Experiments during Chiral Resolution. Three series of chiral resolution experiments, series I, series II, and series III, were performed, with different

ratios of cis-4MPE, 24%, 16%, and 8%, respectively. In each series, solutions with different concentrations of 4MPE-LTA were prepared through reaction crystallization at 40 °C. To be exact, a known amount of LTA, namely, 5.6 g, was dissolved in certain mass of mixed solvent  $v_1/v_2$  varied from 100 to 200 g at 40 °C. Then equimolar amounts of 4MPE, about 6.3 g, were added into the solution. In this way solutions with different concentration of 4MPE-LTA were obtained. Then the solution was gradually cooled down to 5 °C at a fixed cooling rate of 5 °C/h and stood at 5 °C for 5 h. For the experiment that oiled out, we took down the temperature so that oil droplets appeared as  $T_{cloud}$  and then raised the temperature slightly until the solution clarified. We denoted this temperature as  $T_{clear}$  the minimum temperature at which the solution clarified. The average of  $T_{cloud}$  and  $T_{clear}$  was taken as  $T_{L-L}$ . During the whole process, the FBRM and ATR-FTIR, combined with PVM, were used to measure and identify the clouding and clarifying points.

Furthermore, the effects of impurities and the oiling-out process on the final products were studied. When LLPS or crystallization started, the solutions were allowed to undergo a gravity-driven separation into two coexisting phases in quiescent medium at about 20 °C. To allow for an easy comparison, the solutions with a concentration of 4MPE-LTA 11.67 g/100 g solvent in three series were kept quiescent for more than 8 h at 20 °C. Samples of the bottom phases, in the oil phase or crystal form, were withdrawn simultaneously using a rubber buret, followed by a free-basing step that yielded the (2*R*,4*R*)-4MPE free base as the final drug intermediate. The ratio of all of the four isomers was measured by HPLC.

**2.5.** Defining Suitable Peaks for the Salt-Forming Reaction and the Concentration of 4MPE-LTA during the in Situ Oiling-Out Measurement. Selection of a suitable peak for 4MPE-LTA is very essential for in situ measurement.<sup>13</sup> At the beginning of one of the experiments in series, background was taken of the solvent and LTA after LTA was totally dissolved at 40 °C. Then an equimolar amount of 4MPE was added to the solution, at which point the salt-forming reaction started. It allowed for the rapid identification of the special peak to 4MPE-LTA.

#### 3. RESULTS AND DISCUSSION

**3.1. Solubility.** As presented in Figure 3, the solubility of the two diastereomer salt exhibits a conservative pattern of increasing solubility with temperature. The desired  $R_r$  form is less soluble than the  $S_r$  form, which indicates that the  $R_r$  form would precipitate more easily than the  $S_r$  form. Furthermore, to obtain a better resolution efficiency, the end point of cooling crystallization was set at 20 °C in our chiral separation, below which the difference in solubility is getting smaller and it becomes difficult for resolution. No oiling-out was observed to take place in any of the experiments. However, given the limited materials, here only some of the solubility data was presented.

The resolution of pure *trans*-diastereomers (the ratio of *trans*-form is 97.8%) is given here as supplementation at 20 °C. According to the report of HPLC, the purity of (2R,4R)-4MPE-LTA could be increased from 50.3% to 92.7% after two times crystallization. The melting point of final products is between 95 and 98.0 °C, consistent with the result of a Japanese patent.<sup>9</sup>

**3.2. Defining Suitable Peaks for in Situ Measurement.** As shown in Figure 4, 4MPE-LTA produced a distinct FTIR fingerprint, with several peaks available to trace the salt-forming reaction and the concentration of 4MPE-LTA in solution. The



**Figure 3.** Solubility of the *R*,*R*-form, *S*,*S*-form, and typical coarse salt in  $v_1/v_2$  acetone/water.



**Figure 4.** Mid-IR spectra taken at 40 °C to identify the absorption fingerprint of the 4MPE-LTA.

annotation in Figure 4 points out the peak of interest in our study at  $1611 \text{ cm}^{-1}$ . It should be noted that IR peak height is a reflection of absorbed energy corresponding to the vibration and rotation of chemical bonds. Therefore, it is not a good technology to be used to distinguish the difference between all of these diastereomeric salts efficiently. The peak height here actually represents for the total concentration of four kinds of salt we studied.

