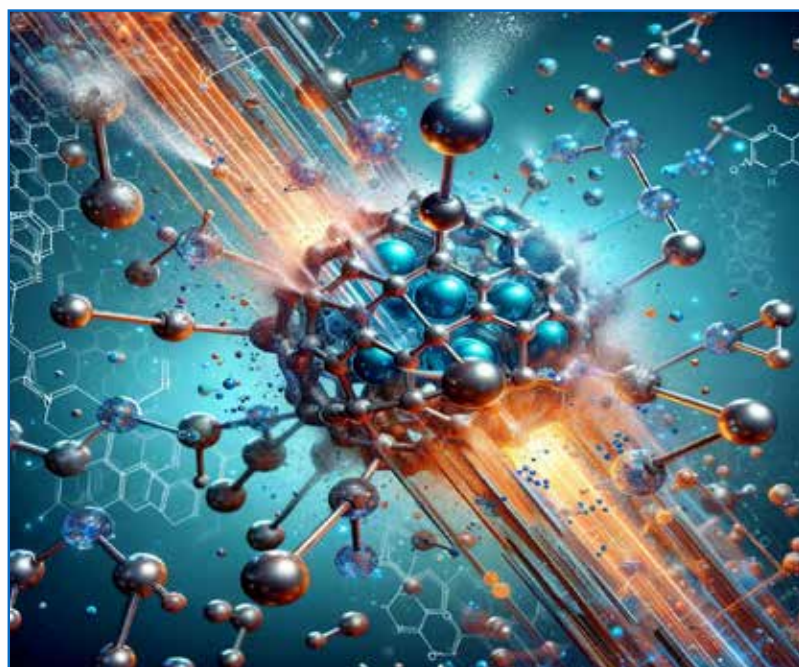


# Advances in Mechanochemistry Processing Enabled By ResonantAcoustic<sup>®</sup> Mixing

Testimonials • Published Articles • Patents & Patent Applications



November 2023

This document is a portfolio of articles, patents/patents pending and user testimonials that reference Resodyn's ResonantAcoustic<sup>®</sup> Mixing (RAM) technology in a variety of mechanochemistry materials industry applications. This collection of abstracts and links to published articles is intended to provide insight into the value of RAM technology as a means of solving challenges, improving quality, and raising productivity in the development of "Green" Chemistry Processes.

# Mechanochemistry

Mechanochemistry is a field of chemistry that focuses on chemical reactions induced by mechanical forces such as grinding, shearing, milling, or mixing. Traditional processing methodologies vary from hand grinding (i.e., mortar and pestle) to shaker and planetary mills for laboratory scale production. Eccentric and horizontal high-energy ball mill devices have been the preferred methodology for scale up to batch production, while twin-screw and single-screw extrusion equipment has been used for continuous mechanochemical processing.

Mechanochemistry reduces, or even eliminates, the use of solvents, heat, electricity and other external elements to reactions. Reactions requiring multiple intermediary products may also be simplified.

Illustrating clear advantages (reduced process times and increased conversion) to the afore mentioned traditional processes, ResonantAcoustic® Mixing is a specialized technology that leverages low frequency acoustic waves to generate controlled mechanical force within a reaction vessel. ResonantAcoustic® Mixing increases the chance of molecular collisions promoting reaction kinetics, supplying the activation energy necessary to break and form chemical bonds. Both acceleration and frequency are precisely controlled elements of ResonantAcoustic® Mixing technology, allowing chemists to tailor the reaction conditions and selectivity. Temperature control and vacuum options are also available. The ability to fine-tune the reaction environment is invaluable toward specific product outcomes.

System and process scale up has been identified as a pressing challenge toward the further advancement of mechanochemistry production. ResonantAcoustic® Mixing provides a consistent platform for both batch and continuous mechanochemical processing scale-up.

