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A THERMODYNAMICALLY GUIDED APPROACH TO CO-CRYSTAL SCREENING: APPLICATION TO MALEIC ACID / CAFFEINE SYSTEM

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Introduction

Co-crystallization of pharmaceutically active molecules allows to enhance the physical properties of a drug substance, such as its solubility, bioavailability... Although dry grinding, solvent drop grinding, and melt crystallization have been reported as key preparative techniques,^[1] the development of a solvent crystallization often remains imperative from an industrial point of view.

Issues encountered during the development of an up-scaled co-crystallization process are often related to a limited understanding of the thermodynamic behavior of a ternary system consisting of two distinct compounds, as well as the solvent.^[2] The distinct pairwise interactions between these components, lead to complex phase diagrams, as shown in Figure 1a.^[3] The thermodynamic conditions under which a pure co-crystal phase can be identified in solution, are often difficult to identify by a trial and error approach and would ideally require the construction of ternary phase diagrams. Construction of such diagrams can, nevertheless, be quite time-consuming, and is often impractical from an industrial point of view. Screening for co-crystal phases in solution can, however, be simplified to a great extent, when using thermodynamic considerations to guide the screening trials.

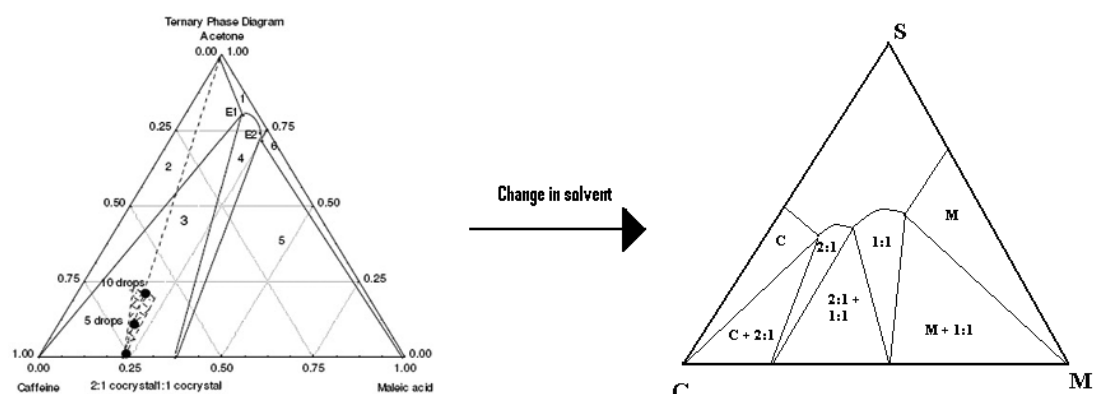


Figure 1. a) Ternary Phase diagram caffeine/maleic acid/acetone at 25°C in mass % (Source: ref 3). b) Hypothetical phase diagram in a solvent showing comparable maleic acid and caffeine solubility.

In this contribution, such an approach was applied to the caffeine/maleic acid co-crystal system. For this system, 1:1 and 2:1 co-crystals have been obtained through wet grinding, but only the former has been obtained in a reproducible manner in solution.^[3-4] A single, non-repeatable, occurrence of a 2:1 co-crystallization in solution has been reported so far. The aim of this contribution is to show that the 2:1 phase can be obtained in solution in a repeatable manner. To achieve this goal, an approach is constructed based on thermodynamic arguments.

Approach

The 1:1 co-crystal phase can easily be obtained from solution crystallization in acetone. In this solvent, maleic acid is about 30 times more soluble compared to caffeine, leading to a twisted ternary phase diagram, as presented in Figure 1a. As shown by this diagram, the 1:1 phase is thermodynamically accessible, but the 2:1 phase is expected to be meta-stable in solution. Spontaneous crystallization of this phase in acetone would require substantial supersaturation levels. To render the 2:1 phase thermodynamically accessible in solution, the ternary phase diagram would have to be altered, as shown in Figure 1b. The most straightforward manner to achieve this transformation is by modifying the solvent used, ideally leading to a diagram as presented in Figure 1b. This would require using a solvent showing comparable solubility of both co-crystal components.

To show the importance of the solvent for the development of an in solution co-crystallization of the 2:1 crystal phase, four different solvents were tested, having respectively maleic acid vs. caffeine solubility ratios of 100, 40, 5, and 0.05. The solvent presenting a relative ratio of 5, is most likely to lead to a ternary phase diagram, as presented in Figure 1b, and is thus most likely of interest for the co-crystallization of the 2:1 phase. Ideally, the complete ternary phase diagram for each solvent should be determined. However, this often turns out to be time-consuming.

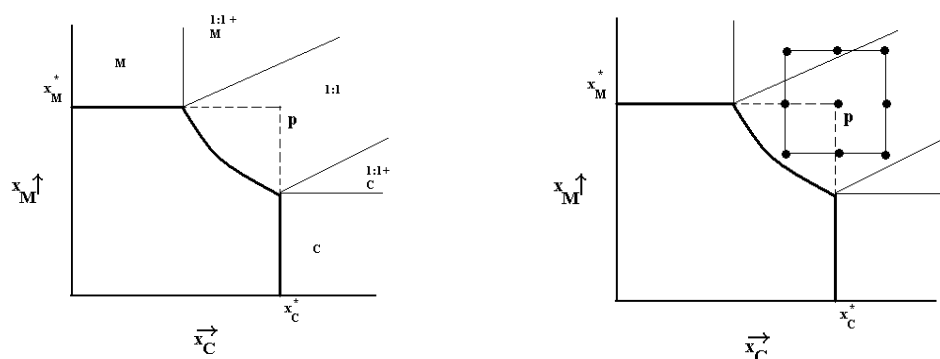


Figure 2. a) Schematic phase diagram for a system leading to a 1:1 co-crystal. b) Experimental design centred around point p.

