Synthesis of caffeine/maleic acid co-crystal by ultrasound assisted slurry co-crystallization

Prafulla P. Apshingekar[a], Suyog Aher[a], Adrian L. Kelly[a,b], Elaine C. Brown[b], Anant Paradkar[a]*

[a] Centre for Pharmaceutical Engineering Science, University of Bradford, Bradford, West Yorkshire, UK.

[b] IRC in Polymer Science and Technology, University of Bradford, Bradford, West Yorkshire, UK.

Correspondence to:

Professor Anant Paradkar (Telephone: +44 1274 233900; E-mail: A.Paradkar1@bradford.ac.uk),

ABSTRACT:

A green approach has been used for co-crystallization of non-congruent co-crystal pair of caffeine – maleic acid using water. Ultrasound is known to affect crystallization hence the effect of high power ultrasound on the ternary phase diagram has been investigated in detail using a slurry co-crystallization approach. A systematic investigation was performed to understand how the accelerated conditions during ultrasound assisted co-crystallization will affect different regions of the ternary phase diagram. Application of ultrasound showed considerable effect on the ternary phase diagram; principally on caffeine/maleic acid 2:1 (disappeared) and 1:1 co-crystal (narrowed) regions. Also, the stability regions for pure caffeine and maleic acid in water were narrowed in the presence of ultrasound, expanding the solution region. The observed effect of ultrasound on the phase diagram was correlated with solubility of caffeine and maleic acid and stability of co-crystal forms in water.

INTRODUCTION

Pharmaceutical co-crystallization has shown potential to overcome challenges associated with the physicochemical properties of active pharmaceutical ingredients (APIs); manipulating solubility, bioavailability and stability.[1,2] One of the important challenges in pharmaceutical co-crystallization is non-congruent solubility of co-crystal crystal components. Caffeine – dicarboxylic acid is the most studied co-crystal pair showing non-congruency.[3-8] Several approaches have been used to overcome the non-congruent solubility of co-crystal components. Friščić et al.[4] carried out ultrasound assisted slurry co-crystallization experiments using different organic solvents for caffeine with l-malic acid or l-tartaric acid. Co-crystal formation was observed in solvents with relatively similar solubilities of both the co-crystal components and anticipated under circumstances where all co-crystal forming components remain saturated. Similarly, Sander et al.[9] used a combination of multiple-solvents and surfactant to reduce non-congruency between caffeine and 2,4-dihydroxybenzoic acid in the presence of ultrasound to obtain co-crystals. High solubility of co-crystal components and use of surfactant was found to increase nucleation rate and form nano-co-crystals. In addition to solvent selection approaches to overcome non-congruency, Aher et al.[6] used stoichiometric variation of the co-crystal forming components in menthol in the presence of ultrasound. In this study, a high solubility component was found to be required in high amounts in solution to keep both co-crystal forming components in a saturated state.

The above reports utilized organic solvents to obtain co-crystals. However, the use of organic solvent is not desirable at industrial scale for environmental reasons. The use of water as a solvent for crystallization is a green approach and there are few reports which used water as a solvent for co-crystallization of non-congruent co-crystals. Pagire et al.[8] synthesized caffeine/maleic acid co-crystals in water using microwave energy. Similar observations were made to the above reports utilizing ultrasound; co-crystallization was found to be dependent on the solubility of co-crystal forming components.

Ultrasound is known have a positive influence on the crystallization processes by providing accelerated conditions. Ultrasound application results in a dramatic reduction in induction period, metastable zone width and altered supersaturation conditions.[10-13] This will have significant effect on co-crystallization process of non-congruent system like caffeine – maleic acid. The sonochemistry reports available to date on co-crystallization of caffeine – maleic acid have used organic solvents.[6] Here, we have carried out a study to understand the effect of ultrasound on caffeine and maleic acid co-crystallization in water. The aqueous solubility of caffeine is 0.101 mM and maleic acid is 7.431 mM.[8] Solubility of maleic acid in water is around 33 times higher compared with caffeine. Considering effects of ultrasound on solution crystallization as mentioned above, we postulate that the accelerated conditions experienced by co-crystal components and co-crystals in the presence of ultrasound can be presumed to have a significant effect on co-crystallization and the ternary phase diagram. Aher et al.[6] also suggested that the application of ultrasound to solution co-crystallization may alter ternary phase diagram regions. The effect of ultrasound on co-crystal ternary phase diagrams has not been reported to date. The present report is a systematic investigation of ultrasound effect on co-crystal synthesis using aqueous ultrasound-assisted slurry co-crystallization of non-congruent caffeine - maleic acid co-crystals.

MATERIALS AND METHODS

Materials

Anhydrous caffeine (99% pure) and maleic acid (99% pure) were purchased from Sigma-Aldrich, UK. De-ionized water was collected from Milli Q system and used as such without any further treatment.

