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ResonantAcoustic® Mixing at Work: Research Driving Change in Pharmaceutical Processing

A Collection of Peer-Reviewed Studies from Across the Pharmaceutical Sector

July 2025

This collection features 37 peer-reviewed research papers showcasing ResonantAcoustic® Mixing (RAM) in real-world pharmaceutical applications. The studies highlight RAM's ability to deliver consistent, repeatable results—especially in complex scenarios like **low-dose API blends**, nanoparticle coatings, nanosuspensions, and cocrystal screening. Whether in early-stage formulation or scale-up, RAM demonstrates measurable improvements in uniformity, versatility, and speed across the board.

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Featured: Use of Resonant Acoustic Mixing Technology for Ultra-Low-Dose Blending in a Single-Step Mixing Process

RAM was used to accurately prepare homogeneous mixtures of <0.1% CAF in dilutions of up to 1 part per 8,000. This study presents the first instance of a homogenously mixed <0.1% (w/w) blend using RAM technology and demonstrates the suitability for reproducible dosing of single-digit microgram drug amounts.

See the Report

Featured: Sample preparation techniques to enhance uniformity of Low-Dose blends mixed by resonant acoustic mixing technology

We introduce several effective methods to improve BU results for a lesser compatible formulation for which we had thus far been unable to prepare to acceptable levels of homogeneity to meet AV specification criteria. Simple, practical strategies for overcoming BU issues are proposed assessing a range of techniques, with results demonstrating a powerful potential for RAM performance to be improved upon through only small adjustments to initial sample conditions.

See the Report

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HIGHLIGHTED PUBLISHED ARTICLES

Key Research Findings Using RAM Technology

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High-Throughput Reaction Screening with Nanomoles of Solid Reagents Coated on Glass Beads

Noah P. Tu, Dr. Amanda W. Dombrowski, Dr. Gashaw M. Goshu, Dr. Anil Vasudevan, Dr. Stevan W. Djuric, Dr. Ying Wang

Angewandte Chemie

Glass beads coated with solid chemical reagents (ChemBeads) were developed using RAM technology to enable the delivery of nanomolar quantities of solid chemical reagents efficiently. By exploring the concept of preferred screening sets, the flexibility and generality of this technology for high-throughput reaction screening was validated.

A new and improved method for the preparation of drug nanosuspension formulations using acoustic mixing technology

Dennis H. Leung, David J. Lamberto, Lina Liu, Elizabeth Kwong, Todd Nelson, Timothy Rhodes & Annette Bak

International Journal of Pharmaceutics

We report on a new drug sparing technology utilizing low shear **acoustic mixing** to rapidly identify optimized nanosuspension formulations for a wide range of compounds with dramatically improved material and time efficiencies.

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

Karthik Nagapudi, Evelyn Yanez Umanzor & Colin Masui

International Journal of Pharmaceutics

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.

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Assessment of Resonant Acoustic Mixing for Low-Dose Pharmaceutical Powder Blends
Shashwat Gupta, Yu Elaine Pu, Minglu Li, Zhengmao Li & Juan G. Osorio
AAPS PharmSciTech
Obtaining a homogeneous low-dose pharmaceutical powder blend without multi-step processing remains a challenge. One promising technology to address this risk is **resonant acoustic mixing (RAM**).

A scalable photo-mechanochemical platform for sustainable photoredox catalysis by resonant acoustic mixing
Deshen Kong, Liang Yi, Alice Nanni & Magnus Rueping
Nature Communications
Herein, we present a scalable photo-mechanochemical platform that combines visible-light photocatalysis with **Resonant Acoustic Mixing (RAM)**, enabling efficient cross-coupling reactions under solvent-minimised conditions. This approach demonstrates broad substrate tolerance, accommodating a variety of aryl (hetero) halides and N-, O-, P-, S-nucleophiles. The protocol supports scaling up to 300 mmol, representing a 1500-fold increase, while maintaining exceptionally low catalyst loading and achieving up to 9800 turnover numbers (TON)

Photochemical Stabilization of Self-Assembled Spherical Nucleic Acids
Sepideh Kaviani, Haochen Bai, Trishalina Das, Jathavan Asohan, Abdelrahman Elmanzalawy, Julian Marlyn, Lea El Choueiri, Masad J. Damha, Quentin Laurent & Hanadi F. Sleiman
Nano Micro Small
We selected **resonant acoustic mixing (RAM)**, a solventless mechanochemical method, to accomplish conjugation. RAM exposes materials to high acceleration forces (0–100 g, g = 9.81 m s−2) along a vertical axis by vibrating a reaction vessel at moderate frequency (≈60 Hz), and moderate amplitude (0–1.4 cm).