**3.3.** In Situ Measurement of Oiling-Out and Subsequent Crystallization. When oiling-out took place, the transparent solution would become cloudy, and oil droplets appeared on the wall of the crystallizer (Figure 5a). However, it was difficult to discriminate if the cloudiness of the solution was caused by droplets or crystal particles with naked eyes, and when the stirrer was turned off, two liquid phases separated, and the oil phase sank to the bottom after several seconds<sup>15</sup> (Figure 5b). Figure 5c shows a photograph of oil droplets with a microscope.



Figure 5. Images of oiling-out: (a) Oil droplets appeared on the wall of the crystallizer; (b) after the agitation was stopped, a visible phase separation interface appeared gradually; (c) optical microscope images of oil droplets.



Figure 6. Time course of FBRM and FTIR measurements during the liquid-liquid phase separation and crystallization of 4MPE-LTA.

The combination of FBRM, IR, and PVM measurements<sup>16,17</sup> was used in one of the experiments that oiled out to have a better understanding of this phenomenon. According to those PVM images, the dimensions of the droplets or particles throughout the process are smaller than 150  $\mu$ m. Therefore, the statistical interval for the time course FBRM was selected as 0 to 150  $\mu$ m, as shown in Figure 6.

Upon cooling the clear solution (Figure 7a) after reaction, the specific IR peak of 4MPE-LTA was seen to have a very sharp increase whilst the counts for small dimension ( $\leq$ 50  $\mu$ m) detected by FBRM had a very sudden increase in total counts at about 3090s (point B). Examination of the PVM images (Figure 7b) showed that this corresponded to the generation of amorphous-like aggregates. As for the sudden increase in IR measurement, although similar measurements were observed in the work of Deneau and Veesler et al.,<sup>18,19</sup> they simply ascribed it to be due to transient oiling-out on heating or generation of droplets upon cooling and did not give any further interpretation. Although FTIR will not respond to the presence of either droplets or crystals in suspension for its the detection limit (about 2  $\mu$ m), The ATR probe is sensitive to the film in contact with the probe surface. Here we do think that the sudden increase might be a respond to the generation of films of oil phase, which may initially form on the vessel and probe surface and be detected by the ATR probe. With the quantity of amorphous growing, the visible droplets, which were beyond the detection limit of FTIR. Then the IR probe began to detect the concentration in the lean phase.

At about 4520 s (point C), both IR peak height and counts for dimension  $\leq$ 50  $\mu$ m, as well as the total counts (summing up all the counts in different intervals), were seen to have a sharp decrease. It could be interpreted as the coalescence of small oil droplets. As the visible droplets were formed (Figure 7c), the IR probe began to detect the concentration in the lean phase. The speculation was further affirmed by the slightly increase of the particle counts for larger particles between 50 and 150  $\mu$ m at 4710 s.

Upon further cooling, it slowly began to generate many needle-like crystals. At first, it seems that the particle appeared to hold at a constant level, with a slight decline in the IR measurements. By the examination of Figure 7d (point D, at about 15180 s), it was found that almost all of the fine crystals generated were confined to the oil droplets, and FBRM might still detect the counts of droplets that contain fine crystals. As the droplets gradually transformed into crystals, an apparent increase in particle counts of all of the statistical intervals was observed by FBRM at 22410 s (point E). This can be explained by the release of crystals into the solution as shown in Figure 7e. Then those crystals began to grow at the consumption of concentration just like the process in normal crystallization,



Figure 7. PVM images for the evolution of oiling-out.

which was in line with the subsequent decrease of the IR peak height. At the end of this measurement, all of the droplets transformed into the normal crystals. Compared with Figure 7e, there were more crystals within view, and the particle dimension had significantly increased in Figure 7f. It indicted the generation and the growth of more crystals outside the oil droplets.

