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A Practical Solid Form Screen Approach To Identify a Pharmaceutical Glutaric Acid Cocrystal for Development

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Abstract:

Pharmaceutical cocrystals could be used to improve the physicochemical properties of active pharmaceutical ingredients. Here, a practical solid form screen approach to identify pharmaceutical cocrystals in the early development stage is proposed. This approach first used a cogrinding screen to identify potential cocrystal former leads that could form cocrystals with the compound of interest, followed by a solvent-based screen to identify, evaluate, and generate the cocrystal candidates. This approach not only allows fast identification of the cocrystal candidates but also provides insights on their scalability. Using this approach for the development drug candidate, a glutaric acid cocrystal was identified that provided an improved intrinsic dissolution rate in comparison to that of the free form, and therefore this cocrystal is potentially a better solid form for development. The effects of solvents and structures of cocrystal formers on the cocrystal formation and the rationales for this approach are also discussed.

Introduction

Pharmaceutical cocrystals are well-defined crystalline solids generated from active pharmaceutical ingredients (API) and cocrystal formers (CCF). In recent years, identification and development of pharmaceutical cocrystals gained increasing interest in the pharmaceutical industry.[1−4] The approach of cocrystal formation can diversify the solid form choices and increase the chances to identify suitable development candidates, especially for APIs with no crystalline form, nonionizable functional groups, or low pK_a values (to maintain as a stable salt). Examples of pharmaceutical cocrystals have been demonstrated in the literature to provide improved properties such as physical stability,[5,6] dissolution rate, and solubility,[7−9] and thus they can be used as an alternative solid dosage form for an API.

Due to the nature of the pharmaceutical industry, special criteria, such as crystallinity, stability, reproducibility, solubility, hygroscopicity, particle size, flow, filtration, etc., need to be considered for the selection of a solid form for development. In the case of pharmaceutical cocrystals, hydrogen-bonding is generally required to yield stable crystalline solids suitable for development. To identify a cocrystal candidate, different methods have been reported, including thermal methods,[10,11] cogrinding (dry grinding) or liquid-assisted grinding,[12,13] evaporation,[14,15] slurry,[16,17] and solution crystallization.[18,19] Regardless of the pathways for cocrystal identification, when

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(1) Blagden, N.; Berry, D. J.; Parkin, A.; Javed, H.; Ibrahim, A.; Gavan, P. T.; De Matos, L. L.; Seaton, C. C. Current directions in co-crystal growth. *New J. Chem.* **2008**, *32* (10), 1659–1672.

(2) Trask Andrew, V. An overview of pharmaceutical cocrystals as intellectual property. *Mol. Pharm.* **2007**, *4* (3), 301–9.

(3) Vishweshwar, P.; McMahon, J. A.; Bis, J. A.; Zaworotko, M. J. Pharmaceutical co-crystals. *J. Pharm. Sci.* **2006**, *95* (3), 499–516.

(4) Almarsson, O.; Zaworotko, M. J. Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines? *Chem. Commun. (Cambridge)* **2004**, *17*, 1889–1896.

(5) Trask, A. V.; Motherwell, W. D. S.; Jones, W. Pharmaceutical Cocrystallization: Engineering a Remedy for Caffeine Hydration. *Cryst. Growth Des.* **2005**, *5* (3), 1013–1021.

(6) Trask, A. V.; Motherwell, W. D. S.; Jones, W. Physical stability enhancement of theophylline via cocrystallization. *Int. J. Pharm.* **2006**, *320* (1−2), 114–123.

(7) McNamara, D. P.; Childs, S. L.; Giordano, J.; Iarriccio, A.; Cassidy, J.; Shet Manjunath, S.; Mannion, R.; O'Donnell, E.; Park, A. Use of a glutaric acid cocrystal to improve oral bioavailability of a low solubility API. *Pharm. Res.* **2006**, *23* (8), 1888–97.

(8) Remenar, J. F.; Morissette, S. L.; Peterson, M. L.; Moulton, B.; MacPhee, J. M.; Guzman, H. R.; Almarsson, O. Crystal engineering of novel cocrystals of a triazole drug with 1,4-dicarboxylic acids. *J. Am. Chem. Soc.* **2003**, *125* (28), 8456–8457.

(9) Good, D. J.; Rodriguez-Hornedo, N. Solubility Advantage of Pharmaceutical Cocrystals. *Cryst. Growth Des.* **2009**, *9* (5), 2252–2264.

(10) Berry, D. J.; Seaton, C. C.; Clegg, W.; Harrington, R. W.; Coles, S. J.; Horton, P. N.; Hursthouse, M. B.; Storey, R.; Jones, W.; Friscic, T.; Blagden, N. Applying Hot-Stage Microscopy to Co-Crystal Screening: A Study of Nicotinamide with Seven Active Pharmaceutical Ingredients. *Cryst. Growth Des.* **2008**, *8* (5), 1697–1712.

(11) Lu, E.; Rodriguez-Hornedo, N.; Suryanarayanan, R. A rapid thermal method for cocrystal screening. *CrystEngComm* **2008**, *10* (6), 665–668.

(12) Trask, A. V.; Jones, W. Crystal engineering of organic cocrystals by the solid-state grinding approach. (Organic Solid State Reactions) *Top. Curr. Chem.* **2005**, *254*, 41−70.

(13) Shan, N.; Toda, F.; Jones, W. Mechanochemistry and co-crystal formation: effect of solvent on reaction kinetics. *Chem. Commun. (Cambridge)* **2002**, *20*, 2372–2373.

(14) Weyna, D. R.; Shattock, T.; Vishweshwar, P.; Zaworotko, M. J. Synthesis and Structural Characterization of Cocrystals and Pharmaceutical Cocrystals: Mechanochemistry vs. Slow Evaporation from Solution. *Cryst. Growth Des.* **2009**, *9* (2), 1106–1123.