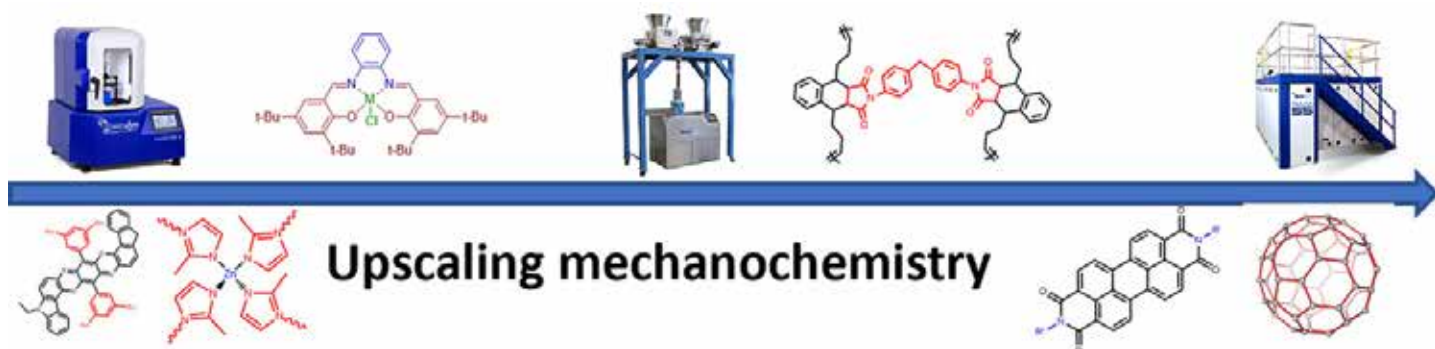
## Companies all over the world rely upon RAM technology for mechanochemistry research and development

Australia  
Belgium  
Brazil  
Canada  
China  
Czechia  
Costa Rica  
France  
Germany  
Greece  
Hungary  
India  
Indonesia  
Ireland  
Israel  
Italy  
Japan  
Latvia  
Liechtenstein



Mexico  
Morocco  
Netherlands  
New Zealand  
Norway  
Saudi Arabia  
Singapore  
South Africa  
South Korea  
Spain  
Sweden  
Switzerland  
Taiwan  
Thailand  
Turkey  
United Arab Emirates  
United Kingdom  
United States

**RAM technology is making Mechanochemistry a Global Reality.**



# What “Green” Chemistry professionals are saying about RAM

*“... RAM mechanosynthesis is shown to be faster, operationally simpler than conventional ball-milling, while also providing the first example of a mechanochemical strategy for ruthenium-catalyzed ene-yne metathesis. Reactions by RAM are readily and directly scaled-up ...”*

-Dr. Tomislav Friščić, et al  
University of Birmingham, U.K.

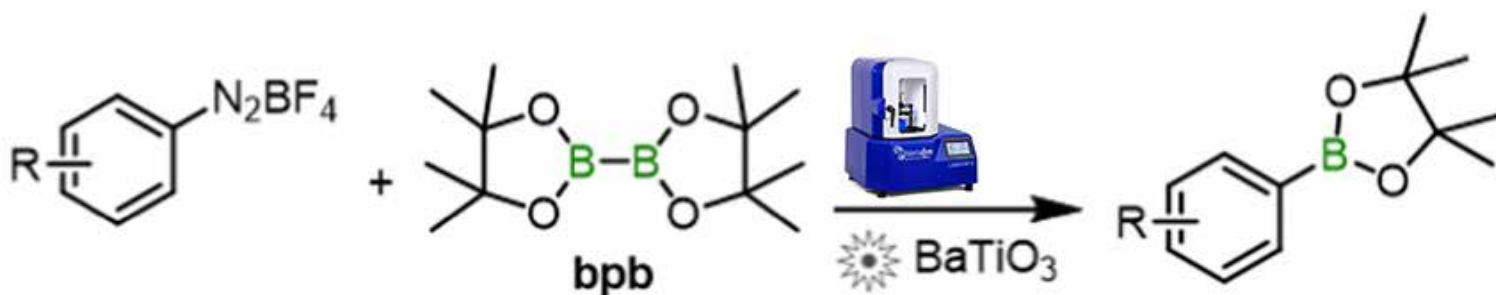
*“The RAM exhibited remarkable performance in the Suzuki coupling reaction, achieving yields of approximately 90 % after 60 min and complete conversion after 90 min. The longevity of the milling vessel in the RAM was significantly extended compared to previous systems, thus offering increased durability for multiple reactions without deterioration ...”*

-Maxmilian Wohlgemuth, et al  
Ruhr-Universität Bochum, Germany

*“ ... it was shown that resonant acoustic mixing provides the mixing intensity required of lab-scale mechanochemical methods, such as liquid -assisted grinding, but now on a platform more amenable to larger-scale manufacture. Resonant acoustic mixing in general has been demonstrated to be scalable to volumes greater than 200 L and thus affords a potential new platform for co-crystallization processes.”*

-David J. am Ende, et al  
Nalas Engineering Services, Essex, Conn., U.S.

























