

Development of a High Throughput Methodology of a Mechanoredox Free Radical
Polymerization Procedure

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Abstract

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High-throughput methodologies are widely applied in polymer research because they enable the efficient exploration of large and complex design spaces. These approaches allow researchers to rapidly test and evaluate diverse reaction conditions, formulations, and polymer architectures. However, many existing high-throughput strategies face notable limitations, including a high degree of specialization that restricts broader applicability, low polymer yield that constrains downstream characterization, and reliance on solution-based reactions that may not be suitable for all systems. Ball mill mechanoredox polymerization is a novel radical based polymerization pathway that produces large volumes of polymers and is virtually solvent free, allowing for the access of unique polymer architectures. This workflow offers a way of producing ball mill mechanoredox polymers in a high throughput capacity. This workflow utilized the Science Jubilee automation platform with custom reaction hardware to produce up to 64 formulations at a time. Results from a polymerization campaign show this methods accuracy, precision, and viability to synthesis polymers in a high throughput manner.

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Chapter 1: Introduction

1.1 High Throughput Polymer Workflows

In recent decades, polymer science has advanced rapidly through innovations in synthesis methodologies, fabrication technologies, and polymer architecture design. These developments have significantly expanded the performance, functionality, and accessibility of polymer-based materials¹. As a result of these advancements, researchers have been transitioning towards high throughput workflows as they provide a systematic way of formulating within a large design space. High throughput methodologies are ideal for targeting optimal reaction conditions, new polymer material screening, and efficient exploration of polymer libraries.

Continuous flow reactors offer advantages over traditional batch-based synthesis. Their modular design can allow for specific reactions in quasi-isothermal conditions which allow for the access of unique kinetic windows. Their small internal volume and high flow rates allow for safe handling of hazardous materials and offer the ability to produce large amounts of polymers daily. Unfortunately, reactors like these can cost several tens of thousands of dollars. Due to their continuous flow, transitioning between formulations is a suboptimal process. Flushing, cleaning, and re-stabilizing the flow adds time and complexity to experimental campaigns. This can limit their suitability for high-throughput screening applications, where rapid testing of many formulations is required².

High throughput flow reactors take advantage of continuous flowing material by attaching characterization labware onto the product stream. For example, these workflows incorporate inline dynamic light scattering, ¹HNMR, and/or Size Exclusion Chromatography (SEC) to characterize polymers immediately after they are synthesized. This method is a very advantageous way of screening through multiple iterations of formulas in a very efficient way. However, these systems are highly specialized as they are limited to the specific inline characterization tests. And even if these polymers were extracted from the reactor workflow, they only produce polymers in small quantities^{3,4}. To test the mechanical, physical, and chemical properties of materials a larger quantity of material is required.

A large number of established high throughput polymerization techniques involve the use of a robotic motion platform. Robotic high-throughput platforms offer substantial advantages in the field of polymer research by supporting high-speed, parallelized formulation with high precision and reproducibility. These systems reduce material consumption, accelerate the exploration of chemical design space, and generate expansive datasets that can be used in combination with machine learning for data-driven new material research. Despite these strengths, robotic platforms can require considerable financial investment and specialized technical expertise for operation and maintenance, presenting a barrier to accessibility. They often exhibit reduced flexibility when transitioning between distinct chemistries, solvents, or

reaction conditions. Certain processes such as oxygen-sensitive or highly viscous polymerizations remain challenging to automate effectively⁵.

1.2 Mechanoredox Polymerization Reactions

Mechanoredox based chemistry has been utilized in many scientific fields of study such as crystal engineering and material science. Recently it has sparked interest in the polymer research as a new synthesis method that offers benefits over traditional thermal and solution-based methods⁶.

As the name implies, mechanoredox involves mechanically inducing the redox step in radical based polymerization processes such as free radical polymerization (FRP) and Reversible Addition Fragmentation Chain Transfer (RAFT). Common mechanical energy sources that have been tested in this application include mortar and pestles, sonication horns, ultrasonic baths, bench top vortexes, and ball mills⁷.

The key to this mechanism is the addition of piezoelectric nanoparticles (PNPs). When a mechanical energy is applied to PNPs, their crystal structure deforms, inducing a dipole that produces an electrical potential. This electrical potential is strong enough to radicalize an initiator within the reaction and leads to monomer chain initiation and polymer chain propagation. An example of a mechanoredox formulation would include monomer(s), PNPs, an initiator salt, and a small amount of solvent for Liquid-Assisted Grinding (LAG). Added liquid content from the LAG solvent help improve the kinetics of the reaction.

Utilizing a ball mill as a mechanical energy source offers the unique benefit of being a virtually solvent free reaction. This makes ball mill mechanoredox polymerization an attractive method for researchers focusing on green chemistry and limiting hazardous solvents. Solvent-free polymerizations also open the door to interesting architectures that previously were not trivial to access. For example, producing a semifluorinated diblock copolymer which contains both a hydrophilic and hydrophobic block is nearly impossible using traditional solution-based techniques due to the lack of a common solvent. Yet block copolymers with this architecture can be synthesized using mechanoredox chemistry due to lack of needing a common solvent. This access to new polymer architectures could mark a massive leap forward in new materials research⁸.

The current process of producing FRP polymers on a ball mill involves individually setting up reactions in 1.5mL stainless steel reaction vials either in open air or an inert glovebox depending on the chemistry. Both the solid and liquid components of the reaction were manually added to each vial along with a 5 mm stainless steel ball bearing. The vials are then individually sealed with a threaded cap to ensure an airtight enclosure.



Figure 1. Traditional reaction vial with ball bearing and threaded cap

The capped vials are then placed into an acrylic block that holds up to 24 vials. Aluminum caps are added to the top and bottom of the holder to contain all the vials and couple to the ball mill. The holder is then inserted between 2 aluminum ball mill clamps that contain the vials while milling and couple to the ball mill arms.

