Journal of Pharmaceutical Sciences xxx (2016) 1-5

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Rapid Communication

# Synthesis of Caffeine/Maleic Acid Co-crystal by Ultrasound-assisted Slurry Co-crystallization

Prafulla P. Apshingekar [1], Suyog Aher [1], Adrian L. Kelly [1,2], Elaine C. Brown [2], Anant Paradkar [1,*]

[1] Centre for Pharmaceutical Engineering Science, University of Bradford, Bradford, West Yorkshire, UK
[2] IRC in Polymer Science and Technology, University of Bradford, Bradford, West Yorkshire, UK

ARTICLE INFO

*Article history:*
Received 6 July 2016
Revised 1 September 2016
Accepted 9 September 2016

*Keywords:*
co-crystals
solubility
stability
supersaturation
ultrasound
phase diagram
crystallization

ABSTRACT

A green approach has been used for co-crystallization of noncongruent 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, manipulating solubility, bioavailability, and stability.[1,2] One of the important challenges in pharmaceutical co-crystallization is noncongruent solubility of co-crystal crystal components. Caffeine/dicarboxylic acid is the most studied co-crystal pair showing noncongruency.[3-8] Several approaches have been used to overcome the noncongruent 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 surfactants to reduce noncongruency 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 were found to increase nucleation rate and form nano-co-crystals. In addition to solvent selection approaches to overcome noncongruency, 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 used 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 noncongruent 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 using 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,

*Abbreviations used:* PXRD, powder X-ray diffraction.
This article contains supplementary material available from the authors by request or via the Internet at http://dx.doi.org/10.1016/j.xphs.2016.09.009.
* *Correspondence to:* Anant Paradkar (Telephone: +44 1274 233900).
*E-mail address:* A.Paradkar1@bradford.ac.uk (A. Paradkar).

http://dx.doi.org/10.1016/j.xphs.2016.09.009

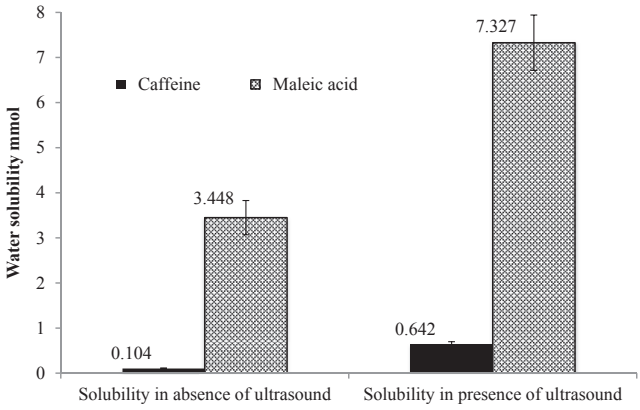


**Figure 1.** Effect of ultrasound on solubility of caffeine and maleic acid in water.

metastable zone width, and altered supersaturation conditions.[10-13] This will have a significant effect on co-crystallization process of noncongruent 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 noncongruent caffeine/maleic acid co-crystals.

## Materials and Methods

### *Materials*

Anhydrous caffeine (99% pure) and maleic acid (99% pure) were purchased from Sigma-Aldrich (Irvine, UK). Deionized 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 h under stirring (400 rpm) in a jacketed vessel at 25°C. Supernatant in equilibrium with caffeine or maleic acid slurries was analyzed by HPLC to determine solubility. Similarly to understand effect of ultrasound on solubility, caffeine and maleic acid slurries

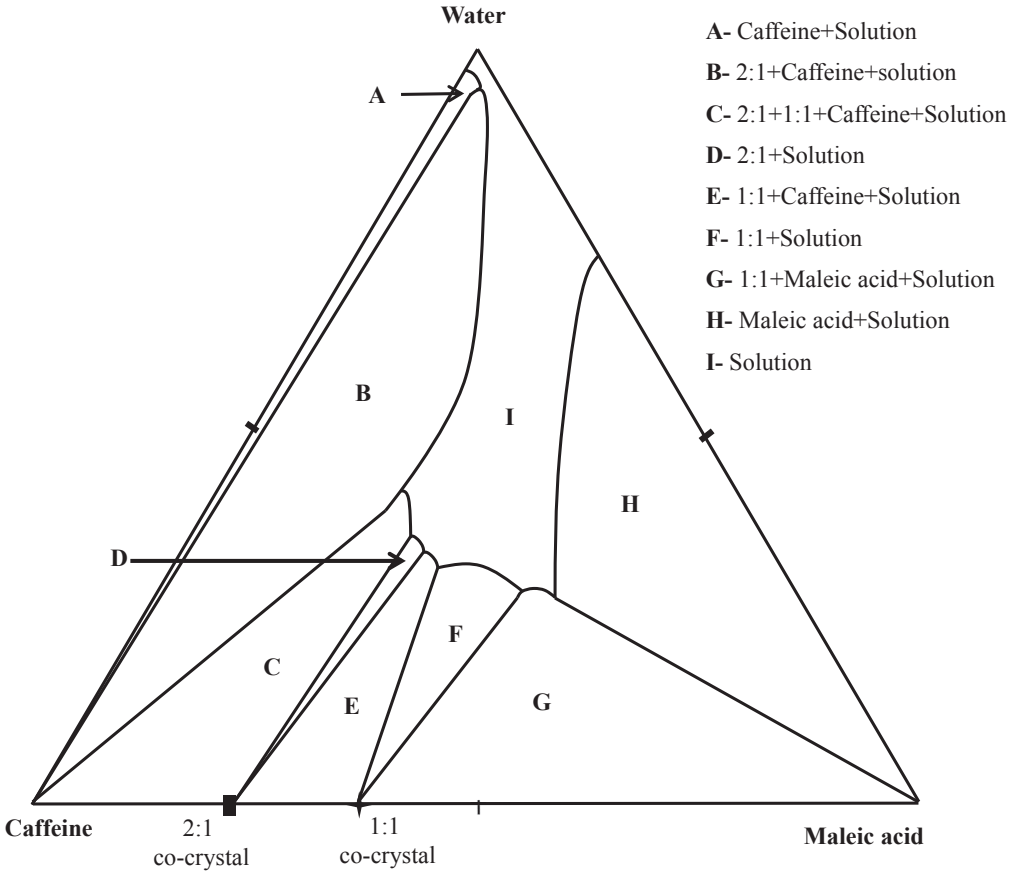


**Figure 2.** The ternary phase diagram for caffeine/maleic acid/water co-crystallization in the absence of ultrasound.