Exploring new mechanochemical methodologies using SpeedMixer technology

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ABSTRACT

Mechanochemistry, the study of the effect of mechanical forces such as grinding or milling on chemical change, has seen an explosive growth in popularity for the past two decades. This growth coincided with the recent focus on green, renewable and sustainable chemistry as mechanochemistry is able to drive chemical changes in the absence of expensive, toxic and environmentally damaging bulk solvents. Beyond green credentials, mechanochemistry can also provide unique selectivity and grant access to compounds that are otherwise difficult or impossible to synthesize using conventional techniques. Ball mills, extruders, and mixers form the backbone of these mechanochemical transformations and synthesis. Initially, these devices were not designed to cater to the specific needs of mechanochemical synthesis, but to mix and/or comminute various materials on a manufacturing or industrial scale. As the field develops, a diverse range of sophisticated modifications and setups based on these devices sprung up, catering to needs such as scaling-up, temperature control or *in situ* measurements. In recent years, several new devices that may cater better to mechanochemical needs have also been introduced and experimented on.

With the ongoing rapid growth of the field, it is important for mechanochemists to pause and identify key features that are essential for any device operating in the near future. This thesis explores the development of mechanochemical devices and their essential features, with a focus on their application in the synthesis of cocrystals and metal-organic frameworks (MOFs). The SpeedMixer is also introduced as a new mechanochemical tool for the synthesis of cocrystals and MOFs.

The SpeedMixer employs powerful centrifugal forces to blend mixtures, performing various mechanochemical transformations through intense shearing and mixing of the components. To better understand the mechanochemical effects of these forces, the SpeedMixer was employed to synthesize various model pharmaceutical cocrystals without bulk solvent or milling media in a technique termed 'SpeedMixing'. Through the addition of catalytic amounts of liquid additives, different cocrystal polymorphs and stoichiomorphs were selectively synthesized, alongside the discovery of the first solvate of the well-known model pharmaceutical cocrystal of carbamazepine and saccharin.

An alternative technique, termed 'SpeedMilling', incorporates milling rings into the blending process, to greatly increase the mechanical energy input in the system. This new approach was employed to synthesize MOFs with extremely high space-time yields. HKUST-

1, MgMOF-74, and ZIF-8 were among the MOFs synthesized using this method in just one minute, on a 5 g to 10 g scale.

RÉSUMÉ

La mécano-chimie, l'étude de l'effet des forces mécaniques telles que le broyage ou le fraisage sur les changements chimiques, a connu une croissance exponentielle de popularité au cours des deux dernières décennies. Cette croissance a coïncidé avec l'accent mis récemment sur la chimie verte, renouvelable et durable car la mécano-chimie est capable de conduire des changements chimiques en l'absence de solvants en vrac coûteux, toxiques et environnementalement dommageables. Au-delà de ses crédits environnementaux, la mécanochimie peut également fournir une sélectivité unique et accéder à des composés qui sont autrement difficiles ou impossibles à synthétiser en utilisant des techniques conventionnelles. Les broyeurs à boulets, les extrudeurs et les mélangeurs forment l'épine dorsale de ces transformations et synthèses mécano-chimiques. À l'origine, ces dispositifs n'étaient pas conçus pour répondre aux besoins spécifiques de la synthèse mécano-chimique, mais pour mélanger et/ou comminuer divers matériaux à une échelle de fabrication ou industrielle. Au fur et à mesure que le domaine se développe, une gamme diversifiée de modifications sophistiquées et de configurations basées sur ces dispositifs ont surgi, répondant à des besoins tels que la mise à l'échelle, la régulation de la température ou les mesures in situ. Au cours des dernières années, plusieurs nouveaux dispositifs qui pourraient mieux répondre aux besoins mécano-chimiques ont également été introduits et expérimentés.

Alors que le domaine continue de se développer rapidement, il est important pour les mécano-chimistes de faire une pause et d'identifier les caractéristiques clés qui sont essentielles pour tout dispositif fonctionnant dans un avenir proche. Cet article explore le développement des dispositifs mécano-chimiques et leurs caractéristiques essentielles, en mettant l'accent sur leur application dans la synthèse de cocristaux et de cadres organométalliques (MOF). Dans cette thèse, le SpeedMixer est présenté comme un nouvel outil mécano-chimique pour la synthèse de cocristaux et de MOF.

Le SpeedMixer utilise de puissantes forces centrifuges doubles pour mélanger les mélanges, effectuant diverses transformations mécano-chimiques par cisaillement et mélange intensifs entre les composants. Pour mieux comprendre les effets mécano-chimiques de ces forces, le SpeedMixer a été utilisé pour synthétiser différents cocristaux pharmaceutiques

modèles sans solvant en vrac ou support de fraisage dans une technique appelée "SpeedMixing". Grâce à l'ajout de quantités catalytiques d'additifs liquides, différents polymorphes de cocristaux et des stœchiomorphes ont été sélectivement synthétisés, ainsi que la découverte du premier solvate du cocrystal pharmaceutique commun carbamazépine-saccharine.

Une technique alternative, appelée "SpeedMilling", intègre des anneaux de fraisage dans le processus de mélange pour augmenter considérablement l'énergie transférée par le système. Cette nouvelle approche est utilisée pour la synthèse de MOF avec un excellent rendement espace-temps. HKUST-1, MgMOF-74 et ZIF-8 ont été ainsi préparés en moins d'une minute en utilisant cette nouvelle méthode, sur une échelle de 5 à 10g.

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"Life is what happens when you're busy making other plans." — John Lennon

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Preface and contribution of authors

This Thesis, titled 'Exploring new mechanochemical methodologies using SpeedMixer technology' describes the research conducted by Yong Teoh alongside guidance from Professor Tomislav Friščić from January 2021 to December 2022. The main body of this Thesis consists of three chapters (Chapter 2 and Chapter 3). Dr Thomas Auvray made significant contribution to the translation of the abstract into French, correcting the grammatical and sentence structure issues.

Chapter 1 is divided into two different sections. The first section is a literature review on the development of mechanochemical equipment, and their application in the chemistry of MOFs and cocrystals. The second section of Chapter 1 is a perspective on the essential features that should be included in any future mechanochemical devices introduced into the field, derived from the . The perspective is derived from an extrapolation of the development of the machines covered earlier.

The research of Chapter 2 has been published in the journal Angewandte Chemie, International Edition (*Angew. Chem. Int. Ed. Int. Ed.* **2022**, *61*, *e202206293*) under the title: **SpeedMixing: Rapid Tribochemical Synthesis and Discovery of Pharmaceutical Cocrystals without Milling or Grinding Media**. The paper is co-authored by: Yong Teoh, Dr Ghada Ayoub, Dr Igor Huskić, Dr Hatem M. Titi, Christopher W. Nickels, Brad Herrmann and Prof Tomislav Friščić. Preliminary experiments were conducted by Dr Ayoub, Dr Huskić and Mr Herrmann. Single crystal X-ray diffraction by conducted with assistance from Dr Titi. Scanning electron microscopy was performed with the help of Mr D. Liu and Mr K. Sears at the Facility for Electron Microscopy Research of McGill University. Dr R. S. Stein is conducted and provided data for solid-state Nuclear Magnetic Resonance spectroscopy. All the experiments were complied, reproduced, conducted, and expanded upon by Yong Teoh, including all of the following analysis: powder X-ray diffraction, Fourier-transform infrared attenuated total reflectance spectroscopy, thermogravimetric analysis. This communication explored a novel, media-free mechanochemical technique, SpeedMixing on the synthesis of various pharmaceutical cocrystals.

Chapter 3 describes results prepared for publication, entitled: SpeedMilling: Minute synthesis of Metal-Organic Frameworks. This is co-authored by: Dr Hatem M. Titi, Joseph M. Marrett, Christopher W. Nickels, Prof Tomislav Friščić. Preliminary results were obtained by Joseph M. Marrett and Christopher W. Nickels. Reproduction of preliminary results and all subsequent

experiments and analysis such as powder X-ray diffraction and Fourier-transform infrared attenuated total reflection spectroscopy were performed by Yong Teoh, with guidance from Dr Titi and Prof Friščić. Brunauer-Emmett-Teller surface area analysis was conducted by Dr Titi. This Chapter describe the effects of adding milling rings to the SpeedMixing process to create another technique termed SpeedMilling. SpeedMilling was performed on the synthesis of various MOFs to better understand its effectiveness as a mechanochemical technique.

List of abbreviations

AG	autogenous
API	active pharmaceutical ingredients
bipy	4,4-dipyridyl
bpe	trans1,2-bis(4-pyridyl)-ethylene
CBZ	carbamazepine
COD	1,5-cyclooctadiene
CP-MAS ssNMR	cross-polarization magic angle spinning solid state nuclear magnetic resonance
dabco	1,4-diazabicyclo[2.2.2]octane
DHCBZ	dihydrocarbamazepine
FTIR-ATR	Fourier-transform infrared attenuated total reflectance spectroscopy
fum	fumaric acid
HKUST	Hong Kong University of Science and Technology
H ₂ dta	2,5-dihydroxyterephaltic acid
ILAG	ion- and liquid- assisted grinding
IL-AG	ionic liquid assisted grinding
INA	isonicotinamide
LAG	liquid-assisted grinding
MALE	mechanochemistry-assisted linker exchange
MeOH	methanol
MOF	metal-organic framework
NIC	nicotinamide
ODS	oxide-dispersion strengthened

PMMA	poly(methyl acrylate)		
POLAG	polymer- and liquid- asssisted grinding		
PXRD	powder X-ray diffraction		
RAM	resonant acoustic mixer/mixing		
RHO	zeolitic RHO topology		
rpm	rounds per minute		
SAC	saccharin		
SALE	solvent-assisted ligand exchange		
SEM	scanning electron microscopy		
STY	space-time-yield		
ssNMR	solid-state nuclear magnetic resonance		
SUB	suberic acid		
ta	terephthalic acid		
TGA	thermogravimetric analysis		
ZIF	zeolitic imidazolate framework		

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Chapter 1: Literature review

Mechanochemistry is a rapidly growing field of research on how mechanical treatment such as grinding, milling, or extrusion can initiate or drive chemical transformations, seemingly blurring the line between chemical reactions and physical changes.¹ The physical fracturing of elemental metals into finer powder by milling is viewed as a physical change by most, but tribochemists and mechanochemists may perceive the resultant powder to be in a higher energy state as the newly exposed surfaces are highly reactive interfaces. An example of this 'blurred' line is in the work of M. Carey Lea, one of the earliest recorded mechanochemists.² Lea studied the decomposition of silver and mercuric halides by scratching or grinding. Like many chemists at the time, Lea initially rejected the premise that the decomposition of the halides was due to mechanical forces and believed the decomposition was a physical change or a result of thermal effects from the grinding.³ This ran contrary to other observations, such as chemists obtaining identical products when irritating the halides with light, or that heating the halides results in melting rather than decomposition. This was a subject of intense debate at the time, with Lea only changing his opinion much later in life and devoting himself to the study of mechanochemical effects.⁴

Mechanochemistry has been in use since ancient times, with one of the classical examples being the reduction of cinnabar, which is composed of mercury sulfide, into mercury with a bronze mortar and pestle, recorded by Theophrastus of Eresos in the 4th century BCE.² The presence of mechanochemical effects may have been observed throughout the early development of modern sciences but these effects are seldom recorded. An early record of organic mechanochemical synthesis is a report by Ling et.al., who used grinding to synthesize halogenated quinhydrones in 1893.⁵ There were also studies of mechanochemical effects by Lea and Spring that were documented at a similar time, although such studies were not commonplace.² The beginning of the industrial era led to the development of new mechanical mills, such as the tumbling mill (Figure 1.1a), which consists of a horizontal, rotating drum used to tumble the feed and milling media such as milling balls, rods or cylpebs (tapered cylindrical grinding media with equal length and diameter, and rounded edges) (Figure 1.1b).^{6a,7} This comminutes the fed material, grinding them into microscopic sizes.^{6b} These mills were utilised in extractive metallurgy and used to process the ores and minerals required to fuel the industrial revolution. Newer types of mills, created later in the 20th century, provided a mix of impact and sheer forces magnitudes higher than tumbling mills.⁸ These mills are highly efficient at comminution, pulverizing powders into nanoparticulate sizes at a fraction of the

time required for conventional, gravity-driven mills to attain microparticles.^{2,9} The application of these mills was largely in the areas of metallurgy and alloy engineering, but soon found applications in numerous other fields such as physical, inorganic, organic, and colloid chemistry, materials, and geological sciences.^{1,2} Throughout the mid- to late-20th century, mechanochemical methodologies in each of these fields have advanced independently, developing unique methods and terminology based on particular research objectives and applications.²



Figure 1.1. Tumbling mills, their accessories, and the mechanism of comminution. (**a**) A tumbling mill, filled with milling balls which tumbles to crush the feed when the cylinder is rotated.⁶ (**b**) Schematic illustration of the mechanism of comminution. From left to right: Direct impact or compression, chipping or attrition from shear stress, abrasion from shear stress.⁶ (**c**) Different milling media used to crush and grind down materials fed into the mills: (**i**) cylpebs (**ii**) milling balls (**iii**) milling rods. Image obtained from 911 Metallurgist process equipment.⁷

The focus on green chemistry for the past two decades has renewed interest in mechanochemistry.^{10,11} Mechanochemical processes are generally considered greener than conventional solvothermal methods as they do not require bulk quantities of toxic, environmentally-damaging, and/or expensive solvents.¹² Alongside the generally observed acceleration of reaction kinetics compared to solution-based methods, using mechanochemistry also results in improved space-time yield (STY), the product yield per unit volume of the reaction and per unit time, ¹³ For example, the mechanochemical synthesis of perylenediimide-based dyes was established by Cao *et al.* to have a STY of 30×10^{-3} kg m⁻³ day⁻¹. This value is one to two orders of magnitude greater than the currently used solvent-based methodologies.¹⁴

Mechanochemical processes often operate at lower temperatures and pressures compared to solvothermal synthesis, allowing reactions to proceed under milder conditions.¹⁰ For instance, the iron-catalysed synthesis of ammonia from nitrogen was found to proceed at 45 °C and atmospheric pressure under mechanochemical conditions, while the industrially-established Haber-Bosch process operates at 450 °C and 200 bars of pressure. While the mechanochemical process has only been performed on a laboratory scale compared to the million ton scale of the Haber-Bosch process, it still holds great potential, yielding three times the conversion compared to the industrial process.¹⁵ Another example is the mechanochemical synthesis of ZIF-62, which was found to be complete in 30 minutes under ambient conditions, compared to 48 hours at 130 °C that is required for conventional solvothermal synthesis (Figure 1.2c).¹⁶ Mechanochemistry also has potential application in waste treatment or polymer degradation, as shear and impact forces (figure 1.1b) can break down unreactive molecules such as polychlorinated aromatics or polymers without harsh chemical conditions.¹⁷⁻²⁰

Beyond just green, mechanochemistry also enables the synthesis of previously inaccessible molecules and compounds, novel supramolecular assemblies, and new chemical selectivity (figure 1.2).²¹⁻²⁴ These are often serendipitous discoveries, such as the dimerization of buckyball C₆₀ when milled with potassium cyanide, or the trapping and isolation in the solid state of aryl N-thiocarbamoylbenzotriazoles, previously known only as non-isolatable intermediates in solution-phased reactions.^{23,24} Given the solventless nature of mechanochemistry, it can effectively overcome solubility issues that hinder conventional synthesis methods. In particular, mechanochemistry can resolve two types of solubility issues: one is when the reaction is impeded due to the low solubility of starting materials, and the other one is when the products have similar solubilities, making it difficult to isolate individual compounds. This is highly applicable in inorganic synthesis such as high-entropy oxides,²⁵ perovskites,²⁶ battery materials,²⁷ zeolites²⁸, or chemistry involving other highly insoluble compounds such as polyaromatic molecules or graphite.^{27,29} One of the earliest recorded examples is the mechanochemical salt metathesis between barium sulfate and sodium carbonate, which is not feasible in solvent-based methods due to the poor solubility of barium sulfate.²



Figure 1.2. Advantages of mechanochemistry. (**a**) Schematic illustration of the mechanochemical synthesis (left) of ZIF-62 when compared to solution-based methods (right).¹⁶ (**b**) Examples of molecules previously categorised as inaccessible, made available via mechanochemistry.¹⁰ (**c**) Unstable intermediates isolated by mechanochemical methods.¹⁰ (**d**) Schematic illustration of the mechanochemical synthesis of perylene diimides dyes.

A significant portion of the early research of mechanochemistry occurred independently and separately between research groups. As a result, there is a disconnect between the techniques and terminology used between the various fields.² An example is the parallel use of additives during milling between different chemistry and materials processing fields. As additives were usually added for different purposes or objectives across different fields, there is no unifying theory or terminology for the use of additives. For instance, within the field of mechanical alloying, additives are used as process control agents (PCA). Such additives may include polymers, solvents, surfactants, or salts, which are added to embrittle ductile metal powders without the need for cryo-cooling.³⁰ The process of embrittlement through the contact of additives to the surface of metal particles is known as the Rehbinder effect, named after P. A. Rehbinder for his contributions in studying the role of additives in mechanical processing.³¹ On the other hand, synthetic chemists developed the use of milling additives with little knowledge of their utilisation in other fields, although the purpose of the additives differs significantly. If the additive used was a liquid or solvent, they were termed liquid-assisted grinding (LAG)^{32,33}, a combination of a salt and a liquid was termed ion-and

liquid-assisted grinding (ILAG),³⁴ and the addition of polymers and liquids was termed polymer- and liquid-assisted grinding (POLAG).³⁵ The use of salts or other inert solids as additives to alter the texture or rheology of the reaction mixture is termed as grinding or milling auxiliaries in the context of ball milling, but termed as glidants or lubricants in the context of extrusion of pharmaceutical formulations.^{13,36} In the case of synthetic chemistry, the additives are known to accelerate the reaction, control the selectivity of the reaction, or help alter the rheology of the mixture, although the specific mechanism is not well understood.^{1,32} A recent review addressed the overlapping usage of the terms mechanochemistry, tribochemistry, and mechanical alloying to help bridge the gap between chemists, engineers, and material scientists who use the different terms in related research.³⁷ A standardised set of scientific notations was proposed to help with communication between the fields.

With thousands of years spent developing equipment for crushing, grinding and milling, there exists a large assortment of mechanochemical equipment available to chemists.³⁸ Combined with the lack of communication between the diverse fields utilising mechanochemistry, this creates a disorganised situation whereby a wide variety of different mechanochemical tools are used across various fields.^{2,37-38} Individual mechanochemical tools input a different combination of shear, impact, and mixing forces, and can result in different chemical outcomes. An example is the cocrystallisation of piroxam with succinic acid, which proceeds by mixing the components and subjecting them to repeated impact, but the cocrystals decompose into individual components when subjected to shear forces.³⁹ Without a throughout understanding of how different forces can affect mechanochemical outcomes, it will be difficult to identify an ideal mill for mechanochemical reactions. However, while finding a one-size fits all machine is a difficult task given the difference in mechanochemical reactivity between inorganic and organic systems, understanding the use, development, and modification of mechanochemical mills within the field can help identify traits and feature that every mechanochemical device needs to perform modern mechanochemistry.⁴⁰

In this introductory overview, I investigate the recent development of mechanochemical equipment and study the application of mechanochemistry in the fields of cocrystallisation and metal-organic frameworks (MOFs). By looking at the evolution of milling tools and the direction the fields are moving in, I aim to highlight the essential features required for any future mechanochemical devices.