Preliminary solubility study

A preliminary study was carried out to understand the effect of ultrasound on caffeine and maleic acid solubility in water. An excess of solid was added to water to form slurries, which were equilibrated for 24 hr under stirring (400 rpm) in a jacketed vessel at 25 °C. Supernatant in equilibrium with caffeine or maleic acid slurries were analyzed by HPLC to determine solubility. Similarly to understand effect of ultrasound on solubility, caffeine and maleic acid slurries were subjected to 12 ultrasound pulses of 5 sec each separated by a gap of 1 sec, using a 20 kHz high power ultrasound set at 50 % amplitude (amplitude range 0-100 %) delivered using a sonotrode with tip diameter 13 mm (Sonics Vibra-Cell VCX 500 with net power output ~ 500 Watts) in a jacketed vessel maintained at 25 °C. Supernatant were analyzed by HPLC to determine solubility.

Ternary phase diagram construction

Two phase diagrams were constructed using slurry co-crystallization, one in the absence of and one in the presence of ultrasound. We believe this is the first report of its kind. Firstly, a ternary phase diagram for caffeine-maleic acid-water was constructed using slurry co-crystallization in the absence of ultrasound. Different concentrations of slurries were prepared (SI 1) by mixing varying amounts of caffeine, maleic acid and water. Caffeine and maleic acid were sieved using a sieve with mesh size 355 µm before slurry experiments and characterized by powder X-ray diffraction (PXRD) (Bruker D8 Diffractometer, wavelength of X-rays 0.154 nm Cu source, voltage 40 kV, and filament emission 40 mA). Water (w/w) was added to pre-weighed physical mixtures of caffeine and maleic acid (w/w) to form slurries, which were equilibrated for 24 hr under stirring (400 rpm) in a jacketed vessel at 25 °C. The solid was filtered; air dried at room temperature, analyzed by PXRD allowing the phase diagram to be constructed.

We hypothesized that ultrasound will affect solubility of the caffeine, maleic acid and co-crystal phases causing shifts in the ternary phase diagram regions. Therefore, subsequent experiments were performed to study the effect of high power ultrasound on the ternary phase diagram.

Different slurry concentrations (SI 2) were subjected to 12 ultrasound pulses of 5 sec each separated by a gap of 1 sec, using a 20 kHz high power ultrasound set at 50 % amplitude (amplitude range 0-100 %) in a jacketed vessel maintained at 25 °C. The solid was filtered; air dried at room temperature, analyzed by PXRD and the phase diagram was constructed.

RESULTS AND DISCUSSION

A preliminary solubility study was conducted showing that the approximate solubility of caffeine in water was 0.104 ± 0.011 mmol/ml, and that this increased to 0.642 ± 0.071 mmol/ml in the presence of ultrasound. Similarly, the approximate solubility of maleic acid in water was increased from 3.448 ± 0.299 mmol/ml to 7.327 ± 0.613 mmol/ml upon application of ultrasound. **The solubility of caffeine and maleic acid in water increases in presence of ultrasound only.** The aqueous solubility of maleic acid in water was found to around 33 times high compare to caffeine (Fig. 1). However, the solubility of maleic acid in water in the presence of ultrasound was found to be around 11 times high compared to caffeine (Fig. 1). This preliminary study indicates that ultrasound helps to achieve congruency in the case of non-congruently soluble co-crystal pairs.

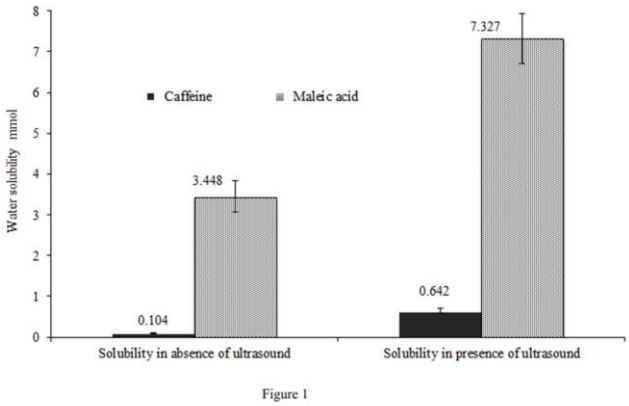

Figure 1

Figure 1. Effect of ultrasound on solubility of caffeine and maleic acid in water

Phase diagram

The ternary phase diagram for co-crystallization without ultrasound gives a clear picture of the formation of different co-crystal regions at different slurry concentrations (Fig. 2). A total of 9 different regions including phase pure 2:1 and phase pure 1:1 co-crystal (form I) were observed (SI 5). A clear shift in the regions for caffeine to 2:1 co-crystal to 1:1 co-crystal was observed as the amount of caffeine was reduced and maleic acid was increased.