(15) Basavoju, S.; Bostrom, D.; Velaga Sitaram, P. Indomethacin-saccharin cocrystal: design, synthesis and preliminary pharmaceutical characterization. *Pharm. Res.* **2008**, *25* (3), 530–41.

(16) Takata, N.; Shiraki, K.; Takano, R.; Hayashi, Y.; Terada, K. Cocrystal Screening of Stanolone and Mestanolone Using Slurry Crystallization. *Cryst. Growth Des.* **2008**, *8* (8), 3032–3037.

(17) Zhang, G. G. Z.; Henry, R. F.; Borchardt, T. B.; Lou, X. Efficient co-crystal screening using solution-mediated phase transformation. *J. Pharm. Sci.* **2007**, *96* (5), 990–995.

(18) Chadwick, K.; Davey, R. J.; Dent, G.; Pritchard, R. G.; Hunter, C. A.; Musumeci, D. Cocrystallization: A Solution Chemistry Perspective and the Case of Benzophenone and Diphenylamine. *Cryst. Growth Des.* **2009**, *9* (4), 1990–1999.

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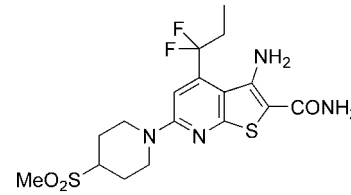
taking the reproducibility and scalability of a development candidate into consideration, solution crystallization is the preferred method for cocrystal formation. In order to develop a scalable solution for cocrystal formation process, the solubility and crystallization kinetics of API, CCF, and cocrystal in a selected solvent system need to be understood.[1,18,20]

During the drug development, the solid-state stability of a cocrystal candidate needs to be evaluated. Cocrystals of the drug candidates may not be as stable as the salts or the free form of API. One argument is that water in the formulation or excipients could interfere with the hydrogen bonding(s) between API and CCF. For example, it has been reported on one hand that the celecoxib:nicotinamide cocrystal dissociates in the presence of water and excipients.[21] On the other hand, some cocrystals are very stable and are not as water soluble as their parent compounds such as the cocrystals of melamine and cyanuric acid.[22,23]

Because of the hydrogen-bonding nature of the cocrystals, structure-based design could be used to help design potential cocrystals based on the interactions between functional group motifs.[24−28] However, experiments are still required to confirm those choices resulted from the structure-based design and sometimes experimental approaches may be necessary to provide additional hits, even with CCFs that are not identified by the design. The structure-based design could also become more challenging as the complexity of API increases, e.g. higher molecular weight, multiple function groups, etc. Other critical factors that are considered for identifying a potential pharmaceutical solid form for development are time and resources. In addition to identifying a potential cocrystal candidate for development, it is preferable that the processability (e.g., reproducibility and scalability) of this candidate is assessed in order to provide sufficient information for the selection of a suitable solid form for development.



Mw: 432.5, pKa: 1.80

Figure 1. **Structure of compound 1.**

For a development drug candidate, different screening approaches have been adapted across the pharmaceutical industry. In general, in the early development stage (e.g., before the end of Phase I), the solid-form screen is focused on the identification and evaluation of a suitable solid form for development. In terms of a cocrystal screen at the early development stage, the purpose could be exploratory and feasibility assessment, and normally, time and resources are limited. In this contribution, a practical approach for identifying and assessing the developability of suitable cocrystal candidates in the early development stage is proposed and demonstrated with a development candidate. Compound **1**, as shown in Figure 1, a BCS (Biopharmaceutics Classification System) Class II compound, has a low intrinsic water solubility of ~1.9 μg/mL. The low solubility and poor dissolution behavior made the formulation development challenging. A request was made to search for an alternative solid form that can provide better dissolution behavior. However, compound **1** is an extremely weak base with measured pK_a value of 1.8, and therefore, salt formation is difficult. Attempts to form salts with strong acids, such as hydrochloric, hydrobromic, and sulfuric acids, were unsuccessful. Compound **1** was considered a good candidate for cocrystal formation as it has multiple hydrogen bond donors/acceptors. As a result, the cocrystal screen was attempted.

Materials and Methods

Chemicals. Compound **1** was produced in house with HPLC area purity 98.2%. Compound **1** used in this study is a highly crystalline anhydrous form with melting point of 212 °C. FDA's GRAS (general considered as safe) list and Handbook of Pharmaceutical Salt[29] were used to select the CCFs. All the CCFs were purchased from Sigma-Aldrich with a minimum chemical purity of 98% and were used as received.

Characterization. X-ray powder diffraction (XRPD) was conducted using a Bruker AXS X-ray powder diffractometer with a Vantec 2000 detector. For each sample, XRPD pattern was collected from 2θ of 3° to 40° using a total of a 2 min scan. In order to facilitate the data interpretation, an XRPD pattern database of the CCFs was established. Although both new peak(s) and amorphous bumps in the XRPD data could imply the existence of interactions between API and CCF, for simplicity, only the former was classified as positive of potential cocrystal formation in this study. The form purity of the identified cocrystal could also be qualitatively obtained from

