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Applicability of Phenolic Acids as Effective Enhancers of Cocrystal Solubility of Methylxanthines

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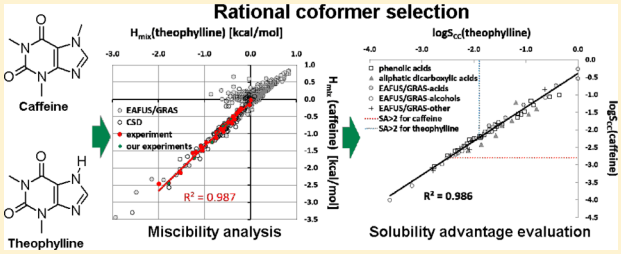
Supporting Information

ABSTRACT: Applicability of phenolic acids as potential cocrystal formers for methylxanthine derivatives was analyzed both in terms of cocrystallization probabilities and solubility advantage. The cocrystal formation abilities were evaluated using mixing enthalpy estimated within the conductor like screening model for real solvents (COSMO-RS) framework. The solubility improvement of potential cocrystals was estimated by formulation of the model relating experimental values to predicted solubilities. This enabled for ranking of potential cocrystals formers according to their solubility enhancement potential. According to the calculation results, a highly linear relationship (R^2 = 0.989) was found between estimated theophylline and caffeine cocrystal solubility values. It has been found that many phenolic acids, especially ones with several hydroxyl groups attached to phenyl ring, are the most promising candidates for cocrystallization with caffeine or theophylline. Experimental verification of the proposed protocol for caffeine and theophylline resulted in eight new molecular complexes, which were synthesized via a mechanochemical approach. All new solids were characterized using powder X-ray diffractometry and Fourier transform infrared spectroscopy combined with a attenuated total reflection technique.



INTRODUCTION

Pharmaceutically interesting substances are very often poorly or very poorly soluble in water. This is a source of serious problems, especially from the perspective of the route of drugs administration and consequently their bioavailability. That is why many methods have been invented for improving the physicochemical properties of new forms of drugs. Among them one of the most promising routes is multicomponent crystals synthesis.[1] There are many spectacular examples of improvements in pharmaceutically relevant properties achieved through cocrystallization such as solubility,[2−4] dissolution rate,[5−9] mechanical compressibility, tabletability,[10,11] stability,[12−14] or hygroscopicity.[15,16] A promising class of cocrystal formers are nutraceuticals, such as flavonoids, vitamins, and phenolic acids. According to our experimental and theoretical studies, the latter compounds were found to have a high affinity for amides such as urea, benzamide, salicylamide, and ethenzamide.[17−19] Because of antioxidant activities, phenolic acids are often added to food, pharmaceuticals, and cosmetics in order to enhance their stability.[20−23]

There are many efficient cocrystallization methods[24−26] which can be classified into two main groups: slow thermodynamic methods and fast kinetic approaches. All popular techniques of cocrystals preparation, namely, slurry cocrystallization, solvent evaporation, and grinding have some limitations. Therefore, the choice of method is dependent on the specifics of the particular system. In the case of poorly soluble drugs, there are some difficulties in applying solution cocrystallization methods coming from low concentrations of dissolved components. However, this can be overcome by using popular mechanochemical cogrinding methods. As it was demonstrated in many papers,[27−36] this approach was applied also in the case of methylxanthines including theophylline and caffeine. In this paper, the liquid-assisted cogrinding method was utilized for synthesis of new cocrystals of these two popular drugs.

Many theoretical methods of rational cocrystal former selection have been developed and tested against experimental data sets.[17,19,37−41] Recent approaches based on the analysis of coformers similarity were expressed in terms of the intermolecular interactions[38,42,43] and mixing enthalpy of supercooled liquids[37] under ambient conditions. The latter approach is based on the conductor like screening model for real solvents (COSMO-RS), developed by Klamt et al.,[44] whereby the likelihood of cocrystal formationcan be evaluated by the heat of mixing enthalpies (H_{mix}) analysis.[41] The more negative H_{mix}, the highest probability of cocrystal formation. The application of cocrystallization similarity concept offers

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very fast theoretical screening by inferring cocrystallization of one compound based on similarities between chemical species. This in turns allows for filling gaps in the lists of known cocrystals without the necessity of performing experiments of all possible combinations of coformers pairs.

The aim of this paper is two-fold. First, further experimental confirmation of the transferability of cocrystal formation potential in the case of caffeine and theophylline was performed. Since not all potential cocrystals are interesting from the practical application, apart from high cocrystallization probability, the second criterion was imposed on cocrystals screening results. In this part of the study phenolic acids were selected as potentially efficient cocrystal formers. Thus, the conjuncture of two criterions defines the complete cocrystal screening procedure presented below and applied in the case of methylxanthine derivatives.