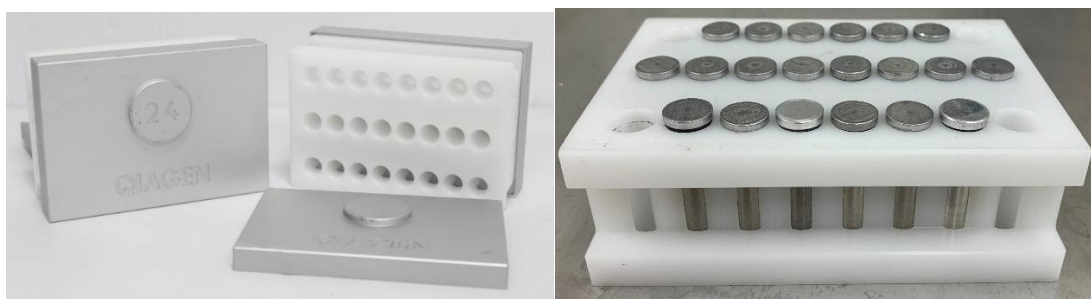


Figure 2. Traditional vial holder and ball mill clamps for a Retsch Mixer Mill (MM 400)

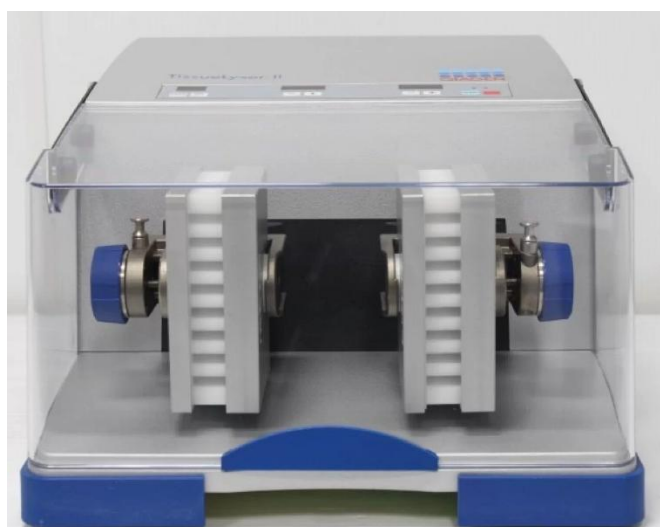


Figure 3. Retsch Mixer Mill (MM 400)

After ball mill processing, each reaction vial contains synthesized polymer, unreacted reactants, PNPs, the ball bearing, and ball mill residue. The synthesized polymers are extracted

from the reaction vials manually or with a solvent such as acetone. Once removed from the reaction vials, the polymers are centrifuged to remove the ball mill residue and some portion of the PNPs. They are then filtered through neutral alumina to eliminate the remaining PNPs and residual reactants. Further trituration in cold methanol is required to remove unreacted monomer and purify the polymer.

1.3 High Throughput Process Limitations

As this process stands, there are three main factors that are keeping it from being high throughput. First is the need for individually capped reaction vials. This process is highly dexterous and time-consuming when dealing with large numbers of formulations. The second limitation is the need for an oxygen free environment. High throughput equipment could theoretically be added inside of a glovebox, but this imposes a critical size and maneuverability constraint that is less than ideal. This also poses an issue when addressing electronic and mechanical maintenance on equipment and hardware. The third limitation is the handling of different reaction components. Mechanoredox reactions involve liquid and solid reactants to achieve polymerization. Most high throughput equipment only can handle one or the other. While very complex and expensive equipment may be capable of performing both tasks, this workflow is designed to provide a more economical alternative.

1.4 Proposed Workflow

This proposed new workflow offers a high throughput methodology of formulating and synthesizing acrylate polymers using ball mill based mechanoredox techniques. By utilizing a robotic platform and custom hardware, this workflow offers an efficient and extensive synthesis method compared to the current state of mechanoredox polymerizations techniques.

This workflow is split up into a solid material and a liquid material handling phase to distribute all the components of the reaction. These reactions are then processed in a ball mill after which they will be processed manually for characterization.

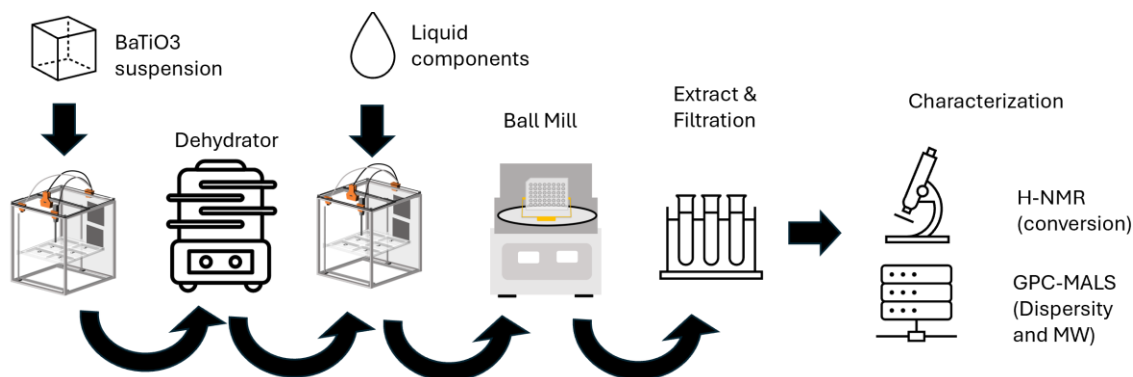


Figure 4. Proposed HTP mechanoredox workflow.

Chapter 2: Materials and Method

2.1 Science Jubilee

Jubilee is an open-sourced, 3-axial motion platform developed by Machine Agency, the research group of Prof. Nadya Peek, at the University of Washington⁹. Jubilee originated as a multilateral 3D printer, but because of its relatively low cost (~1700\$), active community, and tool-changing capabilities, it has also been adopted by researchers to explore high throughput laboratory techniques. Transforming a Jubilee into a “Science Jubilee” involves switching out the 3D printing extruders with various laboratory tools such as pipettes, camera, syringes, and sonication horns. The heated bed plate is replaced with a lab automation deck that secures laboratory hardware to the platform. This workflow will utilize the liquid handling capabilities of Science Jubilee and was interacted with through a Jupyter Notebook interface.