(19) Jayasankar, A.; Reddy, L. S.; Bethune, S. J.; Rodriguez-Hornedo, N. Role of Cocrystal and Solution Chemistry on the Formation and Stability of Cocrystals with Different Stoichiometry. *Cryst. Growth Des.* **2009**, *9* (2), 889–897.
(20) Rodriguez-Hornedo, N.; Nehm, S. J.; Seefeldt, K. F.; Pagan-Torres, Y.; Falkiewicz, C. J. Reaction Crystallization of Pharmaceutical Molecular Complexes. *Mol. Pharm.* **2006**, *3* (3), 362–367.
(21) Remenar, J. F.; Peterson, M. L.; Stephens, P. W.; Zhang, Z.; Zimenkov, Y.; Hickey, M. B. Celecoxib:nicotinamide dissociation: using excipients to capture the cocrystal's potential. *Mol. Pharm.* **2007**, *4* (3), 386–400.
(22) Simanek, E. E.; Mammen, M.; Gordon, D. M.; Chin, D.; Mathias, J. P.; Seto, C. T.; Whitesides, G. M. Design and synthesis of hydrogen-bonded aggregates. Theory and computation applied to three systems based on the cyanuric acid-melamine lattice. *Tetrahedron* **1995**, *51* (2), 607–19.
(23) Seto, C. T.; Whitesides, G. M. Self-assembly based on the cyanuric acid-melamine lattice. *J. Am. Chem. Soc.* **1990**, *112* (17), 6409–11.
(24) Aakeroy, C. B.; Beatty, A. M.; Zou, M. Building organic assemblies with 2-pyridone and dicarboxylic acids: relating molecular conformation and synthon stability to crystal structure. *Cryst. Eng.* **1999**, *1* (3/4), 225–241.
(25) Bis, J. A.; Vishweshwar, P.; Weyna, D.; Zaworotko, M. J. Hierarchy of Supramolecular Synthons: Persistent Hydroxyl···Pyridine Hydrogen Bonds in Cocrystals That Contain a Cyano Acceptor. *Mol. Pharm.* **2007**, *4* (3), 401–416.
(26) Oswald, I. D. H.; Motherwell, W. D. S.; Parsons, S.; Pidcock, E.; Pulham, C. R. Rationalisation of co-crystal formation through knowledge-mining. *Crystallogr. Rev.* **2004**, *10* (1), 57–66.
(27) Allen, F. H. The Cambridge Structural Database: a quarter of a million crystal structures and rising. *Acta Crystallogr., Sect. B* **2002**, *B58* (3, No. 1), 380–388.
(28) Fabian, L. Cambridge Structural Database Analysis of Molecular Complementarity in Cocrystals. *Cryst. Growth Des.* **2009**, *9* (3), 1436–1443.
(29) Stahl, H. P., Wermuth, C. G.; Eds. *Handbook of Pharmaceutical Salts; Properties, Selection, and Use.* 2008; p 374.

Table 1. **List of CCFs used in stage I screen and the DSC and XRPD responses after cogrinding with compound 1**

cocrystal formers (CCFs)[a]	response after cogrinding		cocrystal formers (CCFs)[a]	response after cogrinding	
	DSC	XRPD		DSC	XRPD
L-tartaric acid	+	−	L-proline	−	−
citric acid	+	−	saccharin	+	−
orotic acid	−	−	nicotinamide	+	−
fumaric acid	+	+	isonicotinamide	−	−
salicylic acid	+	+	D-valine	−	−
succinic acid	+	+	tromethamine	+	−
maleic acid	+	+	succinamide	−	−
D-tartaric acid	+	−	uracil	−	−
hippuric acid	+	−	*N*-methyl-D-glucamine	−	−
L-pyroglutamic acid	+	−	L-arginine	−	−
L-ascorbic acid	+	−	**piperazine**	+	+
nicotinic acid	+	−	glycine	−	−
L-lysine monohydrate	−	−			

[a] Positive responses for both XRPD and DSC are classified as leads and are in bold-faced text.

the selected compound **1** and CCF that showed disappearing or decreasing XRPD peak intensity.

Differential scanning calorimetry (DSC) measurements were performed using a TA Instruments model Q1000 V6.21 DSC. Two to four mg of obtained solids was accurately weighed and loaded into an aluminum sample pan. Samples were equilibrated at 10 °C, followed by heating from 10 to 300 °C at rate of 10 °C per minute. Appearance of new DSC endothermic event(s), other than the melting of compound **1** or CCF, indicates "positive" result of the screen. Once the cocrystal formation was confirmed by XRPD and ^{1}H NMR, the T_{onset} of the newly identified endothermic event was assigned as the melting temperature of this cocrystal.

In addition to XRPD and DSC, which provide the indication of the existence and purity of a potential new solid form, ^{1}H NMR was also used on those solids that were obtained from the solvent-based screen. All ^{1}H NMR spectra were collected from Bruker 400 MHz NMR using *d*-DMSO as solvent. The stoichiometric ratios between compound **1** and CCFs were calculated on the basis of integrations of representative peaks. These ratios were also used as one of the key criteria to assess the robustness and developability of the identified cocrystal, and this will be further discussed in Results and Discussion section.

Methods. The proposed cocrystal screen approach includes two stages of screening activities: stage I cogrinding and stage II solvent-based screen. In stage I, cogrinding was used as the primary method to identify the CCF "leads" that had interaction with the compound of interest. Cogrinding was performed by first mixing the solids of API (∼ 60 mg) and CCF, in an equimolar ratio, followed by grinding for 20 min at a frequency of 30 Hz on a Retsch mixer ball mill MM301. The resultant solids were collected and characterized, and the potential "leads" after drying grinding were identified with both XRPD and DSC analysis showing positive results.

In stage II, the "leads" identified from stage I together with structurally similar CCFs were used to form cocrystals with the compound via. solution crystallization or slurry conversion. In detail, API (∼ 200 mg) and CCFs, with 1:1 molar ratio, were dissolved or slurried in 3 mL of solvent or solvent mixture at elevated temperatures (70 °C, or 5 °C below the boiling point of the solvent). The solution or slurry was maintained at elevated temperature for 4 h, followed by cooling down to 15 °C in 8 h. The solids obtained from solution crystallization or slurry experiments were isolated by filtration, then dried and characterized with XRPD, DSC, and ^{1}H NMR.