Formation of the 2:1 co-crystal from solution is kinetically driven and reports suggest that it can only be achieved by techniques which can generate high levels of supersaturation.[5,6,7] Similarly, the caffeine/maleic acid 2:1 co-crystal observed in the current study can be assumed to be formed due to high levels of supersaturation achieved mainly because of slurry co-crystallization. Supersaturation levels are achieved more effectively in slurry techniques and hence have the potential to address challenges associated with many other co-crystallization techniques. Friščić et al.[4] suggested that co-crystal formation can be expected when co-crystal components remain at saturated levels in slurry experiments and co-crystal formation is mediated through solution phase. Similarly, in the present study, solids always remained in equilibrium with solution, keeping the solution phase saturated with respect to caffeine and maleic acid and allowing formation of co-crystals. Secondly, the apparent enhancement in caffeine solubility in the presence of maleic acid must have also contributed to high levels of supersaturation forming 2:1 co-crystal (SI 3 and SI 4). This has been verified experimentally. The solubility of caffeine in the presence of different (%) mole fractions of maleic acid in water and solubility of maleic acid in the presence of different (%) mole fractions of caffeine in water were also investigated. Caffeine was added to the solutions prepared with different amounts of maleic acid. The addition of caffeine was continued until caffeine started precipitating out from solution. The solution was filtered and analysed by HPLC to quantify the amount of caffeine present in that solution. A

similar procedure was used to calculate the amount of maleic acid soluble in presence of different known concentrations of caffeine in water. The solubility of caffeine increased in the presence of maleic acid (SI 3) until an equimolar ratio of caffeine and maleic acid was attained. Further increase in maleic acid resulted in decreased solubility of caffeine. Similarly, the presence of caffeine in water also has an effect on the solubility of maleic acid (SI 4).

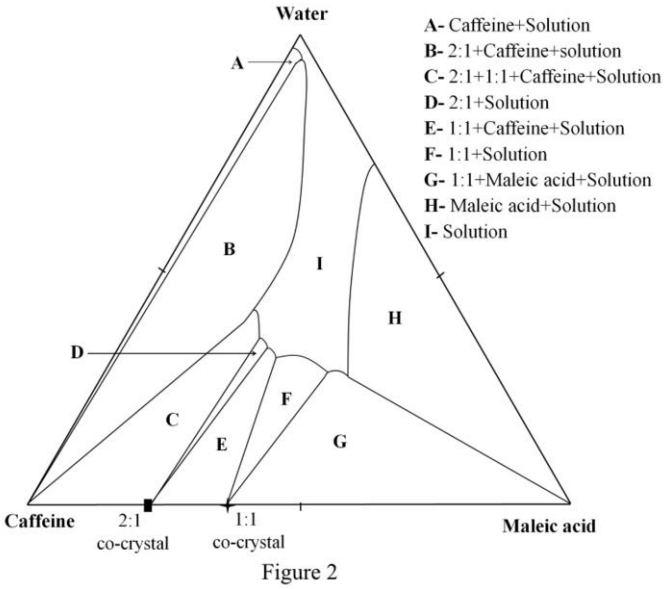

Figure 2

Figure 2. Ternary phase diagram for caffeine-maleic acid-water co-crystallization in the absence of ultrasound.

Effect of ultrasound on phase diagram

Ultrasound application has been shown to cause significant deviations in the phase diagram of Caffeine-maleic acid-water. The ternary phase diagram obtained without ultrasound (Fig. 2) shows 9 well defined regions; however Fig. 3 shows 8 regions, highlighting the effect of ultrasound on co-crystallization. In both cases, caffeine hydrate was not observed as caffeine hydrate is formed mainly at high temperature (50 °C approximately).[14] Additionally, only

caffeine/maleic acid 1:1 co-crystal form I was detected and not form II. The comparison of these two ternary phase diagrams shows that the overall pattern of co-crystal formation remained the same but that ultrasound application showed a considerable effect on different regions of the phase diagram. The overall 'solution' region was widened in the presence of ultrasound, suppressing all other regions with prominent effect on the 'maleic acid + solution' and '2:1 co-crystal + caffeine + solution' regions. This indicates that the individual solubility of caffeine and maleic acid was increased due to application of ultrasound. This is evident from the preliminary solubility study. Also as discussed previously, the solubility of caffeine was altered due to the presence of maleic acid in the solution. This collectively resulted in increased solubility of each component thus expanding the solution region.

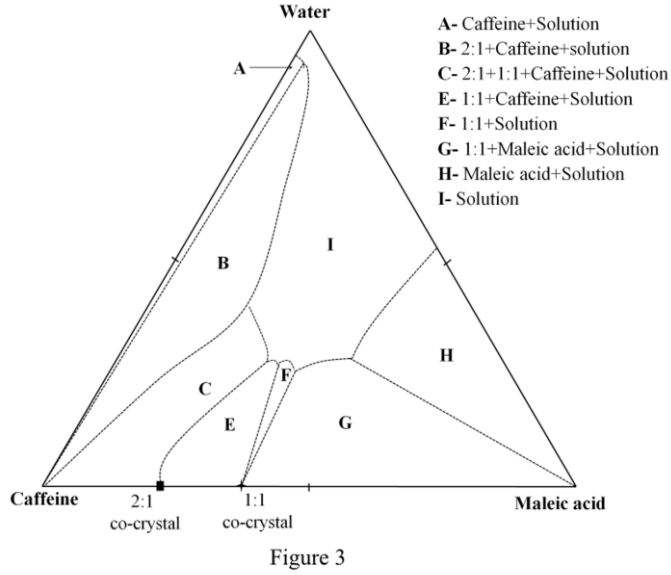

Figure 3

Figure 3. The ternary phase diagram for caffeine-maleic acid-water in the presence of ultrasound.