This workflow utilizes 6 hardware slots on the Science Jubilee platform that house the reactions vials at various stages of the workflow and other necessary hardware. Each hardware slot has the dimensions to accommodate a standard 96 well plate and allows a few millimeters of tolerance.

An upgraded version of Science Jubilee was also used for this workflow as part of a collaboration with Duke Vierra at the University of Hawaii Manoa. This version of Science Jubilee replaced the a majority of the 3D printed components of the platform with more robust resin or machine aluminum upgrades, to improve chemical compatibility, and a solid base plate to replace aluminum extrusions. This version of Science Jubilee offers an easier alignment and assembly framework that is chemical resistant and durable.

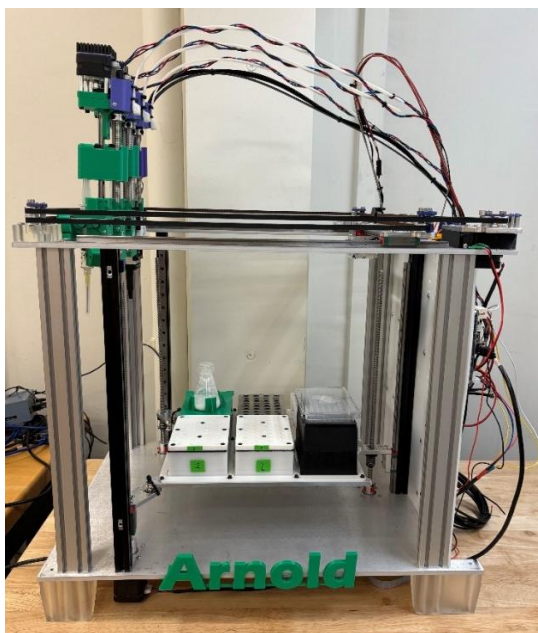


Figure 5. The upgrade Science Jubilee “Arnold” which was used for this workflow.

2.2 Reaction Hardware

The current hardware being used in ball mill mehanoredox reations has limitations that prevent it from being utilized in a high throughput manner. Each reaction vial was indiviually capped before being manually placed into a vial holder. If handling a large quantity of formulations, screwing on caps can be tedious and time consuming. Since Sience Jubilee does not have the capabilities of picking up and screwing on caps onto reaction vials, the new hardware design must address this issue. The hardware needs to beable to accomidate both oxygen tolerent and oxgyen free reactions. To perform oxygen free reactions without setting up a Science Jubilee insde a glovebox, the hardware needs to be capable of adding reaction compenents while maintaining an inert envirnment inside the reaction vials.

2.2.1 Reaction Holder

The new reaction vial holder was dimensionally scaled to integrate onto the Science Jubilee automation deck. Luckily, this scaling still allows for the use of the original top and bottom clamps used to attach to the ball mill. The holder's capacity was optimized to hold a total of 32 reaction vials per holder, allowing for a total of 64 formulations per synthesis. The holder was constructed from a block of Delrin, a high-strength thermoplastic that is chemical resistant and can handle the mechanical forces of repeated ball mill processing.

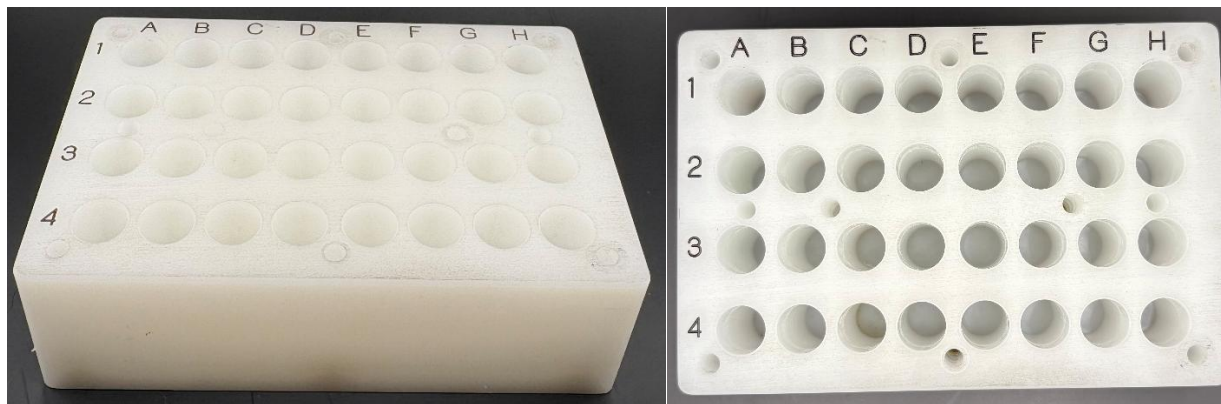


Figure 6. Delrin reaction vial holder

2.2.2 Reaction Holder Lid

A simplified lid assembly was developed to seal the reaction vials to replace the need for individual caps. The lid is secured using 8 M3 socket bolts that screw into heat inserts placed in the base of the reaction vial holder. A layer of 60A, 1/16-inch ethylene propylene diene monomer (EPDM) elastomer is placed in between the vials and the lid. When compressed, the EPDM allows for an airtight seal around each vial. Individual injection sites are located at the top of lid. A syringe can dispense liquid components to reaction vials by piercing though the EPDM elastomer. EPDM is chemically inert to the components in FRP reactions. At this thickness and durometer, the elastomer layer acts like a septa and can withstand the induced forces of the milling process while still allowing the puncturing and sealing from a non-coring needle. The

EPDM elastomers were cut from a 12x12 inch sheet using a Fusion Pro 48 laser machine at default speed and 80% power.