1.1. Mechanochemical devices

1.1.1. Automation of traditional equipment

The mortar and pestle (Figure 1.3a) approach has been used to perform mechanochemical transformations since antiquity. This approach remains relevant due to low cost and simplicity, with a mortar and pestle being found in most research laboratories. The mechanochemical synthesis of the well-known dark blue pigment Prussian blue was recently replicated using mortar and pestle by the Kwak group for the removal of caesium ions from an aqueous solution.⁴¹ The Biswas group also recently synthesized and modified caesium lead halide perovskites using a mortar and pestle.⁴² Mortar and pestle methods have also been used to synthesize cocrystals,⁴³ deep eutectic solvents,⁴⁴ organic compounds,⁴⁵ supramolecular assemblies,⁴⁶, and nucleotides.⁴⁷ Given that mortar and pestle are widely available, they are the ideal equipment to introduce mechanochemistry to students.⁴⁸ Despite being extensively used, manual grinding is labour-intensive and susceptible to variation from environmental and human factors.^{1c,49-50} Automation of the milling processes can alleviate inconsistency issues while simultaneously improving the efficiency. Automated mortar mills (Figure 1.3b), powered by electroical motors are the machine equivalents of a mortar and pestle. Examples of mortar mill usage includes oxidation and cleavage of lignin studied by Saumya and her coworkers, and the synthesis of barium titanate from barium oxide and titanium oxide accomplished by the Mukheriee group.^{51,52}



Figure 1.3. Traditional mechanochemical tools and their automated counterparts. (**a**) A mortar and pestle. (**b**) An automated mortar mill. Image obtained from Retsch. (**c**) A stone mill. Image obtained from Koper Regional Museum, Slovenia. (**d**) Motorised pan mill and a cross section diagram of the milling pan.⁵⁴

Another traditional milling technique automated through motorisation is pan-milling, a form of solid-state shear milling (S³M). An archetypal example of traditional pan milling is the use of a rotating quern, which is also known as a stone mill, (Figure 1.3c) used to grind wheat or soybeans which can be powered by humans, animals, wind, or water. Material is fed inbetween two jagged pans, with one of the pans rotating to generate powerful shear forces to pulverise solids. Powering modern pan mills with motors increases the rotating speed and greatly increases the shearing strength, making them suitable for the shearing of tough, elastic polymers such as rubber or the exfoliation of graphite (Figure 1.3d).⁵³⁻⁵⁵ Pan milling has been heavily utilised to generate polymer composites, such as poly(ethyleneterephthalate)/Na-montmorillonite, polylactic acid with various chemical foaming agents, or polyvinylidene fluoride/barium titanate piezoelectric composite.⁵⁶⁻⁵⁸ Pan milling also has been used for the exfoliation and doping of graphite with melamine and NaCl, and the continuous synthesis of carbamazepine-salicylic acid cocrystals.⁵⁹⁻⁶⁰

1.1.2. Ball milling

The use of tumbling mills is still common in many industries because such mills are less expensive to build, operate, and maintain. Most of the published and academic research on tumbling mills for the past few years are focused on improving their energy efficiency, with few e.^{6,9a,61} Most research into mechanochemistry nowadays is based on high-energy milling, a term loosely associated with milling processes whereby the media is agitated at velocities magnitudes greater than the gravitational acceleration within traditional ball mills.^{8,62} This results in blending and comminution to take place on a nanoscopic scale within a much shorter timeframe compared to conventional ball mills.⁸ Although the mills are classified according to their output motion, their naming terminology may be used interchangeably with other similar mills depending on the manufacturer or research group. The following section outlines few of the most commonly used ball mills within the mechanochemistry field and their applications.

All the mills outlined in the following section are capable of rapid comminution and homogenisation of powders, which results in overlap in their application. Therefore, the examples provided below may have been and can be applied to any type of mill, rather than being specific to the mill being discussed.

Planetary mill

Laboratory-scale planetary mills consist of a sun disc that supports two to four milling jars (in the case whereby there is only one jar, a counter-balancing weight needs to be installed), which rotate in a dual centrifugal motion around their axis (figure 1.4).^{8-9,62-63} Because the jars and disc rotate in opposite directions, the generated centrifugal force causes milling balls and material within the jars to cascade or cataract across the jar at high speeds and force. The intensity of centrifugal acceleration exerted on the feed, which can reach 150 g (150 times gravitational acceleration, with g being 9.81 m s⁻²), is determined by the speed of the rotation, the size of the sun disc, and the ratio of revolution between jar and disc (usually 2:1 or 4:1).^{9b} Planetary mills were initially used (and continues to be used) for mechanical alloying, a process whereby a mixture of metal powders undergoes continuous fracturing and cold welding under the tremendous stress generated by the mill.⁶² This is used to generate new alloys, such as oxide-dispersion strengthened (ODS) nickel- and iron-based superalloys for the aerospace industry.^{9a} Being effective at both comminution and homogenising mixtures, planetary mills also found application in other fields such as zeolites,⁶⁴ perovskites,⁶⁵ nanoparticles,⁶⁶ metal-organic frameworks (MOFs),⁶⁷ organic synthesis,⁶⁸ waste degradation and recycling, ^{69,70} and

renewable feedstocks.⁷¹ He *et al.* combined polymer degradation and MOF synthesis by milling waste poly(ethyleneterephthalate) (PET) into UiO-66.⁷² Another fascinating field of study that has seen extensive use of planetary mills is mechanochemistry involving gases. The aforementioned mechanochemical trapping of nitrogen in the form of ammonia is performed with a planetary mill.¹⁵ Another example is the generation of hydrogen gas by grinding diether ether in the planetary mill with chromium-containing jars or balls, such as type SUS304 stainless steel. The hydrogen gas can also be generated *in situ* and milled with alkenes for hydrogenation.⁷³



Figure 1.4. Planetary mills. (a) A schematic diagram illustrating the movement and operation of a planetary mill.⁶³ (b) Possible movement of balls within the jar, depending on the force exerted by the mill. (i) cascading, whereby the balls slide over each other. (ii) cataracting, when the balls are flung across the jar.⁶³ (iii) rolling, where the balls roll on the wall of the jar due to the centrifugal force. (c) A planetary mill.^{1c}

Vibratory mills

Vibratory mills grind down materials by subjecting the materials alongside the milling media to high-frequency vibrations.^{8,9a} The vibrations are generated by an eccentric weight, driven by a motor, and balanced by springs (Figure 1.4a, b). Vibratory are defined by their relatively (compared to the milling jars) small displacement values (aka vibrating), with older and larger vibratory mills having circular or elliptical motions while some newer mills vibrate vertically.^{8,75} Developed in the 1930s for the comminution of minerals and ores, vibratory mills were initially used for mineral processing and extractive metallurgy.³⁸ Miniaturisation enabled the implementation of the mill within the laboratory to screen for reaction conditions (Figure 1.4c). For example, the discovery of dumb-bell-shaped C_{120} by Wang *et al.* through the grinding of C_{60} with 20 equivalents of KCN in a vibratory mill,⁷⁴ the direct synthesis of

alkoxysilanes,⁷⁵ catalytic materials such as CuO-CeO₂,⁷⁶ bulk synthesis of metal nanoparticles attached carbon nanotubes,⁷⁷ palladium(II) pincer complexes,⁷⁸ the mineral ettringite⁷⁹ and organic synthesis of bicyclononyne tosylate⁸⁰ are all recent examples of mechanochemical synthesis using a vibratory mill. Benchtop vibratory mills have also been used extensively for various *in situ* studies of mechanochemical reactions.⁸¹ For example, Kulla *et al.* conducted an *in situ* triple coupling of synchrotron powder X-ray diffraction (PXRD) with Raman spectroscopy, and thermography to study the cocrystallisation of theobromine with oxalic acid dihydrate, the Knoevenagel condensation of p-nitrobenzaldehyde with malononitrile, and the formation of a manganese(II) phosphonate.⁸²



Figure 1.5. Vibratory and mixer mills. (**a**) A schematic diagram of a vibratory mill.⁸ (**b**) An industrial scale vibratory mill.⁸ (**c**) A benchtop vibratory mill. Image obtained from FRITCH (**d**) A SPEX mixer mill, which oscillates the milling vessel in a figure of eight.^{1e} (**e**) A Retsch mixer mill, which has a horizontal oscillation.^{1e}

Mixer mills

Mixer ball mills, also known as shaker mills, grind and homogenise materials by shaking the milling jar and media (Figure 1.5d, e).^{8,62} Their benchtop sizes make them suitable for processing small samples within the lab. Their motion and effects are almost identical to some benchtop vibratory mills, causing the terms to be used interchangeably. Mixer mills usually have a larger amplitude of displacement compared to vibratory mills and move in a

linear or figure-of-eight motion horizontally instead of the vertical motion in a vibratory mill. The easy operation and small sample scale of mixer mills make it convenient to scan for reaction conditions within laboratory settings. They are consequently used for a wide range of applications, including the numerous small-scale organic and inorganic mechano-synthesis,^{1,83} gaseous mechanochemistry,⁸⁴ direct catalysis,⁸⁵ enzymatic reactions,⁸⁶ and polymer synthesis⁸⁷ among others. The widespread use of mixer mills has led to significant modifications and additions being installed on the mixer mills. For example, the first *in situ* synchrotron PXRD on the mechanochemical synthesis of zeolite imidazole frameworks (ZIFs) by Friščić *et al.* on a mixer mill.⁸⁸ The process was accomplished by modifying the mill so that it positions a poly(methylacrylate) (PMMA) milling jar in the trajectory of a high-energy synchrotron X-ray beam (about 90 keV) during the milling process. A similar modification also enabled *in situ* monitoring of the formation of coordination polymers of cadmium chloride with cyanoguanidine, and cocrystals of nicotinamide with suberic acid by Raman spectroscopy on a mixer mill.⁸⁹

Several different temperature control configurations for mixer mills have also been built over the years, which include heating and cooling jackets attached to the milling jars, heat guns pointed directly at the jars, and even mini ovens mounted on the milling arms of the mills.^{90-^{92,84} These modifications allowed mechanochemists to better understand the effects of temperature on the outcome of mechanochemical reactions. Andersen *et al.* used cooling jackets to cool milling jars and study the effects of sub-ambient temperatures on the enantioselectivity of mechanochemical reduction of 4-tert-butylcylohexanone with sodium borohydride.⁹⁰ The scope of mechanochemical reactions conducted under sub-ambient temperatures was expanded in a later study involving aldol condensations, Diels-Alders, and A³ Click reactions.⁹³ Temperature control also enabled the mechanochemical synthesis of molecules otherwise not attainable by milling at ambient conditions. As an example, Cindro *et al.* used a heating jacket to mill at elevated temperatures, synthesizing a series of amides and urea-containing compounds that are not attainable by milling at room temperatures.⁹⁰ *In situ* monitoring of the mechanochemical reaction at elevated temperatures was also conducted using Raman spectroscopy.}

The user-friendly design of a mixer mill, featuring easy attachment and compact, handheld-sized jars, enables the customization of jars to suit specific milling requirements. For example, the Schüth group built a plug flow milling jar for gaseous mechanochemistry (Figure 1.6c). The jar was used for the mechanochemical, selective synthesis of monochloromethane at 90 °C (achieved by the mini oven attachment mentioned above), and for the study of oscillatory oxidation between carbon monoxide and carbon dioxide when milled over chromium (iii) oxide or cerium (IV) oxides.^{84,94} Mixer mill jars can also be coated with or constructed from catalytic metals. The Mack group constructed a nickel jar specifically designed for a mixer mill, directly catalysing the mechanochemical [2 + 2 + 2 + 2] cycloaddition of alkynes to cyclooctatetraene without the need to add air sensitive Ni(COD)₂ catalyst.⁹⁵ The group also built copper jars and silver-lined steel jars for the [2 + 1] cycloaddition between a diazo-compound to an unsaturated hydrocarbon.⁹⁶ To reduce wear and tear from abrasion during milling processes, Pickhardt *et al.* suggest using harder and more abrasion-resistant alloys like brass or monel (alloys of nickel) instead of soft catalytic metals such as silver, copper, and nickel. This can enhance the efficiency and lifespan of the milling equipment.⁸⁵



Figure 1.6. Mechanochemistry using customised milling media. (a) Nickel catalysed [2 + 2 + 2 + 2] cycloaddition using nickel pellets as milling balls or a nickel jar.⁸⁵ (b) Silver or copper jar catalysed [1 + 2] cycloadditions.⁸⁵ (c) Schematic for a custom-built gas flow jar for the mixer mill.^{84,217} (d) Jars lined with silver or copper metal used in reactions mentioned in (b).⁸⁵

Attritor mills

Attritor mills, otherwise known as stirred media mills, consists of a rotating shaft with arms to agitate the milling material and media (figure 1.7).^{9,98} Invented in 1922 by Klein and Szegvari for the rapid dispersion of hydrocarbons, lead oxides, or sulfur particles within the rubber to complete the vulcanisation of rubber.⁹⁹ Attritor mills are a versatile type of grinding equipment that find extensive use in a range of industries, including mining, agrochemicals, electronics, coatings, and more. Table 1 provides a non-exhaustive list of the industries where these mills are commonly used. Depending on the design and speed of the rotating shaft, stirred media mill can either be classified as a conventional (some may refer to as low energy) or high energy ball mill.



Figure 1.7. Attritor mills. (a) Schematic of an attritor mill with a cooling jacket.⁶ (b) A three-storey tall tower mill, an industrial scale conventional mill of which has a propeller shaft which lifts and drop the milling balls. Image obtained from Metso Outotec cooperation. (c) Table with schematic representation of different of attritor shafts and inner shells.⁶

Industry	Product	Industry	Product
Paint + lacquer	-primer coatings -lacquer -dispersion paints	Agrochemical	-pesticides -insecticides -herbicides -fungicides
Ink	-printing inks -dyestuffs -textile inks -activating of pigment crudes	Food industry	-cocoa nibs -milk chocolate -peanuts -sesame
Chemical and pharmaceutical	-various products		
Electronics	-high-grade ceramics -oxides for electronic components -ferrites for permanent magnets	Biotechnology	-cell disruption of microorganism -disruption of yeast cells for enzyme extraction
	-audio + video coatings	Rubber	–continuous dissolving of polymers in solvent
Minerals	-limestone -filler industry -paper coatings -flue gas desulfurization -kaoline	Coal, energy	-coal-oil mixtures -coal-water slurries -utilities (mill grind) -gas turbines (micronized)
	-gypsum		-diesel engines (micronized)
	-aluminium hydroxide		-benefication
	-precious metals liberation		-desulfurization

Table 1.1. Products processed on attritor mills.98

In the context of laboratory research, high energy attritor mills are used largely for mechanical alloying or the synthesis of inorganic, catalytic materials. Attritor mills generate high levels of media contamination and heat due to frequent high-energy collisions between the rotating shaft and balls during the milling process. This limits the use of attritor mills for the synthesis of fine chemicals within laboratories.¹⁰⁰ To alleviate the generation of high temperatures, industrial attritor mills are frequently equipped with complex cooling systems that incorporate cooling jackets and a water circulation system within the shafts and arms, enabling effectively dissipation of the heat generated during operation (Figure 1.7a).^{100a}

1.1.3. Sonication

Ultrasonication, which involves the application of acoustic cavitation to produce mechanical energy, is widely recognized as a branch of mechanochemistry known as sonochemistry (Figure 1.8).¹⁰¹ Acoustic cavitation is the growth and collapse of microbubbles that are generated when high-frequency sound waves travel through a liquid, building up high temperature and pressure within the microbubbles, which transfers the energy to molecules when the bubbles collapse.^{102,103} While ultrasonication has been used in numerous synthetic procedures and utilised extensively for molecular mechanochemistry (the study of direct mechanical force on a molecule on a molecular scale), sonochemistry remains distant from other mechanochemical fields.¹⁰³⁻¹⁰⁷ This is because sonochemistry often requires a liquid medium to transfer the energies through cavitation compared to the mechanochemical fields which relies on solid milling media. This difference in operating mechanism hampers the understanding of any unifying rationale to explain common reactivities between the fields, separating the study of mechanochemistry from sonochemistry.¹⁰¹



Figure 1.8. An ultrasound probe sonicator and a schematic illustration of the setup.⁹⁷

1.1.4. Vortex mixers

Traditionally, Vortex mixers have been utilized for mixing and preparing biological samples using high-speed oscillations, but the MacGillivray group has introduced a novel method called vortex grinding, which involves adding one or two milling balls to the system (figure 1.9). The group built a photo-mechanochemical setup using the vortex mill, whereby UV radiation was irradiated onto a transparent milling jar.¹⁰⁸ Photoactive 2(4,6dichlororesorcinol) •2**bpe** cocrystal was synthesized and photo-dimerised *in situ* using the

setup.¹⁰⁸ The MOF [Cu(INA)₂] (INA = isonicotinamide) was also synthesized using vortex milling.¹⁰⁸ Yelgaonkar *et al.* also used vortex milling to conduct a cascading reaction involving a Diels-Alder reaction, cocrystallisation to form a photoactive cocrystal, and a [2 + 2] cyclodimersation, further demonstrating the viability of vortex milling.¹⁰⁹



Figure 1.9. A schematic illustration of vortex grinding, a vortex mixer and the application of vortex mixing.¹⁰⁸

1.1.5. Extruders

Continuous manufacturing refers to a process where chemical reactions are continuously performed in a system, rather than in batches, with the constant feeding of reactants and removal of products from the system.⁸ Most industrial-sized vibratory, attritor, and tumbling mills can be operated in continuous modes.^{8,98,110} In laboratory settings where continuous manufacturing is required, both pan mills and extruders can be utilized, although the latter is far more prevalent.^{60,111} The twin screw extruder is one of the most commonly utilized types of extruders, consisting of two intermeshing, rotating (either co- or counter-

rotating) screws within a barrel. The feed injected at the start or along the screws is ground up, mixed, and extruded out at the other end by the shear forces generated by the rotation of the screws. The threads along the screw can be customised to adjust the residence time and the amount of shear pressure applied to the material. Extrusion is a common method of mass transport for solids in factories and has been used extensively for the manufacturing of plastic products.¹¹² Extrusion has been applied to the mechanochemical synthesis of cocrystals, MOFs, deep eutectic solvents, and a wide array of organic molecules.^{67,111,113-115} For example, Deborah synthesized the metal complexes Ni(salen) and Ni(NCS)₂(PPh₃)₂ as well as the MOFs HKUST-1, ZIF-8, and Al(fumarate)(OH) on a multi-gram scale using the twin screw extruder.¹¹⁶ Karadeniz et al. also used the extruder to synthesize 100g of zirconium MOFs UiO-66-NH₂ at a rate of 1.4kg h^{-1.67} Bolt *et al.* studied the scaling up of nickel catalysed Suzuki Miyaura coupling using a twin screw extruder. The conversion rate during the 3-hour extrusion process (with a 3-minute residence time) was observed to be 10-60 % lower during the initial hour and final 30 minutes, in comparison to the more productive 150 minutes period in the middle of the extrusion operation.¹¹⁷ This was attributed to the incomplete filling of kneading sections with milling material at the start and end of the extrusion. Synthesis through extrusion is therefore much more effective for longer, large-scale manufacturing when the productive period is elongated, compared to shorter runs.



Figure 1.10. Single and twin-screw extruders. (a) A schematic representation of a single screw extruder.(b) A twin-screw extruder.

1.1.6. Media-less techniques

Most mechanochemistry is performed using milling media or with extrusion techniques as mentioned earlier. However, the use of these methods can result in significant contamination due to the wear and tear caused by the abrasion of the media, particularly when operating at high speeds and intensity.¹⁰⁰ Although measures can be employed to minimise contamination, the most straightforward solution is a media-less mill. A classic example is the autogenous (AG) mill, a media-less tumbling mill that uses the coarser fraction of the fed material to crush and comminute itself via a tumbling motion.¹¹⁸ AG mills are mostly used by the mining industry as a low-cost, energy-efficient technique to crush ores before further processing or grinding.⁶



Figure 1.11. Media-less mechanochemical devices. (**a**) An industrial autogenous mill which can process 70,000 tons of copper sulfide ore at the Tintaya Antapaccay copper mine, Peru.⁶ (**b**) Exterior of a LabRAM II resonant acoustic mixer.¹²⁴ (**c**) Photograph of the mixing station of a SpeedMixer.¹⁸⁸ (**d**) Interior of a LabRAM II resonant acoustic mixer.¹²⁴

In recent years, mechanochemists have been experimenting with new media-less techniques such as Resonant Acoustic Mixers (RAM) to conduct mechanochemistry (Figure 1.11b, d). Similar to how high-energy ball milling achieves rapid milling by accelerating the media at speeds magnitudes greater than a traditional ball mill, RAM oscillates the mixing vessel at its resonant frequency to generate high-intensity vibrations of up to 100g, blending the powders quickly and efficiently.¹¹⁹ Initially used for the mixing of impact sensitive explosive, RAM was brought to the attention of mechanochemists by am Ende *et al.*, who used RAM to synthesize and scale-up model pharmaceutical cocrystal compositions based on

carbamazepine and nicotinamide, carbamazepine and saccharin, as well as carbamazepine and 4-aminobenzoic acid.^{120,121} Individual screens were performed using eight different solvents as LAG. Cocrystal formation was observed with all solvents, except for cyclohexane. At around the same period, Anderson et al. reported the use of RAM to safely synthesize a cocrystal consisting of two highly energetic components, octahydro-1,3,5,7-tetranitro-1,3,5,7tetrazocine, and 2,4,6,8,10,12-hexanitro2,4,6,8,10,12-hexaazaisowurtzitane.¹²² Compared to conventional milling methods, RAM is thought to be much safer for the mechanochemical preparation of such explosive cocrystals due to the minimisation of impact forces that might detonate the cocrystal. Michalchuk and co-workers conducted the first in situ synchrotron PXRD study on the cocrystallisation of carbamazepine and nicotinamide on the RAM and proved that LAG is essential for the formation of cocrystals when using RAM, compared to neat alternatives for ball milling.¹²⁰ Nagapudi *et al.* created a high throughput holder for RAM and used it to screen for cocrystals.¹²³ Titi *et al.* used RAM in the presence of liquid additives to synthesize imidazolate MOFs from zinc oxide, proving that the use of RAM is not limited to soft organic materials, while Gonnet, Lennox and co-workers applied RAM to a series of catalytic organic reactions, proving the viability of RAM for organic synthesis.¹²⁴⁻¹²⁵ Most recently, Effaty et al. used RAM for mechanoredox catalysis, using barium titanate as the piezoelectric catalyst to activate diazonium salts for coupling.¹²⁶ RAM has certainly seen a rapid rise over the past few years, quickly adapting most techniques and setups used in conventional mechanochemistry, with great potential for future applications. In the following chapter, the use of another media-less technique, termed SpeedMixing (Figure 1.11c), in explored in the context of synthesizing pharmaceutical cocrystals.