Recently, alternative phase diagrams drawing have been developed,^[5,6] which zoom-in onto the region of the ternary phase diagram where the co-crystal phases possibly appear. These phase diagrams are constructed by considering how the solubility of one component varies, if the amount of the other component is altered, leading to diagrams as presented in Figure 2a. With respect to classical screening methods, based on

stoichiometric ratios of both components, the idea behind these diagrams is to consider the respective saturation concentrations of both components as a starting point. As shown in this diagram, a solution saturated in both components is likely to be supersaturated with respect to the co-crystal phase (point **p**). Figure 2a shows an ideal situation, for which the solubility of one component is independent on the presence of the other. This is, however, rarely the case, especially for co-crystal systems, as both components are assumed to interact with one another. To identify possible co-crystal phases, an experimental plan was therefore designed, centred around point **p**, as shown on Figure 2b.

As the phase diagram presented Figure 2 is temperature dependent, the experimental plan can be created at different temperatures, under the condition that the solubility of both components is known at these temperatures.

At first, the solubility curves for maleic acid and caffeine were measured for the different solvents selected. A multiwell set-up with video microscopy, as shown in Figure 3, was used to determine the solubility curves. Standard 1ml HPLC glass vials were inserted into two blocks that were temperature controlled by Peltier elements. The whole assembly is mounted on a translation table to allow scanning of the different vials.

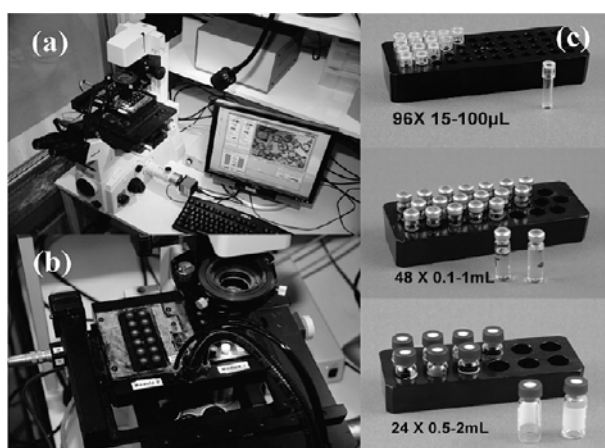


Figure 3. a) Multiwell set-up used b) translational stage c) blocks containing vials.^[7]

Once the solubility curves were determined, an experimental plan such as presented in Figure 2b, was created for each solvent, at two different reference temperatures. The Multiwell device was used, to check for spontaneous crystallization. Crystalline phases were identified by XRPD.

Both 1:1 and 2:1 phases crystallized spontaneously in the solvent showing a maleic acid/caffeine solubility ratio of 5. Both forms show needle-shaped habits as shown in Figure 4.

This solvent was then selected to determine conditions for which the 2:1 phase is kinetically favoured, as well as conditions for which this phase is thermodynamically favoured. The spontaneous crystallization of the 2:1 phase is achieved by extending the experimental plan presented in Figure 2b. Moreover, to study the thermodynamic stability, the experimental plan is repeated, and all samples are seeded with both the 1:1

and 2:1 phases, and left to equilibrate for over two weeks. Based on these findings, repeatable 2:1 co-crystallization conditions were determined, with the ultimate goal of growing a single 2:1 co-crystal for structure determination.

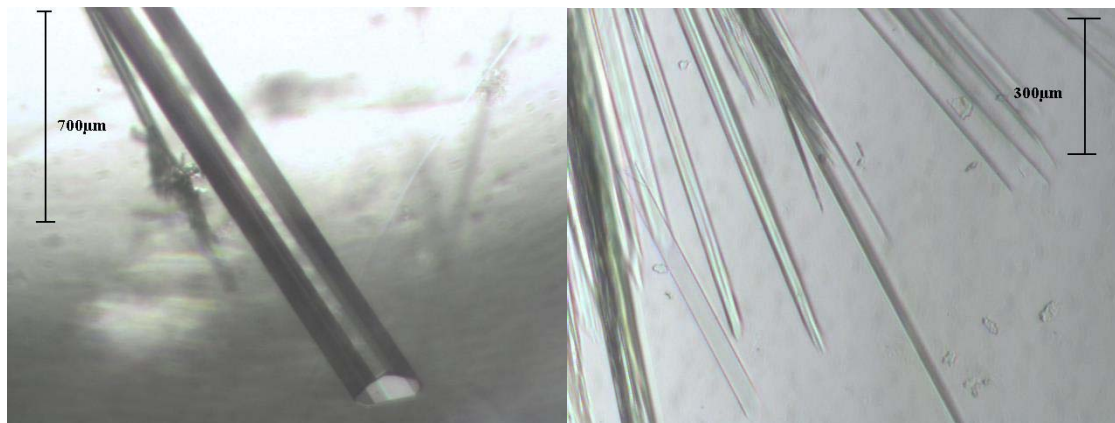


Figure 4. Optical microscopy images (left 1:1 co-crystal, right 2:1 co-crystal).

Conclusion

In this contribution, a thermodynamically guided approach is applied for the screening of co-crystals in solution. The methodology used, allowed us for a rapid screening of crystallization conditions of potential co-crystals. In less than 6 weeks, conditions for the co-crystallization of the caffeine/maleic acid 2:1 co-crystal in solution were defined, showing the interest of the developed approach, especially from an industrial and commercial point of view.

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