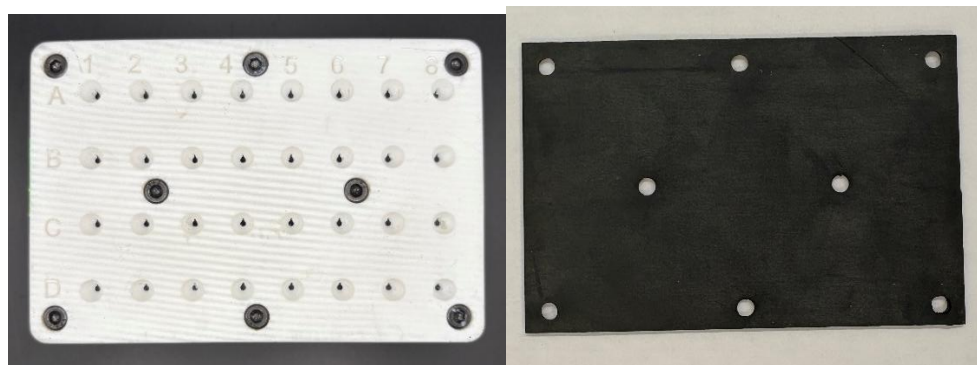


Figure 7. Laser-cut EPDM elastomer sheet

Figure X. New vial holder lid with individual injection sites bolted to vial holder

The injection sites are 1.6mm in diameter and are shaped like a cone at the top to help position a syringe needle for injection.

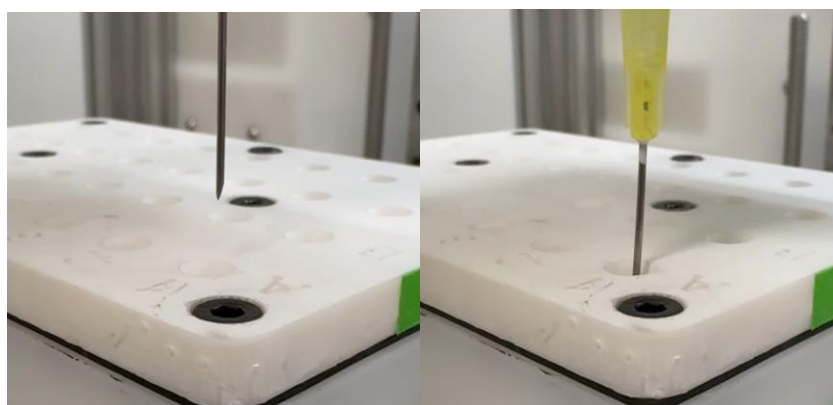


Figure 8. The sloped injection site diverting a syringe needle into a reaction vial.

Initial testing with this design caused material to be expelled from the reaction vials through the injection site during ball mill processing.



Figure 9. The contents inside the reaction vials sprayed out of the injection sites after ball mill processing.

While the ball mill was operating, the ball bearing was impacting the perforated EPDM elastomer as the injection site. By off centering the injection sites to the edge of the reaction vials, the contents of the reaction vials remained inside during ball mill operation.

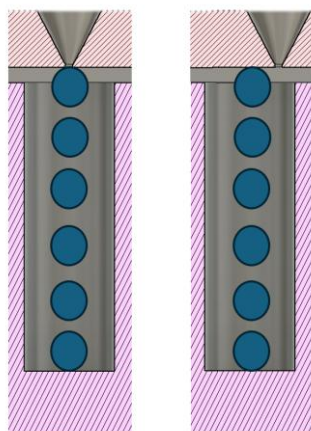


Figure 10. The ball bearing impacts the injection site during ball mill processing (left). Off-centered injection sites avoid these impacts (right).

2.2.3 Ball mill clamp

An updated version of the top clamp was designed to incorporate conical plugs on the inner surface. These plug seal off the injection sites on the lid to help further contain the contents with the reaction vials.

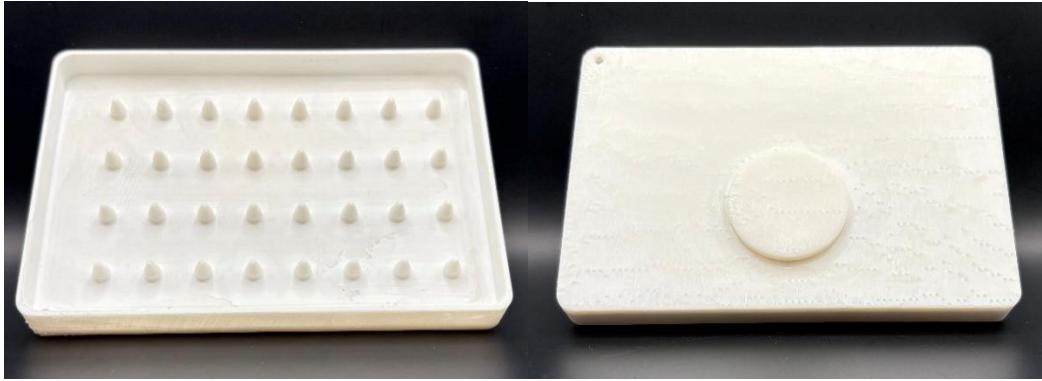


Figure 11. New top ball mill clamp with conical plugs

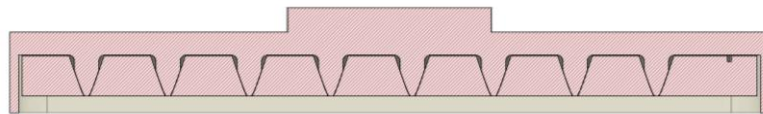


Figure 12. Cross section of the ball mill top clamp plugging the injection sites in the lid.

The lid and top clamp were modeled in Fusion 360 and then prototyped on a Prusa i3 MK3 3D printer in PLA and a Form Lab 3B+ in clear 4K resin. The final versions were resin printed on a Form Lab 3B+ in rigid 10K resin. CAD files for the hardware can be found on this projects GitHub repository ¹⁰.