MATERIALS AND METHODS

Chemicals Used for Cocrystals Synthesis. All chemicals were used without purification, as received from suppliers. Analytical grade active pharmaceutical ingredients were used, namely, theophylline (CAS: 58-55-9) and caffeine (CAS: 58-08-2). Also the following cocrystal formers were utilized, namely, 4-amino-2-hydroxybenzoic acid (4-aminosalicylic acid, CAS: 65-49-6), 4-nitrophenol (CAS: 100-02-7), 2-hydroxy-1-naphthoic acid (CAS: 2283-08-1), 3-hydroxy-2-naphthoic acid (β-hydroxynaphtoic acid, CAS: 92-70-6), 4-hydroxy-3-methoxycinnamic acid (ferulic acid, CAS: 537-98-4), 1,2,4,5-benzenetetracarboxylic acid (pyromellitic acid, CAS: 89-05-4), 2-fluorobenzoic acid (CAS: 445-29-4), 3,4-dihydroxycinnamic acid (3,4-dihydroxybenzeneacrylic acid and caffeic acid, CAS: 331-39-5) as supplied by Sigma-Aldrich. Methanol (99.9%) was purchased from Avantor Performance Materials Poland (Gliwice, Poland).

Experimental Cocrystals Screening. The procedure taking advantage of mechanochemical synthesis utilized 0.1 g of methylxanthine (theophylline or caffeine) mixed together with coformer in a molar ratio of 1:1 and milled in a porcelain mortar for an hour. During this procedure 20 μL portions of methanol were added to the mixture at intervals of 2 min. The obtained samples were analyzed using powder X-ray diffraction (PXRD) and Fourier transform infrared spectroscopy combined with an attenuated total reflection (ATR) technique (FTIR-ATR). Diffraction patterns were recorded using PW3050/60 goniometer equipped with Empyrean XRD tube Cu LFF DK303072. The range of 2θ angle was from 5° to 40° with 0.02° step. The obtained raw diffractograms were processed including Kα2 stripping, background subtraction, smoothing, and normalization with the use of the Reflex module of the Material Studio 8.0 package.[45] FTIR-ATR spectra were measured on a Bruker Alpha-PFT-IR spectrometer equipped with diamond attenuated total reflectance accessory.

Calculation Details. The geometries in both gas and condensed phases of all compounds were optimized using BP-RI/TZVP scheme, which was followed by σ-profiles computation by means of BP-RI/TZVPD approach taking advantage of TURBOMOLE software.[46] Prior to this stage conformational analysis of all compounds was performed using Materials Studio 8.0.[45] Postquantum-mechanical miscibility and aqueous solubility analyses were performed with COSMOtherm software[47] using BP_TZVPD_FINE_C30_1601.ctd parametrization. The likelihood of cocrystal formation was estimated based on the working paradigm of the correspondence between miscibility in the solid state and in liquids quantified by the mixing enthalpy.

RESULTS AND DISCUSSION

The two-step procedure for comprehensive cocrystals screening started from estimation of similarities between cocrystals landscapes of caffeine and theophylline and was followed by experimental synthesis of new solids. The final step was devoted to ranking of coformers with high probability of cocrystallization using criterions of predicted solubility advantage.

Transferability of Cocrystallization Landscapes between Theophylline and Caffeine. Since structures of caffeine and theophylline are quite analogous, it is reasonable to expect that they can exhibit similar abilities to cocrystal formation. Indeed, as it can be inferred from Figure 1, there is

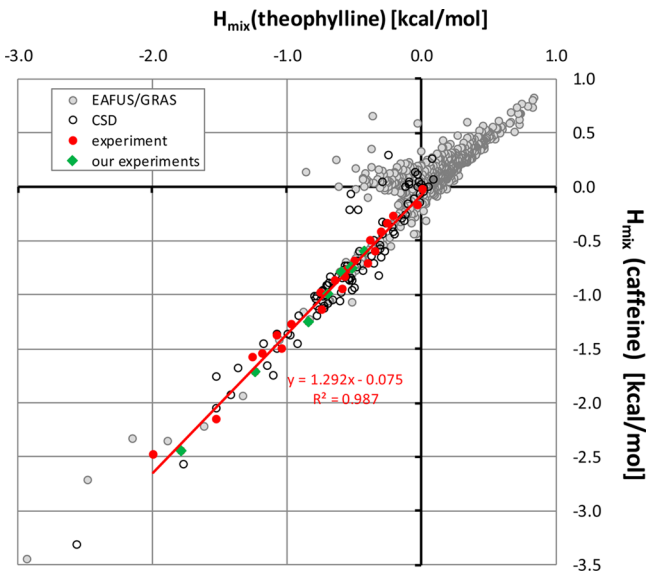

Figure 1. Correlation between mixing enthalpies of caffeine and theophylline. The four series corresponds to different sets of coformers mixed in the liquid state under supercooled conditions.

