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ESRF

Experiment Report Form

The double page inside this form is to be filled in by all users or groups of users who have had access to beam time for measurements at the ESRF.

Once completed, the report should be submitted electronically to the User Office via the User Portal:

https://wwws.esrf.fr/misapps/SMISWebClient/protected/welcome.do

Reports supporting requests for additional beam time

Reports can be submitted independently of new proposals – it is necessary simply to indicate the number of the report(s) supporting a new proposal on the proposal form.

The Review Committees reserve the right to reject new proposals from groups who have not reported on the use of beam time allocated previously.

Reports on experiments relating to long term projects

Proposers awarded beam time for a long term project are required to submit an interim report at the end of each year, irrespective of the number of shifts of beam time they have used.

Published papers

All users must give proper credit to ESRF staff members and proper mention to ESRF facilities which were essential for the results described in any ensuing publication. Further, they are obliged to send to the Joint ESRF/ ILL library the complete reference and the abstract of all papers appearing in print, and resulting from the use of the ESRF.

Should you wish to make more general comments on the experiment, please note them on the User Evaluation Form, and send both the Report and the Evaluation Form to the User Office.

Deadlines for submission of Experimental Reports

- 1st March for experiments carried out up until June of the previous year;
- 1st September for experiments carried out up until January of the same year.

Instructions for preparing your Report

- fill in a separate form for each project or series of measurements.
- type your report, in English.
- include the reference number of the proposal to which the report refers.
- make sure that the text, tables and figures fit into the space available.
- if your work is published or is in press, you may prefer to paste in the abstract, and add full reference details. If the abstract is in a language other than English, please include an English translation.

ESRF	**Experiment title:** Time- and space-resolved studies of mechanochemical transformations of pharmaceutical materials and molecules in situ	**Experiment number**: SC-3821
Beamline: ID11	**Date of experiment**: from: 10/07/2015 to: 14/07/2015	**Date of report**: 17/08/2015
Shifts: 12	**Local contact(s)**: Simon Arthur John Kimber (email: kimber@esrf.fr)	*Received at ESRF:*

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Report:

The experiment was using a new methodology for real-time in situ monitoring of reaction induced by mechanical milling (mechanochemical reactions). The following three important aspects of mechanochemical processing of drugs were addressed: 1) distribution of reactivity and transformations across the milling vessel; 2) reversibility and equilibration of polymorphic forms during milling and 3) mechanochemical, solvent-free synthesis of APIs as a highly attractive new opportunity for pharmaceutical development. We directly monitored the cocrystallization reactions of selected APIs in particular areas of the milling jar that are dominated by different types of mechanical action. This lead to the first mapping of the distribution of mechanical reactivity across the milling vessel. The second aim of the proposed research was to in situ follow the stages of a stepwise milling transformation, in cases when the accumulation of the product was not monotonic with the time of treatment, but went through an extremum (the phase transition in sulphatiazole, the reactions of co-crystallization involving amino acids and carboxylic acids. The third aim of proposed work was the real-time and in situ observation of the mechanochemical synthesis of APIs.
Experiments included monitoring transformations at systematically varied intensity of treatment, on variable composition of the mixtures if reactants. We have followed the effects of adding inert components on the reaction outcome. The data are being processed and prepared for publication.

1. Amorphization and phase transitions by milling

The available time at the ESRF has enabled us to systematically examine the amoprhization behavior and reactivity of simple organic molecules in the solid state, primarily imidazoles and carbohydrates.

1.1 Imidazole substrates

For imidazoles, our study systematically explored the effect of substituent choice and position on the solid-state behavior of ca. 15 different imidazoles. Preliminary screening revealed the absence of amorphization or other types of phase transitions under conventional screening conditions (30 min milling in a 14 mL Perspex milling jar, 300 mg sample, 10 mm diameter stainless steel ball of 3.9 grams weight, corresponding to $m_{\text{milling media}}/m_{\text{sample}}$ ratio of 13) for all explored imidazoles except 4-nitroimidazole, 5-chloroimidazole, 2-iodo and 2-isopropylimidazole. While milling of 4-nitroimidazole and 5-chlorobenzimidazole revealed mechanochemical amorphization, the 2-iodo and 2-isopropylimidazoles underwent polymorphic transformations. These model systems enabled a unique opportunity to directly explore, for the first time, the effect of conventional mechanochemical parameters, such as milling frequency, ratio of the weight of milling media to the weight of sample, and the choice of milling media, on the course of a mechanochemically-induced phase transition. The most complete set of results, with duplicate measurements that attest to reproducibility, has been obtained for the phase transformation of 2-isopropylimidazole. It was clearly established that phase transition is dependent on the milling frequency, as well as on the size of utilized milling media. Surprisingly, phase transition was readily induced by milling media of 10 mm diameter or higher (3.9 grams or more weight), but not by smaller miling media, even if their total weight exceeded 4 grams. Crystal structure determination of the new polymorphs of 2-iodo- and 2-isopropylimidazole, made by milling, are underway and we except that the first publication arising from this work will be submitted by October. It is important to stress that these measurements are first examples of direct evaluation of the effect of well-known parameters of mechanochemistry on kinetics of structural transformations and should be publishable in a high-impact journal.