1.2. Mechanochemistry of Cocrystals

A cocrystal is a crystalline single-phase material composed of two or more different molecular or ionic compounds, which are solids at ambient conditions, in a particular, well-defined stoichiometric ratio (figure 1.12).¹²⁷ The crystal structure of a cocrystal typically differs from those of its underlying components, giving rise to new and/or different physical properties.¹²⁷ Cocrystallisation has been applied to improve the performance of explosives, agrochemicals, and active pharmaceutical ingredients (API).¹²⁷ Mechanochemical methods are attractive for the screening and synthesis of cocrystals as they bypass the solubility requirements of the individual cocrystal components, allowing cocrystals to be synthesized from poorly soluble components.^{127,128} An example is the drug molecule brexpiprazole is an

antipsychotic for the treatment of mental disorders, like schizophrenia and depression, but suffers from poor solubility in various solvents.¹²⁹ Recent studies have demonstrated that the formation of cocrystals of brexpiprazole with fumaric acid or catechol via the process of grinding together stoichiometric quantities of the components can lead to significant improvements in the drug's solubility by up to 2.6 times or enhanced stability respectively.¹²⁹ To the best of my knowledge, this is currently the only method to obtain brexpiprazole cocrystals.



Figure 1.12. Schematic illustration of various multicomponent pharmaceutical cocrystals.^{127c}

Another advantage mechanochemical methods offer over solution-based synthesis is the elimination of the need for cocrystal components to be soluble in the same solvents.¹³⁰ This is particularly relevant in cases where the components have vastly different solubility profiles, which can complicate the synthesis process. The synthesis of phenazine•mesaconic acid cocrystals by Eddleston *et al.* encountered difficulties due to the poor solubility of phenazine in polar solvents and mesaconic acid in non-polar solvents.¹³¹ The use of solution-based methods only yielded cocrystals of phenazine•mesaconic acid in solutions whereby the solubility of both components are similar. However, forms of the cocrystal can be readily synthesized within 30 minutes via simple grinding, either neat or using LAG. Notably, this approach also yielded the greatest number of different solid forms of phenazine•mesaconic acid cocrystals.

Besides neat grinding, the addition of additives for LAG, ionic liquid-assisted grinding (IL-AG), or POLAG can alter the kinetics or outcome of cocrystallisation.¹³²⁻¹³³ Additives can increase the reaction rate, increase product crystallinity, or change chemical selectivity through enhanced mass transfer or templating effects.¹³⁴ Initially known as solvent-drop grinding¹³⁵ or kneading,¹ LAG is used to describe the addition of liquids during the grinding process.¹ The

term LAG was coined to remove the implication that the liquid additives in the process were intended to dissolve the components.^{1b} To the best of my knowledge, one of the pioneering studies of the effects of LAG on cocrystal formation was done by Shan *et al.*, who noted that the addition of a small amount of methanol during the grinding process can greatly accelerate the formation of cocrystals of cyclohexane-1,3cis,5cis-tricarboxylic acid.¹³⁶ Trask et al. theorised solvent polarity as an important factor in determining the polymorphic outcome of caffeine glutaric acid cocrystals when it comes to LAG.¹³⁵ Using non-polar cyclohexane as a liquid additive when grinding with anhydrous caffeine and glutaric acid yielded predominantly form I of caffeine glutaric acid cocrystals, which has methyl and methylene groups exposed on its cleavage plane, which would preferentially stabilise by non-polar solvent upon grindinginduced cleavage. On the other hand, the use of polar chloroform in the grinding process yielded form II of caffeine glutaric acid cocrystals, which do not have a non-polar cleavage plane. Other studies have explored the use of various liquids for LAG and their impact on polymorphic outcomes. For instance, Chierotti et al. investigated the interconversion of the five polymorphic/tautomeric forms of 2-thiobarbituric acid forms, while Trask et al. examined the transformation between three polymorphs of anthranilic acid and the two polymorphs of succinic acid when grinding with liquid additives. ¹³⁷⁻¹³⁸



Figure 1.13. Summary of the LAG experiments performed by Hasa *et al.* on the effect of η and liquid additive on the polymorphic outcome of caffeine-anthranilic cocrystals.¹⁴⁰

The amount of liquid additive used for LAG also has a large impact on the kinetics and outcomes of cocrystallisation. Friščić *et al.* studied the effects of different amounts of various liquid additives on the formation of theophylline•L-malic acid, theophylline•L-tartaric acid, caffeine•L-malic acid, and caffeine•L-tartaric acid cocrystals.¹³⁹ The amount of liquid added

was defined by the η parameter, which is the ratio of the volume of liquid additive added to the mass of the solids milled. At low η values of less than 0.05 μ L mg⁻¹, rates of formation of all four cocrystals were slow and the rates increased as η was increased. Each cocrystal had an optimal range of η for corrystal formation and at η values above that range, the corrystal was not formed. The effect of η is the most pronounced in systems where the solubilities of the components of the cocrystal do not match. Building upon the research of Friščić et al., Hasa et al. conducted a comprehensive investigation on the impact of η and liquid additives on the polymorphic outcome of cocrystallization between caffeine and anthranilic acid, exploring a more detailed range of η values in the study.¹⁴⁰ For 11 of the 15 liquid additives studied, the polymorphic outcome of the mechanochemical reaction changed as η was increased. For instance, when using 1-dodecanol as LAG, when $\eta = 0.04$, form III of caffeine anthranilic acid cocrystal was obtained, when $0.08 \le \eta \le 0.12$, form II was obtained, and for η values above 0.15, a mixture of form I and III are obtained. Some liquid additives such as acetonitrile or ethylene glycol are highly selective for metastable form II, regardless of the amount of liquid additive used in the grinding. These data suggest a more nuanced view of the effects of LAG and its mechanism, raising the question of how a small variation in the volume of liquid additives can have a huge impact on reaction outcomes. The exact mechanism of LAG remains a topic of many studies and discussions.¹⁴¹



Figure 10. An overview of solid-state reactions of hydrated and nonhydrated forms of caffeine and citric acid.⁶⁸

Figure 1.14. Schematic overview of using hydrated forms of caffeine or citric acid to obtain caffeine•citric acid cocrystals.^{33a}

Another interesting method to perform LAG to introduce the liquid additive is in the form of hydrates or solvates.^{33a} Karki *et al.* demonstrated in the synthesis of theophylline-citric acid monohydrate that milling either theophylline monohydrate or citric acid monohydrate with their anhydrous counterpart produces the same effect having water for LAG (Figure 1.14).¹⁴² Another demonstration of the transfer of solvents from solvates was done by the Hasa group, using POLAG for the stepwise desolvation of the theophylline-2-pyrrolidinone solvate.¹⁴³ Theophylline can be solvated stepwise by controlling the stoichiometry of 2-pyrrolidinone added.¹⁴⁴ This can result in pure mono-solvate being obtained when one equivalent of 2-pyrrolidinone is used, at the sesquisolvate obtained when 1.5 equivalent of pyrrolidinone is applied. The reverse desolvation by grinding the solvates with small quantities of poly(acrylic acid) added is 10% of the total mass of sesquisolvate, it desolvates into the mono-solvate and fully converts to anhydrous theophylline when the mass of poly(acrylic acid) added reaches 35 to 75%.¹⁴³



Figure 1.15. The stepwise solvation and desolvation of theophylline 2-pyrrolidinone solvate. By increasing the amount of 2-pyrrolidinone used as LAG, the mono-solvate or sesquisolvate (1.5 eq of 2-pyrrolidinone for each equivalent of theophylline) can be selectively obtained. The solvates do not desolvate readily when ground neat, but the addition of poly(acrylic acid) can be used to selectively desolvate the solvate. δ = mass ratio of polymer additive to reactant mass. ^{143,144}

Other than varying the additives, changing the material of the milling media can also alter the kinetics and outcomes of mechanochemical cocrystallisation.¹⁴⁵ While it is known that increased kinetics of mechanochemical processes are usually correlated with increased ball mass and diameter, interactions between the milling media and milled materials may distort the trend.¹⁴⁶ The Boldyreva group studied the mechanochemical cocrystallisation of theophylline and nicotinamide using balls of different mass, sizes, and materials to help disentangle the effects of mass and surface areas of milling balls. The rate of reactions

correlated well with the total ball mass and density of ball material. The nylon ball was an outlier in the study, possessing the fastest cocrystallisation rates despite being the lightest. This led to Michalchuk *et al.* theorising that the accelerated kinetics was due to the sorption of the liquid additive, ethanol to the milling ball.¹⁴⁶ Germann *et al.* discovered a new polymorph of a 1:1 cocrystal of nicotinamide and adipic acid (termed form II, while the original 1:1 cocrystal is termed form I) by increasing total ball mass during the milling process.¹⁴⁷ Although DSC and VTPXRD have determined that the new form is an enantiotropically-related hightemperature polymorph of the stable form I, the mechanochemical conversion of form I to form II takes place at room temperature, significantly lower than the polymorphic transition temperature of 93.7 °C. Furthermore, milling form I in a stainless-steel jar generates form II, while milling in a PMMA jar converts form II into form I, highlighting the importance of milling media in polymorphic conversion and mechanochemical cocrystallisation outcomes (Figure 1.16). A similar study was conducted by Linberg *et al.*, who studied the polymorphic conversion between form I and II carbamazepine isonicotinamide cocrystals.¹⁴⁸ Milling using a PMMA jar accelerates the conversion from form I to form II by ca. 110-fold when compared to milling using a stainless steel jar. This conversion was, however, attributed to the elevated temperature when using PMMA jars which retain more heat from the milling.



Figure 1.16. Schematic illustration of the polymorphic conversion between form I and II of nicotinamide adipic acid when milled using PMMA or steel jars.¹⁴⁷

Mechanochemical processes are also efficient at screening for cocrystals, obtaining cocrystals that are difficult to synthesize using conventional methods, and manufacturing cocrystals without the need for a ternary phase diagram.^{130b,149-151} Patil *et al.* used a mortar and a pestle to synthesize benzoquinone hydroquinone cocrystals with ease, charge transfer complexes which tend to undergo redox isomerisation when synthesized using solution
means.¹⁵² The related cocrystal system of bis-naphthol and benzoquinone is also obtainable only through mechanochemical methods.¹⁵³ Friščić et al. conducted a systematic study by synthesizing a series of three-component cocrystals through solution, neat grinding, and LAG methodologies.¹⁵⁴ However, synthesizing multicomponent cocrystals posed a challenge as the components needed to be equally and reasonably soluble in the same solvent, which became increasingly difficult to balance with multiple molecular species. Unsurprisingly, initial screens using solution-based methodology is only able to isolate 4 different cocrystals. Some of the cocrystals not obtained in the initial solution-based scan were later successfully grown, albeit through the identification of a suitable binary solvent system. This contrasts with the use of LAG, which resulted in the discovery 18 different cocrystals. The application of neat grinding also led to the production of 15 of the 18 cocrystals obtained using LAG, demonstrating the effectiveness of mechanochemical methods in isolating new solid forms. Novel ternary and quaternary cocrystals have also been synthesized via mechanochemical means, including a quaternary cocrystal consisting of organic and inorganic components.¹⁵⁵⁻¹⁵⁷ These advancements highlight the potential of mechanochemical processes in cocrystal screening and synthesis, especially in addressing challenges encountered in multicomponent cocrystal synthesis.

1.3. Mechanochemistry of Metal-Organic Frameworks

Metal-organic frameworks (MOFs) are organic/inorganic hybrid materials comprising of metal clusters or centers held together by organic, multidentate ligands in three-dimensional polymeric structures.¹⁵⁸ While the term MOF is used interchangeably with the term coordination polymers, MOFs are usually defined by their two- or three-dimensional structure and potential voids or pores in the structure. Pores of MOFs range from 3Å to 100 Å, making them the most porous materials to be developed, with the most porous MOF nearing surface areas of 8000 m² g⁻¹.¹⁵⁹ The porosity makes MOFs highly suitable for a range of applications, including gas and liquid storage, purification, and carbon capture.¹⁶⁰⁻¹⁶² Additionally, MOF materials can potentially serve as a platform for drug delivery and as a support structure for catalysts in various chemical reactions.¹⁶³⁻¹⁶⁴ Other interesting applications of MOFs include energy storage, chemical sensing and even harvesting water from the atmosphere.¹⁶⁵⁻¹⁶⁷



Figure 1.17. Schematic illustration of a passive, cyclic water harvesting using MOFs.¹⁶⁷

The continuous discovery of new MOF structures and applications necessitates the development of greener methodologies, to screen and manufacture these materials on an industrial scale.^{165,168} MOFs are usually synthesized via solvothermal methods which require large quantities of toxic and costly solvents, alongside long reaction times, and elevated temperatures and pressures. This generates concerns about the cost, environmental impact, and safety of the synthesis of MOFs. Mechanochemistry can help remove the need for bulk solvents in the synthesis of MOFs. I was known for a long time that complexes and coordination polymers can be produced mechanochemically,¹⁶⁹ but it was not until 2006 that the James group synthesized the Cu(INA)₂] (INA = isonicotinamide) by grinding – the first MOF made mechanochemically.¹⁷⁰ Pichon *et al.* then conducted an array-based study to scan for MOFs, milling 60 different combinations of metal salts and ligands for 15 minutes. Forty of the combinations resulted in conversions, twenty-nine of those conversions were complete, and six products were identified, including HKUST-1. This validates the viability of mechanochemistry in MOF synthesis and hints at the possibility of using mechanochemical means to scan and discover new MOFs.

The number of MOFs synthesized mechanochemically expanded rapidly thereafter, with at least 70 different MOFs such as MOF-74, ZIFs, CPL, MOF-5, MOF-14, and UiO-66.¹⁷² A few MOFs can be synthesized by neat milling, while most MOFs require LAG accomplished either by addition of an external liquid or by using a metal salt hydrate as the starting material. Other than being solventless, mechanochemical synthesis of MOFs also takes place under milder conditions, while the reaction times are significantly shorter than solvothermal synthesis in most cases.^{10,172} For example, the synthesis of UiO-66 and its analogues takes 12 to 14 hours

at 150 °C under solvothermal conditions while Užarević *et al.* was able to synthesize UiO-66 mechanochemically within 90 minutes under ambient conditions.¹⁷³



Figure 1.18. Schematic illustration of the structures of some of the MOFs synthesized using mechanochemistry.

Another advantage of synthesizing MOFs mechanochemically is the availability of poorly soluble oxides or hydroxides as precursors. This bypasses the need for soluble metal complexes such as chlorides or nitrates, which are often corrosive or toxic. One of the earliest examples was the work by Friščić and Fabian, who milled poorly soluble zinc oxide with fumaric acid (**fum**) and 4,4-dipyridyl (**bipy**) or trans1,2-bis(4-pyridyl)-ethylene (**bpe**) to form two different pillared MOFs.¹⁷⁴

The addition of salts in the mechanochemical ILAG strategy can also greatly accelerate the mechanochemical synthesis of MOFs. For example, Friščić *et al.* milled zinc oxide with terephthalic acid (**ta**), 1,4-diazabicyclo[2.2.2]octane (**dabco**) together with the addition of DMF as the liquid additive to synthesize the pillared MOF [$Zn_2(ta)_2(dabco)$].¹⁷⁵ As the reaction was only partially complete after 60 minutes, Friščić *et al.* experimented with the addition of catalytic amounts of salts as templating agents accelerate the reaction. By varying the salt used in ILAG, a complete conversion to pillared MOFs of different topology were obtained within 20 to 45 minutes. Grinding the reactants with catalytic amounts of ammonium or potassium nitrate generates the pillar MOF with tetragonal layers while grinding with sulfate salts generates hexagonal layered MOF(figure 1.17). Another example of ILAG being used as a templating agent to control the topology of the MOF was done by Julien *et al.* on zinc ethylimidazole MOFs.¹⁷⁶ By milling with zinc oxide and 2-ethylimidazole with dimethylformamide with sub-stoichiometric amounts of ammonium sulfate or ammonium methylsulfate generated either a MOF with zeolite RHO topology or ZIF-14 with the analcime topology respectively. Interestingly, using ammonium nitrate as an additive resulted in the formation of a crystalline material that was previously unknown. Crystal structure determination from PXRD assisted by solid-state Nuclear Magnetic Resonance (ssNMR) revealed the ZIF adopted a non-porous β -quartz (*qtz*) topology.



Figure 1.19. Schematic illustration of the two pillared MOFs synthesized by Friščić et al..¹⁷⁵

Mechanochemistry can also be used to exchange ligands in a MOF, using the framework as a template to potentially generate new, complex MOF structures.¹⁷⁷ This has conventionally been done through solvent-assisted ligand exchange (SALE),¹⁷⁸ but requires large amounts of organic solvents and is an energy-intensive process. The Zhong group used a mortar and pestle and ground ZIF-8 with a series of 2-substituted imidazoles to obtain various mixed linked ZIFs. The degree of substitution increases with milling time, although it reaches a plateau at 29% to 66%, as equilibrium is achieved. A similar methodology was also applied to UiO-66, substituting 38% **ta** with 2-amino terephthalic acid successfully, while retaining the same topology. The paper attributes the substitution and the differences in equilibrium to the thermodynamic stability of the MOF products. This technique was termed by the group as mechanochemistry-assisted linker exchange (MALE) and appears to have great potential in the

synthesis of MOFs with diverse and complex architectures, although much work is still needed to ensure applicability and a better understanding of the mechanisms.

1.4. Perspective on essential features of future mechanochemical machines

Mechanochemistry has been gaining popularity in recent years due to its potential for more sustainable synthesis and unique reactivities. ^{1c,179} While the majority of mechanochemical discoveries are still conducted directly with commercially available mills and devices, many groups have been experimenting with modification of mills to better suit their needs. There is also research based on custom-made mills and even highly established groups are experimenting with new devices.^{30,180-181}

Looking at the modification and development of these devices within the mechanochemical field, there are a few features that are increasingly essential for mechanochemical synthesis. These features include scalability, versatility to modifications and add-ons, availability, adaptability to materials and mixtures with different rheology, minimisation of 'void zones', and consistency in applied forces, alongside the basic expectations of the ability to vary reaction time and force. I will go through each of these points below.

