CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

Title	Tracking cocrystallization of active pharmaceutical ingredients with Bbenzoic acid coformer using Broadband Acoustic resonance Dissolution Spectroscopy (BARDS)
Authors	Kent, Christopher;Rao Khandavilli, Udaya B. Rao;Alfarsi, Anas;Hanna-Brown, Melissa;McSweeney, Seán;Krüse, Jacob;Lawrence, Simon E.;Fitzpatrick, Dara
Publication date	2018-09-18
Original Citation	Kent, C., Rao Khandavilli, U. B., Alfarsi, A., Hanna-Brown, M., McSweeney, S., Krüse, J., Lawrence, S. and Fitzpatrick, D. (2018) 'Tracking Cocrystallization of Active Pharmaceutical Ingredients with Benzoic Acid Coformer Using Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS)', Crystal Growth & Design, 18(11), pp. 6528-6537. doi: 10.1021/acs.cgd.8b00668
Type of publication	Article (peer-reviewed)
Link to publisher's version	https://pubs.acs.org/doi/10.1021/acs.cgd.8b00668 - 10.1021/acs.cgd.8b00668
Rights	© 2018 American Chemical Society. This document is the Accepted Manuscript version of a Published Work that appeared in final form in Crystal Growth & Design, copyright © American Chemical Society after peer review and technical editing by the publisher. To access the final edited and published work see https://pubs.acs.org/doi/pdf/10.1021/acs.cgd.8b00668
Download date	2026-11-15 02:07:03
Item downloaded from	https://hdl.handle.net/10468/9648

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

CRYSTAL GROWTH & DESIGN

Subscriber access provided by UNIV COLL CORK

Article

Tracking Cocrystallization of Active Pharmaceutical Ingredients with Benzoic Acid Coformer using Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS)

Christopher Kent, Uday B. Rao Khandavilli, Anas Alfarsi, Melissa Hanna-Brown, Sean McSweeney, Jacob Krüse, Simon Lawrence, and Dara Fitzpatrick

Cryst. Growth Des., **Just Accepted Manuscript** • DOI: 10.1021/acs.cgd.8b00668 • Publication Date (Web): 19 Sep 2018

Downloaded from http://pubs.acs.org on September 26, 2018

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Tracking Cocrystallization of Active Pharmaceutical Ingredients with Benzoic Acid Coformer using Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS)

*Christopher Kent‡, Uday B. Rao Khandavilli† Anas Alfarsi‡, Melissa Hanna-Brown#, Seán McSweeney¥, Jacob Krüse, Simon Lawrence‡†, and Dara Fitzpatrick‡**

‡ School of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland.

† Synthesis and Solid State Pharmaceutical Cluster, University College Cork, Ireland.

Pfizer, Sandwich, Kent, United Kingdom.

¥ BARDS Acoustic Science Labs, Bio-Innovation Centre, University College Cork

AUTHOR EMAIL ADDRESS: d.fitzpatrick@ucc.ie

Address: School of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland

Email: d.fitzpatrick@ucc.ie. Tel.: +353 21 490 3299

ABSTRACT

This study investigates the use of Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS) as a detection method for the formation of cocrystals. BARDS is a novel approach which uses reproducible changes in the compressibility of a solvent as a sample dissolves to characterize and differentiate between materials and in this case co-crystallization. Two cocrystal systems with a 1:1 stoichiometry were examined which used benzoic acid as a co-former with isonicotinamide, and with theophylline. Cocrystals were prepared using dry and wet milling for periods from 1 to 40 min and samples were analyzed using infrared spectroscopy, powder X-Ray diffraction and BARDS. Comparison of the BARDS data with the IR and PXRD data cross-validated the BARDS results. This study shows that BARDS can be used to rapidly assess the formation of these cocrystals at-line when

milling or as a relatively low cost tool in pre-formulation product development. The data can also be used to gauge the unique entrained gas and gas volume generation of the co-crystal samples during dissolution and their dissolution kinetics.

INTRODUCTION

Cocrystallization is the formation of a crystalline sample comprised of two or more compounds.[1] Over the last two decades it has evolved into a mature science that is increasingly popular in the pharmaceutical industry as a method to improve drug delivery through the formation of a new entity with improved physiochemical properties.

Solid state grinding is one method that has been used to synthesize cocrystals.[2] One of the main advantages of this method is that solvent is not required, which means the solubility of the starting materials is not an issue and doesn't require as much experimental development. The risk of forming solvates is removed, and there is no solvent waste. There are some disadvantages as well; the solid-state cocrystal cannot be analyzed using single crystal X-ray diffraction, meaning that alternative ways to identify structural features, such as the hydrogen bond motifs present within the cocrystal, are required. The physical grinding of components together may cause a change to the degree of crystallinity and may lead to changes in the physicochemical properties.

Solution based cocrystallization methods involve evaporation or cooling and they have some clear advantages over solid state grinding such as high yields of well-defined crystals with high purity that can be structurally analyzed relatively easily.[3] However, there are disadvantages to solution crystallization, for example the formation of solvates that can be challenging to handle or have regulatory issues. Another obstacle is the solubility of the starting materials with the solvent system; both must dissolve into solution before cocrystallization may occur. The solvent can interfere with the cocrystallization by being involved with the cocrystal intermolecular interactions, therefore forming part of the crystal lattice and altering the design of the cocrystal. When a polymorphic cocrystal system is an

option, the solution may lead to an unwanted kinetically controlled metastable polymorphs. The cost associated with the amount of solvent required to form the cocrystal can also be an issue.[2]

Infrared spectroscopy and powder x-ray diffraction are routinely used for the analysis of cocrystals, although other methods have been employed, for example terahertz spectroscopy.[4] Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS) is based on an acoustic phenomenon that has been long established,[5] but has only recently been harnessed for analytical purposes.[6]

It is founded on reproducible changes in the compressibility of a solvent during dissolution of a sample. Entrained gas between and within particles creates gas evolution in conjunction with the reduction solubility of gas already in solution due to the dissolution of the solute. This leads to an increase in compressibility and a decrease in the speed of sound. The frequency change in induced resonant sound waves are used to capture changes in compressibility.

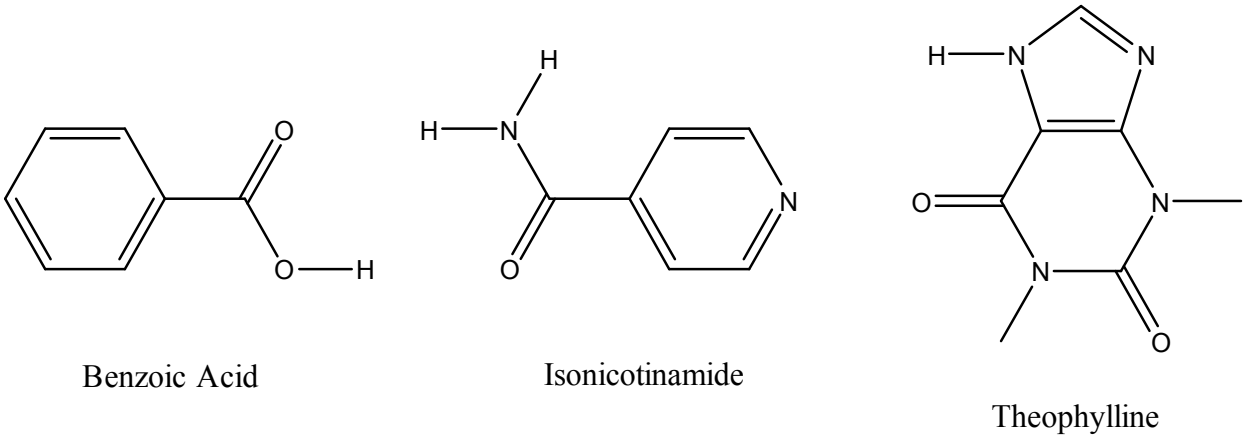
A more detailed and comprehensive outline of the underlying processes and equations involved in BARDS analysis is given by Fitzpatrick and coworkers (2012).[6]