quite a linear relationship between values of mixing enthalpies of these two methylxanthines calculated for a common set of coformers. In Figure 1 there are overlaid three sets of data. The first one comprises coformers which were collected after searching of the Cambridge Structural Database[48] (CSD) for binary solids comprising compounds listed in Table 1. As a

Table 1. Experimental Cocrystal Screening Results Performed for Caffeine and Theophylline[a]

coformer	caffeine	theophylline
ferulic acid	ref 53	+
	−0.98	−0.69
4-amino-2-hydroxybenzoic acid	+	ref 54
	−1.25	−0.84
4-nitrophenol	+	TOPPNP[55b]
	−0.59	−0.42
2-hydroxy-1-naphthoic acid	LAKXUS[25b]	+
	−0.75	−0.52
3-hydroxy-2-naphthoic acid	KIGKOB[56b]	+
	−0.74	−0.52
1,2,4,5-benzenetetracarboxylic acid	NINXAL[57b]	+
	−2.44	−1.78
2-fluorobenzoic acid	AFERAG[58b]	+
	−0.78	−0.59
caffeic acid	ref 53	+
	−1.71	−1.23

[a]Plus symbol indicates cocrystals synthesized in this study. Values of H_{mix} (in kcal/mol) are provided for each pair. [b]Cocrystal reported in CSD.

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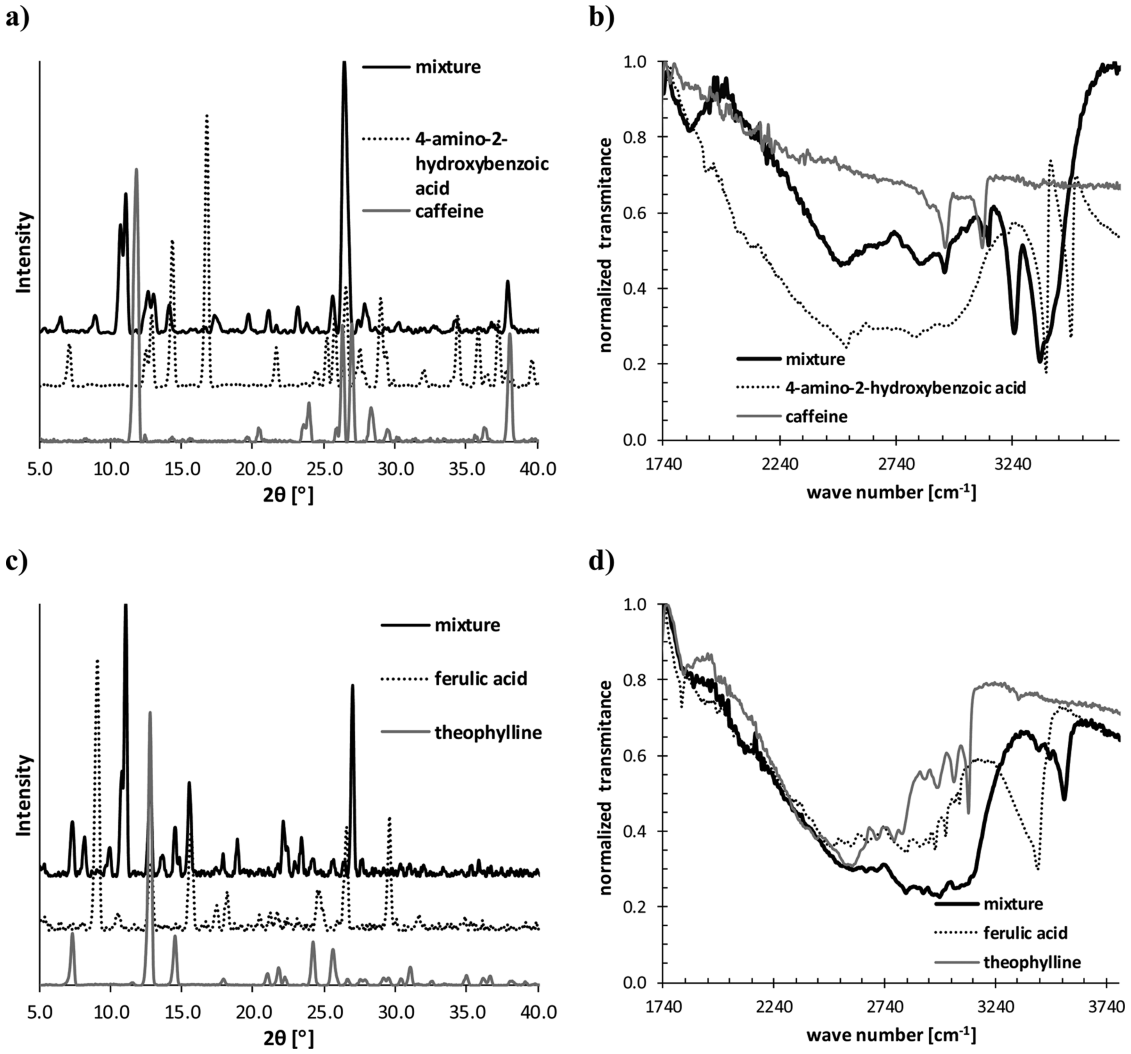