## RAM: The Future of Mechanochemistry













## Icon Legend

	RAM testing, evaluation		Liquid/powder
	Material/chemical properties		Materials processing
	Powder/powder		Materials/product quality

Icons	Publication Title (Live Links)*	RAM Application Summary	Year
   	<a href="#">Milling Media-Free Suzuki Coupling by Direct Mechanocatalysis- From Mixer Mills to Resonant Acoustic Mixers</a>	"The RAM exhibits excellent performance in the Suzuki reaction, achieving yields of 90% after 60 minutes and complete conversion after 90 minutes. The longevity of the milling vessel is significantly improved in the RAM. . ."	2023
   	<a href="#">Direct mechanocatalysis by resonant acoustic mixing (RAM)</a>	"... RAM-based direct mechanocatalysis methodology is simple, enables the effective one-pot, two-step synthesis of triazoles via a combination of benzyl azide formation and CuAAC reactions on a wide scope of reagents, provides control over reaction stoichiometry that is herein shown to be superior ..."	2023
   	<a href="#">The "η-sweet-spot" (η<sub>max</sub>) in liquid-assisted mechanochemistry: polymorph control and the role of a liquid additive as either a catalyst or an inhibitor in resonant acoustic mixing (RAM)</a>	"Resonant acoustic mixing (RAM) offers a simple, efficient route for mechanochemical synthesis in the absence of milling media or bulk solvents. Here, we show the use of RAM to conduct the copper-catalysed coupling of sulfonamides and carbodiimides."	2023
   	<a href="#">Application of resonant acoustic mixing in the synthesis of vitamin C–nicotinamide variable stoichiometry cocrystals</a>	"The use of resonant acoustic mixing (RAM) to synthesize variable stoichiometry cocrystals of nicotinamide and vitamin C was investigated...LA-RAM is demonstrated to be a scalable, environmentally friendly, ball-free method to make variable stoichiometry cocrystals."	2023
   	<a href="#">Concluding remarks: Fundamentals, applications and future of mechanochemistry</a>	"This paper provides a summary ... mechanochemistry, 2 whereas the papers that have been presented in this meeting are dominated by work in ball-mill grinding, resonant acoustic mixing..."	2023
   	<a href="#">Tinkering with Mechanochemical Tools for Scale Up</a>	"... other mechanochemical syntheses.[37] Liquid-assisted resonant acoustic mixing (LARAM) ... rapid adoption at the R&D stage is evidenced by the increasing number of patents filed in the ..."	2023

Icons	Publication Title (Live Links)*	RAM Application Summary	Year
	<a href="#">Metal-Catalyzed Organic Reactions by Resonant Acoustic ...</a>	"...catalytic organic synthesis by Resonant Acoustic Mixing (RAM): a mechanochemical methodology that does not require bulk solvent or milling media... Reactions by RAM are readily and directly scaled-up without any significant changes in reaction conditions..."	2022
	<a href="#">Resonant acoustic-mixing technology as a novel method for production of negative-temperature coefficient thermistors</a>	"...This study will be the lead to guide future studies into the cost-effective fast fabrication of negative-temperature coefficient thermistors by resonant acoustic mixing technology due to reduction of manufacturing costs by reducing processing time."	2022
	<a href="#">Time-resolved in situ monitoring of mechanochemical reactions</a>	"... resonant acoustic mixing (RAM) cocrystallization of carbamazepine and nicotinamide by TRIS-XRD, the degree of bulk powder ..."	2022
	<a href="#">Application of mechanochemical activation in synthetic organic chemistry</a>	" ... A recently emerged technique is Resonant Acoustic Mixing (RAM), which uses low-..."	2021
	<a href="#">Simple, scalable mechanosynthesis of metal–organic frameworks using liquid-assisted resonant acoustic mixing (LA-RAM)</a>	"... mechanochemical syntheses. We demonstrate the use of liquid-assisted resonant acoustic mixing ... never been previously obtained in a mechanochemical environment ..."	2020
	<a href="#">Mechanochemistry for organic chemists: An update</a>	"... A recently emerged technique is Resonant Acoustic Mixing (RAM), which uses low-frequency, high-amplitude acoustic resonance to agitate powder samples."	2018
	<a href="#">Ball-free mechanochemistry: in situ real-time monitoring of pharmaceutical co-crystal formation by resonant acoustic mixing</a>	"We present here the first in situ study of RAM-induced co-crystallisation monitored using synchrotron X-ray powder diffraction."	2018
	<a href="#">High-throughput screening and scale-up of cocrystals using resonant acoustic mixing</a>	"This paper explores the effectiveness of resonant acoustic mixing RAM for screening and scale up of cocrystals. . . . Theophylline Oxalic acid cocrystals at an 80 gram scale with a net yield of 94%. RAM is thus established as an environmentally friendly mechanochemical technique for both high throughput screening and scaled up production of cocrystals."	2017