To summarize, five main areas could be identified for the process in this work: (a) clear solution after reaction; (b) generation of oil droplets or a amorphous aggregates; (c) coalescence of small oil droplets; (d) oil droplets converting into crystal particles; (e) crystal growth. The observations were similar to the work made by others.<sup>18,19</sup>

The generation of some amorphous aggregates before oilingout was first observed in our work, and it could be best interpreted by Ostwald's law of stages.<sup>20</sup> According to Ostwald's law, if a multitude of solid-state forms is possible, the most unstable form will nucleate first. This can either be an unstable crystallization form or even amorphous solid or even oil (Figure 8). Besides, it was not difficult to find that the nucleation and growth of crystals were significantly hindered when LLPS took place. The final products obtained from oiling-out were more like "fine feathers", and other characterizations were discussed in section 3.5.

**3.4. Effect of Diastereomer Impurities on Oiling-Out during Resolution.** Generally, the solution is supersaturated, and crystal nucleation and growth can occur in the region above the solubility curve. However, we found that it would undergo different crystallization process when different ratios of impurity existed. Experiments in series III preceded a normal crystallization without oil droplets, while, in series I and II, oiling-out would be observed distinctly upon cooling, and it seems that crystallization seems to be so hindered.

To have an better understanding of the reactive crystallization,  $T_{L-L}$  curves for series I and II (the pink and olive curves), the solubility curves discussed before and expected solubility curve for a typical raw salt above 40 °C (the green dashed line) was also plotted in Figure 9. The region between



Figure 8. Visualization of Ostwald's law of stages.

 $T_{\rm L-L}$  curve and supersolubility curves was defined as the demixing region in this work.

It can be seen that the  $T_{L-L}$  point is much higher than the spontaneous nucleation points in the presence of the oil phase. For instance, the systems began to oil out from 44.51 and 35.86 °C, respectively, at the concentration of 11.67 g in 100 g mixture solvent in series I and II, and only by holding the whole systems at 5–8 °C for more than 5 h could the solid products be expected to be obtained, which indicates that the kinetics of crystal nucleation is rather slow relative to the LLPS process. The schematic supersolubility curve for the two series was represented by the red dashed line. However, in series III the spontaneous nucleation points were at about 15–21 °C at the concentrations of interest (see the dark blue curve).

Since LLPS is the concentration at which the substance exceeds its miscibility limit with the mixed solvent, most compounds show the expected increase of miscibility with the solvent with the temperature increase.<sup>21</sup> As exemplified by 4MPE-LTA in series I and II, the phase transition concentration in this study increased with temperature over

the temperature range studied, and miscibility increases with an increase in temperature.

Oiling-out is an intermediate undercooled liquid phase and can be regarded as a preferred kinetic route to crystallization when the kinetic processes of nucleation and growth are so hindered.<sup>7</sup> According to that logic, a higher  $T_{L-L}$  point might indicate a lower energy barrier for a new phase, and the presence of impurities would promote the generation of the oil phase, since that  $T_{L-L}$  curve not only depends on the initial supersaturation but also the level of diastereomer impurities.

**3.5. Influence of Oiling-Out on Final Products.** Typical optical microscope images of final products obtained from oiling-out and true crystallization are shown in Figure 10 for comparison. Figure 10a is a typical micrograph of the needle-like crystallization product in the absence of oiling-out. Figure 10b is a typical micrograph of the products from oil droplets. It can be seen that particles yielded from oil phase are so small and tend to melt even at ambient temperature, which may be attributed to the inclusion of solvents. The molecular rearrangement required for growth seems to be so hindered in the heavy viscous oil-like phase.