Figure 2. PXRD and FTIR spectra recorded for 1:1 caffeine/4-amino-2-hydroxybenzoic acid mixture (a, b) and 1:1 theophylline/ferulic acid mixture (c, d) obtained via liquid-assisted grinding.

result a set of 162 cocrystals formed with 126 coformers was found. Caffeine was used for the synthesis of 91 cocrystals, and 67 binary solids comprised theophylline. The other methylxanthines were rarely used since seven cocrystals were found for pentoxiphylline, six for theobromine, five for etophylline, and one for doxophylline. The cocrystals of other methylxanthines have been not deposited in the CSD. Using the set of 126 coformers, all possible combinations of binary mixtures were considered for which H_{mix} values were computed. The resulting distributions were collected in Figure 1 as black open circles characterizing caffeine and theophylline. The second and the most comprehensive set of coformers comes from the EAFUS/GRAS lists comprising 835 species. Among them one can find many naturally occurring nutraceuticals like vitamins, flavonoids, polyphenols, and phenolic acids, which are regarded as potentially interesting and pharmaceutically relevant cocrystal ingredients.[49−52] This set was used for ensuring that the extension of a coformers list beyond the one used in the experiment also leads to similar linear relationships. Despite a confirmative answer to this question, there are many pairs for which the cocrystallization probability seems to be quite low as indicated by high H_{mix} values. It was documented[40] that in such a case the region of low predictability of mixing enthalpy corresponds to the values of H_{mix} higherthan −0.17 kcal/mol when the BP-TZVPD-FINE level of computation is used. Contrary to the first two sets comprising many hypothetical pairs, the third collection was restricted only to experimentally synthesized binary solids. In Figure 1 red circles document cocrystals found in the literature. Additionally our experiments enriched the collection of cocrystals formed by caffeine and theophylline as documented by green diamonds.

New Cocrystals Synthesis. Although enormous reports on the caffeine and theophylline cocrystals were published, there are several gaps in their cocrystallization landscapes. Therefore, experimental cocrystal screening studies using a popular mechanochemical approach were performed for several exemplary mixtures including phenolic acids. The screening procedure was based on filling the gaps in the cocrystallization landscapes of caffeine and theophylline comprising known examples from CSD and the literature. As a result of cogrinding experiments, eight new cocrystals were identified. These results along with the mixing enthalpy values and structurally similar cocrystals are summarized in Table 1. The complete documentation of theophylline and caffeine cocrystal screening results are provided in the Figure 2 and Supporting Information (Figures S1−S6). In the case of all examined systems, the

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cocrystal phase can be identified by the appearance of several new peaks on each diffraction pattern recorded for the coground mixture. For instance, the caffeine-4-amino-2-hydroxybenzoic acid cocrystal can be detected by two new diffraction peaks of high intensity located at 2θ angle values equal to 10.7° and 11.1° and by several small signals at 14.5°, 19.7°, 21.1°, and 26.6° which cannot be assigned to the known forms of the pure components (Figure 2a). In the case of theophylline−ferulic acid system, cocrystal formation can be evidenced by the appearance of a new signals on the diffraction pattern, located at 8.2°, 9.9°, 11.1°, 13.7°, and 27° (Figure 2c). Additional confirmation related to the new hydrogen bonding motifs between coformers is provided by the FTIR-ATR spectra analysis of coground mixtures and pure components. As one can see from Figure 2b,d and Supplementary Figures S1−S6, in each case several absorption bands appeared on the vibrational spectra of mixtures which cannot be assigned to the cocrystal formers. This is associated with absorption bands shifts that indicate formation of a new molecular complex stabilized by the OH···N interactions. As one can see, a blue-shift of absorption bands in the OH stretching region, namely, from 3491 to 3381 cm^{-1} and from 3385 to 3249 cm^{-1} can be observed for the 4-amino-2-hydroxybenzoic−caffeine system (Figure 2b). On the other hand, in the case of the exemplary spectra recorded for theophylline−ferulic acid system, a characteristic ν(OH) absorption band red-shift from 3432 to 3550 cm^{-1} probably indicates formation of a new molecular complex (Figure 2d).