\* Article links maybe limited by copyright restrictions. Detailed links on following pages

^ Results excerpted/paraphrased from articles.

Partial (edited) selection of searched technical articles using the following search terms (articles are live links):

- “Resonant Acoustic Mixing” AND/OR
- “mechanochemistry”

### **Milling Media-Free Suzuki Coupling by Direct Mechanocatalysis- From Mixer Mills to Resonant Acoustic Mixers**

**Maximilian Wohlgemuth, Sarah Schmidt, Maïke Mayer, Dr. Wilm Pickhardt, Dr. Sven Grätz, Prof. Dr. Lars Borchardt**

Here we describe the development of a sustainable and cost-effective approach for catalytic cross-coupling reactions in mechanochemistry. It is found that the substrate's impact with the vessel wall alone is sufficient to initiate the reaction, thus indicating that milling balls function primarily as a mixing agent for direct mechanocatalytic Suzuki coupling. The absence of milling balls can be offset by adjusting the rheology using liquid-assisted grinding (LAG). The LAG sweet spot of  $0.25 \mu\text{L mg}^{-1}$  is confirmed for both resonance acoustic mixers (RAMs) and ball-free mixer mills, and is higher than in the presence of milling balls. RAMs exhibit excellent performance in the Suzuki reaction, achieving yields of 90% after 60 min and complete conversion after 90 min. The longevity of the milling vessel is significantly improved in a RAM, allowing for at least 20 reactions without deterioration.

### **Direct Mechanocatalysis without Milling Media – From Mixer Mills to Resonant Acoustic Mixers**

**Maximilian Wohlgemuth, Sarah Schmidt, Maïke Mayer, Wilm Pickhardt, Sven Graetz, Lars Borchardt**

Here we describe the development of a sustainable and cost-effective approach for catalytic cross-coupling reactions in mechanochemistry. It is found that the substrate's impact with the vessel wall alone is sufficient to initiate the reaction, indicating that milling balls primarily serve as mixing agents rather than energy carriers. The absence of milling balls can be offset by adjusting the rheology using liquid-assisted grinding (LAG). The  $\eta$ -sweet spot of  $0.25 \mu\text{L/mg}$  is confirmed for both resonance acoustic mixer (RAM) and ball-free mixer mills and is higher than in the presence of milling balls. The RAM exhibits excellent performance in the Suzuki reaction, achieving yields of 90% after 60 minutes and complete conversion after 90 minutes. The longevity of the milling vessel is significantly improved in the RAM, allowing for at least 20 reactions without deterioration.

### **The “ $\eta$ -sweet-spot” ( $\eta_{\text{max}}$ ) in liquid-assisted mechanochemistry: polymorph control and the role of a liquid additive as either a catalyst or an inhibitor in resonant acoustic mixing (RAM)**

**Lori Gonnet, Tristan H. Borchers, Cameron B. Lennox, Jogirdas Vainauskas, Yong Teoh, Hatem M. Titi, Christopher J. Barrett, Stefan G. Koenig, Karthik Nagapudi, and Tomislav Friščić**