In addition to the effect on the solution region, the application of ultrasound during slurry co-crystallisation showed a distinct effect on the phase pure co-crystal regions (region D and F), which were either narrowed or disappeared completely. Fig. 2 shows a narrow region for caffeine/maleic acid 2:1 co-crystal (region D), which was not detected when ultrasound was

present. The region for pure caffeine/maleic acid 1:1 co-crystals (region F) was also narrowed in the presence of ultrasound. The region for 'maleic acid + 1:1 co-crystal + solution' was broadened at the expense of the pure 1:1 co-crystal region. The effect of ultrasound on these regions of phase diagram can be attributed to the change in solubility of the co-crystal components and stability of co-crystal phases in the presence of ultrasound. Although the equilibrium time was significantly reduced in the presence of ultrasound, the ultrasound assisted slurry co-crystallization process did not provide broader regions of phase pure co-crystals; rather regions for pure co-crystal phases were narrowed further or disappeared. This may be due to solvent mediated instability of co-crystal in the slurry co-crystallization process. Fig. 4 shows a schematic for overall effect of ultrasound on caffeine-maleic acid-water system. Ultrasound application is expected to reduce non-congruency shows alteration in phase diagram regions.

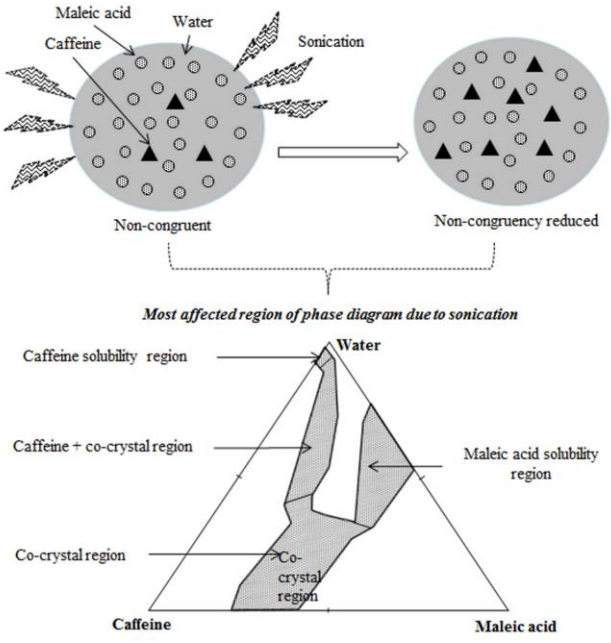

Figure 4

Figure 4. Schematic for overall effect of ultrasound application on caffeine-maleic acid-water system.

Stability of co-crystals

A further study was designed to investigate the stability of caffeine/maleic acid 2:1 and 1:1 co-crystals in slurry. Pure co-crystal solid was added to water with or without subsequent ultrasound treatment of the slurry. The PXRD results (SI 6, SI 7 and SI 8) for this stability study are summarized in Tables 1 and 2 respectively.

Table 1. Slurry stability data for phase pure 1:1 co-crystals and phase pure 2:1 co-crystals (+++: Major amount).

Sample	**Slurry concentration**	**PXRD results**				
		2hr	**4hr**	**8hr**	**12hr**	**24hr**
Phase pure 1:1 CC	5 gm + 1.5 ml water	1:1 CC	1:1 CC	1:1 CC	1:1 CC	Caf hydrate, Mal
Phase pure 2:1 CC	5 gm + 2.5 ml water	2:1 CC +++, Caf	2:1 CC +++, Caf	2:1 CC +++, Caf	2:1 CC +++, Caf	2:1 CC +++, Caf

Caffeine (Caf), Maleic acid (Mal) and co-crystal (CC)

Table 2. Ultrasound assisted slurry stability data for phase pure 1:1 co-crystals and phase pure 2:1 co-crystals (+++: Major amount).

Sample	**Slurry concentration**	**PXRD results**
Phase pure 1:1 CC	15gms + 4.5ml water	1:1 CC
Phase pure 2:1 CC	15gms + 7.5 ml water	2:1 CC+++, Caffeine

Caffeine (Caf), Maleic acid (Mal) and co-crystal (CC)

The data clearly show that 1:1 co-crystal was more stable compared to 2:1, both with and without application of ultrasound to the slurry. It has been reported that caffeine co-crystals with a series of dicarboxylic acids dissociate upon exposure to humidity, which was supposed to be due to the partial dissolution of acid.[15] This was mainly attributed to solubility differences between caffeine and its co-formers. Similarly in the present study, caffeine/maleic acid 2:1 co-crystal was found to be unstable and dissociated providing caffeine as an additional product. In slurry, caffeine/maleic acid 2:1 co-crystals dissociated into individual components, leaving caffeine and maleic acid molecules in co-crystal stoichiometric ratio in the solution. But due to the high solubility of maleic acid compared to caffeine, supersaturation levels of maleic acid were not achieved as with caffeine. Therefore, caffeine precipitates out from the slurry of caffeine/maleic acid 2:1 co-crystal. Caffeine/maleic acid 1:1 co-crystals were dissociated after 12 hr when prepared without ultrasound, but did not show any effect of sonification. This stability study indicates that 2:1 co-crystals exhibit poor stability compared to the 1:1 co-crystal form and hence supports the fact that the region for phase pure 2:1 co-crystal could not be found and the region for pure 1:1 co-crystals was narrowed in the presence of ultrasound. Region C remained mostly unaffected by application of ultrasound. However, region E was slightly broadened by ultrasound, as a region for phase pure 2:1 was not detected. Overall, the application of ultrasound during co-crystallization significantly altered several ternary phase diagram regions.