Scalability. Most industrial-scale mills such as tumbling, vibratory, and attritor mills are capable of circulation, continuous or semi-continuous manufacturing, processing materials on the multi-ton scale. Even the planetary mill, which has been touted as difficult to scale-up on an industrial scale due to its complex motion, can be engineered for continuous manufacturing within pilot plants (figure 1.18).¹⁸² On the laboratory scale, the twin screw extruder, and its widespread application, have been explored in the above sections. Therefore, the challenge of scaling-up mechanochemistry should not be attributed to its inability to operate on a large scale for industrial applications.^{111b} Instead, the main issue arises from the need for a different mechanochemical device to scale up efficiently, which often requires the reoptimization of experimental conditions, resulting in significant costs. Few machines are versatile enough to operate efficiently and handle the different scales demanded by synthetic chemists. Additionally, it is uncommon for research groups outside the mechanochemistry field to have access to multiple devices capable of operating at different scales. This may help explain why most multi-step reactions using mechanochemical techniques are limited to two or five steps, rather than the total synthesis of complex molecules.¹⁸³



Figure 1.20. Photo of industrial continuous flow planetary mill MP-4.8

Steps are being taken to reduce the cost and effort required to switch between machines when scaling. An example is the mechanochemical nucleophilic aromatic substitution of 2-bromo-1-fluoro-4-nitrobenzene by benzylamine, conducted on the milligram scale by Andersen *et al.* using a mixer mill and scaled up on a multigram scale was done using a twinscrew extruder. ¹⁸⁴ As direct optimisation using an extruder is resource-intensive given the scale (> 10g), Andersen *et al.* optimised the conditions on the mixer mills to match the requirements of the extruder. As the extruder has a short retention time of a few minutes, the reaction on the mixer mills was shortened to 15 minutes by raising the milling temperature. However, it should be noted that scaling between mixer mills and extruders is not perfectly synchronized, with different conversions between the two devices at the exact temperature. This is because the extruder functions on different parameters, such as residence time instead of milling time, rotational speed instead of milling speed, and a different mechanical motion compared to mixer mills. Bolt *et al.* also scaled up the mechanochemical manufacturing of nickel-catalysed Suzuki-Miyaura reaction on the twin screw extruder based on temperature parameters obtained from conducting the reaction on the mixer mill. ¹¹⁷

Another possible solution to reducing the expense and labour when scaling up is to use devices with similar motions so that the type of mechanical force and controlled parameters remain consistent. In most cases, this simply involves bigger-sized versions of the original mill. Gomes *et al.* took an innovative approach to 'shrinking' an extruder while removing the disadvantage of a short residence time by converting the operation into a batch process.¹⁸⁰ This

was accomplished by using a bench drill as a single drill device (figure 1.23d). The drill is lowered into a cylindrical chamber filled with the reaction material, mixing and shearing the components using the high-speed rotation of the drill bit. This simple yet effective approach has been applied to the synthesis of chalcones, dihydropyrimidinones, dihydropyrimidinethiones, pyrazolines, and porphyrins, proving its effectiveness. While there need to be upgrades to the machine to create a closed system during the milling process, the simplicity of this approach allows the low-cost miniaturisation of extrusion processes.

The most direct solution is to have a mechanochemical machine flexible enough to operate comfortably from the milligram to multigram scales. This range is adequate for most laboratories, compared to the multi-kilogram or ton scales in pilot or manufacturing plants. Some laboratory-based mills meet these requirements. For instance, planetary mills often operate jar sizes between 12 mL to 500 mL, and have been used for multi-scaled, multi-step reactions.,^{183,185} However, handling large-scale reactions on planetary mills can be inconvenient, with a large number of milling balls complicating operations such as separation of media from the product, wear and tear or simply being heavy and bulky to handle.¹⁸⁶⁻¹⁸⁷ Alternatively, media-less techniques such as RAM or SpeedMixing are convenient for scaling up reactions, only requiring the use of larger containers. RAM has been applied to the scale-up of cocrystals and MOFs, scaling up by 146- and 125-fold respectively with ease.^{121,124} SpeedMixing has also been explored as a convenient approach to scale up cocrystallisation by the Friščić group, scaling up of manufacturing of a cocrystal of suberic acid with nicotinamide from 200 mg to 22 g scale comfortably.¹⁸⁸ Moreover, the amount of liquid additive relative to the cocrystal components decreased as the scale increased. With larger variations of both the RAM and SpeedMixers commercially available, there is much potential to explore.¹⁸⁹

Versatility to modifications and add-ons. As mechanochemistry progresses, increasingly complex setups are created to perform the functions or reactions done in conventional chemical processes. This may include energy inputs such as temperature controls, light irradiation, and electric discharge.¹⁹⁰ The use of such setups has opened up possibilities for chemical reactions that were previously unattainable through conventional mechanochemistry, and in certain instances, has even led to the discovery of chemical reactions impossible by any other means.²¹ Seo *et al.* utilized a heating setup, consisting of a heat gun secured above a mixer mill, positioning it directly over a milling jar (figure 1.20g).⁹² The high temperatures achieved by the setup during milling enabled the Suzuki coupling of practically insoluble aryl halides, synthesizing novel pigment molecules that is impossible to produce

using any other method. Modifications and add-ons may also be in the form of *in situ* monitoring devices such as Raman spectroscopy, ssNMR spectroscopy, synchrotron PXRD, or pressure probes.⁸¹ These setups are essential for gaining insights into mechanochemical processes. Other modifications to mechanochemical devices include using milling media made up of catalytically active materials,⁸⁵ or the gaseous setups.¹⁹² The technical details of the setups are the focus of the current discussion, with the chemistry involved being covered earlier in the chapter.



Figure 1.21. Electric discharge milling on a tumbling mill. (a) Schematic illustration of electric discharge milling. (b-c) Photos of electric discharge milling.^{134,191}

Most of these setups (except for electric discharge done on tumbling mills (figure 1.19) and some gaseous setups) are built on the mixer, vibratory, or vortex mills - machines with smallscale, user-friendly designs that operate on simple mechanical motions with low displacements. These features make modifications and add-ons a lot simpler as the add-ons can be easily mounted, either in a stationary fashion or onto the milling vessel itself. This may have contributed to the diverse range of temperature control setups observed on mixer mills and benchtop vibration mills. Both the Kaupp and Mack group cooled their mechanochemical reactions by building individual, custom, double-walled milling jars, with tubing circulating a coolant wrapped between the walls.^{91,193} Heating can be done by a heat gun fixed above the milling jar by Ito group, or through variations of PID-coupled heating jackets mounted onto the milling vessels, used by the Užarević, Browne, Stuparu, and Michalchuk groups (Figure 1.20e, h).^{92,117,194-196} Due to the small displacement amplitude of the jars during the milling process, the thermocouple and heating element can be easily wired to the PID without the risk of damaging the connections. Recently, the Laurencin group also created a temperature control setup for a benchtop vibratory mill based on induction heating (Figure 1.21).¹⁹⁷ While temperature-controlled mills are not a new addition,^{8,98,193} the variety of temperature-controlled setups alongside its widespread application into mixer and vibratory mills for numerous

mechanochemical studies is a testament to the flexibility of the mixer and vibratory mills for modification and add-on.



Figure 1.22. Photos of modifications, add ons and setups based on the mixer mills. (**a**) *In situ* Raman spectroscopy setup.⁸⁹ (**b**) Gas flow with mounted oven setup.⁸⁴ (**c**) Cryo-cooling setup which flows coolant liquid through a jacket.¹⁹³ (**d**) A photo-mechanochemical setup, of which LED light strips are coiled over PMMA milling jars.¹⁷¹ (**e**) A temperature control setup using silicone heat pads as heating jackets.¹⁹⁵ (**f**) Another cooling setup, of which a hose with circulating coolant is coiled around the milling jar.¹⁹⁰ (**g**) Heating setup with heat gun mounted directly over milling jar.¹⁹⁰ (**h**) A heating jacket used for temperature control.¹⁹⁰

To perform photo-mechanochemistry and *in situ* spectroscopy during milling processes, complex setups are required. These setups must enable transparency to electromagnetic radiation, as well as accurate positioning of the irradiation source and detector around the mill.¹⁹⁸ In all available literature on *in situ* monitoring using synchrotron PXRD or Raman spectroscopy, the irradiation source and detectors are fixed in position, which is possible due to the simple motions with low displacement of the mixer or vibratory mill used.⁸⁸⁻⁸⁹ Transparency was primarily achieved using PMMA jars (steel and aluminium jars can be permeable to high energy X-rays from a synchrotron source).⁸⁸ Although there are concerns on the solubility of the material in certain solvents, physical deformation or wear and tear from milling, and alteration of chemical reactivity when using the jar,¹⁴⁵⁻¹⁴⁸. PMMA jars remain the most used due to its straightforward design, inexpensive material, and low cost of

manufacturing. An alternative jar design consists of a hard but brittle transparent tube (usually glass or sapphire) with Teflon end caps.¹⁹⁹ This type of jar was recently used for real-time monitoring of the mechanochemical synthesis of calcium urea phosphate ionic cocrystal by Raman spectroscopy. In both cases, the ease of operation of the mills facilitated the use of custom-made jars, enabling users to bypass the restrictions of pre-made, commercial jars. In a drastic example of this flexibility use any custom-made milling vessels, Štrukil *et al.* mounted a Duran glass vessel with Teflon balls onto a mixer mill for photo-milling (figure 1.21a,b).²⁰⁰





As mechanochemistry progresses, the setups and add-ons will increase in complexity, with multiple inputs or *in situ* data collection taking place at the same time. Krunoslav conducted a temperature-controlled, *in situ* synchrotron PXRD study on the effects of temperature on the kinetics of the formation of cadmium cyanoguanidine chloride coordination polymers.¹⁹⁴ There is also the above-mentioned triple coupling of synchrotron PXRD, Raman spectroscopy, and thermography to track reaction progress by Hannes.⁸²



Figure 1.24. Photo-mechanochemical setup and high throughput scanning setups. (a) Schematic illustration of five led strips fixed and mounted adjacent to the milling trajectory.²⁰⁰ (b) photos of the setup. (c) 96-well high throughput assembly for RAM.¹²³ (d) 12-jar high throughput setup for planetary milling.²⁰²

High throughput mechanochemical screening is another area of interest requiring intricate setups, with potential application in cocrystal or reaction scanning. Bysouth *et al.* was able to scan 48 samples for cocrystalliation conditions simultaneously using a vial adaptor on the planetary mill (figure 1.22d).²⁰¹ The system was used by Rotolo *et al.* for the parallel synthesis of benzoxazine derivatives.²⁰² Nagapudi *et al.* created a 96-well high throughput assembly for RAM, using it to scan for pharmaceutical cocrystals under different LAG conditions (figure 1.22c).¹²³ The widespread application of high throughput screening in mechanochemistry has thus far been limited compared to the other fields.²⁰³ In the case of cocrystal screening, the large amount of sample required (~100 milligrams) when compared to other conventional methods such as encapsulated nanodroplet crystallisation or microbatch under-oil crystallisation, which only require micrograms of material for each sample.²⁰⁴ Further miniaturisation and optimisation of milling or mixing vials for the mills will be required to make this methodology competitive. Another obstacle high throughput mechanochemistry needs to overcome to attain efficiency comparable to other solution-based methods is the integration of automated systems, from loading to milling and analysis.²⁰⁵ Current methods of

loading the milling vessels may be simple for chemists to operate, but they still represent a challenge to robots, requiring complex coordination and movement to fix or remove the vessels from the mill. Although resolving the issue of the multiplex is a task for the engineers, the feasibility of increasingly sophisticated mechanochemical setups will rely on simplifying every aspect of the machines' operation, from loading to milling to unloading.

Devices with uncomplicated movement are not only more adaptable but also easier to modify and attach add-ons and adaptors, which is essential for achieving increased sophistication and functionality. One of the best illustrations of this point is the RAM, which has a very simple vertical motion with modular and expandable features. This may explain how RAM is able to rapidly adapt the developments in mechanochemistry such as *in situ* measurements,¹²⁰ hundred-fold scaling up, ^{121,124} temperature control²⁰⁶, and high throughput scanning¹²³ within a short span of nine years since its initial introduction. A streamlined, modular, and expandable operation is therefore essential for any future mechanochemical machines to allow for customization and modifications that meet changing needs over time, without requiring extensive retooling or replacement of major components.

Readily or commercially available. The availability and accessibility of commercially available mechanochemical devices often determine their widespread use among chemists. Compared to in-house mills, commercial devices offer improved accessibility, standardization, and certification for safety, making them the preferred choice for many chemists. With the long history of mechanochemistry, most commercially available mills have been tested or considered for their viability in this field. Consequently, new mechanochemical devices or equipment are either introduced via market innovations or repurposed from existing machines.

An example of market innovation is planetary milling jars for *in situ* measurements of mechanochemistry on gaseous reactants.¹⁹² Specialised milling jars that can withstand high pressures and/or have gas valves are required to run these reactions in batches, given that a flow setup is difficult with the complex movement of a planetary mill. While some groups did not explicitly state the source of their gaseous milling jars and most likely used in-house-built jars,²⁰⁷⁻²⁰⁸ commercially available gaseous jars, and their accessories are compatible with commonly used planetary mills, supplied by the respective manufacturers.²⁰⁹ This has enabled other groups to approach this field readily and safely. These companies also engineered sophisticated accessories mounted on the milling jar that can take *in situ* measurements of temperature and pressure, before transmitting the data wirelessly to a remote desktop. This

improved the safety of the milling process and helped mechanochemists gain insights into the kinetics and thermodynamics of the mechanochemical reaction. ^{73,210} Cyro-mills which mill samples at liquid nitrogen (-196 °C) temperatures is another example of complex but commercially available setups. ²¹¹ They have been applied to the preparation of biological samples, embrittlement of inorganic materials, metals, and polymers, and mechanistic studies of mechanochemical reactions. ^{100a,212-214} Given the complexity of these setups, it is difficult for individual groups without a specialised workshop to run such reactions. Having research groups working with commercial partners is also greatly beneficial to the field, allowing the equipment to be tailored to the current needs of mechanochemists. Examples include the light, user-friendly SmartSnapTM milling jars from Form Tech Scientific^{1c} and Insolido's IST mills and jars⁶⁷ that were adapted for *in situ* monitoring.²¹⁵





Most mechanochemical devices are technically repurposed from other applications rather than being designed for mechanochemistry. For instance, twin-screw extruders are originally for the extrusion of plastic pellets, RAM was designed for the mixing of explosive powders and SpeedMixing was initially employed to homogenise viscous liquids such as paints. The single screw mechanochemical reactor was created out of a benchtop drill press. Similarly, mills were originally designed for comminution and mixing, and their use in mechanochemistry has evolved over time. The advantage of repurposing these devices is that they are already commercially available or accessible, making it easier for other research groups to adopt the technology and promote widespread standardization of mechanochemical devices. Making use of existing technology and repurposing devices should therefore take priority over building a brand new mechanochemical device from scratch to accelerate the development of mechanochemistry.

In the case whereby the device is not commercially available, a detailed schematic of the device should be provided to allow other chemists to replicate it easily. For example, Užarević *et al.* made the design of his group's PID-coupled heating jacket available online, allowing other groups to replicate the setup. ^{117,194-196} Another notable schematic online is the specialised jar for gaseous flow mechanochemistry on a mixer mill, offered in detail by the Schüth group,^{84,94,216} although its complexity has limited its manufacturing by other groups. It is important to note that commercially unavailable devices are still less desirable as in-house manufacturing has a greater risk for variability in the production process which can result in differences in performance between different copies of the device. This can make it difficult to reproduce results and can lead to inconsistencies in data and conclusions.¹⁹²

Ability to process materials and mixtures with vastly different rheology. All substances have different material properties which respond differently when placed under mechanical strain. When the powders are milled, they can undergo elastic or plastic deformation, and transform into amorphous or fluid phases. ^{37,40} This meant that the rheology of the reaction mixture changes over the course of the mechanochemical process. Hutchings et al. observed that during the mechanochemical Knoevenagel condensation between vanillin and barbituric acid performed using a mixer mill, the reaction mixture changed from a dry, free flowing powder to a cohesive rubber-like state which coated the milling ball.²¹⁴ The mixture returned to a free-flowing powder at the end of the reaction. This observation aligns with earlier research by Stolle *et al.*, who performed the same reaction on a planetary mill.¹⁸⁶ Stolle *et al.* noted that the enclosure of milling balls with cohesive substrate-product mixtures prevented movement during milling and hindered the completion of the reaction. This was only resolved by using balls of higher mass which exerts a higher force when accelerated. The addition of other liquid additives also further alters the rheology of the mixture, which can create more complications, although. It is therefore important to note that milled mixtures often do not conform to the characteristics of a perfect powder, as assumed in most simulations.²¹⁷⁻²¹⁸ Rather, they may agglomerate, forming clumps that can obstruct or block the milling process. This is detrimental to most mechanochemical processes as mechanical strain can no longer be applied to drive the

chemical transformation. Any new mechanochemical device needs to cater to a wide range of different material properties to perform a wider range of mechanochemical reactions.

Consistency, force measurements, and calibration. The reproducibility of published work is of great concern and importance to the scientific community. Michalchuk *et al.* suggested the standardisation of symbols such as milling motion, temperature, and atmosphere to help mechanochemists better communicate their milling procedures to help ensure reproducibility.³⁷ For example, the three-ball symbol was introduced by Rightmire et al. to denote any mechanochemical transformation.²¹⁹ Another example is the Bolt *et al.* also made an explicit effort to highlight the volume of the milling jar and the weight of the milling balls when illustrating the mechanochemical nickel catalysed Suzuki Miyaura reaction, given the importance of jar fill in affecting reaction outcome.¹¹⁷



Figure 1.26. (a) A piezoelectric harvesting jar²²⁰ (b) Schematic illustration of an all directional, 3D planetary mill.²²⁴

When considering the standardization and communication of mechanochemical parameters, it is important to measure and standardise the force applied by the mill on the system. Wear and tear of the machinery or incorrect milling speeds due to malfunctions are factors affecting the consistency of the milling process, even between exact copies of the same mill. However, this is rarely discussed even though variation in mechanical force is known to cause differences in reaction outcomes. In the case of a manual calibration or measurement of mechanical force, a suggestion was made by Richard Blair during the 2022 Faraday discussions, whereby a piezoelectric jar can be used to measure the amount of force applied during the milling process (figure 1.26a).²²⁰ Since the force is proportionate to the voltage generated within the jar, voltage measurements can help chemists calculate the force applied and compare it amongst machines of the same design. Another simple but effective method is to make use of slow-motion

videography, which can be done with cameras on mobile phones.²²¹ Both the displacement and the cycles per second can be measured from the video with relative ease, which can help the mechanochemist ensure the same amount of force applied between the same mills.

Some machines have inbuilt, automated systems which can provide feedback and recalibrate themselves. Examples can be found in user manuals of machines such as RAM or Restch mixer mills. It is important for users to be aware that not all mechanochemical devices are equipped with automated correction and calibration, and any future mechanochemical device need to be designed with such systems in-built.

Void zones. The last attribute any new mechanochemical device introduced needs is the minimisation or elimination of void zones. This refers to areas in which mechanochemical motion or strain does not reach. Examples include corners of cylindrical milling jars which are too small for larger milling balls to shear, preventing any mechanochemical reaction from taking place in that region. Minimisation of this zone helps to ensure homogenous dispersion within the jar, therefore improving the reproducibility of mechanochemical reactions. One of the more novel methods used to address the issue of void zones through the creation of a 3-dimension planetary mill, whereby the jars continue their dual centrifugal motion while the sun disc is rotated around a horizontal axis (figure 1.26b).²²²⁻²²⁴ Another solution is to alter the shape of the jar itself, such as the spherical design of the benchtop vibratory mill jars.²²⁵ Overall, void zones do not represent a huge hindrance for most mechanochemists and can be resolved through the additives to change the rheology of the system.

In conclusion, as the field of mechanochemistry continues to expand into diverse areas and develops increasingly intricate processes, a greater variety of devices will be designed and customized to meet the specific demands and requirements of the field. It is crucial for these new devices to be designed based on insights and best practices gleaned from the sub-fields of mechanochemistry, rather than developing in isolation, as has been the case in the past. I have identified some of these design features, such as scalability, customisability, availability compatibility with diverse rheological properties, the precision of applied forces, and the minimisation of void zones. By evolving mechanochemical devices to meet modern chemical needs, mechanochemistry can once again become ubiquitous in research labs, much like the mortar and pestle's widespread use in the past.

In the following two chapters, I explore the mechanocemical use of a machine known as the SpeedMixer for carrying out mechanochemical reactions. The SpeedMixer uses powerful dual centrifugal motion to rapidly homogenise mixtures to perform various mechanochemical transformations. In Chapter 2, the SpeedMixer was utilised in a media-less fashion in a technique termed SpeedMixing to synthesize various pharmaceutical cocrystals without the need for bulk solvents. SpeedMixing proved to be an effective technique for rapid, scalable, and selective synthesis of cocrystals, cocrystal polymorphs and stoichiomorphs, with the added benefit of eliminating media contamination concerns. In Chapter 3, the addition of milling rings into the SpeedMixer greatly amplified the mechanical energy input in the system. This new technique, termed SpeedMilling, is utilised for churning out MOFs at very high STYs. MOFs such as HKUST-1, MgMOF-74, and ZIF-8 were synthesized within a minute using this technique.

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Chapter 2: SpeedMixing: Rapid Tribochemical Synthesis and Discovery of Pharmaceutical Cocrystals without Milling or Grinding Media

This paper (*Angew. Chem. Int. Ed.* **2022**, *134*, e202206293, https://onlinelibrary.wiley.com/doi/10.1002/anie.202206293) was reproduced from Wiley. It is co-authored by Ghada Ayoub, Igor Huskić, Hatem M. Titi, Christopher W. Nickels, Brad Herrmann, Tomislav Friščić. The acknowledgement forms from co-authors areseparately provided. The text below is a copy of the published paper with slight modifications to certain abbreviations.