Resonant acoustic mixing (RAM) offers a simple, efficient route for mechanochemical synthesis in the absence of milling media or bulk solvents. Here, we show the use of RAM to conduct the copper-catalysed coupling of sulfonamides and carbodiimides. This coupling was previously reported to take place only by mechanochemical ball milling, while in conventional solution environments it is not efficient, or does not take place at all. The results demonstrate RAM as a suitable methodology to conduct reactions previously accessed only by ball milling and provide a detailed, systematic overview of how the amount of liquid additive, measured by the ratio of liquid volume to weight of reactants ( $\eta$ , in  $\mu\text{L mg}^{-1}$ ), can affect the course of a mechanochemical reaction and the polymorphic composition of its product. Switching from ball milling to RAM allowed for the discovery of a new polymorph of the model sulfonylguanidine obtained by catalytic coupling of di(cyclohexyl)carbodiimide (DCC) and p-toluenesulfonamide, and the ability to control reaction temperature in RAM enabled in situ control of the polymorphic behaviour of this nascent product. We show that the reaction conversion for a given reaction time does not change monotonically but, instead, achieves a maximum for a well-defined  $\eta$ -value. This “ $\eta$ -sweet-spot” of conversion is herein designated  $\eta_{\text{max}}$ . The herein explored reactions demonstrate sensitivity to  $\eta$  on the order of  $0.01 \mu\text{L mg}^{-1}$ , which corresponds to an amount of liquid additive below 5 mol% compared to the reactants, and is at least one to two orders of magnitude lower than the

$\eta$ -value typically considered in the design of liquid-assisted ball milling mechanochemical reactions. Such sensitivity suggests that strategies to optimise liquid-assisted mechanochemical reactions should systematically evaluate  $\eta$ -values at increments of 0.01  $\mu\text{L mg}^{-1}$ , or even finer. At  $\eta$ -values other than  $\eta_{\text{max}}$  the reaction conversion drops off, demonstrating that the same liquid additive can act either as a catalyst or an inhibitor of a mechanochemical reaction, depending on the amount.

### Application of resonant acoustic mixing in the synthesis of vitamin C–nicotinamide variable stoichiometry cocrystals

**Minhthi Bui, Paroma Chakravartya and Karthik Nagapudi**

The use of resonant acoustic mixing (RAM) to synthesize variable stoichiometry cocrystals of nicotinamide and vitamin C was investigated. Liquid assisted RAM (LA-RAM) was used to generate two polymorphs, Form I and II, of the 1 : 1 cocrystal of nicotinamide and vitamin C at a 700 mg scale using ethanol and methanol respectively as the liquid additives. LA-RAM was used to scale up polymorphs I and II of the 1 : 1 cocrystal to 20 grams. Finally, LA-RAM used was to produce a high purity 3 : 1 cocrystal of nicotinamide and vitamin C when either methanol or ethanol was used as the liquid additive. LA-RAM is demonstrated to be a scalable, environmentally friendly, ball-free method to make variable stoichiometry cocrystals.

### Concluding remarks: Fundamentals, applications and future of mechanochemistry

**Stephan L. Craig**

This paper provides a summary of the Faraday Discussions meeting on “Mechanochemistry: fundamentals, applications, and future” in the context of broad themes whose exploration might contribute to a unified framework of mechanochemical phenomena.

### Metal-Catalyzed Organic Reactions by Resonant Acoustic Mixing

**Dr. Lori Gonnet, Cameron B. Lennox, Jean-Louis Do, Ivani Malvestiti, Dr. Stefan G. Koenig, Dr. Karthik Nagapudi, Prof. Tomislav Friščić**

We demonstrate catalytic organic synthesis by Resonant Acoustic Mixing (RAM): a mechanochemical methodology that does not require bulk solvent or milling media. Using as model reactions ruthenium-catalyzed ring-closing metathesis and copper-catalyzed sulfonamide-isocyanate coupling, RAM mechanosynthesis is shown to be faster, operationally simpler than conventional ball-milling, while also providing the first example of a mechanochemical strategy for ruthenium-catalyzed ene-yne metathesis. Reactions by RAM are readily and directly scaled-up without any significant changes in reaction conditions, as shown by the straightforward 200-fold scaling-up of the synthesis of the antidiabetic drug Tolbutamide, from hundreds of milligrams directly to 30 grams.