Results and Discussion

In stage I of the proposed protocol, the compound was first screened using cogrinding methods against different cocrystal formers to identify the potential "leads". The main purpose of cogrinding was to provide the preliminary experimental assessment on whether a certain class of CCFs has interaction (mainly through hydrogen bonding) with the API that may lead to cocrystal formation. The selection of CCFs used in stage I was based on the following criteria: (1) CCF needs to be pharmaceutically acceptable, (2) CCF has hydrogen donor/acceptor functional group(s), and (3) the selection covers a wide range of differences in chemical structure and functional groups. The CCFs used for cogrinding experiments are listed in Table 1, and a certain CCF was selected to represent a class of CCFs, e.g. succinic acid was selected to represent saturated dicarboxylic acids including adipic acid and glutaric acid.

The solvent-based screens, e.g., liquid-assisted grinding, evaporation, slurry, or cooling crystallization, were excluded from the stage I screen in the proposed protocol, mainly due to practical consideration of time and resource. Because the purpose for the initial screen was to identify the potential cocrystal formation interaction between the CCF and the compound, addition of solvent could introduce complexity to the system, such as the formation of solvates with compound **1** and/or CCFs (which may make the XRPD and DSC data analyses difficult) and the competition of the solvent for the hydrogen bonding between the API and CCF. In this proposed protocol, the effect of solvent is studied in the stage II screen, where the selection of the solvent could be critical for the cocrystal formation. This protocol uses cogrinding as the main screen method in the initial stage I screen since it provides a simple experimental process and straightforward data analyses and interpretation.

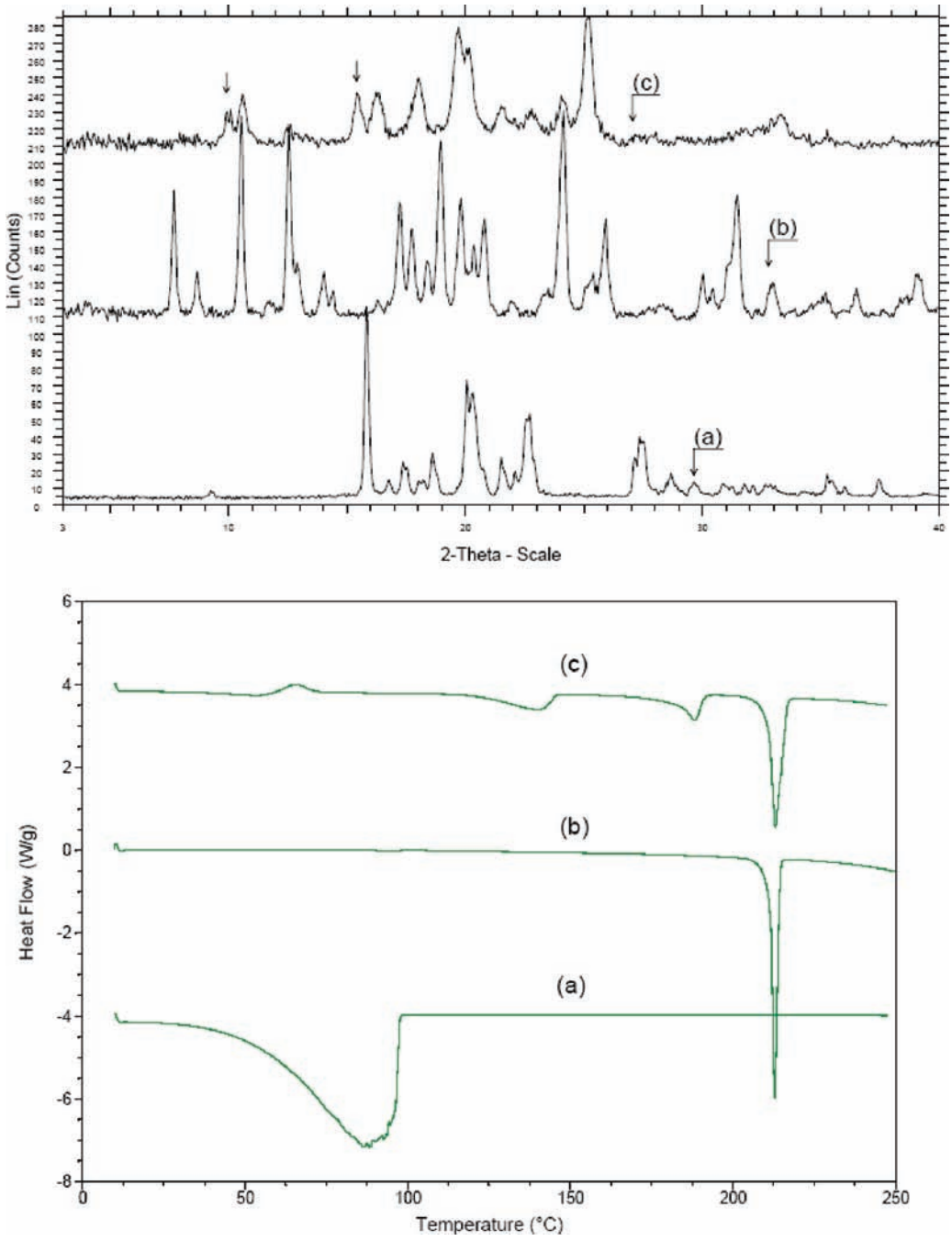


Figure 2. **Example of the use of XRPD (Top) and DSC (Bottom) data to identify a potential cocrystal "lead" after the cogrinding experiment. For both graphs, (a) piperazine, (b) compound 1, and (c) 1:1 mixture of piperazine and compound 1 after cogrinding.**

Different cocrystal screening approaches have been evaluated by different groups,[30,31] and it was well recognized that cogrinding is not the only tool to identify cocrystals. However, for a drug candidate in the early development stage, the purpose of the screen is not to identify as many cocrystals as possible but rather to identify a suitable cocrystal for development in a timely fashion. Using cogrinding, followed by solution screen (the current proposed approach) could potentially be helpful in terms of identifying a robust cocrystal for development. One should be aware that the selection of a screening approach could also be case dependent by considering time, resources, and additional information that might be available before the screening is started. For example, with the help of the solubility data and polymorphism information of the CCF and drug candidate, liquid-assisted grinding and evaporation approaches could be more suitable for the initial screen purpose.