Rapid, Highly Sustainable Ring-Opening Polymerization via Resonant Acoustic Mixing
Harriet R. Fowler, Riley O'Shea, Joseph Sefton, Shaun C. Howard, Benjamin W. Muir, Robert A. Stockman, Vincenzo Taresco & Derek J. Irvine
ACS Sustainable Chemistry & Engineering
Reported herein is the first combination of **resonant acoustic mixing (RAM)** and controlled ring-opening polymerization (ROP) to deliver fully sustainable, end-functionalized, biodegradable polymers via a manufacturing route with a much-reduced environmental impact.

The effects of resonance acoustic mixing modulation on the structural and emulsifying properties of pea protein isolate
Zhaorui Li, Yungang Cao, Yibing Wang, Yingjie Li, Zhenbin Liu, Zhenbao Zhu, Huan Zhang, Junrong Huang & Youling L. Xiong
Food Chemistry
RAM treatments ranging from 0 to 20 min all had obvious positive effects on improving the emulsifying activity of PPI and the stability of the prepared emulsions, and 15–20 min of treatment exhibited the best enhancement.

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An Automated Robotic Interface for Assays: Facilitating Machine Learning in Drug Discovery by the Automation of Physicochemical Property Assays

Newton P. Wu, Wenyi Wang, Dhireshan Gadiagellan, Mike Counsell, Nikkia K. Hamidi, Yuko Koike & Huy Q. Nguyen

ACS Omega

Devices such as the **LabRam II mixer (Resodyne)** are very well-suited for manual human operation but lack automation ability off the shelf. Early decisions in the project to develop custom automation allowing for the incorporation of fit-for-purpose devices such as the **Labram** were instrumental in the success of ARIA.

Parametric effects on the mixing efficiency of resonant acoustic mixing technology for high-viscosity mixture: A numerical study

Imdad Ullah Khan, Rui Guo, Umar Farooq, Suraj Adhikari & Hao Zhou

Processes

...was used to mix several pharmaceutical blends [2] of active pharmaceutical ingredients (APIs) …
This study established a finite element model of the **resonance acoustic mixing system** in …

Acoustic Synthesis (Solvent-Free) and Resonant Acoustic Mixing (RAM)

Maria Elena Rivas

Mechanochemistry and Emerging Technologies for Sustainable Chemical Manufacturing

Analysis of research conducted to date shows that **RAM** technology offers several advantages over traditional mixing techniques, especially in the field of energetic materials. One of the main advantages is related to the gentle mechanism of mixing in the **RAM** technique, where only minor damage occurs to sample particulates, with no blades or impellers being used in the process. Additionally, the process is also relatively thermally benign, although some temperature excursions have been identified.

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

Minhthi Bui, Paroma Chakravarty & Karthik Nagapudi

Faraday Discussions

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.

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Assessing the interrelationship of microstructure, properties, drug release performance, and preparation process for amorphous solid dispersions via noninvasive

Wei Jia, Phillip D. Yawman, Keyur M. Pandya, Kellie Sluga, Tania Ng, Dawen Kou, Karthik Nagapudi, Paul E. Luner, Aiden Zhu, Shawn Zhang & Hao Helen Hou

Faraday Discussions

Both methods of spray drying and co-precipitation produced single-phase ASDs. Distinct differences in microstructure, particle size distribution, specific surface area, bulk and tapped density, were observed between GDC-0810 spray dried dispersion (SDD) and co-precipitated amorphous dispersion (cPAD) materials. The cPAD powders prepared by the **resonant acoustic mixing** process demonstrated superior compactibility compared to the SDD, while the compressibility of the ASDs were comparable. Both SDD powder and tablets showed higher in vitro dissolution than those of cPAD powders.