In this study, BARDS was investigated to see whether it can be used to track cocrystallization. Cross-validation with the more routine methods for monitoring cocrystallization, namely IR spectroscopy and PXRD, was undertaken. Two 1:1 stoichiometry cocrystal systems were examined: benzoic acid with isonicotinamide,[7] and benzoic acid with theophylline.[8]

Isonicotinamide (INA) has five known polymorphs[9,10,11] and has been used in the pharmaceutical industry for its unique set of properties. Mixed salts of INA have a broad range of uses including being a widely used coformer.[12] It is the pyridyl nitrogen atom that acts as a hydrogen bond acceptor when mixed with hydrogen bond donors such as carboxylic acids. The bond between the carboxylic acid and pyridine is thought to be the most adaptable and most stable hydrogen bond and is the main type of bonding even in the presence of other good hydrogen bond donors.[13]

Theophylline (TP) is used to treat chronic obstructive pulmonary disease,[14] and it is also used for its therapeutic effect for the respiratory disease, asthma.[15] It has low solubility and poor bioavailability. When theophylline forms a cocrystal with acids and bases, the solubility can be improved, but the

formation can only occur if the carbonyl groups and aromatic nitrogen atoms become involved in the formation with the cocrystal former.[16] Formulation of TP is difficult because it is known to change from the anhydrate to a monohydrate form and back, depending on the relative humidity. The possibility of crystalline hydrate formation makes it difficult to formulate a design that is consistent and reproducible for this API.[17]



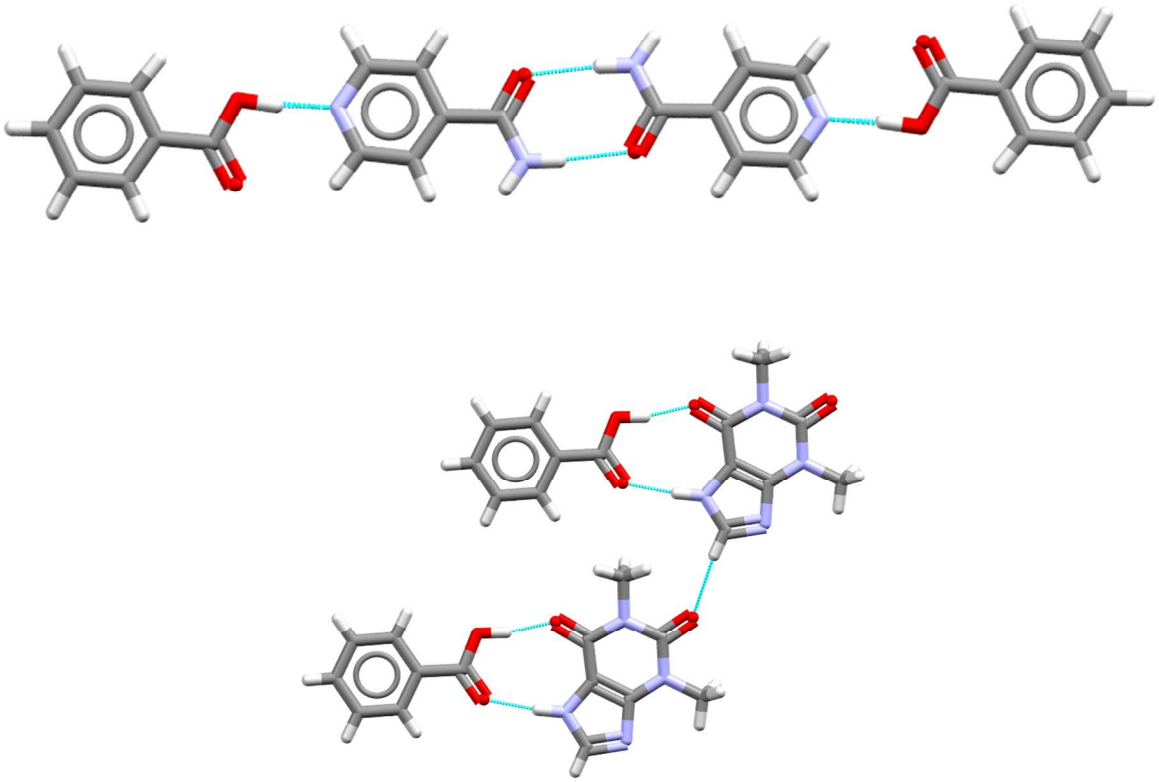


Figure 1: The compounds and co-crystal investigated in this study.

EXPERIMENTAL SECTION

Materials All compounds were purchased from Sigma Aldrich and used without any further purification. Where indicated, distilled water was used.

Grinding Experiments. Mechanical grinding experiments were conducted in a Retsch MM400 Mixer mill, equipped with stainless steel 5 mL grinding jars and one 5 mm stainless steel grinding ball per jar. The mill was operated at a rate of 30 Hz for a variety of different times ranging from 1 min to 40 min. For the BA: INA cocrystal dry grinding was used, with a total sample mass of 0.75 g in a 1:1mole ratio (mass 0.375 g of both was taken which is 0.003 moles of both). For the BA: TP cocrystal liquid assisted grinding was used. For BA: TP a total mass of 0.75 g in a 1:1 mole ratio (mass of theophylline used was 0.45 g/ 0.0025 moles and mass of benzoic acid used was 0.3 g or 0.0025 moles) was used, with the addition of 4 drops of methanol before milling. After milling, the sample was allowed to dry for 24 h.

Solution Crystallization. A 1:1 molar ratio of coformers were mixed together in the solid state, dissolved and allowed to stand at room temperature until the solvent had completely evaporated, typically 3-9 days.

Instrumentation The BARDS instrumentation consists of a dissolution vessel made of borosilicate glass. There is a microphone situated above the borosilicate glass vessel and within the dissolution chamber. Figure 2 shows a schematic of the instrumentation. The dissolution vessel contains 25 mL of a 40: 60 (v/v) ethanol: water mixture. The vessel is placed off-center with the stirrer plate which allows the magnetic follower to gently tap the inner glass wall. This mechanical energy results in an acoustic resonance to occur in three different media, (i.e. the glass, solvent, and the air column above the solvent). The microphone converts this induced acoustic resonance to a spectrum using a PC with a sound card and specialized software. The resonances of the liquid vessel are recorded in a frequency band of 0−20 kHz. The steady state resonance was recorded for thirty seconds at the beginning of each run. At this point the sample was added automatically, from a weighing boat, using a tipper motor to 25 mL of solvent in the dissolution vessel. Each sample run lasts for five hundred seconds and each sample was run in duplicate. Excel data files which contained the experimental data were used to obtain an

average and spread of the duplicate results, for set points along the time axis of the spectra These results were transferred to another graphics program (Sigma Plot) which was used to compile the figures.



Figure 2: (A) Top view schematic diagram representing the contents of the dissolution chamber and (B) photograph of the BARDS dissolution chamber. Note the microphone is not in contact with the vessel. External view of the instrument (D Tipper motor with a sample in a weighing boat ready for addition to the stirring solution below.

IR spectrums were recorded on a Bruker Tensor 37 in the range of 4000 to 500 cm^{-1}motif. PXRD analysis was carried out using a Bruker D2 Phaser over the 2θ range of 5-45˚ using a Lynxeye (1D mode) detector with a scan speed of 0.2 s for 797 steps. The Eva software was used to overlay the experimental data with the reference spectra from the CSD.[18]

RESULTS AND DISCUSSION

Table 1 shows the results of the grinding experiments for the two cocrystals for a variety of different grinding times. Analysis is based on the shift in the ν(CO) for benzoic acid and PXRD analysis, see Supporting Information. In all cases it is the 1:1 cocrystal that is formed.[7,8] Table 1 indicates that the co crystal for INA: BA formed completely after 15 min of dry grinding and the co crystal for TP: BA formed completely after 20 min of liquid assisted grinding.