Extension of Cocrystallization Similarities on Other Methylxanthines. On the basis of the cocrystallization transferability concept,[37] the miscibility of a particular compound with a coformer can be inferred from the miscibility of a structurally similar compound with the same coformer. This is a contestant with the well-known rule "*similia similibus solventur*". Therefore, when the cocrystallization potential of theophylline with a certain class of coformers is known, one can evaluate the ability of cocrystal formation of other methylxanthines. In Figure 3 the relationship between H_{mix} values calculated for different cocrystals of methylxanthines found in the CSD database with respect to H_{mix} values characterizing theophylline are presented. As it can be seen, the highest miscibility expressed by the most negative H_{mix} values can be observed for pentoxiphylline, while the lowest miscibility occurs for theodrenaline. Nevertheless, the differences between H_{mix} values calculated for the most stable cocrystals of theodrenaline and pentoxiphylline are quite small, namely, 1.87 kcal/mol. Noteworthy, in all cases the highest miscibility can be observed for octafluorohexanedioic acid, while the lowest can be observed for urea. Although these systems were sparingly studied experimentally, it seems very plausible that many new cocrystals might be obtained with similar coformers as for theophylline.

Theoretical Solubility Advantage Analysis of Phenolic Acids Methylxanthines Cocrystals. The selection of cocrystal former is not only restricted to ones fulfilling the miscibility criterion but should be also driven by the pharmaceutically relevant properties of new solid formulations. Since solubility enhancement is one of the main challenges of API improvement, theoretical analysis of solubility advantage was performed at the final stage of this study. According to the COSMOtherm approach, multicomponent crystals solubility can be calculated using the following equation:

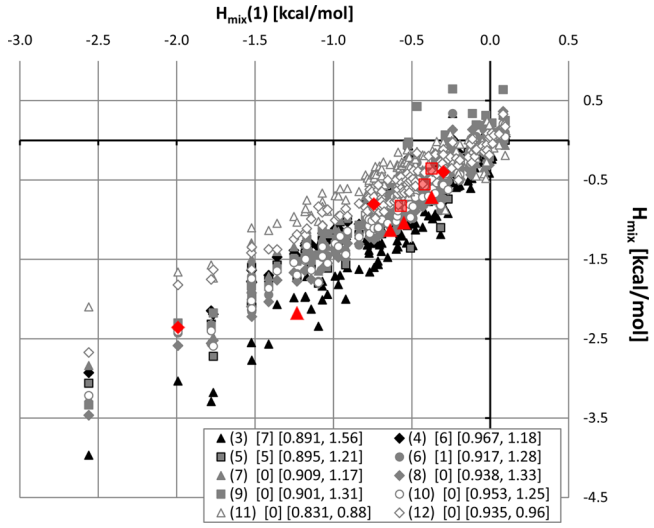

Figure 3. Relative values of mixing enthalpies of methylxanthines with respect to theophylline. The abscissa characterizes H_{mix} of theophylline with a variety of coformers, while the ordinate holds corresponding values of other methylxanthines, namely, (2) caffeine, (3) pentoxiphylline, (4) theobromine, (5) etophylline, (6) doxophylline, (7) dyphylline, (8) lisophylline, (9) pentiphylline, (10) proxyphylline, (11) theodrenaline, and (12) 8-cyclopentyltheophylline. In brackets, the number of cocrystals found in the CSD database, correlation coefficient, and the slope values are given. Series are composed from coformers found in cocrystals deposited in the CSD.[48]

$$\log S_{CC} = \frac{\mu_{CC}^{(0)} - \mu_{CC}^{(S)} - \max(0, \Delta G_{fus})}{\upsilon_{tot} RT \ln(10)} \quad (1)$$

where S_{cc} denotes drug solubility in cocrystal, ΔG_{fus} is the enthalpy of fusion, $\mu_{CC}^{(0)}$ and $\mu_{CC}^{(S)}$ stand for chemical potentials of the binary system in a vacuum (0) and solvent (s), respectively. Since, for cocrystals usually there are no available experimental data of ΔG_{fus} the absolute solubility values cannot be computed directly. Nevertheless, as suggested by Abramov et al.,[59] API cocrystals can be ranked in terms of their solubilities using the relationship between experimental solubility advantage and theoretical drug solubility in cocrystals calculated assuming zeroth contributions from ΔG_{fus}. The solubility advantage SA is typically defined according to the following formula:

$$SA = \frac{S_{CC}}{S_{drug}} \quad (2)$$

where S_{drug} denotes solubility of pure API. As it can be inferred from eq 2, for a certain drug (when S_{drug} = const.) a linear relationship between log SA and log S_{CC} can be obtained. This shows that there is a possibility for formulating models based on known experimental SA data and theoretical S_{CC} values. The relationships between calculated solubility values and experimental data reported in the literature were presented in Figure 4 including methylxanthinesstudied here. The observed trends, although based on a limited number of cases, consistently exhibit a linear increase in experimentally determined log SA with an increase of estimated values of log S_{CC}. This fortunate correspondence enables at least qualitative estimating of solubility advantage in cases of not studied cocrystals. Particularly it is interesting to rank phenolic acids as potential cocrystals formers with methylxanthines studied here. The selection of these compounds was not accidental, since

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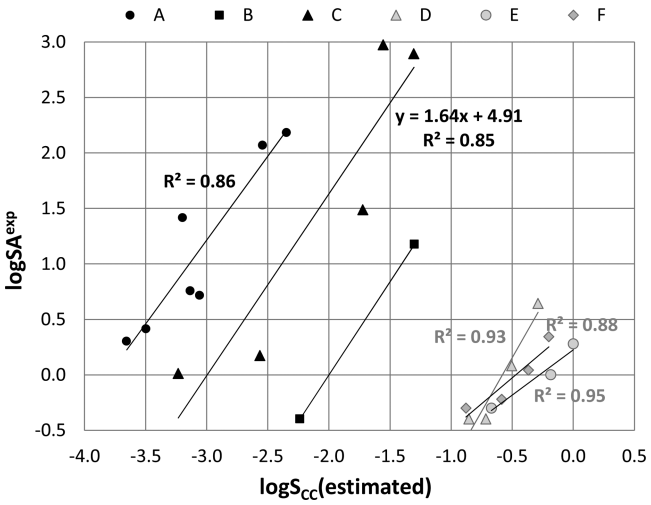

Figure 4. Relationships between experimental values of solubility advantage, log SA^{exp} and computed drug solubilities in cocrystal expressed as log S_{CC}. The following systems were analyzed: A - carbamazepine with saccharin, nicotinamide, succinic acid, malonic acid, oxalic acid, salicylic acid, or glutaric acid in water,[2,78] B - theophylline with nicotinamide or salicylic acid in water,[2,78] C - caffeine with malonic acid, glutaric acid, maleic acid, salicylic acid or 1-hydroxy-2-naphthoic acid in water,[79,53] D, E, and F carbamazepine with glutaric acid, nicotinamide, saccharin, and succinic acid in 2-propanol, ethyl acetate, and ethanol, respectively.[2,78]

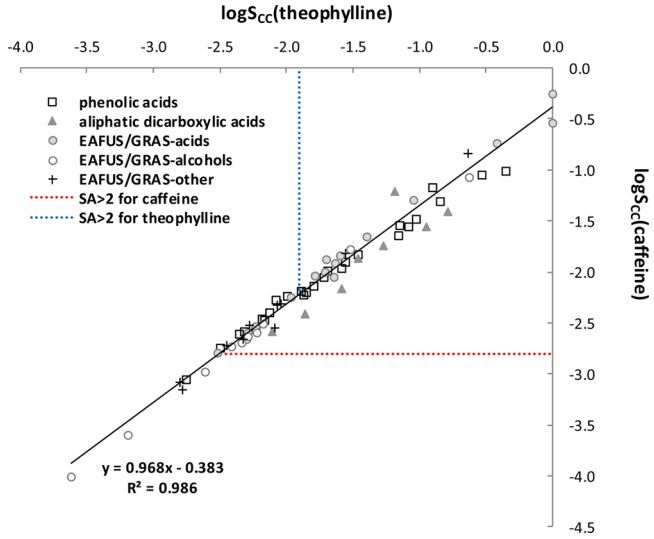

Figure 5. Correlation between estimated solubility values of caffeine and theophylline in the case of cocrystallization with the same coformers in a 1:1 stoichiometry.