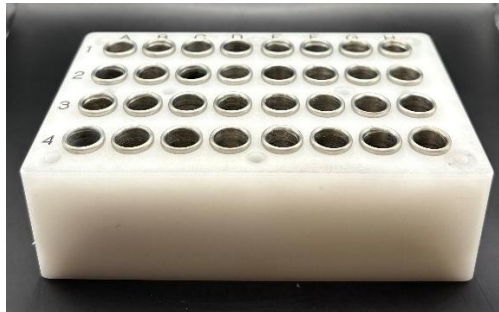


Figure 13. New vial holder with vials, open without lid.

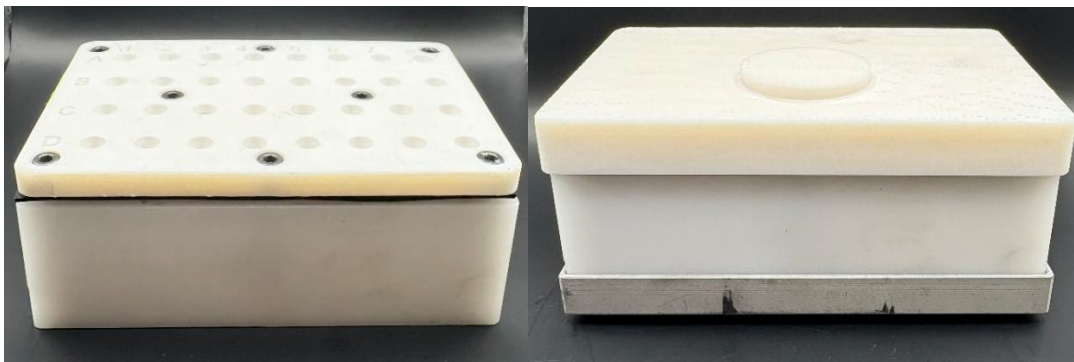


Figure 14. New vial holder with vials, EPDM and lid, sealed with socket screws (left). Sealed vial holder with new top clamp and bottom clamp (right).

2.2.4 Reaction Vials

After numerous cycles of testing this new hardware in the ball mill, a design flaw emerged with the reaction vials that were being used. The original threaded reaction vials contained a thin sharp edge. The compression forces from the lid and mechanical forces from ball mill process were causing the reaction vials to punchout holes in the EPDM elastomer. This exposed the seal around of the vials caused the contents to spill out.



Figure 15. The original reaction vials caused leakage and perforations in the EPDM elastomer.

Alternate elastomer materials and thicknesses were explored but this issue prevailed. This led to needing to find alternate reaction vials. Some aluminum reaction vials were identified as inexpensive and able to be purchased in bulk. These reaction vials contained a rounded edge and kept the elastomer intact during ball mill processing. Unfortunately, due to their thin walls and less durable material, the impacts of the ball bearing caused deformations and perforations in the reaction vials base. Some vials deformed and expanded to the point at which they were unable to be removed from the holder.



Figure 16. Aluminum vials with perforations after ball mill processing (left) and lodged inside a reaction vial holder (right).

As a result, custom vials were commissioned to fit the specifications of the new hardware. These vials were manufactured from a solid rod of 304 stainless steel to retain the durability of the original reaction vials. They include a rounded beveled edge to mimic the edge present on the aluminum vials. After multiple cycles in the ball mill, the custom reaction vials remained intact, and their contents were fully contained.

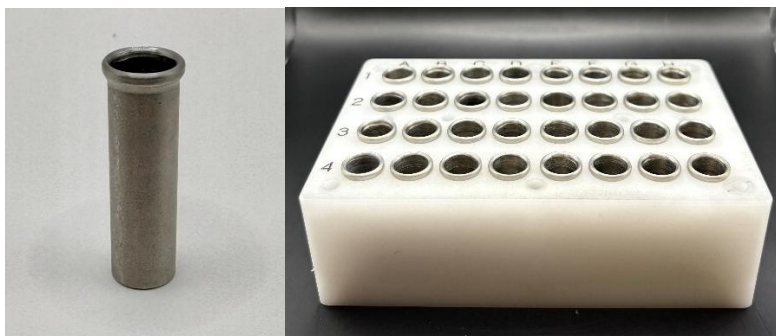


Figure 17. A custom stainless steel reaction vial with rounded beveled rim (left). A full set of vials in a reaction vial holder (right).

2.3 Solid Handling

The first step in this workflow is the handling of the solid components needed for mechanoredox polymerization. Since the initiator salts are typically soluble in the small amount of solvents used for LAG, the PNPs and ball bearing are the only components that need to be delivered as solids. Science Jubilee lacks the ability to independently handle solid components using its current tool library. A solution to this constraint is to suspend the solid PNPs in water using a stir plate. A stir plate was constructed to house a suspension can then be delivered to individual reaction vials in an open vial holder using a liquid handling pipette tool. The reaction vials are then placed in a dehydrator to evaporate off the water overnight for 20 hours at 160 F. Ball bearings are added manually to each reaction vial before or after delivering the PNP.