Table 1: The effect of different grinding times on the synthesis of the cocrystals.

coformer	coformer	Time (min)	Method	Products
BA	INA	1	Dry grinding	Both coformers
BA	INA	2	Dry grinding	Both coformers
BA	INA	5	Dry grinding	Both coformers
BA	INA	10	Dry grinding	Mix of coformers and Co Crystal
BA	INA	15	Dry grinding	Co Crystal
BA	INA	20	Dry grinding	Co Crystal
BA	INA	40	Dry grinding	Co Crystal
BA	TP	5	Liquid assisted grinding	Both coformers
BA	TP	10	Liquid assisted grinding	Both coformers
BA	TP	15	Liquid assisted grinding	Both coformers
BA	TP	20	Liquid assisted grinding	Co Crystal

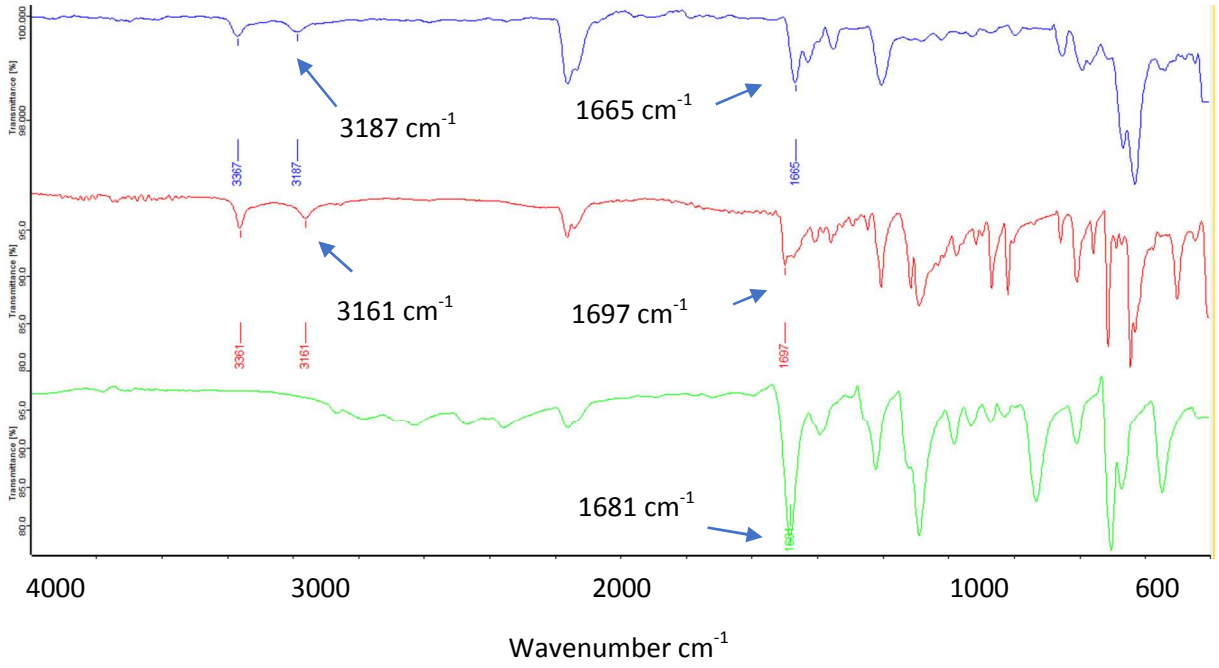


Figure 3: IR analysis for the formation of a 1:1 cocrystal of INA: BA after 15 min of milling (red spectrum) with BA (green spectrum), and INA (blue spectrum). Note the presence of key absorbances in the red spectrum at 3161 cm^{-1} and 1697 cm^{-1}

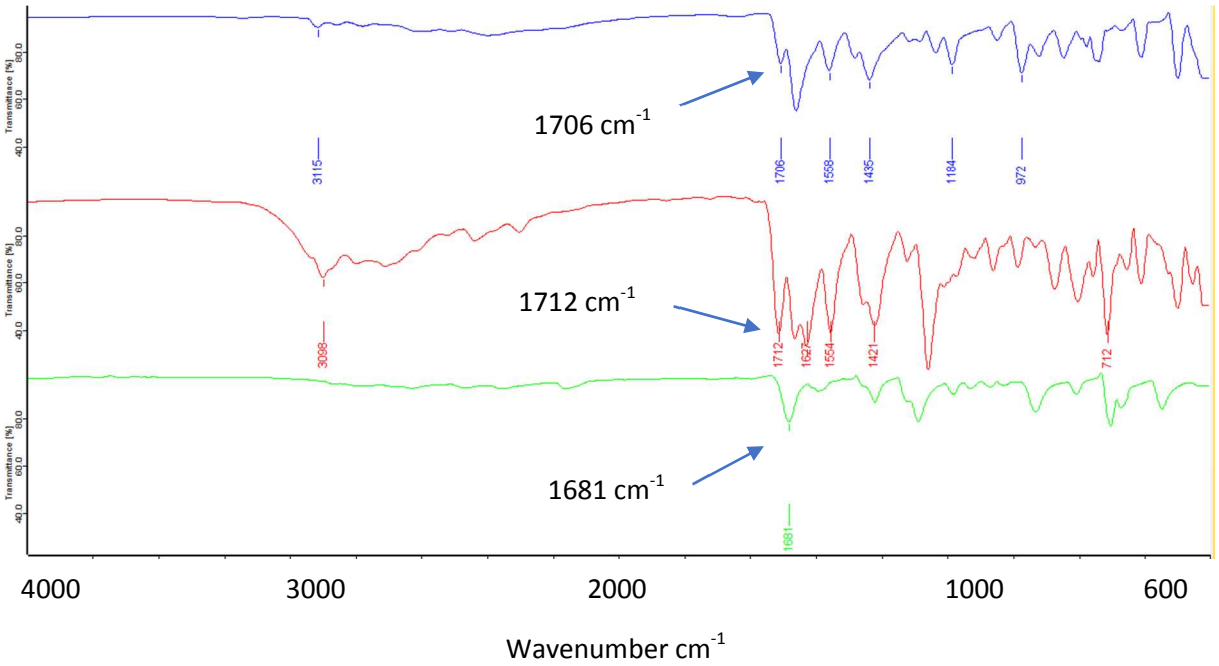


Figure 4: IR analysis for the formation of the 1:1 cocrystal of TP: BA (red spectrum) with BA (green spectrum), and INA (blue spectrum).

In this study, BARDS will be assessed for its ability to track cocrystallization. When assessing a 1:1 blended mixture of API and coformer for cocrystallization, the mixture (300 mg) is added to the solvent.

The process of dissolution introduces gas into the solvent, which changes its compressibility. Each component contributes to the response and a unique acoustic profile for the blend occurs. This is the principle behind tracking the formation of a cocrystal by solution based, solid state and liquid assisted grinding. The dissolution of the mixture changes the speed of sound in the dissolution vessel. The formation of air bubbles from the mixture increases the compressibility of the solution. The frequency is lowered due to the speed of sound being altered to a lower velocity and this is picked up by a microphone within the dissolution chamber.