### Resonant acoustic-mixing technology as a novel method for production of negative-temperature coefficient thermistors

**Berat Yüksel Price & Stuart R. Kennedy**

The 0.1 mol% B<sub>2</sub>O<sub>3</sub>-added NiMn<sub>2</sub>O<sub>4</sub>, Ni<sub>0.5</sub>Co<sub>0.5</sub>Cu<sub>0.3</sub>Mn<sub>1.7</sub>O<sub>4</sub> and 0.1 mol% B<sub>2</sub>O<sub>3</sub>-added Ni<sub>0.5</sub>Co<sub>0.5</sub>Cu<sub>0.3</sub>Mn<sub>1.7</sub>O<sub>4</sub> negative-temperature coefficient thermistors (NTC) prepared by Resonant Acoustic-Mixing (RAM) technology were compared with samples produced by the traditional ball-milling technique. The metal oxide powders were weighed and mixed by a resonant acoustic mixer (LabRAM 1, Resodyn Acoustic Mixers) at 15 and 40 g acceleration for 20 min and 2 h. To prepare the other group of samples, the metal oxide powders were mixed by ball milling for 6 h. The B<sub>2</sub>O<sub>3</sub> addition was chosen in order to reduce processing time by eliminating calcination step. For further comparison, the Ni<sub>0.5</sub>Co<sub>0.5</sub>Cu<sub>0.3</sub>Mn<sub>1.7</sub>O<sub>4</sub> samples without B<sub>2</sub>O<sub>3</sub> addition were calcinated at 900 °C for 2 h and sintered at 1100 °C for 5 h, whereas the sintering process at 1100 °C for 5 h without calcination was applied for the 0.1 mol% B<sub>2</sub>O<sub>3</sub>-added NiMn<sub>2</sub>O<sub>4</sub> and 0.1 mol% B<sub>2</sub>O<sub>3</sub>-added Ni<sub>0.5</sub>Co<sub>0.5</sub>Cu<sub>0.3</sub>Mn<sub>1.7</sub>O<sub>4</sub> samples. To the best of our knowledge, RAM was applied to produce NTC thermistors for the first time in this study. The best electrical resistivity and material constant results were obtained as 79.5  $\Omega\text{ cm}$  and 3180 K for the 0.1 mol% B<sub>2</sub>O<sub>3</sub>-added Ni<sub>0.5</sub>Co<sub>0.5</sub>Cu<sub>0.3</sub>Mn<sub>1.7</sub>O<sub>4</sub> (B8RAM) sample after 40 g 20 min RAM process followed by the sintering at 1100 °C without calcination. This study will be the lead to guide future studies into the cost-effective fast fabrication of negative-temperature coefficient thermistors by resonant acoustic mixing technology due to reduction of manufacturing costs by reducing processing time.

## Time-Resolved In Situ Monitoring of Mechanochemical Reactions

**Dr. Adam A. L. Michalchuk, Priv.-Doz. Dr. Franziska Emmerling**

Mechanochemical transformations offer environmentally benign synthesis routes, whilst enhancing both the speed and selectivity of reactions. In this regard, mechanochemistry promises to transform the way in which chemistry is done in both academia and industry but is greatly hindered by a current lack of mechanistic understanding. The continued development and use of time-resolved in situ (TRIS) approaches to monitor mechanochemical reactions provides a new dimension to elucidate these fascinating transformations. We here discuss recent trends in method development that have pushed the boundaries of mechanochemical research. New features of mechanochemical reactions obtained by TRIS techniques are subsequently discussed, which sheds light on how different TRIS approaches have been used. Emphasis is placed on the strength of combining complementary techniques. Finally, we outline our views on the potential of TRIS methods in mechanochemical research, towards establishing a new, environmentally benign paradigm in the chemical sciences.

## Application of mechanochemical activation in synthetic organic chemistry

**Gábor Varga, Pál Sípó, István Pálinkó**

In recent years the use of mechanochemical activation in promoting synthetic reactions in organic chemistry became remarkably widespread. Indeed, mechanochemical treatment can be a very efficient form of energy transfer, and, often, it may provide with mild reaction conditions for otherwise difficult syntheses.