The results of the cogrinding experiments (stage I) are listed in Table 1. The molar ratio of 1:1 (compound **1**:CCF) was used (as a starting point) during the cogrinding and subsequent

(30) Friscic, T.; Childs, S. L.; Rizvi, S. A. A.; Jones, W. The role of solvent in mechanochemical and sonochemical cocrystal formation: a solubility-based approach for predicting cocrystallisation outcome. *CrystEngComm* **2009**, *11* (3), 418–426.

(31) Childs, S. L.; Rodriguez-Hornedo, N.; Reddy, L. S.; Jayasankar, A.; Maheshwari, C.; McCausland, L.; Shipplett, R.; Stahly, B. C. Screening strategies based on solubility and solution composition generate pharmaceutically acceptable cocrystals of carbamazepine. *CrystEngComm* **2008**, *10* (7), 856–864.

solution crystallization. It should be noted that the selection of 1:1 molar ratio could also yield cocrystals with different ratios, and further evaluation was performed in the solution screen stage to determine the molar ratio between the cocrystal components. The potential "leads" of the cocrystal formation were assigned if both XRPD and DSC analyses provided positive responses. Figure 2 uses piperazine as an example to illustrate the use of XRPD and DSC data to identify potential cocrystal "leads" after the cogrinding experiment. After dry grinding piperazine with compound **1**, new XRPD diffraction peaks at 2θ angles of 10.0° and 15.4° and new DSC endothermic events between 170 and 190 °C were observed, and those were not observed from the CCF or compound **1**. These are indications of the interaction between the CCF and compound **1** that leads to new crystalline species (cocrystal) to form. Although the positive responses from both XRPD and DSC analyses were used as the criteria in this study, the use of DSC alone could also provide additional cocrystal "leads" that were not identified by XRPD, such as amorphous solids. The thermal method using DSC has been demonstrated by Lu et al. through the heating of the physical mixtures of salicylic acid and caffeine solids.[11] CCFs that showed positive on DSC data but negative on XPRD would be considered in the second tier screen if the initial identified "leads" could not yield any suitable cocrystals in the stage II screen. In this study, no CCF showed positive on XRPD and negative on DSC data.

For compound **1**, based on the stage I cogrinding experiments, the potential CCF "leads" are: fumaric acid, salicylic acid, succinic acid, maleic acid, and piperazine. The observation of many "leads" is consistent with the early evaluation that this compound has a high potential to form cocrystals because it has multiple numbers of hydrogen donors and acceptors. Following stage I, cocrystal formation in the presence of solvent (solution crystallization or slurry) was applied in the stage II screen. Solution crystallization or slurry conversion could confirm the cocrystal formation and provide more homogeneous samples compared to those made from cogrinding for physicochemical properties evaluation. Additionally, the understanding of the cocrystal formation with the presence of solvent could help the assessment of the developability of a cocrystal of interest because controlled synthetic processes for pharmaceutical compounds are solution-based. The choices of CCFs for the stage II screen were based on, but not limited to, the "leads" identified in stage I. CCFs structurally similar to the "leads" were also included. For example, since fumaric acid, succinic acid, and maleic acid were identified as potential "leads" for compound **1** from the stage I screen, this indicates that other structurally similar dicarboxylic acids, e.g. adipic acid, glutaric acid, or malonic acid, could also be good candidates for the cocrystal formation for this compound and were therefore included in the stage II screen. Figure 3 shows the chemical structures of CCFs that were used in stage II.

The use of solution crystallization or slurry conversion to generate cocrystals is, in general, more complicated than cogrinding because the solubilities of free form, CCF, and cocrystal in a particular solvent system need to be considered. Ternary phase diagrams of different cocrystals have been illustrated by various research groups, and the solvents could

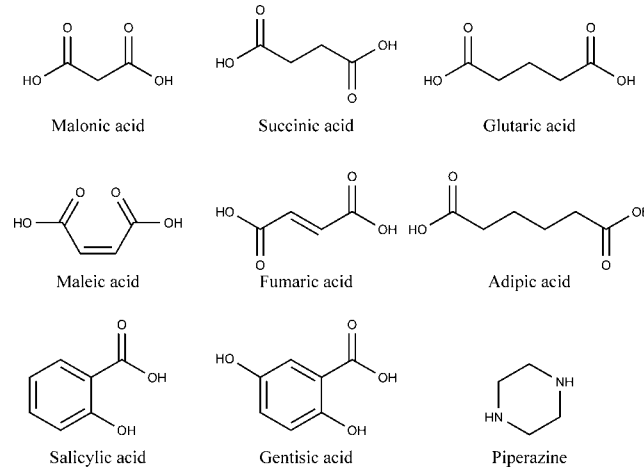


Figure 3. **Structures of CCFs used for the stage II solvent-based cocrystal screen.**

Table 2. **Approximate solubilities (mg/g solvent) of compound 1 and CCFs at 60 °C used in the stage II solvent-based screen[a]**