CONCLUSION

A green approach for co-crystal formation has been applied, using aqueous ultrasound-assisted slurry co-crystallization. Ultrasound application showed a significant effect on several regions of the ternary phase diagram. The study has provided a clear indication that techniques which

impose accelerated conditions on conventional solution co-crystallization can have a significant effect on the phase diagram. It has also yielded information regarding the presence of various metastable states and potential dissolution pathways. Such studies of the complete phase diagram following the application of ultrasound will also assist process scale-up. In similar way, the effect of other processes such as microwave heating on the ternary phase diagram can also be explored.

ACKNOWLEDGEMENT

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ABBREVIATIONS

CC: Co-crystals, PXRD: Powder X-ray Diffraction, SI: supporting information, hr: hour, Caf : Caffeine, Mal : Maleic acid

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Supporting information

SI 1

Table 1. Summary of slurry co-crystallization batches in absence of ultrasound (+++: major, CC: co-crystal).

Batch	Caffeine (gm)	Maleic acid (gm)	Water (ml)	Observation	XRD
A	2.5	0.5	7		2:1 CC, Caffeine
B	4	2	4		2:1 CC+++, Caffeine
C	6	1	3		2:1 CC+++, Caffeine
D	2	4	4	Solution	----------
E	2.2	2	6		2:1CC+++, Caffeine
F	4	3	3		1:1 CC+++
G	3	4	3	Solution	----------
H	2	5	3		Maleic acid
I	4	4	2		1:1 CC+++
J	3	5	2		Maleic Acid
K	5	3	2		1:1 CC+++, Caffeine
L	6	2.5	1.5		1:1 CC+++, Caffeine
M	1	7	2		Maleic acid
N	2	6	2		Maleic acid
O	5	2	3		1:1 CC+++, 2:1 CC++, Caffeine
P	6	2	2		1:1 CC+++, 2:1 CC++, Caffeine
Q	7	2	1		Caffeine+++, 1:1 CC
R	1	4	5	solution	
S	2	1	7		Caffeine +++, 2:1 CC
U	5	4	1		1:1 CC+++
T	1	1	8	solution	
V	4	5	1		1:1 CC+++, Maleic acid
W	3	3	4	solution	
X	1	5	4		Maleic acid
Y	3	6	1		Maleic acid+++, 1:1 CC
Z	8	1	1		1:1 CC+++, Caffeine, 2:1 CC
AA	2	7	1		Maleic acid+++, 1:1 CC
AB	7	1	2		2:1 CC+++, Caffeine
AC	6	3	1		1:1 CC+++, Caffeine
NUS 6-4	9	6	6		2:1 CC+++
Reported neat grinding[5]	0.7699	0.2301	0		2:1 CC
Reported neat grinding[5]	0.6259	0.3741	0		1:1 CC

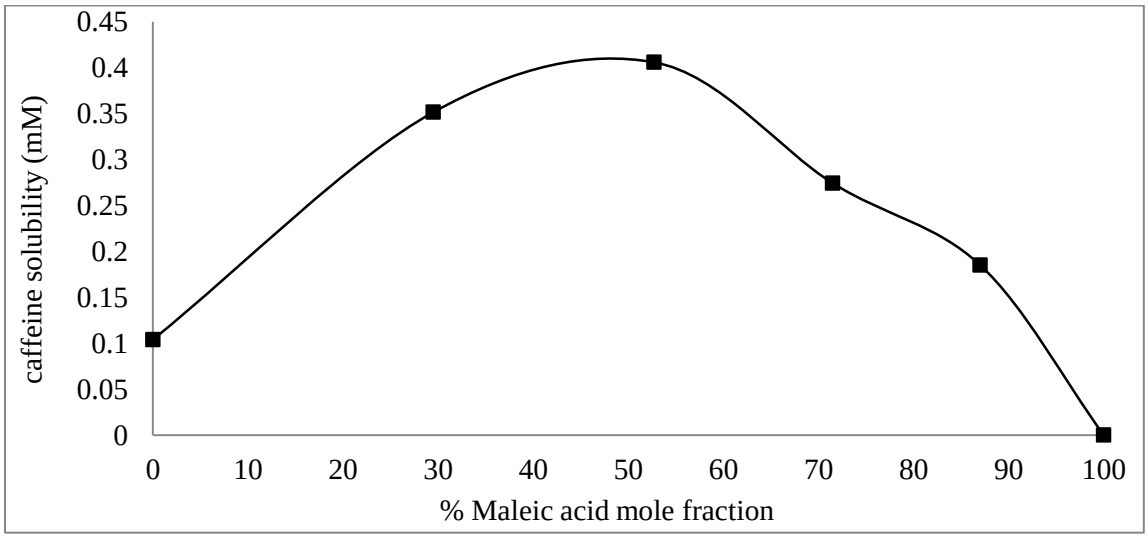
SI 2

Table 2. Summary of ultrasound assisted slurry co-crystallization batches (+++: major, CC: co-crystal).