Investigation on the impact of resonant acoustic mixing parameters and carrier type on the deposition patterns of Budesonide/Formoterol Fumarate DPI combination product

S Radivojev, M Beretta, V Reinisch, V Rehbein, J T Pinto, E Frönlich & A Paudel

Drug Delivery to the Lungs

For this, a **resonant acoustic mixer** was used and short blending times (30 and 90 s) combined with different acceleration levels (30, 45 and 60 g) were applied. Two different carriers were used (α-lactose monohydrate (αLH) and mannitol (MAN)), while the aerosolization performance was investigated using two types of inhalers, namely Cyclohaler® (CH) and Novolizer® (NOV). Finally, the predicted deposition patterns were evaluated. We found that for αLH blends, homogeneity was achieved with lower blending times compared to MAN containing ones.

Coating Processes of Pharmaceutical Applicability: A Glimpse

Mahammed Athar Alli Saikh

Journal of Drug Delivery & Therapeutics

Amongst them state-of-art process are hot-melt coating (HMC) process, aqueous film-coating process, aerosolized coating process, Supercell® coating process, gas-/ vapour-phase process, photo curable coating process, electrical-electrostatic deposition process, **Resonant acoustic** coating process, thermal and mechanical process, thermo-mechanical process, fluidised-bed processes, etc. Herein conventional, specialised, and novel coating processes are briefed, to update professionals.

Effect of magnesium stearate surface coating method on the aerosol performance and permeability of micronized fluticasone propionate

Virender Kuma, Bharti Seth, Evelyn Yanez, Dennis H. Leung, Yashwardhan Y. Ghanwatkar, Jonathan Cheong, Jerry Tso, Ajit S. Narang, Karthik Nagapudi & Ram I. Mahato

International Journal of Pharamaceutics

In this study, we evaluated the aerodynamic performance, dissolution, and permeation behavior of micronized fluticasone propionate (FP) and magnesium stearate (MgSt) binary mixtures. Micronized FP was dry mixed with 2% w/w MgSt using a tumble mixer and a **resonant acoustic mixer (RAM)** with and without heating.

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Resonant acoustic mixing method to produce lipid-based liquid-crystal nanoparticles
Dilek Yalcin, Sarigama Rajesh, Jacinta White, Shaun C. Howard, Paul J. Pigram, Nhiem Tran & Benjamin W. Muir
Journal of Physical Chemistry C
We have found that when compared to traditional sonication-based methods, the use of **resonant acoustic mixing** allows for large-scale synthesis of nanoparticle solutions and the formation of LLC nanoparticles of desirable sizes. We believe this new technique will facilitate the development of lyotropic mesophase materials and new methodologies for the fabrication of nanoparticles. The technique will have a significant impact in shaping the future of nanoscience, providing a rapid and efficient mixing/fabrication platform for a range of materials...

Complete cocrystal formation during resonant acoustic wet granulation: Effect of granulation liquids
Ryoma Tanaka, Supisara Osotprasit, Jomjai Peerapattana, Kazuhide Ashizawa, Yusuke Hattori & Makoto Otsuka
Pharmaceutics
Resonant acoustic wet granulation (RAG) was devised in an effort to complete theophylline-citric acid (THPCIT) cocrystal formation during the granulation process, thereby reducing the number of operations. In addition, the influence of granulation liquid was investigated.

Vibratory mixing of pharmaceutical powders on a single-tablet-scale
Andreas Kottlan, Benjamin J. Glasse & Johannes G. Khinast
Powder Technology
The process relies on the principle of **vibratory mixing** to achieve a homogeneous powder blend in the order of seconds. To investigate the mixing performance under various frequencies and amplitudes, a contactless evaluation method was implemented based on high-speed video recordings, a colored tracer and image analysis.