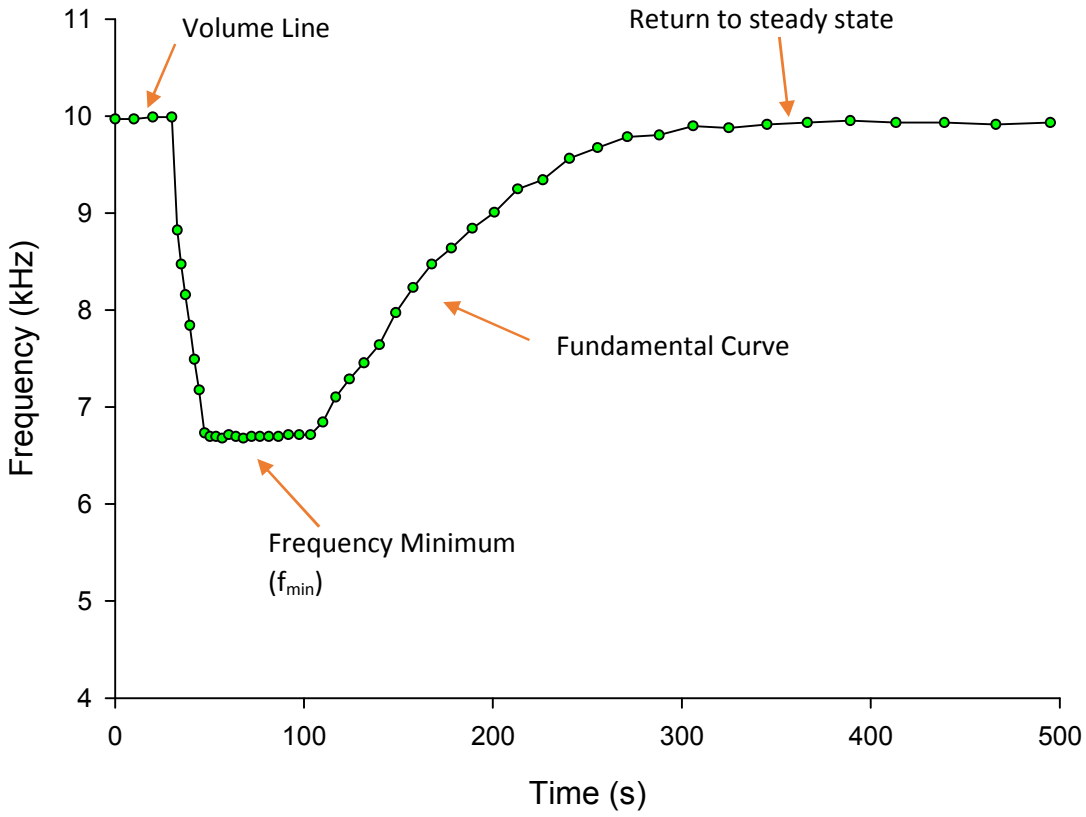


Figure 5: Sigma plot of a BARDS spectrum of benzoic acid dissolved in 25 mL of a 40:60 ethanol: water mixture Note the steady state resonances for 30 s before the addition of the compound.

The steady state resonance was recorded for thirty seconds at the beginning of each run. At this point the sample was added automatically, from a weighing boat, to 25 mL of solvent in the dissolution

vessel. Each sample run lasts for five hundred seconds. Excel data is then transferred to the Sigma Plot program which was used to compile the Bards overlays in Figures 6-9.

The frequency minimum (f_{min}) of the BARDS response in Figure 5 represents an equilibrium between the rate of gas formation and the rate of liberation of gas from the surface of the solvent. Figure 5 shows the BARDS spectrum of Benzoic acid, a well-known coformer used in the formation of both cocrystals in this study. The borosilicate vessel is induced to resonate by the magnetic stirrer as shown in Figure 2. The initial thirty seconds of the spectra represent just the resonance of the vessel containing 25 mL of solvent. The sample is subsequently added which results in a change in the resonant frequency. These changes are hereafter known as the fundamental curve.

After the initial PXRD and IR analysis of the synthesized cocrystals, the next step was to choose a dissolution solvent for BARDS analysis. Deionized water was used initially, however the solubility of the BA was found to be poor and the milled 1:1 mixture of the INA: BA caused the mixture to clump together. Analysis of this sample mixture was unsuccessful due to poor wetting and the sample would sit on the surface of the deionized water after one minute of dry grinding. Therefore, no change to the steady state frequency was observed and hence no acoustic response was obtained. An organic modifier (ethanol) was used to improve the solubility of BA and to achieve a response from the 1:1 mixture. A 40:60 (v/v) ethanol: water mixture was found to be optimum and was used for analysis and this yielded interpretable acoustic responses (Figures 5-9).

The sample mass placed into the milling jar is an important parameter in terms of formation time of cocrystal. The sample mass used throughout this study is 0.75 g. Other important parameters during milling are the frequency used on the Retsch MM400 mixing mill, the size of the milling balls, the size of the milling jar and whether a molecular lubricant is added or not. It is well understood that adding a molecular lubricant such as methanol (i.e. liquid assisted grinding) will increase the reaction rate and increase yield [19].

Baseline Data Analysis

The PXRD spectra n Figure 6 (A) and (B) shows the overlay of the experimental data in red for INA and BA with the reference spectra in black from the Cambridge Structural Database (CSD).

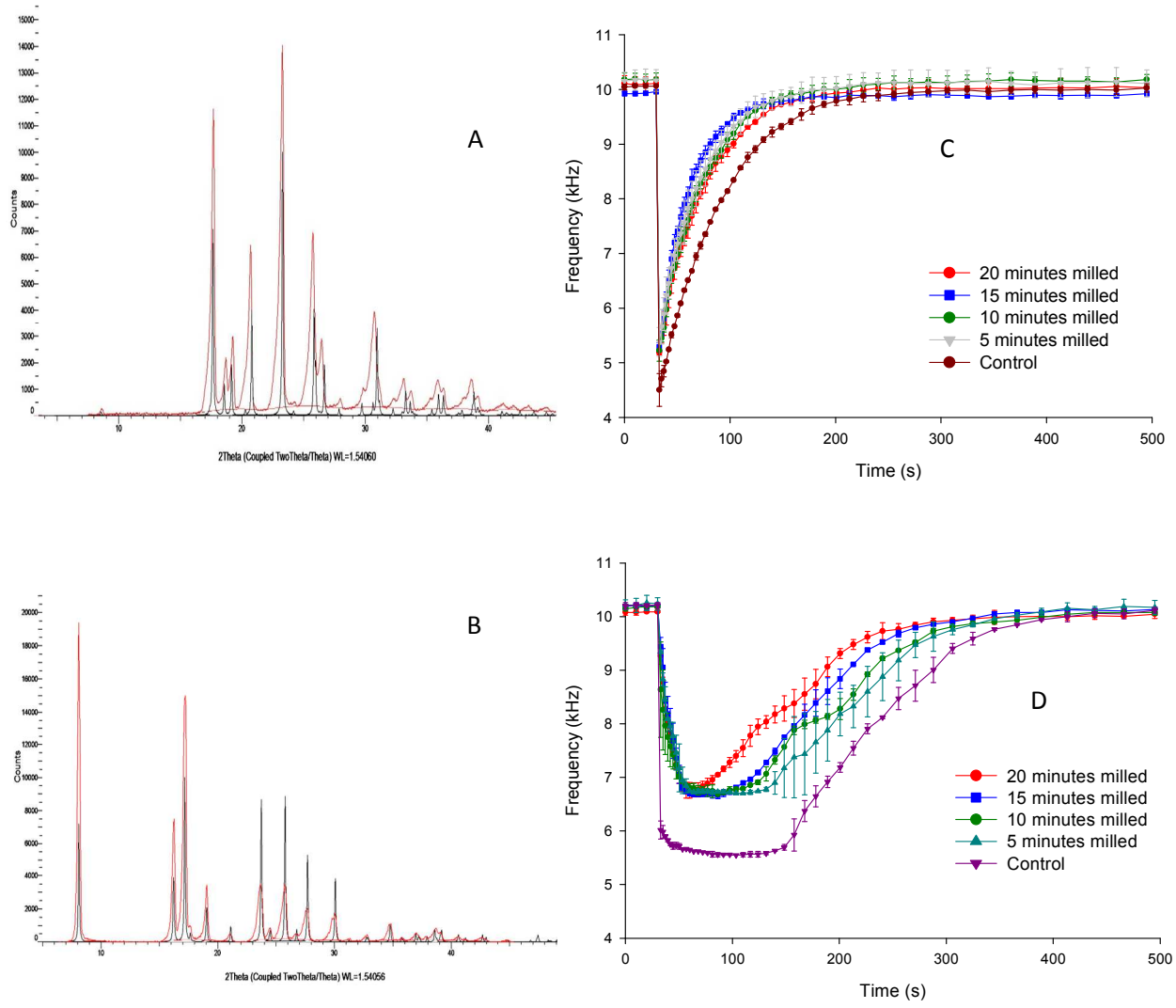


Figure 6: PXRD spectra of (A) INA, and (B) BA (20 min) compared to their corresponding Cambridge Structural Database spectra. The corresponding BARDS spectra (C) and (D) are shown, respectively. Note: the milling process has little effect on the BARDS response for INA, whereas BA changes significantly with increased milling time. . Note: the PXRD analysis yielded the same result throughout the milling process, this indicates that the crystal structure for both BA and INA remained the same. Also, the control in (C) and (D) and in all figures are pre milled samples.