2.1. Abstract

SpeedMixing, a rapid blending technology, is presented as an approach for rapid mechanosynthesis and discovery of model pharmaceutical cocrystals. This approach utilises rapid spinning to synthesize pharmaceutical cocrystals based on the active pharmaceutical ingredients (APIs) carbamazepine, dihydrocarbamazepine, and nicotinamide in the absence of bulk solvents and milling/grinding media. This study demonstrates SpeedMixing as a method for rapid, scalable, as well as controllable and selective synthesis of cocrystals, cocrystal polymorphs and stoichiomorphs, including the discovery of an unexpected methanol solvate of the archetypal cocrystal of carbamazepine and saccharin, which has eluded numerous extensive screens over 20 years.

2.2. Introduction

Mechanochemical transformations, typically conducted by milling, grinding or extrusion, have attracted attention as methods for synthesis and screening of pharmaceutical solid forms (e.g. polymorphs, cocrystals, salts), as well as the synthesis of pharmaceutical fragments and individual active pharmaceutical ingredients (APIs).¹⁻³ Such transformations can be conducted neat or with a catalytic amount of a liquid additive (e.g. liquid-assisted grinding, LAG),⁴ offering a wide range of attractive opportunities for synthesis and screening. Advantages of mechanochemical transformations include fast reaction rates, high screening efficiency, ability to screen for new materials independent of relative solubilities of starting materials, and the overall absence of bulk solvents.^{4,5} However, there are concerns that grinding, milling or extrusion media that can actively participate in the transformation and produce unwanted contamination through abrasion or chipping.⁶ Such considerations have inspired the recent
search for media-free approaches for mechanosynthesis, including ageing of materials in humid air or vapors of organic solvents (e.g. accelerated ageing), enabling the preparation of cocrystals, APIs and metal-organic frameworks.⁷

Here we present a novel technique for media-free mechanosynthesis of pharmaceutical cocrystals by rapidly blending cocrystal components together using a media-less technique termed SpeedMixing, in the absence of bulk solvents. SpeedMixing is based on a dual asymmetric centrifugal (DAC) mixing technology developed for mixing of viscous materials and powders (Figure 2.1a).⁸ By avoiding milling media and mechanical impact, SpeedMixing offers an opportunity to conduct bulk mechanosynthesis in the tribochemical regime, based on fast mixing and shear forces,⁹ instead of grinding or crushing in other mechanochemical techniques.¹⁰ Through the selective synthesis of polymorphs, stoichiomorphs and novel phases of various model pharmaceutical cocrystals, we demonstrate that SpeedMixing is a rapid, highly scalable and selective technique to manufacture pharmaceutical solid forms. In particular, SpeedMixing revealed the unexpected existence of a methanol solvate of the archetypal pharmaceutical cocrystal of carbamazepine (CBZ) and saccharin (SAC): this appears to be the first reported solvate of CBZ·SAC, which is particularly surprising considering that the system has been extensively screened and regularly used as a pharmaceutical cocrystal model for almost two decades.^{11,12}

2.3. Methodology

Materials. All reagents were commercially available (except DHCBZ) and used without further purification. Commercial CBZ (99% stated purity) was purchased from TCI and used without any further purification. Commercial NIC and SAC (both >98% stated purity) were purchased from Sigma Aldrich. Commercial SUB (99% stated purity) was purchased from Alfa Aesar. All cocrystal components were dried under reduced pressure with P_2O_5 for 12 hours before use. Anhydrous methanol was dried using activated 3 Å molecular sieves for three days prior to use, while ACS- (declared water content <0.2%) and HPLC-grade methanol (declared water content <0.1%) were used without prior treatment.

Synthesis of 10,11-dihydrocarbamazepine. In a 25 mL round flask a solution of CBZ (236 mg, 1 mmol) in MeOH (5 mL), 23.5 mg (10% of CBZ by weight) 10% Pd/C and ammonium formate (630 mg, 10 mmol) was added. The mixture was stirred and refluxed for three hours. After cooling, the mixture was filtered through a celite plug and the solvent evaporated under

reduced pressure. To remaining residue a 10 mL CHCl3 was added, and the resulting slurry was filtered through a short silica gel plug. 1H NMR (300 MHz, $cdcl_3$) δ 7.46 – 7.35 (m, 2H), 7.30 – 7.14 (m, 6H), 4.79 (s, 2H), 3.43 (d, J = 6.4 Hz, 2H), 2.83 (d, J = 6.5 Hz, 2H). IR: 3470 cm⁻¹, 3341 cm⁻¹, 1648 cm⁻¹, 1560 cm⁻¹, 1486 cm⁻¹.

SpeedMixing procedure. All experiments were carried out using a Flacktek SpeedMixer, which uses DAC technology.⁸ In SpeedMixing, the sample simultaneously rotates around a central axis at a high rate, typically up to 3,500 rpm, and revolves around its own axis. In the herein developed SpeedMixing cocrystallization approach, a mixture of cocrystal components is placed in an angled polypropylene cup which is then spun clockwise around a central axis while rotating counterclockwise (Figure. 2.1a). In a typical experiment, the reaction mixture is loaded into a cup of 10, 25, or 60 mL volume, pre-mixed by SpeedMixing for 20 seconds at a rate of 3000 rpm, followed by addition of a small amount of a liquid. The quantity of the liquid additive was consistent to that in liquid-assisted mechanochemical techniques, with the η parameter – defined as the ratio of liquid volume (in μ L) to the weight of the reaction mixture (in mg), in the range of ca. 0.1–1.5 μ L/mg.⁴ In developing the SpeedMixing approach to pharmaceutical cocrystals, we focused on liquid additives acceptable in pharmaceutical manufacturing: methanol (MeOH), ethanol (EtOH), and water.¹³ SpeedMixing was performed either in a single cycle of up to 5 minutes, or in multiple 5-minute cycles separated by 3-minute periods.

Synthesis of CBZ·NIC cocrystal. A mixture of NIC (122 mg, 1 mmol) and CBZ (236 mg, 1 mmol) were loaded into a SC12 cup and placed in a speed mixer for 20 seconds at 3000 rpm. This was followed by addition of 100 μ L of MeOH into the SC12 cup and mixed for an additional two 5-minute cycles at 3000 rpm. The resulting powder was then characterized by PXRD and DSC without any further purification.

Synthesis of CBZ·SAC·MeOH. A mixture of SAC (183 mg, 1 mmol) and CBZ (236 mg, 1 mmol) were loaded into a SC12 cup and mixed for 20 seconds at 3000 rpm. Next, 200 μ L of MeOH (laboratory ACS-grade, HPLC grade or in-house dried were all equally effective) was pipetted into the cup and mixed for three minutes at 3000 rpm. The resulting powder was then characterized by PXRD and DSC without any further purification.

Synthesis of CBZ·SAC form I. A mixture of **SAC** (183 mg, 1 mmol) and **CBZ** (236 mg, 1 mmol) were loaded into a SC12 cup and mixed for 20 seconds at 3000 rpm. 200 µL of 5:1

MeOH:H2O (by volume) was then pipetted into the cup and mixed for three minutes at 3000 rpm. The resulting powder was then characterized by PXRD and DSC without any further purification.

Synthesis of CBZ·SAC form II. A mixture of SAC (183 mg, 1 mmol) and CBZ (236 mg, 1 mmol) were loaded into a SC12 cup and mixed for 20 seconds at 3000 rpm. 200 μ L of 1:2 MeOH:H2O (by vol) was then pipetted into the cup and mixed for three minutes at 3000 rpm. The resulting powder was then characterized by PXRD and DSC without any further purification.

Synthesis of DHCBZ·SAC cocrystal. A mixture of SAC (183 mg, 1 mmol) and DHCBZ (238 mg, 1 mmol) were loaded into a SC12 cup and mixed for 20 seconds at 3000 rpm. 200 μ L of MeOH was then pipetted into the cup and mixed for two 5-minute cycles at 3000 rpm, with 3-minutes delay in between. The resulting powder was then characterized by PXRD and DSC without any further purification.

Synthesis of NIC·SUB cocrystal. A mixture of NIC (122 mg, 1 mmol) and SUB (174 mg, 1 mmol) were loaded into a SC12 cup and mixed for 20 seconds at 3000 rpm. 300 μ L of MeOH was then pipetted into the cup and mixed for six 5-minute cycles at 3000 rpm, with 3-minutes of delay in-between. The resulting powder was then characterized by PXRD and DSC without any further purification.

Synthesis of 2NIC-SUB cocrystal. A mixture of NIC (244 mg, 2 mmol) and SUB (174 mg. 1 mmol) were loaded into a SC12 cup and mixed for 20 seconds at 3000 rpm. 300 μ L of MeOH was then pipetted into the cup and mixed for six 5-minute cycles at 3000 rpm, with 3-minutes of delay in-between. The resulting powder was then characterized by PXRD and DSC without any further purification.

2.4. Solid-state characterisation

All products were microcrystalline powders, characterized immediately without prior purification.

Powder X-ray diffraction (PXRD). PXRD patterns were collected on a Bruker D2 Phaser equipped with a using with a LYNXEYE detector and nickel-filtered a CuK α radiation source ($\lambda = 1.54056$ Å). The temperature was not controlled, and was measured to be between 45 °C to 50 °C.

Fourier transformation infrared attenuated total reflectance spectroscopy (FTIR-ATR). Measurements were performed on a Bruker VERTEX 70 instrument equipped with a PLATINUM diamond crystal ATR unit.

Differential scanning calorimetry (DSC). Measurements were done on a TA Instruments DSC2500 differential scanning calorimeter. Measurements were performed under a stream of nitrogen gas (50 mL/min). The sample of the cocrystal (~4 mg) was placed in a hermetically sealed aluminium pan and heated at a rate of 5 °C/min to a temperature 5 to 10 °C above the literature melting point. The sample was held at this temperature for 5 minutes before cooling down to 25 °C at 20 °C/min. For **CBZ·SAC·**MeOH, the cocrystal was rapidly cooled to -20 °C and held for 3 minutes at this temperature. The sample was heated to 150 °C at 5 °C/min. The sample was held at this temperature for 5 minutes before cooling. This cycle was repeated once more to confirm MeOH loss from the solvate.

Thermogravimetric analysis (TGA). Measurements were performed on a TA Instruments TGA5500 thermogravimetric analysis instrument. Measurements were performed under a stream of air (25 mL/min). The sample of the cocrystal (~4 mg) was placed on an open pan and heated to 500 °C at a rate of 10 °C/min.

Solid-state nuclear magnetic resonance spectroscopy (ssNMR). Spectra were acquired on a Varian VNMRS (now Agilent, Santa Clara, CA, USA) spectrometer operating at 499.9 MHz for 1H nuclei with a 3.2 mm probe. 1HNMR spectrum was acquired under spinning at 18 or 24.5 kHz, using a recycle delay of 3 s. Spectra were referenced to adamantane proton at 1.85 ppm. The 13C CPMAS spectrum was acquired on a Varian VNMRS (now Agilent, Santa Clara, CA, USA) spectrometer operating at 399.9 MHz for 1H and 100.5 MHz for 13C nuclei with a 4 mm probe. 13CNMR spectrum was acquired in 64 scans under spinning at 5 kHz, using a

recycle delay of 60 s with a contact time of 2 ms operating at 100 MHz 13C. SPINAL-64 decoupling at a rf field of 95 kHz was applied during acquisition. TOSS was used to suppress spinning side bands. Spectra were referenced using the carbonyl carbon signal in glycine at 176.4 ppm with respect to TMS.

Scanning electron microscopy (SEM). Electron microscopy images were obtained using a FEI Quanta 450 environmental SEM. Before imaging, samples were sputter coated with a 4 nm layer of metallic platinum.

Variable-temperature PXRD (VTPXRD). Experiments were performed on a Bruker D8 Advance instrument equipped with a LYNXEYE XE-T detector using nickel-filtered CuK α radiation. The setup was equipped with Anton Paar CHC plus+ chamber. Diffractograms were collected in a stepwise fashion in a dry environment. After each collection (approx. 15 min) the temperature in the chamber was raised by 1 oC (1 °C/min) and a new collection was started.

Single crystal X-ray Diffraction (SCXRD). SCXRD data were measured on a Bruker D8 Venture diffractometer equipped with a Photon 200 area detector, and IuS microfocus X-ray source (Bruker AXS, CuKα source). The single crystal of CBZ·SAC·MeOH used in the X-ray diffraction experiment was obtained by adding 24 mg of CBZ and 18 mg of SAC to 500 µL of strictly anhydrous MeOH (estimated water content below 50 ppm) in a 1-dram vial, which was then sealed, and the mixture heated until all solid dissolved. The solution was allowed to cool to room temperature and left for 24 hours. Alternatively, high-quality crystals can also be obtained by adding 50 mg of CBZ·SAC·MeOH prepared by SpeedMixing into 200 µL of strictly anhydrous MeOH in a 1-dram vial, which was sealed, heated until all solid material dissolved and then cooled to room temperature and left for 24 hours. The use of anhydrous MeOH is critical for crystal growth, as the use of other types of methanol leads to the formation of non-solvated CBZ·SAC. The measurement was carried out at 180(2)K for CBZ·SAC·MeOH crystals coated with a thin layer of amorphous oil to decrease crystal deterioration, structural disorder, or any related thermal motion effects and to improve the accuracy of the structural results. Structure solution was carried out using the SHELXTL package from Bruker. The parameters were refined for all data by full-matrix-least-squares or F2 using SHELXL. All of the nonhydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atom thermal parameters were constrained to ride on the carrier atom.

2.5. Results and Discussion

As a first trial of cocrystallization via SpeedMixing, we probed the reaction between the API **CBZ** and nicotinamide (**NIC**, Vitamin B6), anticipated to form the known pharmaceutical cocrystal **CBZ**·**NIC** (CSD UNEZES).¹⁴ The parameters affecting cocrystallization rates investigated are volume of liquid additives, mixing speeds, and time. Neat mixing of **CBZ** and **NIC** powders did not lead to cocrystal formation, with the PXRD pattern of the reaction mixture exhibiting Bragg reflections of solid reactants (Figure 2.1d). Next, we explored SpeedMixing in presence of a small amount of MeOH (50 μ L, $\eta = 0.14 \mu$ L/mg), which led to the near complete formation of **CBZ·NIC** within 10 minutes. Increasing the MeOH volume to 200 μ L ($\eta = 0.56 \mu$ L/mg) led to complete conversion. While full conversion was observed upon SpeedMixing for 10 minutes at 1000, 2000, 3000 and 3500 rpm, incomplete formation of **CBZ·NIC** was seen at 500 rpm (see appendix A).



Figure 2.1. (a) Picture of a Flacktek SpeedMixer spinning station: the cup spins in a clockwise fashion while also revolving anticlockwise around a central axis; (b) coformers and APIs used in this study; (c) selected PXRD patterns for SpeedMixing synthesis of the **CBZ**·**NIC** cocrystal, revealing complete conversion in the presence of 200 µL MeOH ($\eta = 0.56 \mu$ L/mg) on a 1 mmol (358 mg) scale, at 3000 rpm (top-to-bottom): reactants **CBZ** (Form III) and **NIC**, simulated for **CBZ**·**NIC** (CSD UNEZES), a 1:1 stoichiometric mixture of **CBZ** and **NIC** after 10 min SpeedMixing neat, 1:1 stoichiometric mixtures of **CBZ** and **NIC** after 10 min SpeedMixing with 50 ($\eta = 0.14 \mu$ L/mg), 100 ($\eta = 0.28 \mu$ L/mg) and 200 µL MeOH ($\eta = 0.56 \mu$ L/mg), and a mixture of **CBZ** and **NIC** after 3 min SpeedMixing in the presence of 200 µL MeOH ($\eta = 0.56 \mu$ L/mg).

Next, we targeted the well-known cocrystal of **CBZ** and saccharin (**SAC**). Introduced by Zaworotko in 2003, **CBZ·SAC** occupies a central place as a model pharmaceutical cocrystal in many studies,^{11,12,14} and provides an opportunity to explore SpeedMixing for selective polymorph synthesis. There are two known polymorphs of **CBZ·SAC**, the thermodynamically stable Form I (CSD UNEZAO) and the metastable Form II (CSD UNEZAO01).^{11,15} Similar to **CBZ·NIC**, neat mixing of a 1:1 stoichiometric mixture of **CBZ** and **SAC** did not lead to cocrystal formation. SpeedMixing with MeOH, however, yielded a material whose PXRD pattern was different from those of any polymorph, hydrate or MeOH solvate forms of **CBZ**, **SAC**, and **CBZ·SAC** found in the Cambridge Structural Database (CSD) (Figure 2a).¹⁶ Subsequent TGA revealed a loss of weight of ca. 5.4% around 70 °C (see appendix A), which could be consistent with a solvate of composition **CBZ·SAC**·MeOH (calc. for MeOH content: 7.1%).



Figure 2.2. (a) Selected PXRD patterns for the SpeedMixing synthesis of **CBZ**·**SAC**·MeOH (top-tobottom): reactants **SAC** and **CBZ** (Form III), simulated for **CBZ**·**SAC** Form I (CSD UNEZAO) and Form II (CSD UNEZAO01), 1:1 stoichiometric mixture of **CBZ** and **SAC** after 3 min SpeedMixing neat, with 200 μ L MeOH ($\eta = 0.48 \mu$ L/mg), and simulated for **CBZ**·**SAC**·MeOH. (b) view of the asymmetric unit of **CBZ**·**SAC**·MeOH structure, with non-hydrogen atoms shown as 50% probability ellipsoids;¹⁹ (c) fragment of the crystal structure of **CBZ**·**SAC**·MeOH, illustrating a hydrogen-bonded tape along the crystallographic b-axis. (d) Temperature-resolved *in situ* X-ray powder diffractogram of **CBZ**·**SAC**·MeOH, demonstrating conversion to **CBZ**·**SAC** Form I at ~69 °C. Crystallographic data

for **CBZ·SAC·**MeOH in CIF format has been deposited with the Cambridge Crystallographic Data Centre (deposition number 2166572).

The presence of MeOH in the product was also supported by ¹³C CP-MAS ssNMR (see appendix A) which revealed a resonance at 48 ppm, consistent with the methyl group carbon of the MeOH molecule.¹⁷ While **CBZ·SAC·**MeOH was readily obtained by SpeedMixing with conventional laboratory-grade MeOH (ACS-grade, declared water content <0.2%), attempts to grow X-ray diffraction-quality single crystals from the same solvent produced **CBZ·SAC** Form II. Only when rigorously in-house dried anhydrous MeOH (estimated water content <50 ppm)¹⁸ was used for either re-crystallization of the SpeedMixing product, or direct cocrystallization of **CBZ** and **SAC**, were crystals of **CBZ·SAC·**MeOH suitable for X-ray diffraction obtained (see appendix A).¹⁹ Importantly, simply ageing of a **CBZ** and **SAC** mixture in vapors of MeOH did not lead to any detectable formation of **CBZ·SAC·**MeOH (see appendix A), only trace amounts of **CBZ·SAC** Form II after 20 minutes. While this is consistent with our previous ageing study,^{20a} it also indicates the importance of SpeedMixing for the rapid formation of **CBZ·SAC·**MeOH and **CBZ·SAC**.

The new form CBZ·SAC·MeOH crystallizes in the P-1 space group and exhibits hydrogen-bonded tapes of CBZ dimers bridged to each other through molecules of SAC and MeOH (Figure 2.2b,c, also SI). Within a tape, each MeOH molecule acts as a donor of an O-H····O hydrogen bond to the neighboring CBZ dimer (O····O separation 2.724(2) Å), and an acceptor of an N-H···O hydrogen bond from the adjacent SAC molecule (N···O separation 2.679(2) Å). Similarly, each **SAC** molecule in a tape participates as an acceptor in an N-H···O hydrogen bond to a neighboring CBZ dimer (N···O separation 2.977(2) Å). The overall hydrogen-bonding pattern within each tape can be described as a combination of a C_3^3 (10) chain with R_2^2 (8) and R_6^8 (20) ring supramolecular synthes.²¹ The structure of CBZ·SAC·MeOH shows similarities to those of CBZ·SAC Forms I and II, which exhibit the presence of CBZ $R_2^2(8)$ dimers and chains of hydrogen-bonded CBZ and SAC molecules, respectively. Upon heating, CBZ·SAC·MeOH loses MeOH around 69 °C and transforms into **CBZ**·**SAC** Form I, as revealed by variable-temperature PXRD analysis (Figure 2.2d). Analysis of **CBZ**·**SAC**·MeOH by DSC in a sealed aluminum pan revealed a broad endothermic signal with a maximum at 68 oC (see appendix A), which was integrated to estimate the **CBZ**·**SAC**·MeOH enthalpy of desolvation of 25.4 kJ/mol.