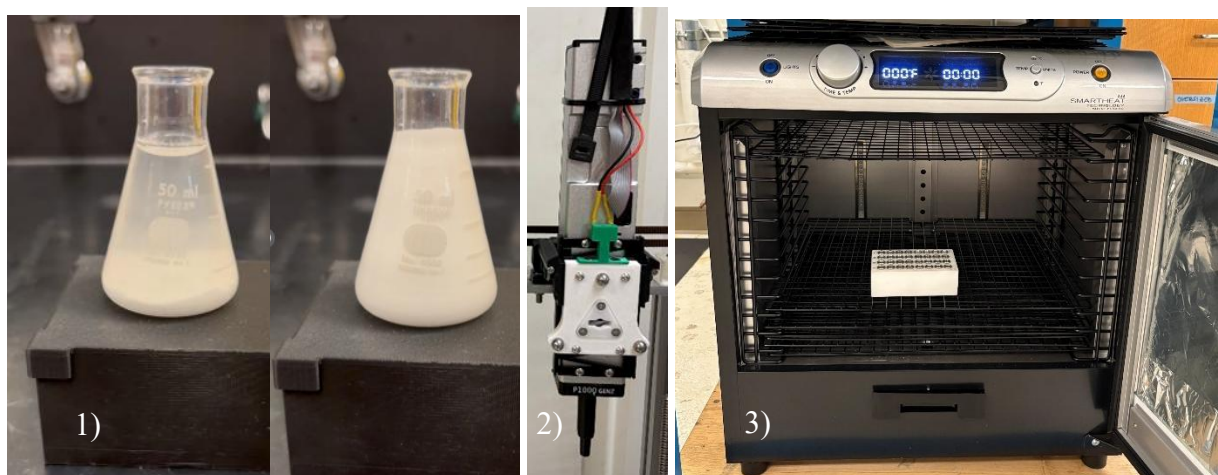


Figure 18. Equipment used in distributing PNPs. 1) A custom-built stir plate used to suspend PNPs in a 50mL Erlenmeyer flask. 2) An Opentron P1000 pipette modified to work on a Science Jubilee. 3) A Cabela's 80-Liter Commercial Food Dehydrator

The required speed and PNP-to-water ratio needed to precisely deposit the desired amount of PNPs to each reaction vial was found using iterative tests. It was found that a ratio of 0.24 parts PNP to 1 part of water in a 50mL Erlenmeyer flask agitated at a moderate rate was able to deliver a large enough and consistent dose of PNP using this method. The results below

are from depositing BaTiO₃ to a full set of 32 vials. This test targeted a mass of 0.14g of BaTiO₃ and measurements were taken every fourth dose.

$$\text{Percent Error (Accuracy)} = 0.49\%$$

$$\text{Percent Error (Precision)} = 7.32\%$$

$$\text{Percent Error (Accuracy)} = \frac{|\bar{M} - M_t|}{M_t}$$

$$\text{Percent Error (Precision)} = \frac{STDM}{\bar{M}}$$

$\bar{M}$ = Mean delivered mass

M_t = Target mass

STDM = Standard deviation of delivered mass

2.4 Liquid Handling

The new ball milling hardware was designed to add liquid components through pierceable injection sites. This implies that this workflow will require syringe tools to distribute the liquid competent of the mechanoredox reaction. There are 2 options for syringe and needle liquid handling on Science Jubilee: the Digital Pipette syringe developed by the University of Toronto and adapted for Jubilee Dr. Brenden Pelkie¹¹ and the 10cc syringe tool developed by Machine Agency by Sonya Vazquez¹². The Digital Pipette syringe tool is assembled using out of the box L16-R miniature linear servos from Actuonix. Its simple design allows for the use of 1 mL, 10 mL, and 20 mL syringes and costs around \$100 per tool. The 10cc syringe tool uses a larger stepper motor and lead screw to dispense from a 10 mL syringe, costing around \$170 per tool.

There are 2 requirements for utilizing a syringe tool in this workflow. First, the syringe tools will be pre-loaded with the total volume required for the full set of 64 reactions. This negates the need for Science Jubilee to aspirate the necessary volume of liquid for each reaction vial before injecting. Secondly, depending on the formulations, the syringe tool is required to accurately dispense volumes on the order of 10 microliters. With these requirements in mind, the minimum deliverable volume of each syringe tool was quantified.

Table 1. Minimum volume dosage data from the 4 options of Science Jubilee syringe tools.

Syringe tool model	Syringe Volume (mL)	Minimum deliverable volume (μL)
Digital Pipette	20	134.11±34.19
Digital Pipette	10	76.43±9.19
Digital Pipette	1	7.59±1.66
10 cc	10	13.91±2.25

$$\text{Percent Error (Accuracy)} = \frac{|\bar{V} - V_t|}{V_t}$$

$$\text{Percent Error (Precision)} = \frac{STDV}{\bar{V}}$$

$\bar{V}$ = Mean delivered volume

V_t = Target volume

STDV = Standard deviation of delivered volume

The 10 and 20 mL Digital Pipette syringe tools minimum deliverable volume was too large for application in a mechanoredox synthesis. Both the 1 mL Digital Pipette syringe tool and 10cc syringe tool fit the small dose resolution required for mechanoredox synthesis. This workflow utilizes 10cc syringe tools due to their larger syringe volume compared to the 1mL Digital Pipette syringe tool to avoid refilling the syringes during the workflow.

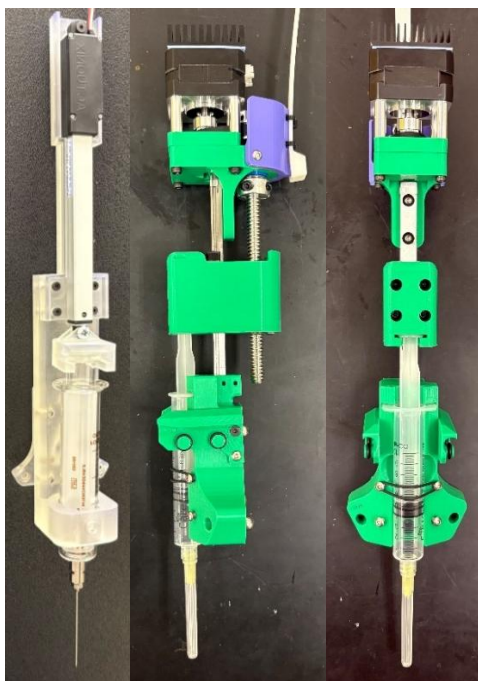


Figure 18. The Digital Pipette syringe tool (left) and 10cc syringe tool (center, right).

Chapter 3: Workflow Validation and Results

3.1 Synthesis Overview

This workflow will target a copolymer FRP campaign containing varying ratios of a low-Tg acrylic monomer N-Butyl acrylate (nBA) with a highly fluorinated monomer 2,2,2-Trifluoroethyl acrylate (TFEA). nBA and TFEA were filtered through basic alumina to remove any MEHQ inhibitor before experimentation. The volume of total monomer volume was held constant at 0.27mL while the ratio of nBA to TFEA varied by 0.03mL.