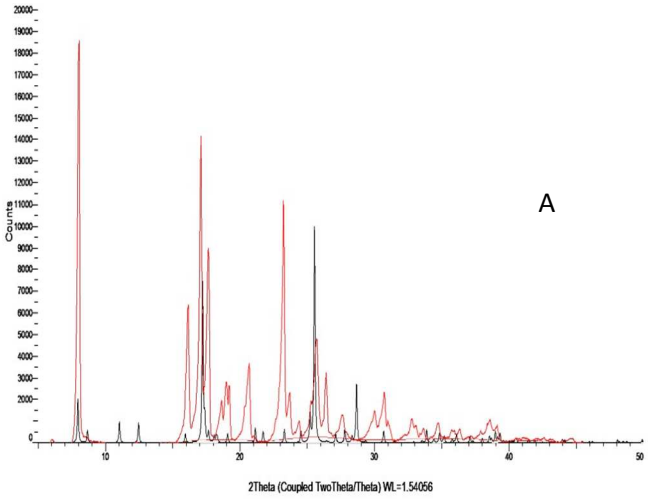
The PXRD pattern suggests there is no change in the crystalline form of either irrespective of the milling time. This means that any changes in the BARDS spectra are caused by other morphological

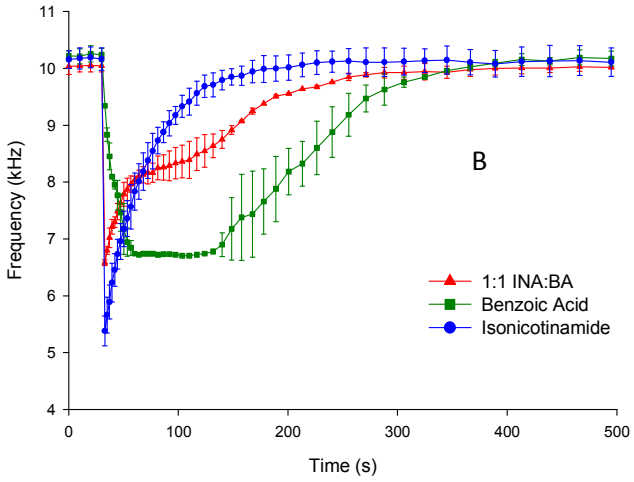
parameters, e.g., particle size or entrained gas. The corresponding BARDS spectra for INA for selected milling times is shown in Figure 6 (C). Note that the spectra change slightly with increased milling time and that there is a decrease in the time taken (ΔT) for the profiles to reach the steady state from the f_{min} value. The lack of change indicates that the milling process has little effect on the dissolution of the INA samples. The f_{min} correspond to an equilibrium between the liberation of gas in solution and the exiting of gas at the surface. It also represents the maximum compressibility of the solution. The PXRD spectrum, in Figure 6 (B), shows the overlay of the experimental data in red for BA with the reference spectrum in black from the CSD. The same PXRD pattern was obtained for each minute of milling, which indicates that the same polymorphic structure of BA was obtained for each minute of milling. The corresponding BARDS spectra for selected milling times are shown beside figure 6 (D). Notice that the spectra change dramatically with increased milling time. This indicates that the milling process has a greater effect on the dissolution of the BA samples. There is an expected increase in dissolution rate of the samples with increasing milling time due to the increase in the overall surface area per unit weight, this is observed at 20 min of milling in the BARDS spectrum in figure 6 (D). The control sample has a frequency minimum of 5.8 kHz. This increases to 6.8 kHz after 5 min of dry grinding. Notice also that there is a plateau within each spectrum up to the 20 min time point of dry grinding. The equilibrium time is reducing as the milling time increases. This means that the BA particles are releasing less gas trapped within and between particles post milling. Baseline data for each co-former is now considered sufficient to proceed with the analysis of the cocrystallisation.

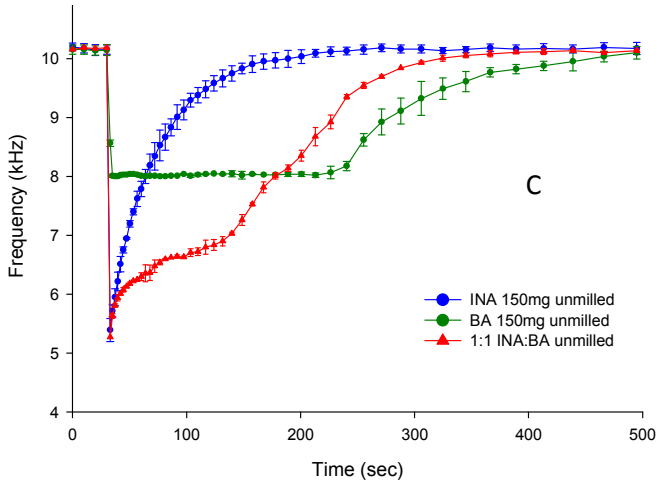
Cocrystallisation Analysis

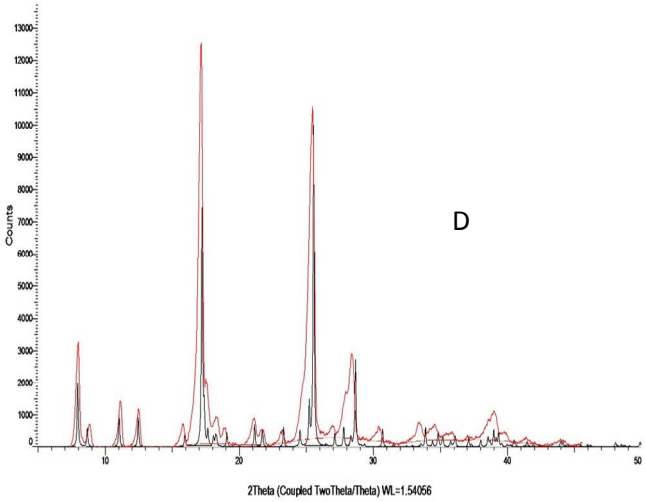
The post milling (5 min and 15 min) PXRD and BARDS data for 0.75 g INA:BA are shown in Figure 7. Figure 7 (A) shows there is little correlation between the coformer samples and the cocrystal reference PXRD spectrum after 5 min of milling. The corresponding BARDS spectrum 7 (B) shows that the red profile associated with the same sample has characteristics of both the INA and the BA spectra, not unlike the mixture of the unmilled material shown in Figure 7 (C red profile) However, after 15 min

of milling, Figure 7 (D) shows there is significant correlation between the sample spectrum and the PXRD reference. Also, the BA features of the BARDS spectrum are now absent in Figure 7 (E). Therefore, the data indicates that it takes 15 to 20 min to form the INA:BA cocrystal with a sample mass of 0.75g.









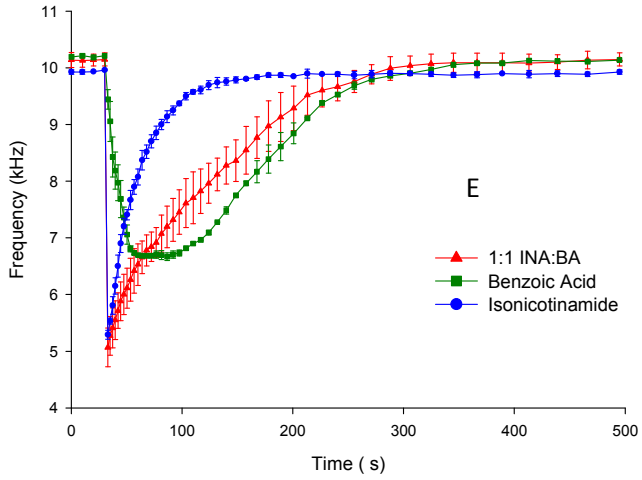


Figure 7: (A) PXRD data after 5 min of solid state grinding for a 1:1 mixture of INA: BA. (B) Corresponding BARDS spectra for (A). Each profile represents 300 mg of material. Note the red profile showing characteristics of BA similar to the unmilled mixture shown by the red profile in (C). (D) PXRD data after 15 min of solid state grinding for a 1:1 mixture of INA: BA. Note: the PXRD spectra match between the experimental and reference indicating the formation of the 1:1 cocrystal. (E) The corresponding BARDS spectra (red) showing the absence of BA characteristics.