1.2. Carbohydrates

In the context of carbohydrates, we have observed and systematically investigated the parameters behind mechanochemical amorphization of sucrose. This data will serve as preliminary results for a more extensive and systematic study of mechanochemical amorphization of sugars, of interest to industries in pharmaceutical and food industries.

2. Assembly of metal-organic frameworks (MOFs)

We have also explored the mechanochemical transformations of MOFs. In particular, our intention was to provide the first *in situ* data for the mechanochemical assembly of a cadmium-based zeolitic imidazolate framework (ZIF). Besides establishing the mechanism of the salt-catalyzed formation of a known close-packed ZIF structure, we have also discovered a rare and potentially unique example of such a close-packed structure being transformed into a previously not known open framework through reaction with excess templating ligand. To the best of our knowledge, such close packed→open framework transformation has never previously been observed in mechanochemical transformation. We are currently following up these results with a systematic solid-state NMR study and expect the publication for a high-impact journal to be ready by October. Importantly, we were already able to establish the crystal structure of the new open framework product from powder X-ray diffraction data, which revealed another surprise – a non-interpenetrated diamondoid topology which is encountered very rarely in MOF chemistry, providing further importance to this unexpected transformation discovered at the ESRF.

3. Mechanisms and Kinetics of Organic Mechanochemistry

With current knowledge of the complexities that underpin mechanochemical reactions, the limitations imposed by stop-start and *ex situ* analytical methodologies have the potential to greatly skew the results of mechanistic and kinetic investigation of mechanochemical processes. The time provided at the ESRF allowed novel insights into mechanochemistry and its mechanisms.

3.1. Mechanisms of Organic Co-Crystallisation

Work on the glycine + oxalic acid dihydrate system focused on exploration of the mechanisms through which it forms the known salts glycinium oxalate (GO) and bis(glycinium) oxalate (G_2O). *Ex situ* kinetics of the co-crystallisation from the reactive components, suggested G_2O to be an intermediate to GO formation. Further, this original work demonstrated the ability to select the final salt product through selection of input reactant stoichiometries. With the capabilities of synchrotron radiation, this system was studied further. In particular,

in situ investigations were two-pronged: (1) understanding how GO and G_2O salt formation occurs, and (2) obtaining insights into parameter effects on mechanochemical reactions.
This work offered unprecedented temporal precision of the salt formation, disproving the current understanding of the process. Combined with similar studies varying reactant particle size, these studies offer the first indication that many of the conventional controls that govern solution crystallisation may not be equally important for mechanochemical crystallisation. In particular, these data suggest that particle mixing is considerably more important for determining the final state of a mechanochemical process than the thermodynamics of the system as a whole. Such results are of paramount importance academically and industrially, showing that current controls over mechanochemical product formation – in particular for pure, fine chemicals – remain far from being understood. This system offered further opportunity to investigate the well-known crystal-growing concept of seeding. These studies reinforce the concept that within a mechanochemical milling jar, the system is not subjected to system-wide thermodynamic controls, but is instead controlled by conditions at the impact point.
The practical and fundamental results of these studies are of critical importance to all who use mechanochemical techniques in academic and industrial applications. These results are therefore publishable in a high-impact factor journal and a publication is currently in preparation.

3.2. Excipients in Mechanochemical Co-Crystallisation

Studying the *in situ* real time milling of simple organic systems, the role of excipients (a common additive in the pharmaceutical industry) could be explored. In particular the benefits and dangers of their addition were explored on the mechanochemical co-crystallisation. Depending on the nature of the co-crystallisation, excipient addition was found to either enhance or inhibit to process. In doing so, these studies not only shed practical light onto the development of novel methodologies to conduct difficult mechanochemistry, but offered fundamental insights into highly disputed mechanisms of these processes. This is the first exploration of excipient effects on the mechanisms of mechanically induced multi-component crystallisation and is of importance to both academic and industrial communities across the discipline. As such these results are publishable in a high impact factor journal and are currently under preparation.

3.3 Comparing Mechanical Stability of Polymorphs

Systematic investigations were performed to compare the mechanical stability of the two anhydrous polymorphs of caffeine. Particular focus was paid to the effects of key mechanochemical parameters: milling frequency and milling ball mass. A change in milling body mass was shown to have drastic consequences on the stability of each polymorph, reducing stability from nearly one hour to seconds. This is a surprisingly non-linear dependence, suggesting a more complex interplay of energy transfer than previously believed. Such investigations made possible at the ESRF pave the way for fundamental advances in our understanding of the physics of mechanochemical processes. In depth kinetic analyses are currently underway alongside detailed thermodynamic investigations to probe deeper into a comparison of relative polymorph stabilities. This is the first example in which the mechanical stability of two polymorphs with the same mechanically induced product has been studied in such detail. We believe these results are of high fundamental importance, systematically exploring the basic mechanochemical parameters of ball mass and milling frequency, as well as the fundamental relationship between polymorphs.