Diphenyl iodonium hexafluorophosphate (DPIHP) was used as an initiator dissolved in a small volume of DMF for liquid assisted grinding (LAG). Cubic BaTiO₃ (<100 nm size) was used as the PNP. This formulation was based off of the published work by Zeitler in *Diaryliodonium salts facilitate metal-free mechanoredox free radical polymerizations*¹³. To monitor the reliability of this new hardware, each formulation was run in triplicate.

Table 2. Composition and dosing of monomers, solvent, initiators, and PNP used in the parametric copolymerization study.

Component			Amount	
n-Butyl Acrylate	nBA	Monomer	0-270 μ L	2.0mmol total
2,2,2-Trifluoroethyl acrylate	TFEA	Monomer	0-270 μ L	
Dimethylformamide	DMF	Solvent	120 μ L	0.030% v/w
Diphenyl iodonium hexafluorophosphate	DPIHP	Initiator	0.017g	0.04 mmol
Barium Titanate	BaTiO ₃	PNP	0.14g	0.60 mmol

Ten monomer formulations were tested: eight copolymerization formulations in which the ratios of TFEA and nBA were varied by 30 μ L, and two photopolymerization formulations of TFEA and nBA. Since this campaign requires only 30 reaction vials, a single reaction vial

holder is sufficient.

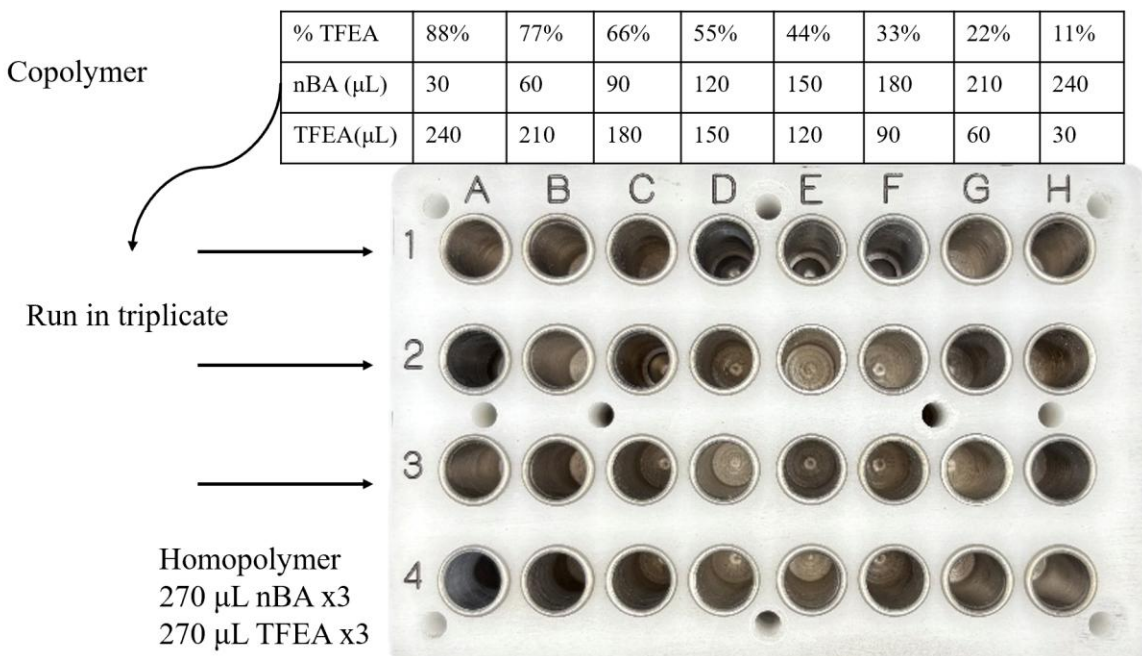


Figure 19. The configuration of formulation for the parametric copolymerization campaign.

Zeitler reported that reactions under these conditions would reach maximum conversion after being processed in the ball mill for 3 hours¹³. Those experiments were performed using the original vials that used stainless steel caps. This workflow removes the stainless-steel cap and replaces with an elastomer layer, effectively halving the number of hard impacts the ball bearing has on the PNPs. Initial testing confirmed this where after 3 hours of milling, no polymerization was observed. Polymerization was observed after increasing the number of hard impacts by increasing the processing time to 4.5 hours. A Retsch Mixer Mill (MM 400) was used to process the polymerization.

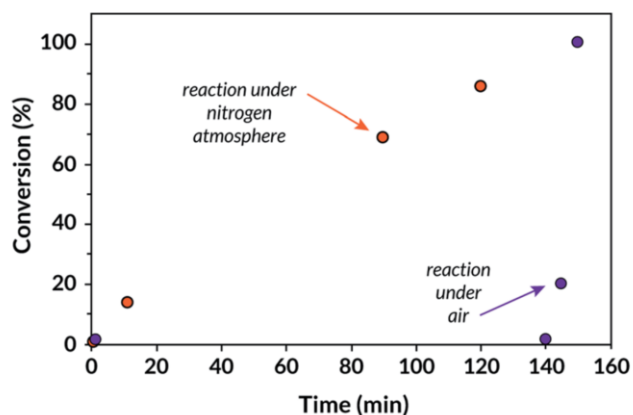


Figure 20. Comparison of BM-mechanoredox kinetics (tBA conversion) in an inert atmosphere and under air¹³.

3.2 Hardware and Tool Setup

This workflow requires 3 separate syringe tools since there are 3 different liquid components in this synthesis. The first two syringes contain the nBA and TFEA monomers and the third syringe contains the DPIHP dissolved in DMF. Each syringe was manually loaded with its component prior to running the workflow. Science Jubilee was programmed to pick up a preloaded syringe and systematically distribute the desired quantity to each reaction vial, starting at the reaction vial located at 'A1' going row by row until reaching 'D6'. Once the first liquid is distributed, the tool was parked, and the second syringe was picked up and distributed. The automation deck includes hardware for distributing BaTiO_3 and for adding the liquid components to 2 sealed reaction vial holders containing BaTiO_3 and a ball bearing. The code used for handling the solid and liquid components of this reaction can be found on this project's GitHub repository¹⁰.