Pharmaceutical Cocrystals—A Review
Sheetal S. Buddhadev & Kevin C. Garala
Proceedings
Resonant acoustic mixing has been used to mix the target … In this method, mechanical energy is transferred acoustically into a wetted powder mixture...

Specialised coating processes finding pharmaceutical applicability
Mahammed Athar Alli Saikh & Prithwiraj Mohapatra
Journal of Drug Delivery & Therapeutics
Amongst them some involves state-of-art process/ technology like Supercell coating technology (SCT), Chemical vapour deposition (CVD), Atomic/molecular layer deposition (AMLD), Electrostatic deposition, Thermo-mechanical process, **Resonant acoustic technology**, Fluidised-bed process, Supercritical fluid (SCF) technology, and others. These foundational for commercially availability of specialised equipments like Magnetically Assisted Impaction Coater (MAIC), **Resodyn acoustic mixer**, Hybridizer®, Theta-composer®. Mechanofusion®, and others.

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A novel method for preparing stabilized amorphous solid dispersion drug formulations using acoustic fusion
Zack Guo, Christopher Boyce, Timothy Rhodes, Lina Liu, Gino M. Salituro, Keun-joong Lee, Annette Bak & Dennis H. Leung
International Journal of Pharmaceutics
Herein, we report a novel approach using heated r**esonant acoustic mixing** or "acoustic fusion" to afford a miniaturized method analogous to hot melt extrusion for the generation of amorphous solid dispersions on milligram scale. The acoustic fusion products were investigated for their physicochemical properties and behavior, including drug loading, particle size distribution, morphology, and in vitro dissolution.

Influence of guest and host particle sizes on dry coating effectiveness: When not to use high mixing intensity
Kai Zheng, Kuriakose Kunnath, Zhipeng Ling, Liang Chen & Rajesh N. Davé
Powder Technology
The effects of material stiffness, host and guest particle sizes, and mixing intensity on dry coating quality were investigated using a **high-intensity vibrational mixer**, using KCl, cornstarch, aluminum silicate and nano-sized silica. The coating quality deteriorated with larger guest particle size at high process intensity, and high material stiffness. Coarse guest particles detached from host particles above certain mixing intensity, indicating higher intensity is not recommended; e.g., the best coating quality for cornstarch was for medium-sized hosts below 30 Gs intensity.

Impact of method of preparation of amorphous solid dispersions on mechanical properties: Comparison of coprecipitation and spray drying
Hao Helen Hou, Aniruddha Rajesh, Keyur M. Pandya, Edward Yost, Wei Jia & Karthik Nagapudi
Journal of Pharmaceutics Sciences
Careful choice of manufacturing process can be used to tune material properties of ASDs to make them more amenable for downstream operations like tableting. **Acoustic mixing** has been demonstrated as a scalable new method to make ASDs through coprecipitation.

Applying Dry Powder Coatings | Pharmaceutical ... - PharmTech
Matthew P. Mullarney, Beth A. Langdon, Mark A. Polizzi & Lauren E. Beach
Pharmaceutical Technology
The authors experiment with a **resonant acoustic mixer** as a method for dry powder coating. Efficient handling and transport of fine-particle powders can be difficult because of the highly cohesive nature of the bulk powder mass.

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

Chemical Communications

Adam A. L. Michalchuk, Karl S. Hope, Stuart R. Kennedy, Maria V. Blanco, Elena V. Boldyreva & 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.

Influence of material properties on the effectiveness of glidants used to improve the flowability of cohesive pharmaceutical powders

Divya Sunkara & Maxx Capece

AAPS PharmSciTech

Three pharmaceutical grade glidants (Aerosil 200, Aerosil R972, and Cab-O-Sil M5P) were evaluated and blended with various pharmaceutical actives as well as cohesive excipients common to capsule and tablet formulation. Flowability enhancement was characterized by the flow function coefficient (ff c). An industry-relevant mixer (Turbula mixer) and a highly efficient and effective mixer (**LabRAM vibratory mixer**) were used to further understand the effect of material properties on glidant effectiveness.

