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Rapid communication

Cocrystallization via planetary milling: Enhancing throughput of solid-state screening methods

Stephen R. Bysouth[a,*], Joanna A. Bis[b], David Igo[b]

[a] Automaxion SARL, L'Auvrairie, 50250 Varenguebec, France
[b] Optiform Technologies™, Catalent Pharma Solutions, 160N Pharma Drive, Morrisville, NC 27560, USA

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ABSTRACT

The application of a novel modified planetary mill, with the capacity to process 48 samples in parallel, to the rapid screening of pharmaceutical cocrystals via grinding is demonstrated for carbamazepine/saccharin, caffeine/oxalic acid, and caffeine/maleic acid cocrystals. Milling is performed directly in standard glass vials therefore no vessel decontamination is needed or sample loss occurs. Furthermore, successive sample processing can be employed without the need for additional material, making the system suitable for screening compounds of limited availability. Use of the system in an automated screening workflow of dispensing, milling, and analysis with high-throughput is also discussed.

The continuing interest in pharmaceutical cocrystals[1] as a means for fine-tuning physicochemical properties of active pharmaceutical ingredients (APIs) (Vishweshwar et al., 2006; Schultheiss and Newman, 2009) has resulted in the need for the development of rapid cocrystal screening methodologies. The current state of the art shows that virtually any crystallization technique has the potential to be successful at generating cocrystals, as exemplified by solvent evaporation (Bis et al., 2007), ultrasonication (Friščić et al., 2009), supercritical fluid crystallization (Padrela et al., 2009), slurry conversion (Zhang et al., 2007), moisture sorption (Jayasankar et al., 2007), melting/cooling (Bis et al., 2007), heating (Berry et al., 2008), co-grinding (Shan et al., 2002), and even simply mixing components together (Maheshwari et al., 2009). However, in pharmaceutical research, the selection of a suitable screening approach is often biased towards strategies that are both productive (proven high success rate) and time-efficient. While recent developments have demonstrated the utility of high-throughput technologies in cocrystal discovery, their application has been limited to traditional solution-phase (e.g., solvent evaporation) or suspension techniques (Porter et al., 2008; Childs et al., 2008; Kojima et al., 2010). Such cocrystallizations can be rapidly executed using automated solvent handling systems that are compatible with robotic procedures such as solid dispensing, phase-separation, and analysis. In contrast, the less conventional but highly productive solid-state cocrystallization, i.e., grinding solid components together in the absence (neat) or presence of small amounts of solvent (solvent-drop grinding, SDG (Shan et al., 2002) or liquid assisted grinding, LAG) (Friščić et al., 2009), is often the preferred cocrystallization method, yet its efficiency remains to be improved. Solid-state grinding represents an attractive approach to cocrystal screening because it is simple, eco-friendly, highly productive (Weyna et al., 2009), and does not require *a priori* knowledge of the solubilities of the cocrystallizing compounds. Indeed, solubility mismatch between the components may prevent solution- and slurry-based cocrystallization, if the thermodynamic stability of the cocrystal falls into a non-central and/or narrow range of the phase diagram. Solid-state screening approaches overcome the solubility issues, however they are time-consuming due to the manual sample preparation and low-throughput. Even though the tedious grinding with a mortar and pestle has been facilitated by mechanised milling devices, including SPEX (Metuchen, NJ, USA) and Retsch (Haan, Germany), most of these systems can process only a few samples simultaneously. Even with the multiple-

* Corresponding author. Tel.: +33 9 64 26 97 39, fax: +33 2 33 45 42 09.
E-mail address: stephen.bysouth@automaxionltd.com (S.R. Bysouth).

[1] For the purpose of this study, cocrystals are defined as multiple-component supramolecular systems consisting of components that are solid under ambient conditions when in pure state. This definition excludes traditional salts and solvates.

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Table 1
Effect of milling parameters on cocrystal formation using a high-throughput planetary mill.

Component 1	Component 2	Solvent	Results		
		(10 μL)	Milling time 0.5 h	Milling time 2 h	Milling time 4 h
Carbamazepine 20.0 ± 0.2 mg (1 equivalent)	Saccharin 15.5 ± 0.2 mg (1 equivalent)	None	UC	UC	UC + CC1
		MeOH	CC1	CC1	CC1
		Toluene	CC1	CC1	CC1
Caffeine 30 ± 0.3 mg (2 equivalents)	Oxalic acid 7 ± 0.1 mg (1 equivalent)	None	UC + CC2	UC + CC2	UC + CC2
		MeOH	CC2	CC2	CC2
		Toluene	UC + CC2	UC + CC2	UC + CC2
Caffeine 25 ± 0.2 mg (1 equivalent)	Maleic Acid 14.9 ± 0.1 mg (1 equivalent)	None	UC + CC1	UC + CC1 + CC2	UC + CC1+ CC2
		MeOH	CC3	CC3	CC3
		Toluene	UC + CC2	UC + CC2	UC + CC1 + CC2
Caffeine 30 ± 0.3mg (2 equivalents)	Maleic Acid 9.0 ± 0.1 mg (1 equivalent)	None	UC + CC2	UC + CC1 + CC2	UC + CC1 + CC2
		MeOH	UC	UC + CC3	UC + CC3
		Toluene	UC + CC2	CC2	CC2

UC: unreacted components; CC1: cocrystal having stoichiometry 1:1; CC2: cocrystal having stoichiometry 2:1; CC3: cocrystal of undetermined composition.

sample adapters that have recently become available, a routine usage of solid-state methods in pharmaceutical cocrystal screening protocols is challenging due to their incompatibility with other automated screening procedures and the time required for sample preparation and decontamination of the milling vessel between experiments.