Batch	Caffeine	Maleic acid	Water	Observation	XRD
1	6	1	3		Caffeine +++, 2:1 CC
2	5	2	3		Caffeine +++, 2:1 CC
3	4	3	3		2:1 CC+++, Caffeine, 1:1 CC traces
4	3	4	3	solution	
5	2	5	3		Maleic acid
6	7	1	2		2:1 CC+++,Caffeine
7	6	2	2		2:1 CC+++,Caffeine, 1:1 CC traces
8	5	3	2		1:1 CC+++,Caffeine
9	4	4	2		1:1 CC+++, Maleic acid
10	3	5	2		Maleic acid +++, 1:1 CC
11	2	6	2		Maleic acid
12	5	4	1		Maleic acid +++, 1:1 CC
13	5.5	3.5	2		1:1 CC+++
14	7	2	1		Caffeine+++, 1:1 CC
15	4	2	4		Caffeine+++,2:1 CC
16	1	5	4		Maleic acid
17	2	1	7		Caffeine+++,2:1 CC
18	2	2	6	solution	
19	3	3	4	solution	
20	2	4	4	solution	
Reported neat grinding[5]	0.7699	0.2301	0		2:1 CC
Reported neat grinding[5]	0.6259	0.3741	0		1:1 CC

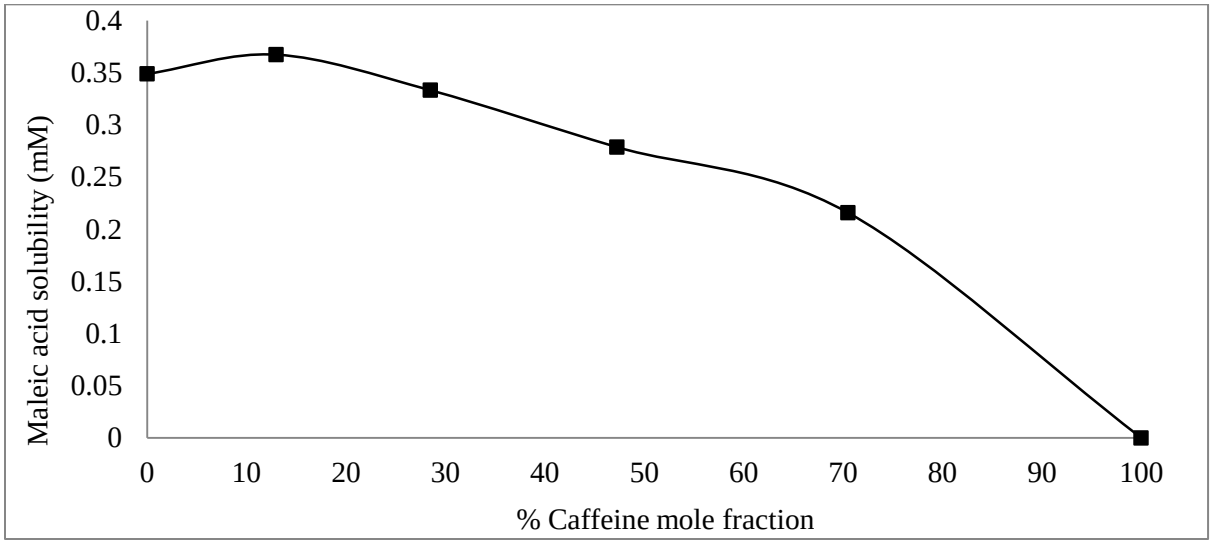
SI 3

Figure 1. Equilibrium solubility of caffeine in water in the presence of % maleic acid mole fraction.