The BARDS spectral data corresponds to the PXRD analysis. Following grinding of the 1:1 mixture components together for 5 min, the characteristic plateau of the BA constituent is evident in Figure 7 (B) whereas, in Figure 7 (E) the formation of a smooth curve and the disappearance of this plateau indicates the formation of the newly formed cocrystal.

The formation of the alternate model cocrystal (1:1 TP: BA) was not achieved after 20 min of solid state grinding. It has been reported that the theophylline cocrystal can be formed in a 10 mL milling jar with two to three 10 mm steel balls using the dry grinding method.[8,19] However, the liquid assisted grinding method was used in this study to help in the formation of the cocrystal by adding four drops of methanol to the total load of 0.75 g. Figure 8 (A) shows the PXRD overlay of the milled samples and the reference spectra for the co-crystal after five min of liquid assisted grinding. The sample spectra shows the characteristics of both unbound TP and BA. The corresponding BARDS spectra in 8 (B) also show the characteristics of both compounds with the presence of a plateau ~ 8 kHz (red profile). This suggests that the structure of the 1:1 cocrystal of TP: BA has not formed with a plateau of un-milled BA similar to the red profile in Figure 8 (C). However, PXRD data in Figure 8 (D) shows evidence that 1:1 cocrystal has formed after 20 minutes of milling.

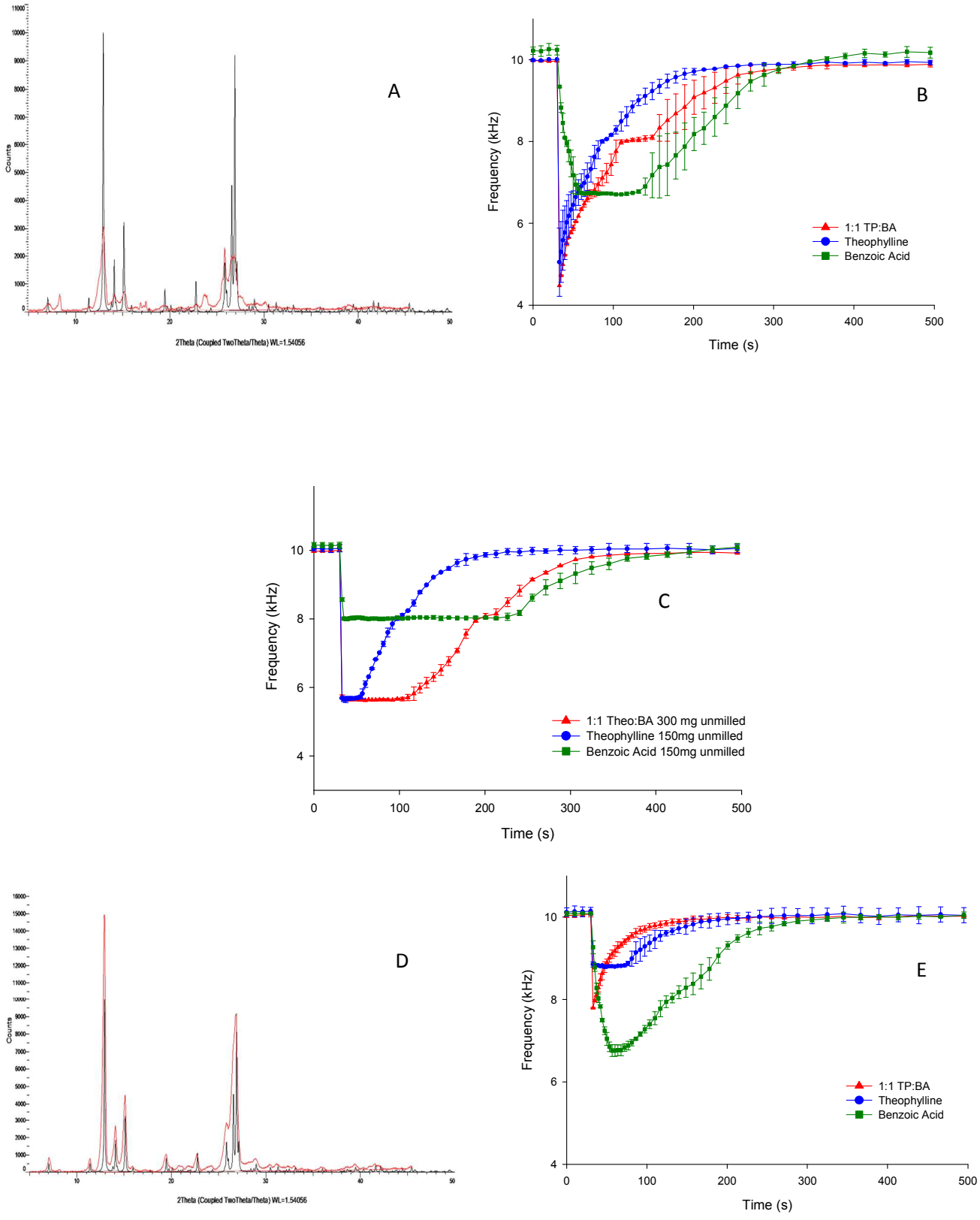


Figure 8: (A) PXRD data and corresponding BARDS data (B) after 5 min of liquid assisted grinding for a 1:1 mixture of TP: BA. Each proile in (B) represents 300 mg of material. (C) BARDS spectra of un-milled

Theophylline and Benzoic Acid and a mixture of both.(D) PXRD data after 20 min of liquid assisted grinding for a 1:1 mixture of TP: BA and (E) the corresponding BARDS data.

The BARDS data in Figure 8 (E) also corresponds to the PXRD analysis in Figure 8 (D). The formation of a smooth curve and the disappearance of the BA plateau indicates the formation of the newly formed cocrystal.

Figure 9 (A and B) shows a clear trend is occurring in the formation of both cocrystals for INA: BA and TP: BA after 15 and 20 min of dry grinding and liquid assisted grinding, respectively. The formation of both 1:1 cocrystal forms is highlighted by the red (TP:BA) and the red and light blue (INA:BA) coloured data points. IR data for samples at all time points are available in the supplementary information.

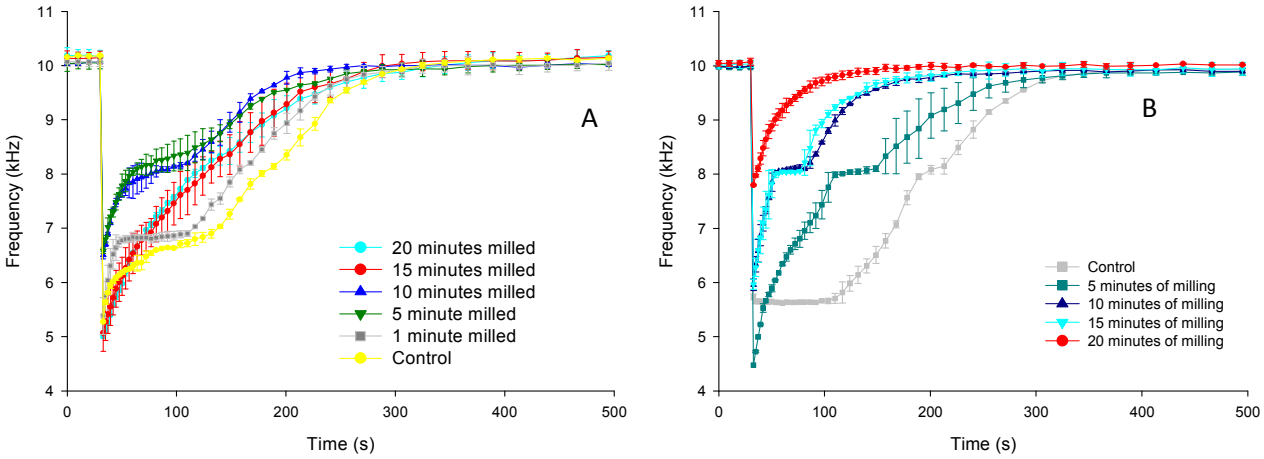


Figure 9: (A) An overlay for selected milling times of 1:1 INA: BA and (B) A similar overlay for 1:1 TP: BA. Note: The BARDS data after 15 and 20 min of grinding indicates the formation of cocrystal as there is a direct overlay. This is also evident between the PXRD data between the experimental and reference spectra in Figures 7 (D) and 8 (D.