phenolic acids and methylxanthines occur together in many natural food products with well proven beneficial properties for human health like yerba mate,[60] cocoa,[61] green coffee,[62] and tea.[63] Compositions containing these compounds such as crude caffeine were found to exhibit significant antioxidant, anti-inflammatory, and glucose uptake enhancement activity.[64] Apart from antioxidant activity, other important aspects of phenolic acids and methylxanthines associated with solubility and bioavailability enhancement can be distinguished. For instance, natural herbal extracts rich in phenolic compounds were found to improve pharmacokinetic properties of theophylline.[65] On the other hand, it has been proven that addition of theophylline and caffeine contributes to the bioavailability increase of many compounds including salicylic acid.[66] It is also worth mentioning that there are many documented examples of solubility and dissolution behavior enhancement achieved through crystallization of sparingly soluble pharmaceuticals with phenolic acids.[51,67−77] Previous work[37] and this study show that the miscibility of the unknown system can be inferred from the similar known cases using miscibility correlation plots (Figures 1 and 3), and, therefore, it seems to be possible to predict solubility in a similar manner. Indeed, there is a linear trend between caffeine and theophylline cocrystals (Figure 5). The similarity of physicochemical properties is the basis of all additive methods including well-known Hansen's and Hildebrandt's solubility calculation approach. It is understandable that structurally similar compounds will exhibit similar solubility and changes in the structure like removing and adding functional groups will have an adequate and predictable influence on the solubility. According to COSMO-RS calculations, the same rule applies to multicomponent crystals.

As it can be inferred from Figure 4, the experimentally proven solubility advantages of caffeine cocrystals are higher compared to the analogous mixtures containing theophylline, which resembles the order of pure drug solubility in water. This is also consistent with observations made by Good.[78] In order to rank the coformers in terms of their solubility advantage potential, the theoretical values of log S_{CC} were calculated for hypothetical 1:1 cocrystals of theophylline and caffeine with several classes of cocrystal formers. The presented results in Figure 5 document a strong correlation between log S_{CC} distributions obtained for both methylxanthines.

In further analysis, it is assumed that the sensible solubility advantage corresponds to SA > 2 that is associated with log S_{CC} > −2.8 in the case of caffeine cocrystals and log S_{CC} > −1.9 in case of the theophylline binary solids. These values were estimated with the aid of trends documented in Figure 4 used further for ranking of potential cocrystals formers. In Figure 5 the dotted line documents these threshold values. Despite the fact that solubility advantage can differ by 1 order of magnitude, it is expected that the same coformers can be used for enhancing of solubility in water of both these methylxanthines. It is interesting to notice that a sensible solubility advantage can be observed for many phenolic acids, especially for ones rich in carboxylic and phenolic groups. This can be explained by the formation of stable complexes in water involving hydrogen bonding between the COOH and OH group attached to the benzene ring and imidazole nitrogen atoms. The highest values of calculated solubility correspond to cocrystals formed by cichoric acid, 3,4,5-trihydroxybenzoic acid (gallic acid), 3,4,5-trihydroxycinnamic acid, and chlorogenic acid. All these four coformers are expected to increase solubility of both caffeine and theophylline cocrystals. The latter compound deserves particular attention since it is present together with caffeine in coffee. According to D'Amelio et al.[80] caffeine forms very stable complexes in the water with chlorogenic acid as evidenced by the high association constant (K = 30 M^{-1}) determined using the nuclear magnetic resonance (NMR) titration method. It is worth mentioning that formation of molecular complex in aqueous solution was also observed using different spectroscopic methods in the case of caffeic acid and caffeine.[81] These facts explain the active role of phenolic acids in enhancing cocrystal solubility.

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Apart from the mentioned phenolic acids, there are also many more potential cocrystal formers worth considering. The full list of performed screening is provided in Table 2.

Table 2. List of Coformers with Sensible Solubility Advantage of Caffeine and Theophylline[a]

coformer	log S_{CC} theophylline	log S_{CC} caffeine
Phenolic Acids		
cichoric acid	−0.36	−1.01
3,4,5-trihydroxybenzoic acid	−0.54	−1.05
3,4,5-trihydroxycinnamic acid	−0.85	−1.31
chlorogenic acid	−0.90	−1.17
caftaric acid	−1.03	−1.48
umbellic acid	−1.09	−1.55
3,4-dihydroxybenzoic acid	−1.15	−1.55
rosmarinic acid	−1.16	−1.65
Apliphatic Dicarboxylic Acids		
oxalic acid	−0.79	−1.19
malonic acid	−1.19	−1.41
succinic acid	−0.95	−1.21
glutaric acid	−1.27	−1.56
adipic acid	−1.46	−1.74
EAFUS/GRAS Acids		
phosphoric acid	0.00	−0.54
sulfamic acid	−0.42	−0.74
1-hydroxyethylidene-1,1-diphosphonic acid	0.00	−0.26
3-hydroxy-2-oxopropionic acid	−1.05	−1.29
hexanedioic acid	−1.39	−1.65
EAFUS/GRAS Alcohols		
myricitrin	−0.63	−1.07
4-hydroxybenzenemethanol	−1.52	−1.78
4-hydroxybenzenemethanol	−1.52	−1.78
other		
azodicarbonamide	−0.64	−0.84

[a]Provided values characterize estimated water solubility of cocrystals.