In this communication, we present a successful cocrystallization screen, executed on a novel planetary milling system, which is amenable to grinding up to 48 samples simultaneously. To our knowledge, small scale production of cocrystals using mechanized aids has relied on the shaking of a reaction vessel parallel to the vessel axis, as exemplified by the Retsch system. In contrast, in planetary milling the horizontal shaking action occurs at right angle to the axis of the milling vessel, which is held vertically. Automaxion (Varenguebec, France) has advanced the planetary milling concept further (Bysouth, 2006, 2008) by modifying the standard milling jars with vial adapters that allow distribution of multiple vials around the jar periphery. This design maintains comparable forces exerted on the milling media and samples as those found in traditional planetary milling. Because the vial adapters are large masses of aluminium, they serve as heat sinks that minimize sample heating. The capacity of the mill is inversely proportional to the size of the vial, such that a standard 4-position laboratory mill is capable of accommodating 16 200-mL vials, 32 20-mL vials, etc. For the experiments described in this study, vial adapters to hold 2-mL glass vials (Agilent, Part number 5182-0864) were produced, thus a capacity of 48 vials was achieved.

The effectiveness of the planetary milling system in producing cocrystals was tested using four known pharmaceutical cocrystals: carbamazepine/saccharin (1:1), caffeine/oxalic acid (2:1), caffeine/maleic acid (1:1), and caffeine/maleic acid (2:1). These model cocrystal cases were chosen due to their well-reported reproducibility, polymorphic and stoichiometric diversity, and availability of characterization data, which served as the basis for validating the outcomes of the study. The cocrystal components were weighed into 2-mL glass vials containing two 4-mm stainless steel beads. Where designated, 10-μL of solvent was added and the samples were subjected to neat grinding or SDG for 0.5, 2 or 4 h at a speed equivalent to a shaking frequency of 10 Hz, using a planetary mill (Fritsch, Idar Oberstein, Germany).

Once milled, the samples were manually transferred onto an analytical plate and subjected to automated analyses via FT-Raman spectroscopy (Nicolet NXR 9650 equipped with a stainless steel 96-well sample stage). The unique screening hits were validated by Powder X-ray Diffraction (PXRD, PANalytical X'Pert Pro). The cocrystal formation was confirmed or refuted based on comparison of the PXRD peaks positions to those reported for the four model cocrystals (Porter et al., 2008; Trask et al., 2005). The sample composition, milling times and results are shown in Table 1.

Table 1 shows that all unique mixtures underwent some degree of cocrystallization under at least one set of applied grinding conditions. Partial cocrystallization was observed within 30 min in the majority of experiments conducted. As expected, SDG was more effective as compared to neat grinding, in that milling times of 0.5–2 h were sufficient to achieve complete cocrystallization in all four cases studied, whereas unreacted starting components were detected in all neatly ground samples, even after 4 h of continuous grinding. While carbamazepine/saccharin and caffeine/oxalic acid cocrystal were obtained in a single solid-state form (polymorphic and/or stoichiometric), grinding caffeine and maleic acid resulted in a total of three solid forms. Two of these forms were identified as 1:1 and 2:1 cocrystals (CC1 and CC2 respectively) and the third solid form (CC3) was new. Thermal analyses confirmed no appreciable solvent loss upon heating CC3, which suggests it is a non-solvated solid form. PXRD analysis of CC3 formed after 4 h using 1:1 ingoing mixture indicated that only traces of unreacted caffeine and maleic acid were present, whereas large excess of caffeine and trace of maleic acid were present in the product obtained using 2:1 ingoing mixture. These data suggest that CC3 is likely a polymorphic form of 1:1 caffeine/maleic acid cocrystal. Detailed studies are underway to understand the mechanism and rate of this cocrystal formation and the results will be reported in a separate manuscript. The milling experiments were performed without sample loss, as the ground material was contained within the vials during the entire course of the milling operation. Such design eliminates cleaning steps between experiments that are otherwise required for the currently known milling vessels and reduces the risk of sample cross-contamination. Although, in this study the samples were manually transferred onto an analytical plate for subsequent FT-Raman analysis, it should be noted that the milled samples could also be analyzed directly through the vial glass, thus preserving an intact sample. The breadth and diversity of the study could then be expanded further by applying additional portions of solvent to the intact sample in order to generate suspensions or solutions for subsequent co crystallizations, without any additional demand on the solid components.