## Simple, scalable mechanosynthesis of metal–organic frameworks using liquid-assisted resonant acoustic mixing (LA-RAM)

**Hatem M. Titi ORCID logo<sup>a</sup>, Jean-Louis Do ORCID logo<sup>a,b</sup>, Ashlee J. Howarth ORCID logo<sup>b</sup>, Karthik Nagapudi ORCID logo<sup>c</sup> and Tomislav Friščić ORCID logo<sup>\*</sup>**

We present a rapid and readily scalable methodology for the mechanosynthesis of diverse metal–organic frameworks (MOFs) in the absence of milling media typically required for other types of mechanochemical syntheses. We demonstrate the use of liquid-assisted resonant acoustic mixing (LA-RAM) methodology for the synthesis of three- and two-dimensional MOFs based on Zn(II), Co(II) and Cu(II), including a mixed ligand system. Importantly, the LA-RAM approach also allowed the synthesis of the ZIF-L framework that has never been previously obtained in a mechanochemical environment, as well as its Co(II) analogue. Straightforward scale-up from milligrams to at least 25 grams is demonstrated using the metastable framework ZIF-L as the model.

## Mechanochemistry for Organic Chemists: An Update

**Davin Tan, Tomislav Friščić**

We provide a brief overview of recent advances in the use of mechanochemical techniques for the synthesis of organic molecules and materials, highlighting selected examples of mechanochemical organic transformations and mechanistic studies, and especially those that illustrate chemical reactions or syntheses of molecular targets that have remained elusive to conventional solution techniques.

## Ball-free mechanochemistry: in situ real-time monitoring of pharmaceutical co-crystal formation by resonant acoustic mixing

**Adam A. L. Michalchuk, Karl S. Hope, Stuart R. Kennedy, Maria V. Blanco, Elena V. Boldyreva, and Colin R. Pulham**

Resonant acoustic mixing (RAM) is a new technology designed for intensive mixing of powders that offers the capability to process powders with minimal damage to particles. This feature is particularly important for mixing impact-sensitive materials such as explosives and propellants. While the RAM technique has been extensively employed for the mixing of powders and viscous polymers, comparatively little is known about its use for mechanosynthesis. We present here the first in situ study of RAM-induced co-crystallisation monitored using synchrotron X-ray powder diffraction. The phase profile of the



reaction between nicotinamide and carbamazepine in the presence of a small amount of water was monitored at two different relative accelerations of the mixer. In marked contrast to ball-milling techniques, the lack of milling bodies in the RAM experiment does not hinder co-crystallisation of the two starting materials, which occurred readily and was independent of the frequency of oscillation. The reaction could be optimised by enhancing the number of reactive contacts through mixing and comminution. These observations provide new insight into the role of various experimental parameters in conventional mechanochemistry using liquid-assisted grinding techniques.

### **High-throughput screening and scale-up of cocrystals using resonant acoustic mixing**

**Karthik Nagapudi, Evelyn Yanez Umanzor, Colin Masui**

This paper explores the effectiveness of resonant acoustic mixing RAM for screening and scale up of cocrystals. 16 cocrystal systems were selected as test cases based on previous literature precedent. A 96 well plate set up in conjunction with zirconia beads was used for cocrystal screening using RAM. A success rate of 80% was obtained in the screen for plates containing solvent or solvent plus Zirconia beads. A proof of concept production of hydrated and anhydrous cocrystals of 1:1 Theophylline Citric acid system at a 400 mg scale was demonstrated using solvent and bead assisted RAM. Finally the parameters affecting the scale up of 2:1 Theophylline Oxalic acid cocrystals was explored in a systematic fashion using a Design of Experiments DOE approach. The RAM parameters of acceleration and mixing time were optimized using the DOE approach. A quantitative XRPD method was developed to determine the extent of conversion to the cocrystal when using RAM. Mixing time of 2 h and an acceleration of 60 G were determined to be optimal. The optimized parameters were used to demonstrate scale up of 2:1 Theophylline Oxalic acid cocrystals at an 80 gram scale with a net yield of 94%. RAM is thus established as an environmentally friendly mechanochemical technique for both high throughput screening and scaled up production of cocrystals.

# Relevant Patents

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Approved and pending applications for work involving the use of ResonantAcoustic® mixing technology.\*

\*With RAM as the preferred embodiment

## Caf2-based fluorination reagents, methods of preparation and uses thereof

WO, WO2023118867A1, Veronique Gouverneur, et al, Oxford University Innovation Limited

Priority 2022-12-21 • Filed 2022-12-21 • Published 2023-6-29

“... least the peaks corresponding to the first and second salt are subtracted). 73. The method of any of claims 44-71, wherein the mechanical force is applied using a ball mill, a mortar and pestle, a twin-screw extruder, using an ultrasonic bath, a resonant acoustic mixer, and/or a mechanical press?