	ACN	THF	MEK	IPA	MeOH	DCE	EtOH/H_2O
compound **1**	~20	~40	~40	<8	~10	~20	<8
fumaric acid	~10	>50	~20	>50	>50	<8	>50
maleic acid	>50	>50	>50	>50	>50	<8	>50
malonic acid	>50	>50	>50	>50	>50	<8	>50
succinic acid	~40	>50	>50	>50	>50	<8	>50
glutaric acid	>50	>50	>50	>50	>50	<8	>50
adipic acid	~40	>50	>50	>50	>50	~20	>50
salicylic acid	>50	>50	>50	>50	>50	>50	>50
gentisic acid	>50	>50	>50	>50	>50	>50	>50
piperazine	>50	>50	~20	>50	>50	<8	>50

[a] ACN: acetonitrile; THF: tetrahydrofuran; MEK: methyl ethyl ketone; IPA: isopropanol; MeOH: methanol; DCE: 1,2-dicholoroethane; EtOH/H_2O: ethanol/water 96/4 (w/w).

have dramatic effects in the cocrystal formation.[18,19] Blagden et al. used ternary diagrams to schematically illustrate the solubility effect of compound and CCF in particular solvent systems.[1] The process window for cocrystal formation could be solvent dependent, and a good understanding of the driving force for the cocrystal formation is required to develop a robust process. Different groups have also evaluated the kinetic and thermodynamic aspects of cocrystal formation in a particular solvent system and demonstrated that cocrystal formation could be controlled through controlling the supersaturation of the cocrystal components.[32−35] However, the complexity introduced by the presence of solvents may require significant resources in terms of time and manpower in the early pharmaceutical

(32) Karki, S.; Friscic, T.; Jones, W. Control and interconversion of cocrystal stoichiometry in grinding: stepwise mechanism for the formation of a hydrogen-bonded cocrystal. *CrystEngComm* **2009**, *11* (3), 470–481.
(33) Nehm, S. J.; Rodriguez-Spong, B.; Rodriguez-Hornedo, N. Phase Solubility Diagrams of Cocrystals Are Explained by Solubility Product and Solution Complexation. *Cryst. Growth Des.* **2006**, *6* (2), 592–600.
(34) Gagniere, E.; Mangin, D.; Puel, F.; Bebon, C.; Klein, J.-P.; Monnier, O.; Garcia, E. Cocrystal Formation in Solution: In Situ Solute Concentration Monitoring of the Two Components and Kinetic Pathways. *Cryst. Growth Des.* **2009**, *9* (8), 3376–3383.
(35) Gagniere, E.; Mangin, D.; Puel, F.; Rivoire, A.; Monnier, O.; Garcia, E.; Klein, J. P. Formation of co-crystals: Kinetic and thermodynamic aspects. *J. Cryst. Growth* **2009**, *311* (9), 2689–2695.

Table 3. **DSC, XRPD, and NMR results[a] after stage II solvent-based screen**

	response of DSC/XRPD/^{1}H NMR ratio of CCF to compound **1**						
	ACN	THF	MEK	IPA	MeOH	DCE	EtOH/H_2O
fumaric acid	+/+/**1:1**	−/−/0.1:1	+/+/0.7:1	−/−/0:1	−/−/0:1	+/+/**1:1**	−/−/0:1
maleic acid	−/−/0:1	−/−/0:1	∓/0:1	−/−/0:1	−/−/0:1	+/+/**1:1**	−/−/0:1
malonic acid	+/+/0.2:1	−/−/0:1	+/+/0.3:1	−/−/0:1	−/−/0:1	+/+/**1:1**	−/−/0:1
succinic acid	+/+/0.7:1	±/0.3:1	+/+/0.6:1	−/−/0.9:1	−/−/0:1	+/+/1.2:1	−/−/0:1
glutaric acid	+/+/**1:1**	+/+/0.6:1	+/+/**1:1**	−/−/0.1:1	−/−/0:1	+/+/**1:1**	−/−/0:1
adipic acid	±/1:1	−/−/0:1	+/+/0.6:1	−/−/0:1	−/−/0:1	+/+/**1:1**	−/−/0:1
salicylic acid	−/−/0:1	−/−/0:1	−/−/0:1	−/−/0:1	−/−/0:1	+/+/0.8:1	−/−/0:1
gentisic acid	+/+/**1:1**	−/−/0:1	−/−/0:1	−/−/0:1	−/−/0:1	+/+/**1:1**	−/−/0:1
piperazine	+/+/0.5:1	+/+/0.4:1	+/+/0.5:1	−/−/0:1	−/−/0:1	−/−/0:1	−/−/0:1

[a] The positive responses for XRPD, DSC, and NMR (1:1) are in bold-faced text.