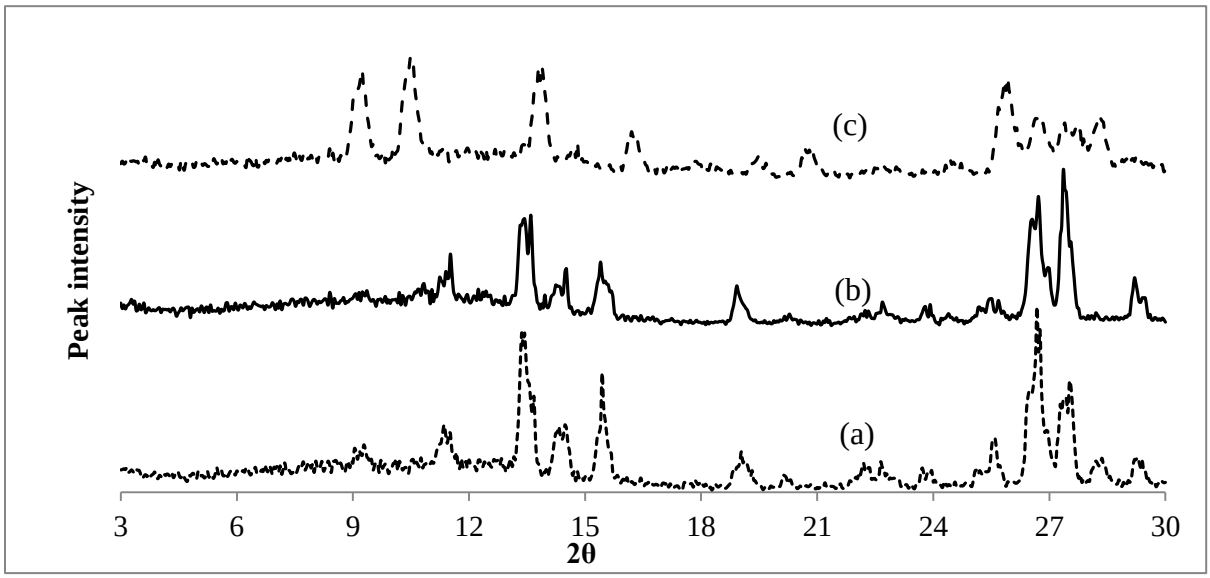
SI 4

Figure 2. Equilibrium solubility of maleic acid in water in presence of % caffeine mole fraction.



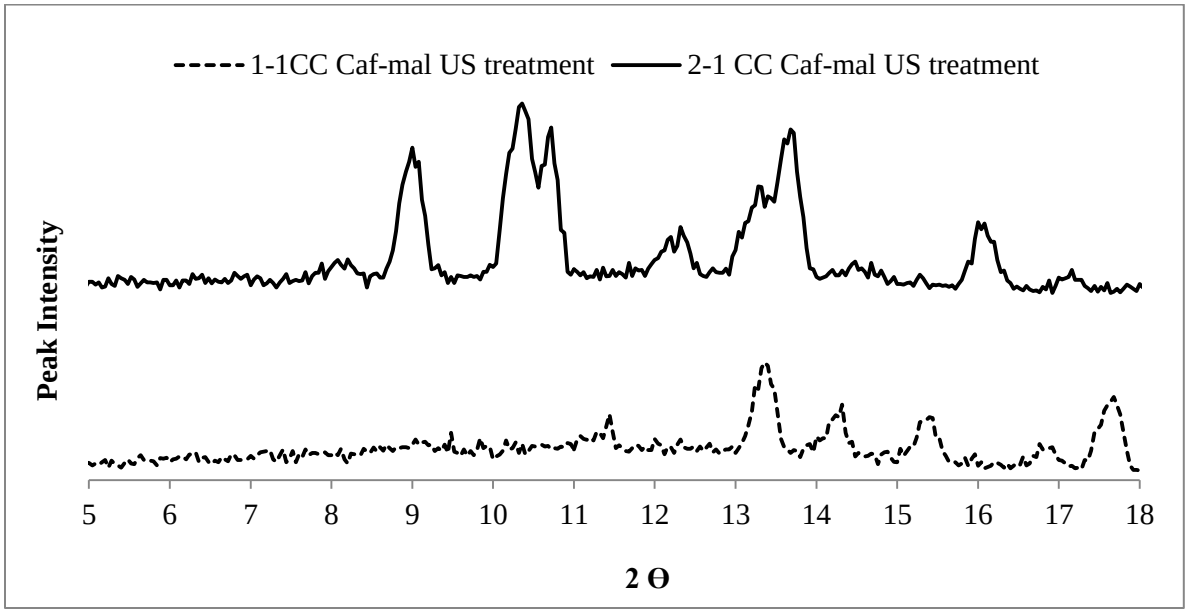
SI 5

Figure 3. PXRD patterns for pure 1:1 co-crystals obtained during in absence of ultrasound (a), pure 1:1 (form I) co-crystals obtained in presence of ultrasound (b) and pure 2:1 co-crystals obtained in absence of ultrasound (c).