To investigate the composition change between the oil phase and the crystals once formed, both the oil products and the solid forms need to be obtained. However, there are many cases that stable oil phase formed, where no nucleation is observed and no solid products can be obtained at 20 °C, unless holding the whole systems at 5-8 °C for more than 5 h, as mentioned before. The composition of all the samples was measured by HPLC.

According to the results of HPLC analysis, shown in Table 1, products obtained from the oil phase are of lower purity. The composition of oil phase was comparable to that of solid products obtained at 5-8 °C, and all of the four enantiomers tend to be involved in the final products with the poor selectivity of oiling-out, resulting a poor separation process. Thus, LLPS occuring in the metastable region of series I and II can be regarded as the precursor of solid products for chiral separation in this work. Moreover, when the purity of 4MPE



Figure 9. Phase diagram for 4MPE-LTA:  $T_{\rm L-L}$  curves and the supersolubility curve of series I, II, and III.



Figure 10. Microscope images: (a) product from normal crystallization and (b) solidification product from oiling-out.

Table 1. Concentration of the ratio of four diastereomers in the bottom phase for three series with an initial composition of the 11.67 g/100 g solvent mixture<sup>a</sup>

series (% initial ratio of trans- form)	layer	temperature samples obtained (°C)	% R,R-form	% S,S-form	% R,S-form	% S,S-form	oiling- out	note
series I (76%)	bottom (oil)	20.2	39.66	39.59	10.49	10.26	much	no crystals at 20.1 °C
	bottom (crystals)	5.0-8.0	40.12	39.60	10.17	10.11		
series II (84%)	bottom (oil)	20.1	47.65	42.38	4.75	5.22	less	no crystals at 20.0 °C
	bottom (crystals)	5.0-8.0	49.51	43.02	3.59	3.88		
series III (92%)	bottom (crystals)	20.0	71.81	23.37	2.16	2.66	none	crystallize at 21.5 °C
trans-4MPE	crystals	23.5	76.33	22.21	0.67	0.79	none	
<sup>a</sup> (2R,4R)-form and (2S,4S)-form are nearly equimolar in trans-4MPE; the rest are (2S,4R)-form and (2R,4S), also equimolar.								

reaches a certain degree, or in other words, when the ratio of impurity decreased to some level, the phenomenon of LLPS will not appear, and a significant improvement on the resolution efficiency will be achieved. Further work will be carried out in our next study in looking for the critical purity of 4MPE-LTA.

Here we have to confess that this is not a good system for the measurement of the composition change between the oil phase and the crystals, since all the crystals through oiling-out were obtained at an extremely low temperature, which will affect the composition greatly.

#### 4. CONCLUSIONS

In industrial crystallization, impurity levels often change during process development and on scale-up. Therefore, it is necessary to take the effect of diastereomeric impurities into consideration when it oiled out during chiral resolution. With the aid of PAT tools, the phase diagram consisting of the solubility curves, the liquid—liquid separation curves, and the supersolubility curves was determined experimentally for three series of interest. We found that the system with a higher ratio of diastereomer impurity is much easier to oil-out, with a higher  $T_{\rm L-L}$  and a wider demixing region. According to the results of HPLC, there were not many changes in the relative content of *R*,*R*-form and *S*,*S*-form both of the oil phase and the crystals, and the amorphous form generated at first might work as the precursor of final solid products.

One area for further study is the identification of a critical purity for the resolution of 4MPE-LTA, since it seems that there may be a critical purity beyond which oiling-out will not appear and the diastereomer separation will become much easier to conduct. Furthermore, the critical purity can be used to determine the least tolerable distillation results and work as guidance for upstream distillation processes. Besides, the identification of the role of impurity on oiling-out will draw some hints on the building of LLPS kinetic models. Much kinetic data need to be measured in our further study.

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#### Notes

The authors declare no competing financial interest.

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