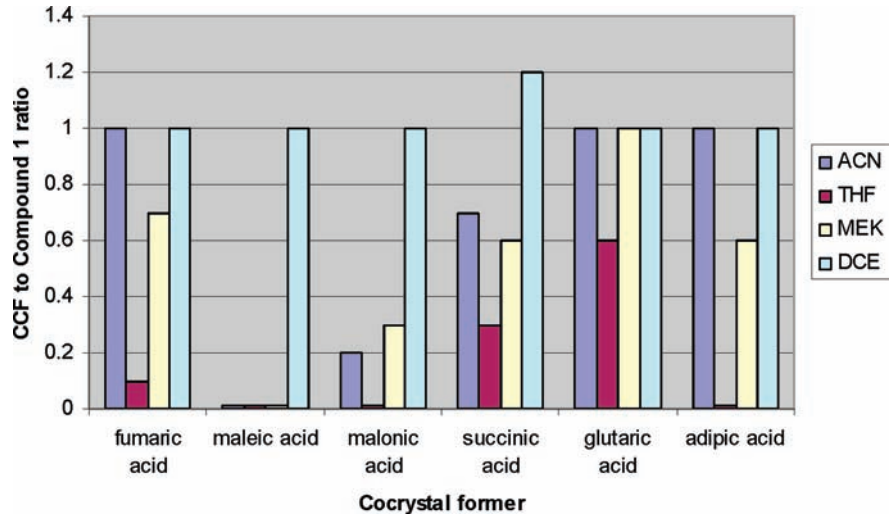


Figure 4. **^{1}H NMR results of different dicarboxylic acids to compound 1 ratios in solvent systems that showed similar solubility. Standard deviations across solvents are 0.42 (fumaric acid), 0.50 (maleic acid), 0.43 (malonic acid), 0.37 (succinic acid), 0.20 (glutaric acid), and 0.47 (adipic acid).**

development which may not be feasible. In this contribution, an alternative practical approach is proposed.

In order to facilitate the solution-based screen, a database of approximate solubility of CCFs in certain common process solvents was first established. In Table 2, the 60 °C solubilities of compound **1** and chosen CCFs for the stage II screen in selected solvents are listed. These solvents were chosen on the basis of a variety of polarities and capabilities of hydrogen-bonding formation. The DSC, XRPD, and NMR data of the isolated solids from the stage II screen are summarized in Table 3. On the basis of Tables 2 and 3, the solubility effect of compound **1** and CCFs on the cocrystal formation in different solvents was observed. In general, the cocrystals were more easily obtained from solvents in which the compound **1** and the CCF have a smaller solubility difference, or a congruently saturating system, such as MEK, THF, ACN, and DCE. In addition to the solubility effect, the effect of solvent properties on the cocrystal formation was also observed for the same CCF among solvents that showed similar solubilities between compound **1** and CCF. For example, glutaric acid cocrystal was favored in certain solvents, e.g., MEK or DCE, than in other solvents, e.g., THF. DCE and acetonitrile solvates of compound **1** were also observed from some of the cocrystal formation attempts. These results further suggest that applying evaporation- or solvent-aided grinding methods in the initial screen could complicate the purpose of identifying the potential interaction between the compound and CCF because of the effect of solvent on the cocrystal formation. In the stage II screen, no cocrystals were formed from solvent systems containing alcohols or H_2O, e.g., MeOH, IPA, or EtOH/H_2O, this could be attributed to, in addition to the solubility effect, the fact that alcohols and H_2O are good hydrogen bond donors and acceptors and they could compete with the H-bonding between the compound and CCF.

The effect of CCF structures on the cocrystal formation was also observed among those cocrystals with similar functional groups. Different results of cocrystal formation were observed among different dicarboxylic acids. For example, in ACN, the cis and trans isomers of unsaturated dicarboxylic acid, maleic and fumaric acids, show totally different cocrystal formation capabilities, with fumaric acid forming cocrystals with compound **1** while maleic acid does not. This effect was also observed for saturated dicarboxylic acids with different chain length, e.g. malonic acid, glutaric acid, succinic acid, and adipic acid showed different cocrystal formation capability in MEK. These results may be associated with the crystal packing energy in these systems and could be further understood, once single-crystal X-ray data are obtained. On the basis of these differences, it might be reasonable to conclude that even though the structure-based design for cocrystal formation could lead to one particular class of the cocrystal formers with certain functional groups, the difference within that particular class might not be predictable.