It is worth mentioning that not all phenolic acids are to be considered as effective solubility enhancers. Indeed, results of our calculations suggest that cocrystals of methylxanthines with salicylic acid exhibit relatively low solubility. This nicely corresponds to experimental log SA values of caffeine−salicylic acid and theophylline−salicylic acid cocrystals, which are as small as 0.17[53] and −0.40,[2,78] respectively. The latter example documents that cocrystallization of theophylline with salicylic acid leads to the solubility reduction. This can be explained by the relatively low affinity of methylxanthines to salicylic acid. It is worth mentioning that salicylic acid−caffeine and salicylic acid−theophylline crystal structures deposited in CSD under refcodes XOBCAT[82] and KIGLES[83] are stabilized by a quite weak synthon formed between COOH···N groups. In these cocrystals, the OH group attached to the benzene ring is not involved in the formation of strong intermolecular interactions due to the competitive intramolecular interaction with the COOH moiety. Another interesting observation can be made by analyzing the number of hydroxyl groups attached to the phenyl ring of coformers. Noteworthy phenolic acids precursors with only one acidic functional group, namely, benzoic acid and cinnamic acid, are less miscible with theophylline and caffeine than their hydroxylated derivatives. A similar observation can be made in the case of methylated phenolic acids. For instance, H_{mix} values calculated for caffeine-3-methoxybenzoic acid are equal to −0.43 kcal/mol, while H_{mix} values calculated for caffeine-3-hydroxybenzoic acid are equal to −1.54 kcal/mol. These observations suggest that the presence of hydroxyl groups attached to the benzene ring enhances the ability of cocrystal formation due to the higher affinity of coformer to methylxanthine and consequently altering of their solubility. A similar effect can be observed in the case of popular solubility enhancers, namely, cyclodextrins. Therefore, it is understandable that cocrystals of the lowest solubilities are formed by the phenolic acid precursor, cinnamic acid and *O*-methylated phenolic acids, namely, 3,4-dimethoxybenzoic acid, 5-bromoferulic acid, and 3,4,5-trimethoxycinnamic acid.

CONCLUSIONS

Theoretical cocrystal screening methods are useful for fast selection of compounds which are the most probable to form a molecular complex in the solid state. This approach is beneficial from an economic viewpoint, since it can be used to minimize the expensive experimental screening studies. Since theophylline and caffeine have been extensively examined in terms of cocrystal formation, it is possible to systematize this information in order to formulate a model of cocrystallization prediction based on the similarity concept. It is important, however, to analyze compounds which are safe and which can improve pharmaceutically relevant properties such solubility or dissolution rate. In this paper, screening studies on the methylxanthines' miscibility with a variety of coformers were performed including nutraceuticals belonging to GRAS and EAFUS lists. The mixing enthalpy of liquids under supercooled conditions estimated using COSMO-RS theory showed that the majority of pharmaceutically acceptable coformers belonging to EAFUS and GRAS lists exhibit relatively low affinity to theophylline and caffeine. This narrows significantly the span of potential coformers. Nevertheless, there are many other compounds regarded as nutraceuticals which potentially can be useful as isolated pure ingredients and compositions obtained using modern extraction methods. In this study, a promising class of cocrystal formers, namely, phenolic acids, were analyzed in terms of their miscibility with methylxanthines and aqueous solubility enhancement power. There are several natural products like coffee, tea, and cocoa containing both methylxanthines and phenolic acids. The wide interest of research studies on these compounds is mainly associated with their antioxidant activity. This study was aimed at a different and also important aspect, which has not been explored in detail elsewhere, namely, the solubility advantage evaluation of a wide spectrum of methylxanthine−phenolic acid binary mixtures. The absolute cocrystal solubility values calculation poses practical difficulties related to the lack of enthalpy of fusion ΔG_{fus} values available in the literature. This cannot be easily overcome. However, on the basis of the approach reported by Abramov et al.,[59] the coformers can be ranked in terms of their solubility improvement potential using values calculated assuming zeroth for ΔG_{fus}. This allows for rational selection of pharmaceutically interesting coformer. The presented information relied on two-stage screening offering suggestions of rational selection of coformers which not only cocrystallize with the API but also will offer a sensible solubility advantage. The application to other systems is only limited by the knowledge of the solubility of some exemplary cocrystals used in the validation step.

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Cryst. Growth Des. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.7b00121.

PXRD patterns and FTIR spectra of 1:1 solid mixtures of caffeine/4-nitrophenol, theophylline/2-hydroxy-1-naphtoic, 1:1 theophylline/3-hydroxy-2-naphtoic acid mixture, 1:1 theophylline/1,2,4,5-benzenetetracarboxylic acid, 1:1 theophylline/2-fluorobenzoic acid, and 1:1 theophylline/caffeic acid (PDF)

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Notes

The authors declare no competing financial interest.

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