BA and INA still retain their characteristic spectrum in their crystallized form using the solvent evaporation method (Figure 10). The plateau is still present at 8 kHz with the crystal sample of BA, Figure 10 (A), and the INA has its characteristic smooth dissolution pattern in the form of a curve. The cocrystal PXRD pattern is not evident and there is a slight plateau at 8 kHz in the BARDS profile which indicates that benzoic acid is still present in its unbound form. The reason for this is due to INA being

less soluble in ethanol compared to BA. This could lead to the INA precipitating before binding to the BA.

This shows the importance of choosing the right solvent system in the formation of cocrystals using this method. When the crystals are ground down using a mortar and pestle the formation of a fine powder causes the dissolution of the crystal samples to occur at an accelerated rate leading to the return to the steady state frequency before the 100s mark figure 10 (B). This makes discrimination more difficult using BARDS.

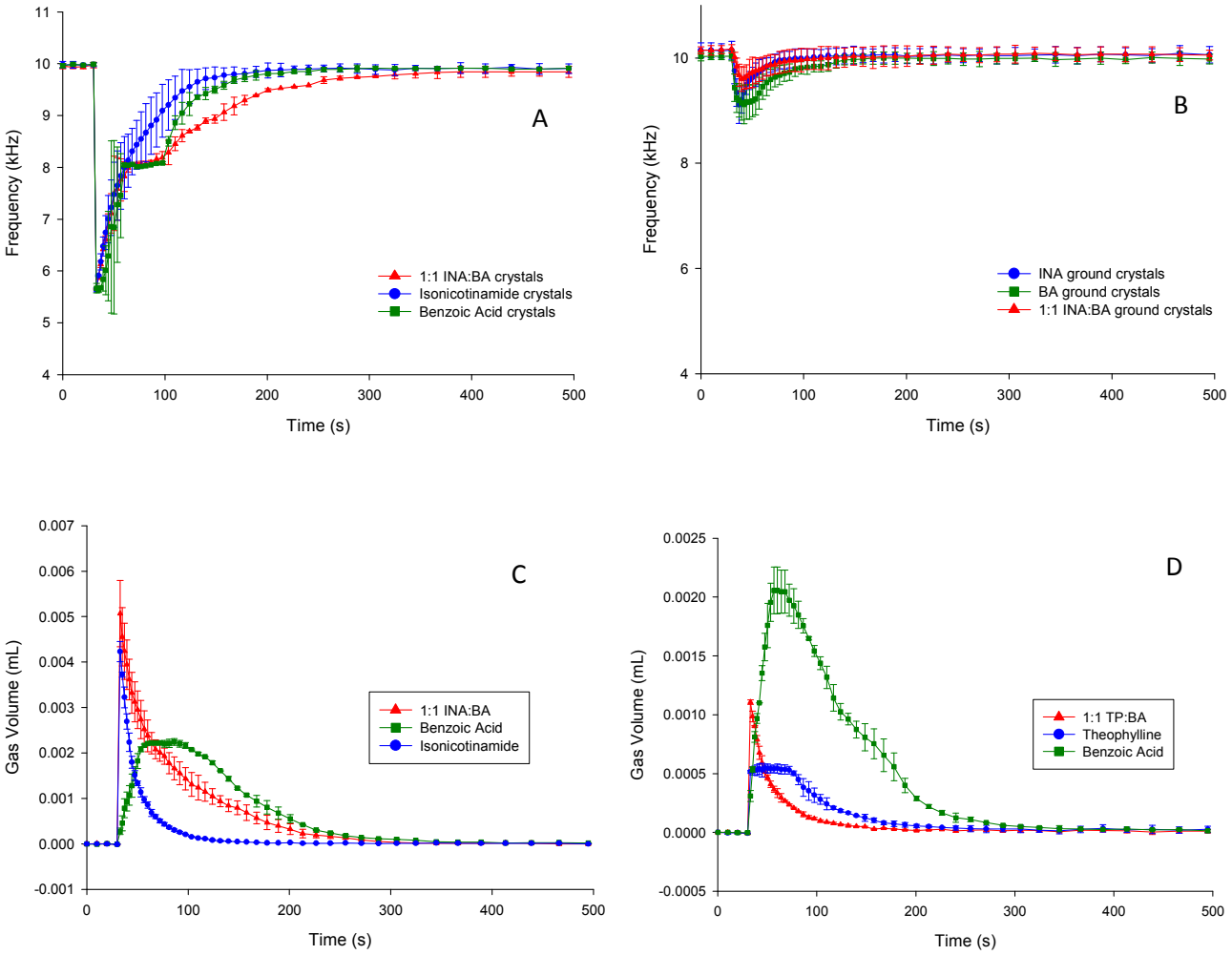


Figure 10: Comparisons of BARDS spectrum for the analysis of 300mg of crystallized 1:1 mixture of INA: BA. Note the formation of a smooth curve indicates the formation of the cocrystal for both. (C) Gas Volume plot after 15 min of solid state grinding for a 1:1 mixture of INA: BA and both coformers. (D) Gas Volume plot after 20 min of liquid assisted grinding for a 1:1 mixture of TP: BA and both coformers.

Finally, the data in Figures 7 (D) and 8 (D) have been parsed through the Crawford equation (ref 6, equation 4) to produce gas volume time course plots for both cocrystal formations. The data gives useful information on how gas is released, in real time, from the cocrystals during dissolution. Note that the release of gas is intermediate between the two coformers of each system. This is unique data which IR or PXRD data does not yield. It provides data for kinetic analysis of dissolution rates and entrained gas within the samples.

DISCUSSION

BARDS analysis of the 1:1 mixture at set time periods through the milling process shows the changes in the acoustic response in the formation of both cocrystal systems, see figure 9 (A) and (B). The disappearance of the characteristic BA plateau and the formation of a smooth BARDS response indicates the formation of both 1:1 cocrystals.

The changes in compressibility of the solvent are evident during dissolution of the 1:1 mixture through the changes of frequency of induced acoustic resonance with the magnetic stirrer. Steady state frequency occurs at 10 kHz and decreases with the addition of the sample mixture after 30s. The frequency subsequently rises back to the steady state frequency after the sample dissolves in the solvent. BARDS data in Figures 6 - 10 demonstrate that all samples yield significantly different acoustic dissolution profiles and are highly reproducible. Different components of the blends produce intrinsic spectra as shown in Figures 6 (A and B). A binary mixture results in frequency profiles which are intermediate to those of the components when analyzed separately [6].

One of the strengths of BARDS is that a control sample (blend) can be made and tested. If a 50:50 binary mixture is made then samples from the blender should match the control spectra if blending or milling has been carried out correctly. Small changes in mass of one component must be made up by another component as a fixed sample mass is used for a BARDS experiment. This leads to intrinsic sensitivity for the technique.

CONCLUSION

It has been shown that BARDS can track the formation of 1:1 cocrystal forms of INA: BA and TP: BA which occurs after 15 and 20 min of solid state and liquid assisted grinding, respectively. BARDS analysis has the potential for usage at-line to track co-crystal formation where BA is the conformer. It is likely other cocrystals may be tracked in a similar way. The sample turnaround time is just a few minutes with minimal sample preparation and method development. The gas volume time courses during dissolution also provide unique insights into the solvation of the cocrystals and starting materials.

The next step in the process of analyzing cocrystals using BARDS is to move to pilot scale analysis. This would allow for sampling from the same batch rather than making up the samples individually and testing them consecutively. Also, to use different conformers, other than benzoic acid, to identify if they can also be tracked during cocrystal formation. Dissolution rates and kinetics will also be investigated.