Based on a search of the CSD, CBZ·SAC·MeOH represents the first reported solvate of the CBZ·SAC cocrystal, and this led us to investigate the possible formation of other such solvates by SpeedMixing. While a cursory screen using a set of solvents (CF₃CH₂OH, CH₃CN, n-BuOH, toluene, ethyleneglycol, CH₃NO₂, see appendix A) did not reveal any new forms of the CBZ·SAC, we observed the known CBZ·CF3CH2OH solvate (CSD SAPDUJ)²² as an intermediate in the formation of CBZ·SAC Form I (see appendix A). These experiments also revealed rapid formation of the CBZ·SAC cocrystal upon SpeedMixing, sometimes within 1 minute (see appendix A). We also expanded our screen to the related API dihydrocarbamazepine (DHCBZ), known to form structurally similar cocrystals to CBZ.²³ However, no new forms were observed beyond the known cocrystal DHCBZ·SAC (CSD code OTESEM, see appendix A).^{24a}

Table 2.1. Outcomes of SpeedMixing cocrystallization of **CBZ** and **SAC** in the presence of different volumes (V, in μ L) of either MeOH or different MeOH:H₂O mixtures as the liquid additive. The η value (in μ L/mg) is also provided for each system, and the ratios of MeOH to H₂O are based on volume. The results are each based on triplicate experiment.

V (µL)	η (μL/mg)	МеОН	5:1 MeOH: H2O	3:1 MeOH: H ₂ O	2:1 MeOH: H ₂ O	1:1 MeOH: H2O	1:2 MeOH: H ₂ O	1:3 MeOH: H ₂ O	1:5 MeOH: H2O
500	1.19	CBZ·SAC· MeOH	Form I	Form I	Form I	Form II	Form II	Form II, CBZ· 2H ₂ O	CBZ·2H ₂ O
200	0.48	CBZ·SAC· MeOH	Form I, trace II	Form I	Form I	Form II	Form II	Form II, CBZ· 2H ₂ O	Form II, CBZ· 2H ₂ O
100	0.24	CBZ·SAC· MeOH	Form I	I, trace II	Form II, trace I	Form II	Form II	Form II, CBZ·2H ₂ O	CBZ·2H ₂ O
50	0.12	CBZ·SAC· MeOH trace I	Form I, II	Form II, trace I	Form II, trace I	Form II	Form II	CBZ· 2H ₂ O , trace II	CBZ·2H ₂ O

Observation of the **CBZ·SAC·**MeOH is highly surprising, considering the central role of **CBZ·SAC** as a model pharmaceutical cocrystal over the past 20 years. Extensive previously reported solution, slurry, mechanochemical and other screens involving MeOH, including the determination of the phase diagram for the ternary system of **CBZ**, **SAC** and MeOH, did not report any other cocrystals except **CBZ·SAC** Form I or II.²⁴⁻²⁷ We note, however, that growth of single crystals of **CBZ·SAC·**MeOH required the use of anhydrous MeOH as a solvent, while analogous experiments using conventional laboratory MeOH produced Form II **CBZ·SAC**. Moreover, in our hands the attempts to synthesize **CBZ·SAC·**MeOH from laboratory- or HPLC-grade MeOH (water content <0.1%) were generally found to produce **CBZ·SAC** Form I and/or II, albeit with occasional, irreproducible appearance of the solvate. These observations indicate that traces of water hinder the solution synthesis of **CBZ·SAC·**MeOH, offering a potential explanation why this form has remained undiscovered for two decades. From that perspective, it is significant that SpeedMixing is more robust and not sensitive to trace water amounts, as seen from reproducible synthesis of **CBZ·SAC·**MeOH using either anhydrous, HPLC- or laboratory-grade MeOH (see appendix A).

Next, we conducted an extensive screen for SpeedMixing cocrystallization of **CBZ** and **SAC** with either anhydrous MeOH, or specific MeOH:H2O mixtures as the liquid additive, at a range of η -values. The screen (Table 2.1, Figure 2.3, also appendix A) showed that the presence of larger amounts of water can be used to drive the selective SpeedMixing synthesis of either Form I or Form II **CBZ·SAC** polymorphs within 3 minutes. Specifically, MeOH with a low water content led to reproducible appearance of Form I, while increased water amounts produced the metastable Form II. Finally, high water contents produced the hydrate **CBZ·2**H2O. In all cases, SpeedMixing for 5 minutes or longer led only to Form I (Figure 2.3). A sample of **CBZ·SAC** Form I, synthesized by SpeedMixing in the presence of a 5:1 by volume mixture of MeOH and H2O, was also significantly smaller (<2µm) than those found, in a physical mixture of **CBZ** and **SAC** which was made by 20-second SpeedMixing without a liquid and exhibited particles tens of micrometers in size.



Figure 2.3. Schematic overview of transformations of **CBZ** and **SAC** by liquid-assisted SpeedMixing in the presence of MeOH or different MeOH:H₂O mixtures, producing **CBZ·SAC** Forms I or II, **CBZ·SAC·**MeOH, or **CBZ·**2H₂O.

Next, we explored the applicability of SpeedMixing to selectively synthesize cocrystals composed of identical components, but in different stoichiometric ratios (stoichiometric variations, stoichiomorphs).²⁸ As a model we selected the well-known system of **NIC** and

suberic acid (**SUB**).²⁹ The two components are known to form cocrystals of compositions **NIC·SUB** and **2NIC·SUB** (CSD NUKZAV01, NUKZES01, respectively). Varying the time and η -value revealed that each cocrystal can be accessed selectively and in complete conversion by SpeedMixing in the presence of MeOH ($\eta = 1.54 \mu$ L/mg) of the components in appropriate stoichiometric ratio within 45 minutes, i.e. through six consecutive cycles of SpeedMixing (Figure 2.4). In contrast, simply ageing^{7,20} the reaction mixtures for 45 minutes in MeOH vapor led to the formation of only small amounts of **NIC·SUB**, regardless of mixture composition (see appendix A). These observations again indicate the importance of SpeedMixing mechanical treatment for both rapid and selective cocrystal formation (see appendix A).

Higher and more selective cocrystal conversions, with only weak signals of reactants in the PXRD pattern, were obtained even if SpeedMixing was conducted for only 1 minute, followed by 44 minutes resting (see appendix A). Importantly, under such conditions PXRD analysis of the mixture with initial 2:1 stoichiometry of **NIC** and **SUB** reveals low-intensity signals of **NIC·SUB** besides the stronger ones of 2NIC**·SUB**. In contrast, no 2NIC**·SUB** was seen in the mixture with initial 1:1 composition. Such behavior at short SpeedMixing times resembles ball milling, where **NIC·SUB** appears during the formation of 2NIC**·SUB**, but synthesis of **NIC·SUB** proceeds without any other forms.^{29,30}



Figure 2.4. (a) Selected PXRD patterns illustrating the selective synthesis and scaling-up of stoichiometric variations of the NIC·SUB cocrystal (top-to-bottom): simulated for 2NIC·SUB (CSD NUKZEZ01); a 2:1 stoichiometric mixture of NIC and SUB (1 mmol scale) after SpeedMixing for six 5-min cycles; a 2:1 stoichiometric mixture of NIC and SUB (1 mmol scale) after SpeedMixing for 1 min and static ageing for 44 min; simulated for NIC·SUB (CSD NUKZAV01); a 1:1 stoichiometric mixture of NIC and SUB (1 mmol scale) after SpeedMixing for 1 mixture of NIC and SUB (1 mmol scale) after SpeedMixing for 3 mixture of NIC and SUB (1 mmol scale) after SpeedMixing for 44 min; simulated for SpeedMixing for six 5-min cycles, 1:1 stoichiometric mixture of NIC and SUB (1 mmol scale) after SpeedMixing for 44 min; a 1:1

stoichiometric mixture of **NIC** and **SUB** (25 mmol scale) after SpeedMixing for six 5-min cycles in a 25 mL cup; a 1:1 stoichiometric mixture of **NIC** and **SUB** (50 mmol scale) after SpeedMixing for six 5-min cycles in a 60 mL cup; a 1:1 stoichiometric mixture of **NIC** and **SUB** (75 mmol scale) after SpeedMixing for six 5-min cycles in a 60 mL cup. (b) Comparison of η -values (lines) and final temperature (vertical bars) in experiments that led to full conversion into **NIC**·**SUB** at different scales, using MeOH (10 mL, 25 mL cup) or EtOH (60 mL cup) as the liquid additive.

Finally, we explored the scaling-up of SpeedMixing cocrystallization, by systematically increasing the sizes of each batch of NIC-SUB. The systematic variation of reaction cup sizes from 10 mL to 60 mL and adjustment of η -values enabled a ca. 70-fold scaling-up of synthesis, from 300 mg to 22 g, within the same time period as smaller scale reactions. The systematic exploration of reaction conditions also revealed that the η -value required for complete conversion into NIC·SUB, based on PXRD analysis, decreases with an increase in reaction scale. Consequently, cocrystal formation by liquid-assisted SpeedMixing appears to become increasingly efficient at larger scales, and required less liquid additive. The increase in efficiency could also be related to a mild increase in the reaction mixture temperature at larger scales: measuring the temperature of the mixing cup immediately after SpeedMixing using an infrared thermometer ³¹ revealed temperatures around 28-30 °C for reactions in a 10 mL cup, and 37-42 °C when using a 60 mL cup (Figure 2.4b). This exploration also reveals that increasing the amount of material to occupy more than ca. one-third of the SpeedMixing cup leads to poorer reactivity and loss of homogeneity. This problem was overcome either by increasing the η -value (Figure 2.4b) or by using a larger cup. The latter approach, however, led to more significant evaporation of the liquid additive which was countered by replacing MeOH with EtOH.

In summary, we have demonstrated the use of the dual asymmetric centrifugal mixing (SpeedMixing), initially developed for blending of viscous and soft materials, as a route to conduct rapid, controllable synthesis, and even discovery, of solid API forms. SpeedMixing cocrystallization operates without bulk solvents, using conditions typically found in liquid-assisted mechanochemistry, but also without grinding or milling media. By relying only on rapid mixing in the absence of any grinding media, the SpeedMixing approach represents a unique⁹ route to bulk synthesis based on tribochemical effects, i.e. by shear and rubbing of particles, without impact and crushing present in other mechanochemical techniques such as milling.¹⁰ Compared to other emergent solvent-free, media-free approaches for synthesis and discovery of solid API forms, e.g. accelerated aging, acoustic mixing or vapor-assisted

tumbling, SpeedMixing is rapid, enables small-scale experiments within 3-5 minutes, and syntheses at tens of grams scale within 45 minutes. We show that SpeedMixing also permits selective synthesis of stoichiomorphs, polymorphs and solvates of APIs or API cocrystals. Notably, SpeedMixing led to the discovery of the first solvate of the archetypal pharmaceutical cocrystal **CBZ·SAC**. The synthesis of this new form from solution appears to be strongly sensitive to traces of water, which has likely played a role in preventing its discovery so far. SpeedMixing, in contrast, was much less sensitive to the presence of moisture, enabling the first observation and reproducible synthesis of **CBZ·SAC**·MeOH. This, and the ability to selectively obtain **CBZ·SAC** polymorphic Forms I and II, present SpeedMixing as a rapid, simple, 'soft' and, importantly, controllable route for the synthesis and discovery of new pharmaceutical forms, even in previously already well-explored cocrystal systems.

2.5. Acknowledgements

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27. The unexpected nature of **CBZ·SAC·**MeOH discovery is illustrated by a report of a previous highthroughput screen which also included MeOH:26 "...in the case of the 1:1 cocrystal of carbamazepine and saccharin (Form I), an extensive polymorphic screen was conducted on one form. By means of high-throughput crystallization, 480 experiments including saccharin and carbamazepine in various solvents and solvent mixtures were performed, yielding 156 solid materials which were characterized by XRPD or Raman spectroscopy. No polymorphic forms of the cocrystal were observed. Additionally, solvent-assisted mechanical grinding experiments were tried, using 24 different solvents. The remaining solids were characterized by XRPD, resulting, once again, in only the original cocrystal form."

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Chapter 3: SpeedMilling: Minute synthesis of Metal Organic Frameworks

The work presented in this chapter has been prepared for publication in a manuscript titled "SpeedMilling: Minute synthesis of Metal Organic Frameworks", co-authored by Dr H.M. Titi, J. Marrett, C. W. Nickels and Prof T. Friščić. The manuscript was written and edited jointly by Y. Teoh, by Dr H.M. Titi and Prof. T. Friščić, and the experiments and subsequent analysis were performed by Y. Teoh and J. Marrett. The results described in the manuscript have been expanded with additional data, including the data from Supplementary Information, for the purpose of being incorporated in this Thesis.

3.1. Abstract

This work introduces SpeedMilling, a novel, high-energy milling technology as an approach for the gram-scale mechanosynthesis of metal-organic frameworks (MOFs) without the need for bulk solvents. Up to 10 grams of archetypal MOFs such as Mg-MOF-74, ZIF-8 and HKUST-1 were synthesized within a minute. The results demonstrate SpeedMilling as a methodology for the synthesis of MOFs at an unprecedented space-time yield.

3.2. Introduction

Mechanochemical synthesis using grinding, milling or extrusion processes, is an attractive method for the large scale synthesis of metal organic frameworks (MOFs).¹⁻⁴ The exclusion of bulk solvents from mechanochemical processes not only makes it a greener approach but also reduces the size of the reaction vessel, therefore greatly improving the space-time-yield (STY) when compared to conventional solution-based solvothermal approaches.^{5,6} In addition, mechanochemical reactions occur independently of the solubilities of the reagents, allowing highly insoluble and cheap starting materials such as metal oxides to be utilized as precursors for MOFs synthesis. Mechanochemical transformations are typically performed at a laboratory scale using vibratory or planetary ball mills. While the milling media (milling balls) is critical in the transfer of mechanical energy within these mills, they occupy a significant volume within the milling vessel. A solution recently explored by our group is the use of media-less mechanochemical methodologies such as SpeedMixing and Resonant acoustic mixing (RAM).^{8,9} These 'soft' or 'gentle' techniques utilizes tribochemical effects, *i.e.* shear and rubbing to drive mechanochemical reactions without any milling media, further

improving the space-time yields and energy efficiency of the reaction compared to conventional mechanochemical techniques.

In cases whereby highly inactivated reagents such as metal oxides are used as precursors to MOFs, the higher energy barriers necessitate the application of harsher mechanochemical conditions.¹⁰ A new methodology, SpeedMilling, adds milling rings to the powerful dual centrifugal motion of SpeedMixing (figure 3.1a and 3.1b) to enhance mechanical energy input.

As a further development for scalable, inorganic mechanochemical synthesis, we applied SpeedMilling to the synthesis of various archetypical MOFs such as ZIF-8, MOF-74 and HKUST-1.¹¹⁻¹⁴ The switch to milling rings increases the surface area of contact between milling media and the milled powder and combined with the effective, high speed mixing motion of SpeedMixing, enables us to rapidly synthesize MOFs from inactivated starting materials (such as metal oxides) within one to three minutes, generating a high STY for MOF synthesis.⁶

3.3. Methodology

Materials. All reagents were commercially available and used without further purification. 2,5-dihydroxyterephalitic acid was purchased from Biosynth, while all other chemicals were purchased from Sigma Aldrich. Magnesium oxide was activated in a furnace at 680 °C for 2 hours.1 All solvents were purchased from Fisher and dried using activated 3 Å molecular sieves for three days prior to use.

SpeedMixing procedure. All experiments were carried out using a Flacktek SpeedMixer. In SpeedMilling the sample jar simultaneously rotates around a central axis and revolves around its own axis at high speeds. In the herein developed SpeedMilling approach, the metal salt, ligand, liquid additive, and three to four milling rings are placed in an angled stainless steel milling jar which is then spun clockwise around a central axis while rotating counterclockwise (Figure. 3.1a, 3.1b), typically at a speed of 2500 rpm for one to three minutes. The quantity of the liquid additive was consistent to that in liquid-assisted mechanochemical techniques, with the η parameter – defined as the ratio of liquid volume (in μ L) to the weight of the reaction mixture (in mg), in the range of ca. 0.37–1.11 μ L/mg. Methanol is typically used as the liquid additive.

SpeedMilling synthesis of Mg-MOF-74. 3.96g of H2dhta (20 mmol, 1 eq) and 1.61g of MgO (40 mmol, 2 eq) were placed in the milling jar along with 4 milling rings (see figure 2). 4 mL of MeOH was added into the jar and the mixture was milled for 1 minute. The crude sample was analysed by PXRD, then washed with DMF twice. The powder was then soaked in 200 mL of DMF for 12 hours, MeOH for 12 hours, then acetone for 12 hours before being dried under vacuum at 120°C overnight to obtain a clean sample of Mg-MOF-74 used for characterisation.

SpeedMilling synthesis of Zn-MOF-74. 2.97g of H2dhta (15 mmol, 1 eq) and 2.44 g of ZnO (30 mmol, 2 eq) were placed in the milling jar along with 4 milling rings (see figure 2). 4 mL of MeOH was added into the jar and the mixture was milled for 3 minutes. The crude sample was analysed by PXRD, then washed with DMF twice. The powder was then soaked in 200 mL of DMF for 12 hours, MeOH for 12 hours, then acetone for 12 hours before being dried under vacuum at 120°C overnight to obtain a clean sample of Zn-MOF-74 used for characterisation.

SpeedMilling synthesis of ZIF-8. 4 g of 2-methylimidazole (48 mmol, 2.1 eq), 1.89 g of ZnO (23.2 mmol, 1 eq) and 295 mg (< 5 wt %) of NH4NO3 were placed in the milling jar along with 4 milling rings (see figure 2). 3 mL of MeOH was added into the jar and the mixture was milled for 1 minutes. The crude sample was analysed by PXRD, then washed with MeOH twice. The powder was then soaked in 200 mL of MeOH for 12 hours, then acetone for 12 hours before being dried under vacuum at 80°C overnight to obtain a clean sample of ZIF-8 used for characterisation.

SpeedMilling synthesis of HKUST-1. 3 g of trimesic acid (15 mmol, 1.5 eq) and 2.1 g of CuSO4·H2O (23.2 mmol, 1 eq) were placed in the milling jar along with 4 milling rings (see figure 2). 2 mL of MeOH was added into the jar and the mixture was milled for 1 minutes. The crude sample was analysed by PXRD, then washed with MeOH twice. The powder was then soaked in 200 mL of MeOH for 12 hours, then acetone for 12 hours before being dried under vacuum at 80°C overnight to for a clean sample of HKUST-1 used for characterisation.

SpeedMilling synthesis of RHO-MOF. 4 g of 2-methylimidazole (42 mmol, 2.1 eq), 1.89 g of ZnO (23.2 mmol, 1 eq) and 295 mg (< 5 wt %) of NH4NO3 were placed in the milling jar along with 4 milling rings (see figure 2). 3.5 mL of MeOH was added into the jar and the mixture was milled for 1 minutes. The crude sample was analysed by PXRD, then washed with MeOH twice. The powder was then soaked in 200 mL of MeOH for 12 hours, then acetone for

12 hours before being dried under vacuum at 80°C overnight to obtain a clean sample of RHO-MOF used for characterisation.

3.4. Solid-state Characterisation

All products were microcrystalline powders, characterized immediately after SpeedMilling without prior purification.

Fourier transformation infrared attenuated total reflectance spectroscopy (FTIR-ATR). Measurements were performed on a Bruker VERTEX 70 instrument equipped with a PLATINUM diamond crystal ATR unit.

Powder X-ray diffraction (PXRD). PXRD patterns were collected on a Bruker D2 Phaser equipped with a using with a LYNXEYE detector and nickel-filtered a CuK α radiation source ($\lambda = 1.54056$ Å). The temperature was not controlled, and was measured to be between 45 °C to 50 °C.

Thermogravimetric analysis (TGA). Measurements were performed on a TA Instruments TGA5500 thermogravimetric analysis instrument. Measurements were performed under a stream of air (25 mL/min). The samples (~5 mg) were placed on an open platinum pan and heated to 700 $^{\circ}$ C at a rate of 10 $^{\circ}$ C/min.

Scanning electron microscopy (SEM). Electron microscopy images were obtained using a FEI Quanta 450 environmental SEM. Before imaging, samples were sputter coated with a 4 nm layer of metallic platinum.