## Method for production of composite magnetic powders by autonomous grinding

SK, SK132021A3, Bureš Radovan, Fáberová Mária

Priority 2021-2-25 • Filed 2021-2-25 • Published 2022-9-14

Ferromagnetism in the form of powdered magnetically soft metal or alloy is placed together with electro-insulating ceramic powder in a cylindrical container. The ratio of the height to the diameter of the container is 2:1. The container is filled with powder to a maximum of 1/3 of the volume. The powder mixture is autonomously ground by the action of resonant acoustic energy for 15 minutes to 360 hours. The particles of the powder mixture are given a gravitational acceleration of at least 20 g. Ferromagnetic particles are at least one order of magnitude larger than ceramic particles. Particles of the powder mixture are precipitated, ceramic particles are fragmented into smaller particles. Ferromagnetic particles act as a grinding medium. Fragmented ceramic particles are attached to the surface of ferromagnetic particles, the size of which does not change significantly during autonomous grinding. The powder composite material is further processed by pressing and sintering into magnetically soft components.

## Complexes Comprising Carbohydrate Polymers and Active Ingredients and Methods for Their Preparation

WO, EP, AU, JP, CA, US, JP2023510089A Felix Polyak, Dmitry Budovich

Priority 2019-12-13 • Filed 2020-12-11 • Published 2023-3-13

Disclosed herein are molecular complexes and compositions containing them. More specifically, carbohydrate polymers such as hyaluronic acid and its salts are bioactive selected from natural products and nutrients (amino acids, amino esters, hydroxy acids, hydroxy esters, vitamins, cannabinoids, etc.) and active pharmaceutical ingredients. Complexes with compounds to form stable molecular complexes. Complexation can be conveniently achieved using resonant acoustic mixing methods.

## A method to produce and scale-up cocrystals and salts via resonant acoustic mixing

US, EP EP2845852A1 Jerry Salan, Stephen R. Anderson, and David J. Am Ende, Nalas Engineering Services Inc.

Priority 2013-9-4 • Filed 2014-9-4 • Published 2015-3-11

A method to produce and manufacture cocrystals and salts is disclosed wherein crystalline solids and other components were combined in the desired proportions into a mixing chamber and mixed at high intensity to afford a cocrystalline product. No grinding media were required. The mixing system consists of a resonant acoustic vibratory system capable of supplying a large amount of energy to the mixture and is tunable to a desired resonance frequency and amplitude. The use of resonant acoustic mixing to assist cocrystallization is novel. This discovery enables the manufacture of cocrystals and salt forms, simplifying their manufacture and scale-up, and avoiding the use of grinding methods or grinding media. The present invention affords the manufacture of cocrystals and salts on kilogram to multi-ton scale and is adaptable to continuous manufacturing through the use of resonant mixing methods.

# Patents (cont.)

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## Mechanoenzymatic degradation of polymers

US, CA, WO, EP, US20220403422A1, Karine Auclair, et al, McGill University, Canada  
Priority 2020-10-27 • Filed 2020-10-27 • Published 2022-12-22

A method of depolymerizing a polymer by combining together the polymer with an enzyme (a hydrolytic enzyme capable of catalyzing cleavage of said (CO)—O bond of an ester or carbonate linkage of the polymer) and an aqueous liquid to provide a reaction mixture. The polymer comprises a (CO)—O bond of an ester or carbonate linkage. The reaction mixture defines a ratio  $\eta$  of liquid volume, in  $\mu\text{L}$ , to total solids, in mg, that is less than 2  $\mu\text{L}/\text{mg}$ . Then, allowing an enzyme-catalyzed reaction of the enzyme with the polymer to take place thereby forming a reaction product.



RAM 5



RAM 5 Continuous



RAM 55



OmniRAM Continuous



OmniRAM H



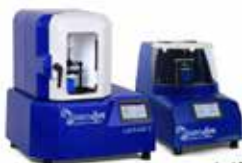
RAM 5 H



RAM 55 H



OmniRAM



LabRAM II



LabRAM I



LabRAM II H



PharmaRAM I



PharmaRAM II

**ResodynMixers.com**