In conclusion, the Automaxion multisample mill was successful at producing the expected cocrystals and led to the discovery of a previously unreported (Trask et al., 2005) solid form in the presence of methanol. The device is capable of carrying out up to 48 experiments at a time, which delivers the highest capacity available for cocrystal screening via mechanochemical methods. Such throughput enables more experimental variables to be investigated in less time enabling faster and more extensive optimisation of conditions for cocrystal formation, e.g., cocrystal formers and stoichiometries, solvents type and amount, and cocrystallization time. In addition to the increased throughput, automated approaches provide greater control of experimental conditions, such as timing and grinding

force exerted on a sample, and therefore improve reproducibility as compared to manual and low-throughput mechanised grinding. The Automaxion system was originally designed to be part of an automated system (Bysouth et al., 2009) and incorporating it into fully automated cocrystal screening work-flows can be envisioned where automated powder, bead, and solvent dispensing would be followed by automated grinding and automated analysis. Such a system would not only be applicable to cocrystal screening but also salt screens (Trask et al., 2006) allowing the pharmaceutical scientists to explore solid-form screening conditions faster.

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References

Berry, D.J., Seaton, C.C., Clegg, W., Harrington, R.W., Coles, S.J., Horton, P.N., Hursthouse, M.B., Storey, R., Jones, W., Fri, T., Blagden, N., 2008. Applying hot-stage microscopy to co-crystal screening: a study of nicotinamide with seven active pharmaceutical ingredients. Cryst. Growth Des. 8, 1697–1712.

Bis, J.A., Vishweshwar, P., Weyna, D., Zaworotko, M.J., 2007. Hierarchy of supramolecular synthons: persistent hydroxyl pyridine hydrogen bonds in cocrystals that contain a cyano acceptor. Mol. Pharm. 4, 401–416.

Bysouth, S.R., 2006. PCT Int Appl.WO2006086567.

Bysouth, S.R., 2008. USPat. 7, 448–566.

Bysouth, S.R., Hite III, S.W., Nettleton-Hammond, J.H., Bergstrom, K.I, Bohara, A, Landham, R.R., and Lukkari, I.G., 2009. US Pat, 7, 501–094.

Childs, S.L., Rodríguez-Hornedo, N., Reddy, L.S., Jayasankar, A., Maheshwari, C., McCausland, L., Shipplett, R., Stahly, B.C., 2008. Screening strategies based on solubility and solution composition generate pharmaceutically acceptable cocrystals of carbamazepine. CrystEngComm 10, 856–864.

Friščić, T., Childs, S.L., Rizvi, S.A., Jones, W., 2009. The role of solvent in mechanochemical and sonochemical cocrystal formation: a solubility-based approach for predicting cocrystallisation outcome. CrystEngComm 11, 418–426.

Jayasankar, A., Good, D.J., Rodríguez-Hornedo, N., 2007. Mechanisms by which moisture generates cocrystals. Mol. Pharm. 4, 360–372.

Kojima, T., Tsutsumi, T., Yamamoto, K., Ikeda, Y., Moriwaki, T., 2010. High-throughput cocrystal slurry screening by use of in situ Raman microscopy and multi-well plate. Int. J. Pharm. 399, 52–59.

Maheshwari, C., Jayasankar, A., Khan, N.A., Amidon, G.E., Rodríguez-Hornedo, N., 2009. Factors that influence the spontaneous formation of pharmaceutical cocrystals by simply mixing solid reactants. CrystEngComm 11, 493–500.

Padrela, L., Rodrigues, M.A., Velaga, S.P., Matos, H.A., Gomes de Azevedo, E., 2009. Formation of indomethacin–saccharin cocrystals using supercritical fluid technology. Eur. J. Pharm. Sci. 38, 9–17.

Porter III, W.W., Elie, S.C., Matzger, A.J., 2008. Polymorphism in carbamazepine cocrystals. Cryst. Growth Des. 8, 14–16.

Schultheiss, N., Newman, A., 2009. Pharmaceutical cocrystals and their physicochemical properties. Cryst. Growth Des. 9, 2950–2967.

Shan, N., Toda, F., Jones, W., 2002. Mechanochemistry and co-crystal formation: effect of solvent on reaction kinetics. Chem. Commun. 20, 2372–2373.

Trask, A.W., Motherwell, S.W.D., Jones, W., 2005. Pharmaceutical cocrystallization: engineering a remedy for caffeine hydration. Cryst. Growth Des. 5, 1013–1021.

Trask, A.V., Haynes, D.A., Motherwell, S.W.D., Jones, W., 2006. Screening for crystalline salts via mechanochemistry. Chem. Commun., 51–53.

Vishweshwar, P., McMahon, J.A., Bis, J.A., Zaworotko, M.J., 2006. Pharmaceutical co-crystals. J. Pharm. Sci. 95, 499–516.

Weyna, D.R., Shattock, T., Vishweshwar, P., Zaworotko, M.J., 2009. Synthesis and structural characterization of cocrystals and pharmaceutical cocrystals: mechanochemistry vs slow evaporation from solution. Cryst. Growth Des. 9, 1106–1123.

Zhang, G.G., Henry, R.F., Borchardt, T.B., Lou, X., 2007. Efficient co-crystal screening using solution-mediated phase transformation. J. Pharm. Sci. 96, 990–995.