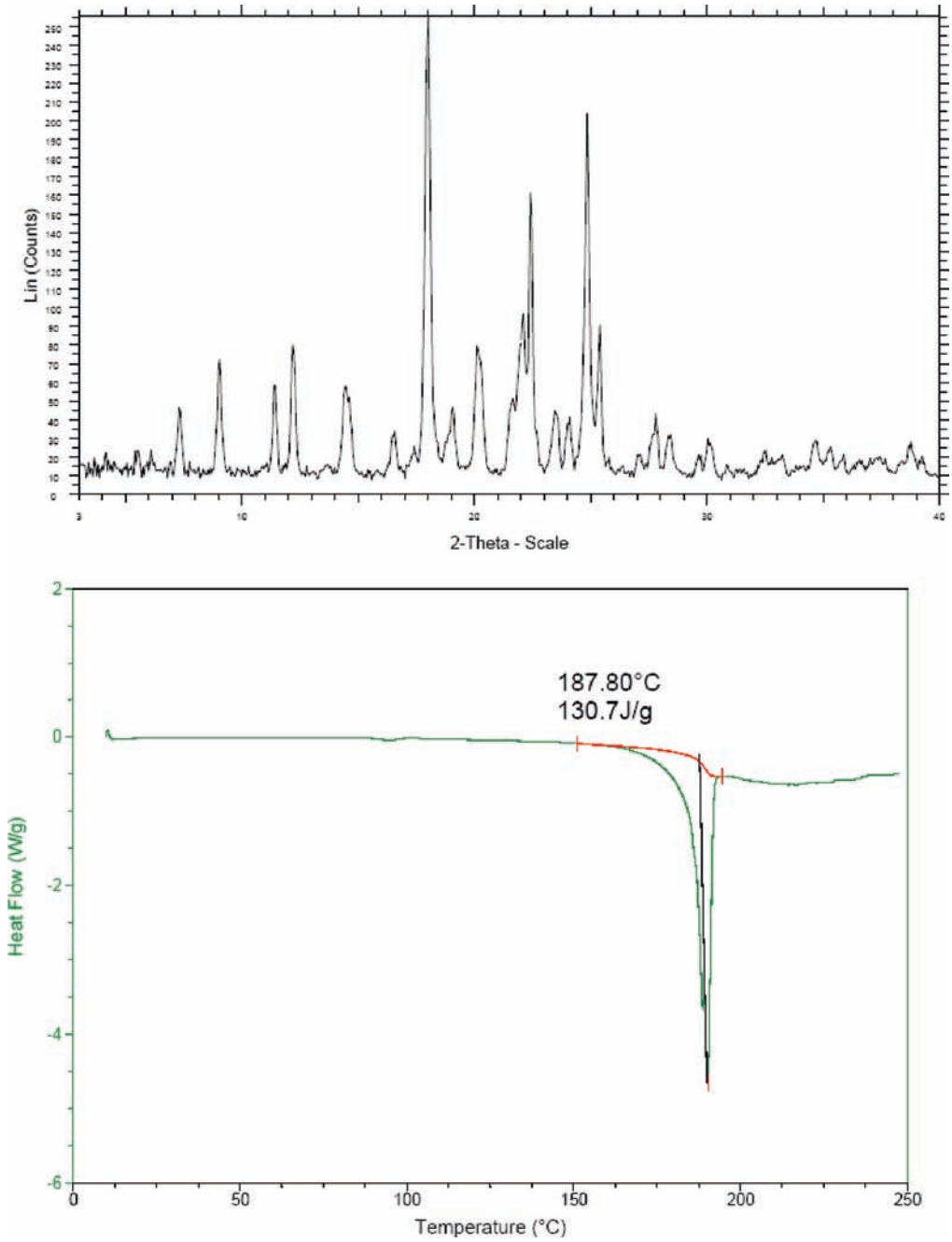


Figure 5. **XRPD (top) and DSC (bottom) data of the glutaric acid cocrystal of compound 1. DSC endothermic peak shows melting T_{onset}: 187.8 °C.**

When the APIs become more complex in terms of molecular weight and functional groups, the possibility of certain functional groups to have intra- or intermolecular interactions could increase. Therefore, together with the effects of solvents and structure variation of CCFs, using a structure-based prediction to identify a good CCF candidate and a suitable solvent to generate pharmaceutical cocrystals could be challenging. Experimental approach might be a more practical and direct approach to identify a "developable" pharmaceutical cocrystal candidate with limited time and resources in this regard.

The feasibility of the cocrystal formation in solution should also be considered at an early stage while evaluating the solid forms (free form, salts, cocrystals) as the developability of the solid form candidates is an important criterion for the solid form selection. In the proposed protocol, the stage II solvent-based screen also provides additional information regarding the scalability of potential cocrystals and solvent choices. Figure 4 shows the ^{1}H NMR results of different dicarboxylic acids to compound **1** ratios in solvent systems that showed smaller solubility difference between the CCFs and compound **1**. From this result, glutaric acid cocrystal of compound **1** was considered the most robust cocrystal candidate because it could be reproduced from different solvent systems with a 1:1 ratio of CCF to compound **1**. Additionally, the standard deviation of the CCF-to-compound **1** ratio can be used as a mathematical tool to assess the feasibility of scaling up different cocrystals. This information produced from the stage II screen could be directly used in subsequent crystallization development once

the cocrystal is selected as the development form, which could greatly reduce development resources and time used.

On the basis of the information obtained in the stage II screen, as shown in Figure 4 and Table 3, glutaric acid cocrystal was the first one to be scaled up for evaluation. MEK was selected as the scale-up solvent because it is a process-friendly solvent (ICH class 3[36]) and has relatively good solubility for both compound **1** and CCFs. A preliminary protocol was developed in MEK to produce gram quantities of the glutaric cocrystal of compound **1**. The solid-state characterizations, including XRPD, DSC, and TGA, of glutaric cocrystal of compound **1** are shown in Figure 5. This cocrystal is a highly crystalline, nonsolvated material with a melting T_{onset} ~188 °C. The intrinsic dissolution rate (IDR) at pH 6.8 and 37 °C of the glutaric cocrystal of compound **1** is 4−5-fold higher than that of the free form. This study demonstrates that the proposed cocrystal screen protocol could quickly identify a suitable cocrystal solid form candidate and provides another example that the cocrystal could be used to improve the physiochemical property, e.g., intrinsic dissolution rate, of the free form.

Conclusions

A systematic and practical cocrystal screen approach was proposed and demonstrated with a development compound. In this approach, a cogrinding screen (stage I) was conducted to identify potential CCF leads, followed by a solvent-based screen (stage II), where the developability of the cocrystals were also assessed. This approach provided an efficient method to identify potential cocrystal candidates for pharmaceutical development within a short period of time (e.g., 6 weeks with one full-time employee to identify the glutaric acid cocrystal for compound **1**). The identified glutaric acid cocrystal of compound **1** provided an improved intrinsic dissolution rate that eased the formulation development challenges. This study also provided an example to use the cocrystal as an alternative form for low solubility drugs.

Effects of solvents and structures of CCFs for cocrystal formation were studied in the stage II screen. These effects further demonstrated that to predict a CCF candidate and a suitable solvent to make a cocrystal for development may be challenging. An experimental approach such as the proposed one may be more feasible and efficient. Scalability of the cocrystals via solution crystallization should be considered at early stage while evaluating the cocrystal candidates. In the stage II screen, cocrystal formation in solution/slurry not only yielded cocrystal candidates but also provided information regarding the developability, potential solvent choices, and crystallization conditions for subsequent crystallization development of the identified cocrystal candidates. This experimental approach was demonstrated to be suitable and practical for pharmaceutical compounds as it provided risk assessment for the developability of the potential cocrystals along with the solid form screen activities.

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(36) http://www.ich.org/LOB/media/MEDIA423.pdf; Guideline for Residual Solvents (Q3C).