AUTHOR INFORMATION

Corresponding Author

Email: d.fitzpatrick@ucc.ie. Tel.: +353 21 490 3299

Notes

Seán McSweeney and Dara Fitzpatrick are directors of BARDS Acoustic Science Labs.

ACKNOWLEDGEMENTS

Thanks to Pfizer, Sandwich UK, for provision of a BARDS instrument for data generation in this project.

References

(1) Duggirala, N. K.; Perry, M. L.; Almarsson, Ö.; Zaworotko, M. J. Pharmaceutical Cocrystals: Along the Path to Improved Medicines. *Chem. Commun.* **2016**, *52*, 640–655.

(2) Trask, A. V.; Jones, W. Crystal Engineering of Organic Cocrystals by the Solid-State Grinding

Approach. *Topics in Current Chemistry*. 2005, pp 41–70.

(3) Pedireddi, V. R.; Jones, W.; Chorlton, a. P.; Docherty, R. Creation of Crystalline Supramolecular Arrays: A Comparison of Co-Crystal Formation from Solution and by Solid-State Grinding. *Chem. Commun.* **1996**, 987–988.

(4) Nguyen, K. L.; Friscić, T.; Day, G. M.; Gladden, L. F.; Jones, W. Terahertz Time-Domain Spectroscopy and the Quantitative Monitoring of Mechanochemical Cocrystal Formation. *Nat. Mater.* **2007**, *6*, 206–209.

(5) Crawford, F. S. The Hot Chocolate Effect. *Am. J. Phys.* **1982**, *50*, 398–404.

(6) Fitzpatrick, D.; Krüse, J.; Vos, B.; Foley, O.; Gleeson, D.; Ogorman, E.; Okeefe, R. Principles and Applications of Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS): A Sound Approach for the Analysis of Compounds. *Anal. Chem.* **2012**, *84* , 2202–2210.

(7) Seaton, C. C.; Parkin, A.; Wilson, C. C.; Blagden, N. Controlling the Formation of Benzoic Acid: Isonicotinamide Molecular Complexes. *Cryst. Growth Des.* **2009**, *9*, 47–56.

(8) Heiden, S.; Tröbs, L.; Wenzel, K.-J.; Emmerling, F. Mechanochemical Synthesis and Structural Characterisation of a Theophylline-Benzoic Acid Cocrystal (1 : 1). *CrystEngComm* **2012**, *14*, 5128–5129.

(9) Aakeröy, C. B.; Beatty, A. M.; Helfrich, B. A.; Nieuwenhuyzen, M. Do Polymorphic Compounds Make Good Cocrystallizing Agents? A Structural Case Study That Demonstrates the Importance of Synthon Flexibility. *Cryst. Growth Des.* **2003**, *3*, 159–165.

(10) Li, J.; Bourne, S. A.; Caira, M. R. New Polymorphs of Isonicotinamide and Nicotinamide. *Chem. Commun.* **2011**, *47*, 1530–1532.

(11) Eccles, K. S.; Deasy, R. E.; Fábián, L.; Braun, D. E.; Maguire, A. R.; Lawrence, S. E. Expanding

the Crystal Landscape of Isonicotinamide: Concomitant Polymorphism and Co-Crystallisation. *CrystEngComm* **2011**, *13*, 6923–6925.

(12) Akalin, E.; Yilmaz, A.; Akyuz, S. Vibrational Analysis of Isonicotinamide. In *Journal of Molecular Structure*; 2005; pp 881–886.

(13) Báthori, N. B.; Lemmerer, A.; Venter, G. A.; Bourne, S. A.; Caira, M. R. Pharmaceutical Co-Crystals with Isonicotinamide-Vitamin B3, Clofibric Acid, and Diclofenac-and Two Isonicotinamide Hydrates. *Cryst. Growth Des.* **2011**, *52*, 640–655.

(14) Barnes, P. J. Theophylline. *American Journal of Respiratory and Critical Care Medicine*. 2013.

(15) Wood, A. J. J.; Weinberger, M.; Hendeles, L. Theophylline in Asthma. *N. Engl. J. Med.* **1996**, *334*, 1380–1388.

(16) Lu, J.; Rohani, S. Preparation and Characterization of Theophylline-Nicotinamide Cocrystal. *Org. Process Res. Dev.* **2009**, *13* (6), 1269–1275.

(17) Clarke, H. D.; Arora, K. K.; Bass, H.; Kavuru, P.; Ong, T. T.; Pujari, T.; Wojtas, L.; Zaworotko, M. J. Structure-Stability Relationships in Cocrystal Hydrates: Does the Promiscuity of Water Make Crystalline Hydrates the Nemesis of Crystal Engineering? *Cryst. Growth Des.* **2010**, *10*, 2152–2167.

(18) Groom, C. R.; Bruno, I. J.; Lightfoot, M. P.; Ward, S. C. The Cambridge Structural Database. *Acta Crystallogr. Sect. B Struct. Sci. Cryst. Eng. Mater.* **2016**, *72*, 171–179.

(19) Kulla, H.; Fischer, F.; Benemann, S.; Rademann, K.; Emmerling, F. The Effect of the Ball to Reactant Ratio on Mechanochemical Reaction Times Studied by in Situ PXRD. *CrystEngComm* **2017**, *19*, 3902–3907.

(20) Fitzpatrick, D.; Scanlon, E.; Krüse, J.; Vos, B.; Evans-Hurson, R.; Fitzpatrick, E.; McSweeney, S.

Blend Uniformity Analysis of Pharmaceutical Products by Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS). *Int. J. Pharm.* **2012**, *438*, 134–139.

(21) Vos, B.; Crowley, S. V.; O'Sullivan, J.; Evans-Hurson, R.; McSweeney, S.; Krüse, J.; Rizwan Ahmed, M.; Fitzpatrick, D.; O'Mahony, J. A. New Insights into the Mechanism of Rehydration of Milk Protein Concentrate Powders Determined by Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS). *Food Hydrocoll.* **2016**, *61*, 933–945.

(22) Peddapatla, R. V. G.; Ahmed, M. R.; Blackshields, C. A.; Sousa-Gallagher, M. J.; McSweeney, S.; Kruse, J.; Crean, A. M.; Fitzpatrick, D. Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS): A Novel Approach to Investigate the Wettability of Pharmaceutical Powder Blends. *Mol. Pharm.* **2018**, *15*, 31–39.

Supporting Information:

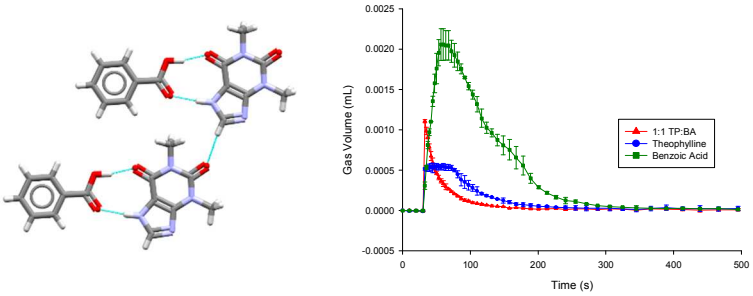
Infrared spectra for mixtures of API and co-former obtained at various milling times are available in the supporting information.

For Table of Contents Use Only.

Tracking Cocrystallization of Active Pharmaceutical Ingredients with Benzoic Acid Coformer using Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS)

Christopher Kent, Uday B. Rao Khandavilli, Anas Alfarsi, Melissa Hanna-Brown, Seán McSweeney, Jacob Krüse, Simon Lawrence, and Dara Fitzpatrick.

Co-crystals of Theophylline and Benzoic Acid produce unique gas evolution profiles during dissolution which can be used to screen for formation and purity.



Broadband Acoustic Resonance Dissolution Spectroscopy (BARDS) is a rapid method for characterising powders, blends and formulations. In this study, it is shown how dissolution of co-crystals produce reproducible gas evolution profiles which are distinct from the starting materials. This new approach has potential as a complimentary test method to confirm the presence of pure co-crystals or mixtures thereof.