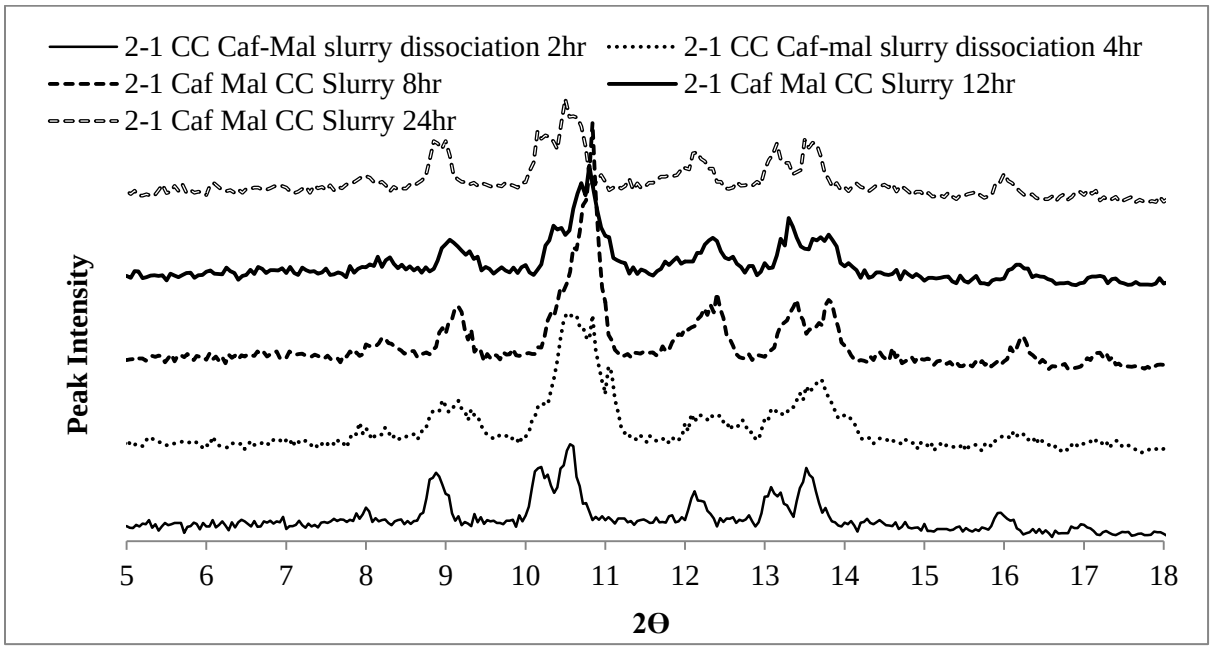
SI 6

Figure 10. Results of dissociation study by high power ultrasound a) Caffeine/ maleic acid 1:1 Co-crystals after ultrasound treatment b) Caffeine/ maleic acid 2:1 Co-crystals after ultrasound treatment



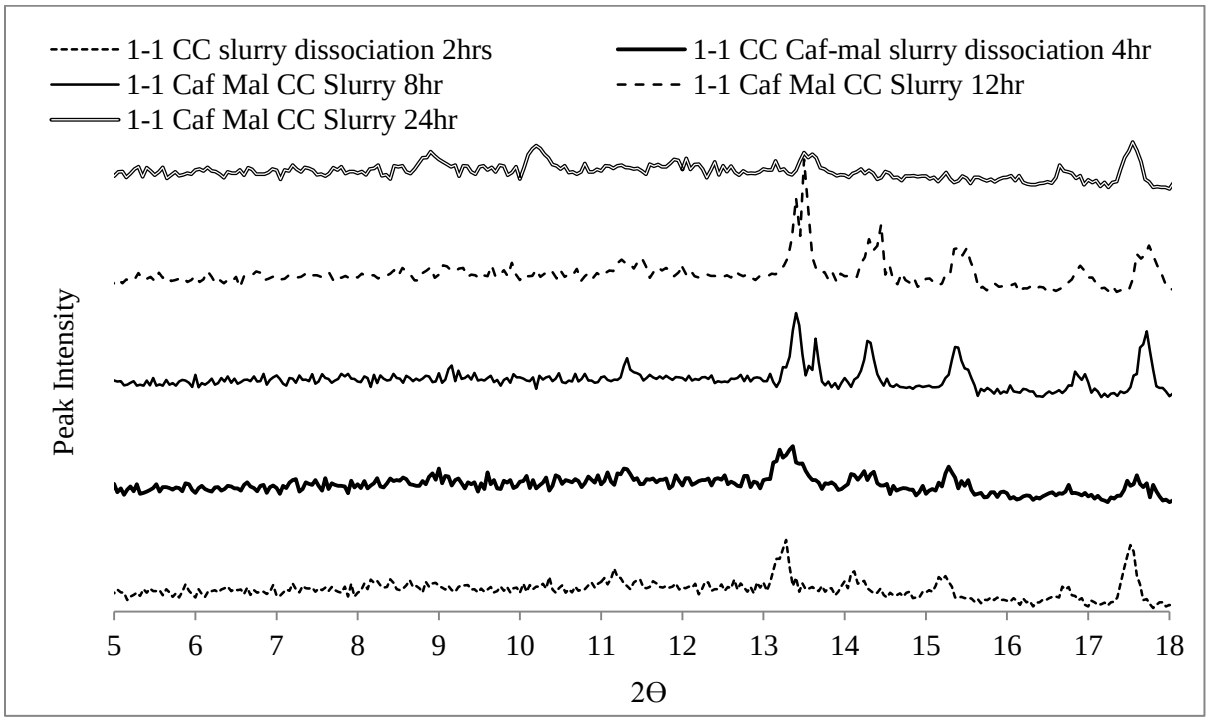
SI 7

Figure 11. Results of dissociation study by slurry treatment; caffeine/ maleic acid 2:1 Co-crystal samples collected at different time intervals.



SI 8

Figure 12. Results of dissociation study by slurry treatment; caffeine/maleic acid 1:1 co-crystal samples collected at different time intervals.



SI 9

Figure 13. Cambridge crystal structure data for caffeine/maleic acid 1:1 co-crystal Form I, caffeine/maleic acid 1:1 co-crystal Form II and caffeine/maleic acid 2:1 co-crystal.