3.5. Results and discussion

As the first trial for SpeedMilling, we used the reaction between magnesium oxide (MgO) and 2,5-dihydroxyterephaltic acid (H₂dta) to form Mg-MOF-74 (figure 3.1c) to investigate the principal parameters expected to affect reaction kinetics, namely the amount of liquid additive, milling speed and configuration of milling rings (see figure 3.2a).¹⁶ Initial neat SpeedMixing (media-less mixing of the reactants using the SpeedMixer) at 3500 rpm for 5 min did not result in any reaction, as evidenced by the PXRD pattern of the reaction mixtures exhibiting only Bragg reflections of solid reactants (figure 3.1d). Note that neat SpeedMilling did not result in the formation of any Mg-MOF-74. Only after the addition of 2 mL of MeOH ($\eta = 0.37 \mu$ L/mg) the formation of Mg-MOF-74 was observed within SpeedMilling di one minute. The reaction was optimized at 4 mL of MeOH ($\eta = 0.74 \mu$ L/mg) enabling the reaction to be completed within a minute on a 5-gram scale. On the other hand, using any excess MeOH of 6 mL or more slows the formation of the MOF.¹⁷

Next, we studied how different combination and arrangement of milling rings affects the rate of the reaction. The three different combinations of milling rings used in this study are shown below in figure 3.2a. The eccentric (4 rings) arrangement was the default arrangement used in the optimization of η value. We first switched to a concentric (3 rings) arrangement of near identical mass to study the effect of ring arrangement on reaction rates, as media mass is strongly correlated to rates of mechanochemical reactions.¹⁶ As the switch from an eccentric arrangement to a concentric arrangement of the rings would most likely alter motion of the rings from an energetic cascading/cataracting motion to a milder rolling motion, we expected the reaction rate to be slightly slower. As expected, the reaction remains incomplete after milling for one minute. In agreement with most mechanochemical studies, when the total mass of milling media was reduced by switching to a 25% lighter eccentric (3 rings) arrangement, the reaction remains incomplete after milling for one minute, although this is beyond the bounds recommended by the manufacturer.



Figure 3.1. (a) Dual asymmetrical centrifugal motion of the SpeedMixer (white and black arrows) acting on the SpeedMilling setup (jar and milling rings in the centre). (b) SpeedMilling rings, jar and adaptors for SpeedMilling setup. (c) Schematic illustration of the synthesis of Mg and Zn-MOF-74. d) Selected PXRD patterns for SpeedMixing synthesis of Mg-MOF-74 revealing a complete conversion within a minute of milling with 4 mL of MeOH ($\eta = 0.73 \mu L/mg$). From top to bottom: Simulated pattern for Mg-MOF-74 (CSD TODYUJ), a 2:1 stoichiometric mixture of H₂dta and MgO i) SpeedMixed (no milling rings) neat for 5 min, ii) SpeedMilled neat for 1 min, iii) SpeedMilled with 2 mL of MeOH for 1 min, iv) SpeedMilled with 5 mL of MeOH for 1 min, v) SpeedMilled with 4 mL of MeOH for 1 min, v) sample of (v) after being washed and dried, commercial MgO, commercial H₂dta.

We were interested in synthesizing Zn-MOF-74, which is a structural analogue of Mg-MOF-74. The product was formed by milling zinc oxide and **H2dta**. Given the lower basicity of ZnO compared to MgO, the reaction was significantly slower, failing to complete within one minute, even after a scan of different liquid additives and η -values. The milling time was progressively extended, and the reaction was complete after milling for 3 one-minute cycles, with 5 minutes of rest in between. Similarly, a single milling cycle of three minutes is required to complete the reaction, indicating the lack of reaction progress with the lack of milling.

Ring system	Total mass of milling media/g	Speed/rpm	Temperature/°C	
Eccentric 4 rings	46	2500	60	
Concentric 3 rings	44.5	2500	56	
Eccentric 3 rings	34.45	2500	55.7	
		2750	65.9	

Table 3.1. Summary of mass of the milling rings and the resulting temperatures when the respective ring systems are used to synthesize Mg-MOF-74.

Switching from ditopic to tritopic carboxylic acid-based linkers, we explored the synthesis of copper(II) trimesate framework material HKUST-1, based on copper(II) paddlewheel nodes, from copper(II) acetate and trimesic acid.¹⁸ The formation of HKUST-1 was rapid, with near complete conversion within one minute when a 3:2 stoichiometric ratio of copper (II) acetate and trimesic acid was SpeedMilled, with some copper (II) acetate left in the system (Figure 3.3). Regardless of the excess of trimesic acid added or extended milling time or even when the liquid additive was changed, copper (II) acetate remains in the system. This is likely due to the rapid formation of the HKUST-1, which results in the trapping of trimesic acid within the pores of the MOF, preventing the complete conversion and leaving residual copper(II) acetate in the system (the excess of copper salt was easily washed off using methanol). Given the ease of formation of HKUST-1, we also doubled the scale of the reaction from 5 g to 10 g without any change in parameters. Further scale-up was limited by the volume of the milling jar.



Figure 3.2. (a) The different arrangement and combination of milling rings. (b) Selected PXRD patterns for the synthesis of Mg-MOF-74 using different ring arrangements and combinations. From top to bottom: Simulated pattern for Mg-MOF-74, a 2:1 stoichiometric mixture of MgO and H_2dta SpeedMilled for 1 minute with i) eccentric (4 rings) at 2500 rpm, ii) concentric (3 rings) at 2500 rpm, iii) eccentric (3 rings) at 2500 rpm, SpeedMilled with eccentric (3 rings) at 2750 rpm, commercial H_2dta and commercial MgO. (c) Selected PXRD patterns for the synthesis of Zn-MOF-74. From top to bottom: Simulated pattern for Zn-MOF-74, a 2:1 stoichiometric mixture of ZnO and H_2dta SpeedMilled with eccentric (4 rings) for i) one minute, ii) two one-minute cycles with 5-minute rest in between, iii) three one minute cycles with 5-minute rest in between, iv) sample from (iii) washed and soaked in MeOH overnight, v) three minutes, commercial sample of H_2dta , a commercial sample of ZnO.



Figure 3.3. (a) Schematic illustration of the synthesis of HKUST-1. (b) Selected PXRD patterns for the synthesis of HKUST-1. From top to bottom: simulated pattern for HKUST-1, a 3:2 stoichiometric mixture of copper(II) acetate and trimesic acid i) speedmilled for one minute, ii) sample of (i) after washing, iii) double the scale SpeedMilled for one minute, iv) sample of (iii) after washing, commercial trimesic acid, commercial copper(ii) acetate hydrate.



Figure 3.4. a) Schematic illustration of the synthesis of ZIF-8 and RHO MOF. b) Selected PXRD patterns for the synthesis of ZIF-8. From top to bottom: simulated pattern for ZIF-8, the simulated pattern for ZIF-L, a 2:1 stoichiometric mixture of 2-methyl imidazole and zinc oxide i) SpeedMilled with catalytic amounts of ammonium nitrate for 1 minute at 2500 rpm, ii) a sample from (i) after washing with methanol and soaking for 12 hours, iii) SpeedMilled with 5 w.t. % of ammonium nitrate for 1 minute at 2500 rpm, iv) SpeedMixed with catalytic amounts of ammonium nitrate for 1 minute at 2500 rpm, commercial 2-methyl imidazole, commercial zinc oxide.

Finally, we also were interested to explore MOFs based on non-carboxylic linkers such as imidazole molecules forming zeolitic imidazolate frameworks (ZIFs), we explored the synthesis of SOD-Zn(2-methylimidazolate)₂, a.k.a. ZIF-8 (Figure 4) from zinc oxide and 2-methyl imidazole to verify if the mehodology is broadly applicable to other types of MOFs.¹⁹ The formation of ZIF-8 was significantly easier and faster than Mg/Zn-MOF-74, and a near complete conversion was attained simply by SpeedMixing at 2500 rpm for one minute a 2:1 stoichiometric mixture of 2-methyl imidazole and zinc oxide, catalyzed by 2.5 w.t.% of ammonium nitrate and methanol as a liquid additive ($\eta = 0.51 \mu L/mg$). However, any further

conversion was slow as the ZIF-8 formed as a single chunk, hindering any further mixing of the unreacted reagents. SpeedMilling the exact composition for one minute at 2500 rpm yields a clean sample of ZIF-8, which was verified after washing by TGA and IR spectroscopy. The addition of an excess of more than 5 w.t.% ammonium nitrate results in the formation of ZIF-L, a two-dimensional zeolitic framework, likely due to the formation of zinc nitrates which are more reactive and selective towards the formation of ZIF-L. Switching 2-methylimidazole for 2-ethylimidazole also yields RHO-Zn(2-ethyl imidazolate)₂ under similar conditions (see Appendix B).



Figure 3.5. SEM images of samples prepared by SpeedMilling. In each case the bar corresponds to 500nm.

The morphology of the SpeedMilling products was studied by SEM (Figure 4a), revealing hexagonal particles for Zn-MOF-74, ZIF-8 and HKUST-1 while Mg-MOF-74 consists of flaky particles. Amongst the MOFs which formed hexagonal particles, Zn-MOF-74 and ZIF-8 tend to form hexagonal rods, while HKUST-1 remains granular. The sizes ranges from 80 to 800nm for Mg-MOF-74 and ZIF-8, while it ranges from 100-400nm for Zn-MOF-74 and HKUST-1. The particles sizes are summarized alongside the measured BET surface area in Table 2 below.

MOF	Measured BET area (m ² g ⁻¹)	Typical literature BET area (m ² g ⁻¹)	Particle size (nm)
Mg(dta) ₂ (Mg-MOF-74)	600	800^{20}	80 - 800
Zn(dta) ₂ (Zn-MOF-74)	1020	702 ²¹	100 - 400
Zn(MeIm) ₂ (ZIF-8)	1240	1413 ²²	80 - 800
Cu ₂ (Tms) ₃ (HKUST-1)	1025	933 ²³	100 - 400
Zn(EtIm) ₂ (RHO)	920	1030 ²⁴	60 - 180

Table 3.2. Measured BET surface areas and typical particle sizes (by SEM) for selected samples of microporous MOFs prepared using SpeedMilling, after washing and evacuation.

In summary, we have demonstrated that the combination of dual centrifugal spinning with milling rings (SpeedMilling) is able to synthesize MOFs on the gram scale within one to three minutes. This rapid synthesis methodology operates without the need for bulk solvents and is broadly applicable to the synthesis of various MOFs.

3.6 References

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Chapter 4: Conclusion and contribution to knowledge

Mechanochemistry is increasingly viewed as a versatile synthetic methodology with advantages such as improved reaction efficacy, elimination of bulk solvents, bypassing solubility concerns and having unique reaction selectivity. However, while looking at the chemical outcomes of mechanochemistry, it is important not to neglect the fact that mechanochemical phenomenon is intrinsically tied to physical and mechanical inputs. The design and operation of mechanochemical devices will have a significant impact on mechanochemical reaction outcomes. In this thesis, mechanochemistry is viewed from the unique viewpoint of mechanochemical devices.

Specifically, the development and modification of the mills was looked at in detail. Drawing lessons from these developments, traits such as scalability, ease of modification, ease of access, adaptability to different rheology and lack of 'deadzones' were identified as critical elements in any future mechanochemical tools for synthesis. These characteristics are not particularly novel, with numerous different examples described in the thesis of equipment built or modified by engineers and mechanochemists with these features. By creating the comprehensive list above, I hope that future introduction of any mechanochemical devices can encompass the features required to exploit developments in the field.

In the context of new mechanochemical devices, the SpeedMixer, which was originally a mixer for highly viscous paints was adapted as a tool for mechanochemical transformation. A new technique, termed 'SpeedMixing' was developed, using the powerful dual centrifugal motion of the SpeedMixer to rapidly blend components together with a catalytic amount of liquid additive. SpeedMixing proved highly efficient in selectively synthesizing various pharmaceutical solid forms such as cocrystals, cocrystal polymorphs and stoichiomorphs. Scanning of various model pharmaceutical cocrystal systems also lead to the discovery of an unexpected methanol solvate of the archetypal cocrystal of carbamazepine and saccharin, which has eluded numerous extensive screens over 20 years.

SpeedMilling, which adds milling rings to the SpeedMixer to enhance the mechanical energy input. SpeedMilling was applied to the synthesis of various MOFs such as ZIFs, MOF-74 and HKUST-1. The significant increase in mechanical energy input from the milling rings, combined with the powerful dual centrifugal motion synthesized the MOFs within one minute, compared to the hours of conventional milling and the days required when using solution-based methods.

Overall, the SpeedMixer fulfils most of the features listed above that are required of modern mechanochemical devices. In the context of SpeedMixing, the work outlined in this Thesis has demonstrated that it is a scalable process, scaling 75-fold without any change to the operating procedure and minimal re-optimisation. The SpeedMixer is also adapted from commercial uses, making it a highly available and accessible option. The ease of operation allowed it to rapidly screen for conditions, which led to the discovery of the novel CBZ·SAC·MeOH cocrystal solvate. It has also been proven to be able to handle a wide range of rheology, from mixing soft materials such as cocrystals, to processing hard, inorganic oxides to form MOFs. Finally, the SpeedMixer is also highly adaptable, able to operate with or without any milling media.

Most mechanochemical devices that are commonly used in laboratories nowadays were designed decades ago. They were not explicitly designed for mechanochemistry, but adapted for the field. Given the recent growth in the mechanochemical field and the numerous developments in mechanochemistry, new devices will have to be developed and adapted to suit the expanding needs of the field. I believe that the future of mechanochemistry depends on new mechanochemical devices.

Appendix A.

This appendix contains additional data, along with additional references, that support findings and conclusions presented in Chapter 2 of this Thesis, but for reasons of brevity and coherence were not included in the main body of the text.

The CBZ·NIC cocrystal system

S1.1 PXRD patterns for the synthesis of CBZ·NIC cocrystal



Figure S1. PXRD patterns relevant for the SpeedMixing synthesis of **CBZ**·**NIC** cocrystal (CSD UNEZES) (top-to-bottom): **a**) simulated for **CBZ**·**NIC**; **b**) a 1:1 stoichiometric mixture of **CBZ** and **NIC** after SpeedMixing for 3 minutes in presence of MeOH, which shows the formation of **CBZ**·**NIC** and traces of **NIC** present in the mixture and **c**) after two 5-minute SpeedMixing cycles in presence of MeOH, which shows the complete formation of **CBZ**·**NIC**; reactants **d**. **NIC** and **e**. **CBZ** (Form III).



Figure S2. PXRD patterns for a 1:1 stoichiometric mixture of CBZ and NIC after SpeedMixing at different mixing rates over two 5-minute cycles in presence of MeOH to form CBZ·NIC (top-to-bottom): a) simulated for CBZ·NIC; a 1:1 stoichiometric mixture of CBZ and NIC after SpeedMixing at b) 500 rpm, which still has traces of NIC present in the mixture, c)1000 rpm, d) 2000 rpm, e) 3000 rpm, f) 3500 rpm; reactants g) CBZ (Form III) and h) NIC.



Figure S3. PXRD patterns for a 1:1 stoichiometric mixture of **CBZ** and **NIC** after SpeedMixing for two 5-min cycles in presence of different volumes of MeOH to form **CBZ·NIC** (top-to-bottom): **a**) simulated for **CBZ·NIC**; reaction mixture after SpeedMixing with **b**) 50 μ L ($\eta = 0.14 \mu$ L/mg), which has trace **NIC** in the mixture, **c**) 100 μ L ($\eta = 0.28 \mu$ L/mg), which has trace **NIC** in the mixture, **and d**) 200 μ L ($\eta = 0.56 \mu$ L/mg) MeOH; reactants **e**) **CBZ** (Form III) and **f**) **NIC**.
S1.2 FTIR-ATR spectra of CBZ, NIC and CBZ·NIC cocrystal



Figure S4. Comparison of FTIR-ATR spectra of (top-to-bottom): CBZ, NIC, and CBZ·NIC cocrystal made by SpeedMixing.



S1.3 Differential scanning calorimetry (DSC) of CBZ·NIC cocrystal

Figure S5. DSC thermogram of **CBZ·NIC** cocrystal. Sample was treated by temperature ramp from 25 °C to 165 °C, 5 °C/min, then held isothermally at 165 °C for 5 mins before cooling down to 25 °C at 20 °C/min. Melting point of 157 °C agrees well with the literature value of 158° C.^[4]



S2.1 PXRD patterns for the synthesis of CBZ·SAC·MeOH, and CBZ·SAC cocrystal forms I and II

Figure S6. Comparison of PXRD patterns for materials synthesized using different MeOH/H₂O volume mixtures as liquid additives (from top-to-bottom): a) reactants CBZ and b) SAC; c) 1:1 stoichiometric mixture of CBZ and SAC after SpeedMixing with 200 μ L anhydrous MeOH forming CBZ·SAC·MeOH, d) simulated for CBZ·SAC·MeOH, e) 1:1 stoichiometric mixture of CBZ and SAC after SpeedMixing with 200 μ L of a 5:1 MeOH:H₂O mixture forming CBZ·SAC Form I, f) simulated for CBZ·SAC Form I, g) 1:1 stoichiometric mixture of CBZ and SAC after SpeedMixing with 200 μ L of 1:2 MeOH:H₂O mixture forming CBZ·SAC Form II, h) simulated for CBZ·SAC Form II, i) 1:1 stoichiometric mixture of CBZ and SAC aged in MeOH vapor for 3 minutes, j) 1:1 stoichiometric mixture of CBZ and SAC aged in MeOH vapor for 20 minutes.



Figure S7. PXRD pattern of different materials obtained by mixing a 1:1 stoichiometric mixture of **CBZ** and **SAC** with 50 µL of different MeOH:H₂O volume mixtures (top-to-bottom): **a**) simulated for **CBZ**·SAC Form I, **b**) simulated for **CBZ**·SAC Form II. <u>Triplicates</u> for reaction mixtures after SpeedMixing with 50µL of **c**-**e**) a 5:1 mixture of MeOH:H₂O, forming **CBZ**·SAC Form I and II, **f**-**h**) a 3:1 mixture of MeOH:H₂O, forming **CBZ**·SAC Form I and II, **i**-**k**) a 2:1 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:1 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:1 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O, forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O forming **CBZ**·SAC Form II, **n** a 1:3 mixture of MeOH:H₂O forming **CBZ**·SAC Form II.



Figure S8. PXRD pattern of a 1:1 stoichiometric mixture of **CBZ** and **SAC** after SpeedMixing with 100µL of different MeOH:H₂O volume mixture (top-to-bottom): **a**) simulated for **CBZ·SAC** Form I, **b**) simulated for **CBZ·SAC** Form II. <u>Triplicates</u> for reaction mixtures after SpeedMixing with 100µL of **c-e**) a 5:1 mixture of MeOH:H₂O, forming **CBZ·2**H₂O, **f-h**) a 3:1 mixture of MeOH:H₂O, forming **CBZ·SAC** Form II, **a**nd **CBZ·2**H₂O, **i-k**) a 2:1 mixture of MeOH:H₂O, forming **CBZ·SAC** Form I, **l-n**) a 1:1 mixture of MeOH:H₂O, forming **CBZ·SAC** Form I and **II**, **r-t**) a 1:2 mixture of MeOH:H₂O, forming **CBZ·SAC** Form I and II, **r-t**) a 1:3 mixture of MeOH:H₂O, forming **CBZ·SAC** Form I and II, **r-t**) a 1:3 mixture of MeOH:H₂O, forming **CBZ·SAC** Form I, **x**) reactant **SAC**, **y**) simulated for **CBZ·2**H₂O, **z**) reactant **CBZ**.



Figure S9. PXRD patterns for 1:1 stoichiometric mixtures of **CBZ** and **SAC** after SpeedMixing with 200 µL of different MeOH:H₂O volume mixtures (top-to-bottom): **a**) simulated for **CBZ·SAC** Form I, **b**) simulated for **CBZ·SAC** Form II; <u>triplicates</u> for mixtures after SpeedMixing with 200µL of **c-e**) a 5:1 mixture of MeOH:H₂O, forming **CBZ·SAC** Form I, **f-h**) a 3:1 mixture of MeOH:H₂O, forming **CBZ·SAC** Form I, **i-h**) a 1:1 mixture of MeOH:H₂O, forming **CBZ·SAC** Form II, **i-n**) a 1:1 mixture of MeOH:H₂O, forming **CBZ·SAC** Form II, **i-n**) a 1:2 mixture of MeOH:H₂O, forming **CBZ·SAC** Form II, **i-t**) a 1:3 mixture of MeOH:H₂O forming **CBZ·SAC** Form II and **CBZ·**2H₂O, **u-w**) a 1:5 mixture of MeOH:H₂O forming **CBZ·SAC** Form II and **CBZ·**2H₂O, **x**) reactant **CBZ**, **y**) simulated for **CBZ·**2H₂O, **z**) reactant **SAC**.