Effect of resonant acoustic mixing on pharmaceutical powder blends and tablets

Juan G. Osorio, Koushik Sowrirajan & Fernando J. Muzzio

Advanced Powder Technology

Blending in a **resonant acoustic mixer (RAM)** was shown to be highly effective for low concentrations of cohesive active pharmaceutical ingredients (APIs) and lubricant (Osorio and Muzzio, 2015). However, changes in material properties of the final blend were observed. Those changes, and their effects on tablet characteristics, are discussed in this paper.

Verification of the mixing processes of the active pharmaceutical ingredient, excipient and lubricant in a pharmaceutical formulation using a resonant acoustic mixing …

Ryoma Tanaka, Naoyuki Takahashi, Yasuaki Nakamura, Yusuke Hattori, Kazuhide Ashizawac & Makoto Otsuka

RSC Advances

In this study, in order to apply the **RAM** method to the pharmaceutical blending process, optimization of the operating conditions of **RAM** (acceleration and frequency) was conducted by numerical simulation. Powder mixing experiments were carried out using various **RAM** conditions and also a modified V-shaped mixing device with a powder material of theophylline powder and lactose or magnesium oxide and lactose.

Characterization of resonant acoustic mixing using near-infrared chemical imaging

Juan G. Osorio, Eduardo Hernández, Rodolfo J. Romañach & Fernando J. Muzzio

Powder Technology

Overall, the resonant acoustic mixing performance increased with increasing acceleration and mixing time. Therefore, larger aggregates of the active pharmaceutical ingredient (API) were found at lower accelerations (mixing intensity) and shorter mixing times.

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In-line and real-time monitoring of resonant acoustic mixing…for process analytical technology applications in pharmaceutical powder blending systems
Ryoma Tanaka, Naoyuki Takahashi, Yasuaki Nakamura, Yusuke Hattori, Kazuhide Ashizawa & Makoto Otsuka
Analytical Sciences
Resonant acoustic® mixing (RAM) technology is a system that performs high-speed mixing by vibration through the control of acceleration and frequency. In recent years, real-time process monitoring and prediction has become of increasing interest, and process analytical technology (PAT) systems will be increasingly introduced into actual manufacturing processes. This study examined the application of PAT with the combination of RAM.

Evaluation of resonant acoustic mixing performance
Juan G. Osorio & Fernando J. Muzzio
Powder Technology
An experimental investigation was carried out to study the mixing performance of a laboratory-scale **ResonantAcoustic® Mixer (LabRAM)**. The first part of the study summarizes the results of a fractional factorial design of experiments used to determine the main effects of process parameters (fill level, acceleration, and blending time) on blend homogeneity. Studies were carried out for several blends having various values of particle size, cohesion and concentration of the active pharmaceutical ingredient. The second part of the study describes the LabRAM mixing performance as a function of process parameters (fill level and acceleration) and total blending time.

Development and scale-up of cocrystals using resonant acoustic mixing
David J. am Ende, Stephen R. Anderson & Jerry S. Salan
Organic Process Research & Development
Thus, 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 cocrystallization processes.

Resonantacoustic ® Mixing; Uniform Distribution Of Minor Materials During Powder Mixing
Aditya Vanarase, Juan G. Osario, Fernando J. Mussio, Scott Coguill
JANNAF 36th Propellant and Explosives Development and Charachterization Joint Subcommittee Meeting
The mix uniformity of lactose and acetaminophen powders blended using **ResonantAcoustic ® Mixing (RAM)** technology is compared to mix results obtained using a double-cone tumble blender. Uniformity is determined by the variance in acetaminophen concentration (as measured by near infrared spectroscopy) obtained from numerous small samples collected over the duration of mixing. The optimal **RAM** operating parameters resulted in relative standard deviation (RSD) values for acetaminophen concentration of 0.04 as opposed to 0.08 for the double cone blender. The **RAM** achieved these minimal RSD results in 30 seconds as opposed to 240 seconds for the double cone blender

RAM 5

RAM 5 Continuous

RAM 55

OmniRAM Continuous

OmniRAM H

RAM 5 H

RAM 55 H

OmniRAM

LabRAM II LabRAM I

PharmaRAM I PharmaRAM II

LabRAM II H

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