Figure S10. PXRD patterns for 1:1 stoichiometric mixtures of **CBZ** and **SAC** after SpeedMixing with 500 µL of different MeOH:H₂O volume mixtures (top-to-bottom): **a**) simulated for **CBZ·SAC** Form I, **b**) simulated for **CBZ·SAC** Form II; <u>triplicates</u> for reaction mixtures after SpeedMixing with 100 µL of **c-e.** a 1:5 mixture of MeOH:H₂O, forming **CBZ·SAC** Form II and **CBZ·**2H₂O, **i-k**) a 1:2 mixture of MeOH:H₂O, forming **CBZ·SAC** Form II, **I-n**) a 1:1 mixture of MeOH:H₂O, forming **CBZ·SAC** Form II, **I-n**) a 1:1 mixture of MeOH:H₂O, forming **CBZ·SAC** Form II, **n-q**) a 2:1 mixture of MeOH:H₂O, forming **CBZ·SAC** Form I, **r-t**) a 3:1 mixture of MeOH:H₂O, forming **CBZ·SAC** Form I, and **u-w**) a 5:1 mixture of MeOH:H₂O, forming **CBZ·SAC** Form I, **x**) simulated for **CBZ·**2H₂O; **y**) reactants **SAC** and **z**) **CBZ**.



Figure S11. PXRD patterns of 1:1 stoichiometric mixtures of **CBZ** and **SAC** after SpeedMixing with different solvents for 1 and 3 minutes (top-to-bottom): **a**) simulated for **CBZ·SAC** Form II, **b**) simulated for **CBZ·SAC** Form I; reaction mixtures after SpeedMixing with 100μ L of **c**) trifluoroethanol for 1 minute, forming **CBZ·CF**₃CH₂OH, **d**) trifluoroethanol for 3 minutes, **e**) acetonitrile for 1 minute, **f**) acetonitrile for 3 minutes, **g**) *n*-butanol for 1 minute, **h**) *n*-butanol for 3 minutes, **i**) reactant **CBZ**, **j**) reactant **SAC**, **k**) simulated for **CBZ·CF**₃CH₂OH.



Figure S12. PXRD patterns for 1:1 stoichiometric mixtures of **CBZ** and **SAC** after SpeedMixing with 100 μ L of a solvent for 1 and 3 minutes (top-to-bottom): **a**) simulated for **CBZ·SAC** Form II, **b**) simulated for **CBZ·SAC** Form I, reaction mixtures after SpeedMixing with **c**) toluene for 1 minute, **d**) toluene for 3 minutes, **e**) ethyleneglycol for 1 minute, **f**) ethyleneglycol for 3 minutes, **g**) nitromethane for 1 minute, **h**) nitromethane for 3 minutes, **i**) reactant **CBZ**, **j**) reactant **SAC**.



Figure S13. Selected PXRD patterns for attempted syntheses of **CBZ·SAC·**MeOH by SpeedMixing or solution cocrystallization of **CBZ** and **SAC** using MeOH of different water contents (top-to-bottom): a) simulated for **CBZ·SAC·**MeOH, b) simulated for **CBZ·SAC** Form I, c) simulated for **CBZ·SAC** Form II. Reaction mixtures after SpeedMixing for 3 minutes using d) in-house dried MeOH (estimated water content <50 ppm), e) HPLC-grade MeOH (declared water content <0.1%), f) laboratory ACS-grade MeOH (declared water content <0.2%), g) crystals synthesized from a solution in anhydrous in-house dried MeOH, h) crystals synthesized from a solution in laboratory ACS-grade MeOH, j) reactant **SAC**, k) reactant **CBZ**.

S2.2 Crystallographic parameters for CBZ·SAC·MeOH

Table S7. Cell parameters of the CBZ·SAC·MeOH.

	CBZ-SAC-MeOH
Formula	$C_{23}H_{21}N_3O_5S$
M_r	451.49
Т	180.0 K
Crystal system	triclinic
Space group	P -1
a/Å	7.2765(11)
b/Å	10.7344(16)
c/Å	15.269(2)
α'°	88.812(5)
$\beta^{\prime\circ}$	77.790(4)
$\gamma/^{\circ}$	72.947(5)
$V(m \AA^3)$	1113.3(3)
Z/Z'	2
$ ho_{calc}~({ m g~cm^{-3}})$	1.347
$\mu (\mathrm{mm}^{-1})$	1.633
F (000)	472
Crystal size (mm ³)	$0.320 \times 0.220 \times 0.210$
Data collection θ -range (°)	8.624 to 146.584
Reflections collected	29833
Independent reflections	4306 [$R_{int} = 0.0498, R_{sigma} = 0.0304$]
Data/restraints/parameters	4306/0/293
Goodness of fit on F^2	1.046
Final <i>R</i> indices (obs data)	$R_I = 0.0479$
Final <i>R</i> indices (all data)	$R_1 = 0.0489 R_2 = 0.1330$
Largest diff. peak/hole (e Å $^{-3}$)	0.487/-0.462

S2.3 Differential scanning calorimetry (DSC) for CBZ·SAC



Figure S14. DSC thermogram of **CBZ**·**SAC** Form I prepared by SpeedMixing. Sample was treated by temperature ramp from 25 °C to 180 °C, at a rate of 5 °C/min, then held isothermally at 180 °C for 5 mins, before cooling down to 25 °C at a rate of 20 °C/min. The melting point of 174 °C matches the literature value.^[4]



Figure S15. DSC thermogram of **CBZ**·**SAC** form II prepared by SpeedMixing. Sample was treated by temperature ramp from 25 °C to 180 °C, at a rate of 5 °C/min, the held Isothermally at 180 °C for 5 mins, before cooling down to 25 °C at a rate of 20 °C/min. The DSC thermogram indicates transformation of Form II to Form I, consistent with previous work.^[5]



Figure S16. DSC thermogram for **CBZ·SAC·**MeOH prepared by 3 minutes SpeedMixing. Complete conversion was confirmed by PXRD right before sample was sealed into a hermetic pan. Sample was treated by a temperature ramp from -20 °C to 150 °C, at rate of 5 °C/min, then held isothermally at 150 °C for 5 mins before cooling to -20 °C at a rate of 5 °C/min. The broad endothermic event around 70 °C is interpreted as loss of MeOH, which is supported by repeating the heating and cooling cycle after holding the sample isothermally for 5 minutes at -20 °C, which revealed no endothermic signals.

S2.4. FTIR-ATR spectra of CBZ·SAC·MeOH, CBZ·SAC Form I and CBZ·SAC Form II



Figure S17. Comparison of FTIR-ATR spectra for (top to bottom): CBZ, SAC, CBZ·SAC Form I, CBZ·SAC Form II and CBZ·SAC·MeOH.



Figure S18. ¹HSSNMR of (top to bottom): CBZ·SAC Form I, CBZ·SAC Form II and CBZ·SAC·MeOH.



Figure S19. ¹³CSSNMR of (top-to-bottom): CBZ·SAC Form I, CBZ·SAC Form II and CBZ·SAC·MeOH, which has a signal at 48 ppm, consistent with the presence of MeOH.

S2.6 SEM images of CBZ·SAC form I



Figure S20. Selected SEM images of a mixture of **CBZ**, **SAC** and **CBZ**·**SAC** form I obtained by SpeedMixing. (top): physical mixture of **CBZ** and **SAC** after 20 seconds of pre-mixing by SpeedMixing in the absence of any solvents; (bottom): **CBZ**·**SAC** Form I cocrystal formed via SpeedMixing in presence of a 5:1 by volume mixture of MeOH and water as the liquid additive.

S2.7 TGA thermogram of CBZ·SAC·MeOH



Figure S21. TGA thermogram of CBZ·SAC·MeOH, illustrating a weight loss of 5.4% at 69.5°C, indicating the loss of MeOH from the solvate.

DHCBZ·SAC cocrystal system



S3.1 PXRD patterns for the synthesis of the DHCBZ·SAC cocrystal

Figure S22. PXRD patterns of **DHCBZ·SAC** synthesized from a 1:1 stoichiometric mixture of **DHCBZ** and **SAC**, with complete cocrystal formation evident only after two 5-minute SpeedMixing cycles with 300μ L of MeOH as the liquid additive, with the remaining patterns indicating the presence of **DHCBZ** and **SAC** in the mixtures (top to bottom): **a**) simulated for **DHCBZ·SAC**; a 1:1 stoichiometric mixture of **DHCBZ** and **SAC** after SpeedMixing for: **b**) 3 minutes with 200μ L of MeOH, **c**) 5 minutes with 200μ L of MeOH, **d**) 5 minutes with 300μ L of MeOH, **e**) two 5-minute cycles with 300μ L of MeOH; **f**) simulated for **DHCBZ** and **g**) simulated for **SAC**.

S3.2. Differential scanning calorimetry (DSC) of DHCBZ·SAC cocrystal



Figure S23. DSC thermogram for **DHCBZ·SAC** prepared by SpeedMixing. Sample was treated by temperature ramp from 25°C to 185°C at a rate of 5°C/min, then held isothermally at 185°C for 5 mins, before cooling down to 25°C at a rate of 20°C/min. Melting point of 174 °C differs from literature value of 181°C, most likely due to a slower heating rate.^[6]



4.3 FTIR-ATR spectra of the DHCBZ·SAC cocrystal

Figure S24. Comparison of FTIR-ATR spectra for (top-to-bottom): DHCBZ, SAC, and DHCBZ·SAC cocrystal.

NIC·SUB cocrystal system



4.1 PXRD patterns for the synthesis of NIC·SUB and 2NIC·SUB

Figure S25. PXRD patterns for the synthesis of NIC·SUB and 2NIC·SUB by SpeedMixing (top-to-bottom): simulated for a) NIC·SUB and b) 2NIC·SUB; c) a 1:1 stoichiometric mixture of NIC and SUB after six 5-minute cycles of SpeedMixing; d) a 2:1 stoichiometric mixture of NIC and SUB after six 5-minute cycles of SpeedMixing; e) reactants NIC and f) SUB. Performed on 1 mmol scale, 296 mg.



Figure S26. Selected PXRD patterns illustrating the effects of time on the synthesis of **SUB**•**NIC** by SpeedMixing a 1:1 stoichiometric mixture of **SUB** and **NIC** at different times (top to bottom): simulated for **a**) **NIC**•**SUB** and **b**) **2NIC**•**SUB**; mixing a 1:1 stoichiometric mixture of **SUB** and **NIC** with 2 mL of MeOH for: **c**) two 5-minute periods, which shows traces of **SUB** and **NIC** in the mixture, **d**) three 5-minute periods which shows traces of **SUB** and **NIC** in the mixture, **e**) six 5-minute periods, reactants **f**) **NIC** and **g**) **SUB**. *Performed on a 10 mmol scale, 2.96 g, η =0.68 mg/µL.



Figure S27. Selected PXRD patterns comparing the cocrystallization of **NIC** and **SUB** by SpeedMixing, brief SpeedMixing (1 minute) followed by ageing, and by ageing in MeOH vapor (top to bottom): simulated for a) **2NIC**•**SUB**; b) a 2:1 stoichiometric mixture of **NIC** and **SUB** after six 5-minute SpeedMixing cycles, forming **2NIC**•**SUB**, c) a 2:1 stoichiometric mixture of **NIC** and **SUB** after six 5-minute followed by resting for 44 minutes, to form **2NIC**•**SUB** with traces of **NIC**•**SUB**, **SUB** and **NIC** in the mixture, d) a 2:1 stoichiometric mixture of **NIC** and **SUB** after ageing in MeOH vapour for 45 minutes, largely consisting of starting materials and **NIC**•**SUB**, e) simulated pattern for **NIC**•**SUB**, f) a 1:1 stoichiometry mixture of **NIC** and **SUB** after six 5-minute SpeedMixing cycles, forming **NIC**•**SUB**, with traces of **SUB** and **NIC** in the mixture, h) a 1:1 stoichiometry mixture of **NIC** and **SUB** after ageing in MeOH vapour for 45 minutes, largely consisting for 1 minute followed by resting for 44 minutes, of **SUB** and **NIC** and **SUB** after six 5-minute SpeedMixing cycles, forming **NIC**•**SUB**, g) a 1:1 stoichiometry mixture of **NIC** and **SUB** after six 5-minute SUB after ageing in MeOH vapour for 45 minutes, largely consisting of **SUB** and **NIC** in the mixture, h) a 1:1 stoichiometry mixture of **NIC** and **SUB** after ageing in MeOH vapour for 45 minutes, largely consisting of starting materials and small amounts of **NIC**•**SUB**, i) **NIC** and **J SUB** reactants.



Figure S28. PXRD patterns illustrating the formation of the **NIC·SUB** cocrystal from a 1:1 stoichiometry mixture of **NIC** and **SUB** by SpeedMixing at different scales in a SC12 (10 mL volume) cup (top to bottom): **a**) simulated pattern for **NIC·SUB**; b) at 1 mmol (296 mg) scale with 200 μ L of MeOH, **c**) at 1 mmol (296 mg) scale with 300 μ L of MeOH, **d**) at 2 mmol (592 mg) scale with 600 μ L of MeOH, **e**) at 2 mmol (592 mg) scale with 500 μ L of MeOH, **f**) at 5 mmol (1.48 g) scale with 900 μ L of MeOH, **g**) at 10 mmol (2.96 g) scale with 1500 μ L of MeOH, **h**) at 10 mmol (2.96 g) scale with 1200 μ L of MeOH, **i**) at 10 mmol (2.96 g) scale with 1000 μ L of MeOH, **j**) at 25 mmol (7.4 g) scale with 5000 μ L of MeOH, reactants **k**) **NIC** and **l**) **SUB**. Underlined patterns were used in Figure 4b based on the minimal amount of MeOH required to produce a pattern without **NIC** or **SUB**.



Figure S29. PXRD patterns illustrating the formation of **NIC·SUB** cocrystal by SpeedMixing of a 1:1 stoichiometry mixture of **NIC** and **SUB** at different scales and using different cups (top to bottom): simulated for **a**) **NIC·SUB** and **b**) **2NIC·SUB**, **c**) at 5 mmol (1.48 g) scale with 900 μ L of MeOH using a 10mL cup, **d**) at 5 mmol (1.48 g) scale with 700 μ L of MeOH using a 25 mL cup, e) at 10 mmol (2.96 g) scale with 1000 μ L of MeOH using a 10 mL cup, **f**) at 10 mmol (2.96 g) scale with 1000 μ L of MeOH using a 25mL cup, e) at 25 mmol (1.48 g) scale with 2500 μ L of MeOH using a 25 mL cup, **h**) at 25 mmol (7.4 g) scale with 2000 μ L of MeOH using a 25 mL cup, **h**) at 25 mmol (7.4 g) scale with 3000 μ L of MeOH using a 25 mL cup, with the sample extracted from the top of the cup. **j**) 50 mmol (14.8 g) scale with 3000 μ L of MeOH using a 25 mL cup, with the sample extracted from the bottom of the cup, reactants **k**) **NIC** and **l**) **SUB**. The PXRD patterns demonstrate that a 25 mL volume cup permits complete synthesis of up to 25 mmol **NIC·SUB**, after which the mixing is no longer sufficiently efficient. Underlined patterns were used in manuscript Figure 4b based on the minimal amount of MeOH required to produce a pattern without **NIC** or **SUB**.



Figure S30. PXRD patterns illustrating the formation of **NIC**·**SUB** cocrystal by SpeedMixing of **NIC** and **SUB** at different scales using a 60 mL cup (top to bottom): simulated for **a**) **NIC**·**SUB** and **b**) **2NIC**·**SUB**, **c**) at 25 mmol (7.4 g) scale with 1800µL of MeOH, **d**) at 50 mmol (14.8 g) scale with 2000 µL of MeOH, **e**) at 50 mmol (14.8 g) scale with 2000 µL of EtOH, **f**) at 75 mmol (22.2 g) scale with 3000 µL of EtOH, sample taken from top of cup, **g**) at 75 mmol (22.2 g) scale with 3000 µL of EtOH, sample taken from top of cup, **g**) at 75 mmol (22.2 g) scale with 3000 µL of EtOH, patterns demonstrate efficient synthesis of up to 75 mmol amount of **NIC**·**SUB** using a 60 mL cup. Underlined patterns were used in the manuscript Figure 4b based on the minimal amount of MeOH required to produce a pattern without **NIC** or **SUB**.

4.2 Differential scanning calorimetry (DSC) of NIC·SUB and 2NIC·SUB



Figure S31. DSC thermogram of **NIC·SUB**. Sample was treated by temperature ramp from 25 °C to 130 °C, 5 °C/min, the held isothermally at 130 °C for 5 mins before cooling down to 25 °C at 20 °C/min. Melting point 119 °C.



Figure S32. DSC thermogram of **SUB-2NIC**. Sample was treated by temperature ramp from 25 °C to 130 °C, 5 °C/min, then held isothermally at 130 °C for 5 minutes before cooling down to 20 °C at 20 °C/min. Melting point 116 °C.





Figure S33. Comparison of FTIR-ATR spectra of (top to bottom): NIC, SUB, 2NIC·SUB, NIC·SUB.

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Appendix B.

This Appendix contains additional data that support findings and conclusions presented in Chapter 3 of this thesis, but for reasons of brevity and coherence were not included in the main body of the text.

S1 Mg-MOF-74



S1.1 TGA thermogram of Mg-MOF-74

Figure S1. TGA thermogram of Mg-MOF-74, Sample was treated by temperature ramp from 25 °C to 700 °C, 10 °C/min. Residue of 26.9 wt % is a close match to the expected value of 28.6 wt %.

S1.2 FTIR spectra of Mg-MOF-74



Figure S2. Comparison of FTIR-ATR spectra for (top to bottom): H₂DHTA, Mg-MOF-74.

S2.3 SEM image of Mg-MOF-74



Figure S3. SEM images of Mg-MOF-74.



S1.4 N2 sorption isotherms for surface area measurements for Mg-MOF-74



S2 Zn-MOF-74



S2.1 TGA thermogram of Zn-MOF-74

Figure S4. TGA thermogram of Zn-MOF-74, Sample was treated by temperature ramp from 25 °C to 700 °C, 10 °C/min. Residue of 40.7 wt % is a close match to the expected value of 40.8 wt %.

S2.2 FTIR spectra of Zn-MOF-74



Figure S5. Comparison of FTIR-ATR spectra for (top to bottom): H₂DHTA, Zn-MOF-74.

S2.3 SEM image of Zn-MOF-74



Figure S6. SEM images of Zn-MOF-74



S2.4 N₂ sorption isotherms for surface area measurements for Zn-MOF-74

Figure S8. Nitrogen desorption and adsorption isotherms run at 77K for Zn-MOF-74 prepared by SpeedMilling.

S3 ZIF-8



S3.1 TGA thermogram of ZIF-8

Figure S7. TGA thermogram of Mg-MOF-74, Sample was treated by temperature ramp from 25 °C to 700 °C, 10 °C/min. Residue of 35.7 wt % is a close match to the expected value of 28.6 wt %.

S3.2 FTIR spectra of ZIF-8



Figure S8. Comparison of FTIR-ATR spectra for (top to bottom): 2-methylimidazole, ZIF-8.

S3.3 SEM image of ZIF-8



Figure S9. SEM images of ZIF-8.



S3.4 N₂ sorption isotherms for surface area measurements for ZIF-8

Figure S12. Nitrogen desorption and adsorption isotherms run at 77K for ZIF-8 prepared by SpeedMilling.

S4 HKUST-1



S4.1 TGA thermogram of HKUST-1

Figure S10. TGA thermogram of HKUST-1, Sample was treated by temperature ramp from 25 °C to 700 °C, 10 °C/min. Residue of 34.7 wt % is a close match to the expected value of 36 wt %.

S4.2 FTIR spectra of HKUST-1



Figure S11. Comparison of FTIR-ATR spectra for (top to bottom): trimesic acid, Cu(OAC)₂·H₂O, HKUST-1.

S4.3 SEM image of HKUST-1



Figure S12. SEM images of HKUST-1.

S5 RHO MOF



S5.1 PXRD patterns of samples of RHO-Zn(EtIm)2 MOF

Figure S13. PXRD patterns of samples of 2:1 stoichiometric mixture of ZnO and 2-ethylimidazole after SpeedMilling with catalytic amounts of NH₄NO₃ (< 5 wt %). From top to bottom: Simulated pattern for RHO MOF, reaction mixture after SpeedMilling with 4mL of MeOH, 3mL of MeOH, after washing, commercial 2-ethylimidazole, commercial ZnO.



S5.2 TGA thermogram of RHO MOF

Figure S14. TGA thermogram of HKUST-1, Sample was treated by temperature ramp from 25 °C to 700 °C, 10 °C/min. Residue of 34.7 wt % is a close match to the expected value of 36 wt %.

S5.3 SEM image of RHO MOF



Figure S16. SEM images of RHO MOF.



S5.4 N₂ sorption isotherms for surface area measurements for RHO-MOF

Figure S21. Nitrogen desorption and adsorption isotherms run at 77K for RHO-MOF prepared by SpeedMilling.