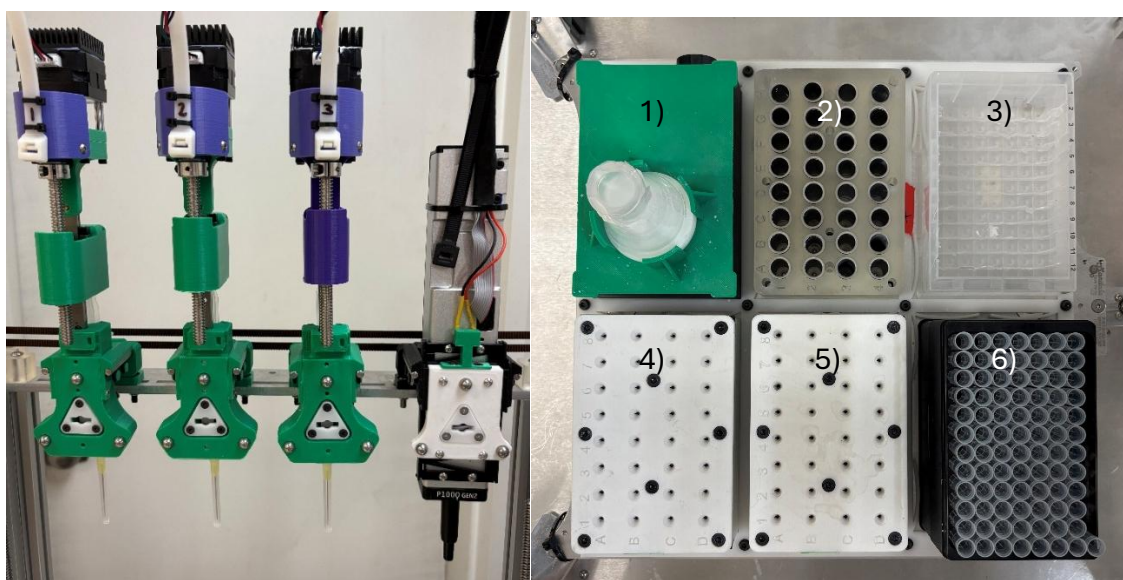


Figure 21. Tool arrangement on a Science Jubilee. Three 10cc syringe tools and an OpenTrons P1000 pipette (left). Science Jubilee's automated lab deck for this workflow (right). 1) Custom stir plate with a 50mL Erlenmeyer flask containing the BaTiO_3 susp

3.2.1 Code and Hardware Check

Before running the campaign, a parametric dye dilution test was run to further confirm the accuracy and precision of the syringe tools and validate the code in charge of controlling the syringe tools. Two syringe tools were loaded with water. The first with DI water and the second with DI water dyed with blue food coloring. By running the same code used for distributing the monomers in this campaign, the total volume of delivered monomers and proper ratios of monomers can be validated. Each reaction vial should contain 0.27g of water and the dye concentration in consecutive vials should change linearly along the row.

This test was run on the first three rows of tared reaction vials. Their final masses were recorded and then a 200-microliter aliquot was taken and dispensed onto a well plate. The plate was taken to a UV-vis spectrometer and absorption data at 630 nm was collected.

$$\text{Percent Error (Accuracy)} = 2.26\%$$

$$\text{Percent Error (Precision)} = 5.03\%$$

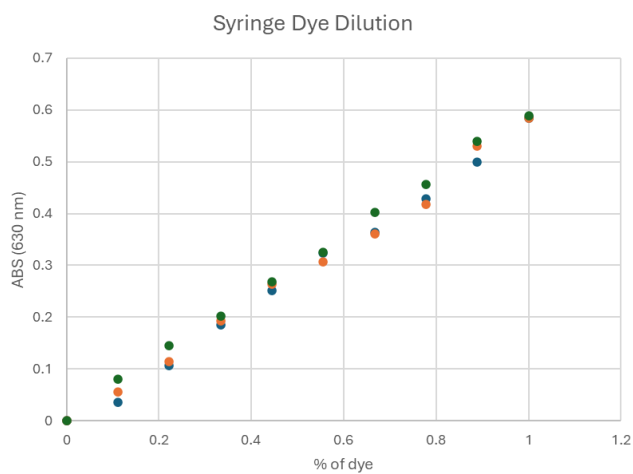


Figure 22. Dye concentration versus Absorbance (630 nm) of a parametric water-dye dilution.

The linear relationship between the dye concentration versus the light absorbance of 630 nm demonstrated the ability of this method to properly conduct a serial dilution of two liquid components. This test demonstrated that the distribution of monomers to each reaction vial exhibited sufficient accuracy and precision to reliably support the parametric campaign.

3.2.2 Processing Modifications

Initial testing of liquid injection into sealed reaction vials revealed that the back pressure was significant enough to expel a small amount of liquid as the needle was withdrawn from the injection site. A needle priming step and aspiration step was added to the code running the syringes to mitigate this from occurring. Reaction vial “D8” was used to prime the syringe before the first injection. The syringe would dispense 60 μ L into the reaction vial and aspirate 80 μ L of air from inside the reaction vial before exiting the injection site. This aspiration technique was utilized after every reaction vial injection. This removed any liquid from the needle and depressurized the reaction vial enough to where no liquid was ejected from the vial or the needle during the liquid handling phase of this workflow. The liquid dispensing code accounts for the absence of liquid in the syringe needle by dispensing an additional 80 μ L per dose. This method of dispensing liquids is still able to achieve high precision and accuracy.

Table 3. Accuracy and precision error calculation of dispensing small volumes of liquids using the Digital Pipette syringe tool and aspiration technique.

Liquid	Target Volume (μL)	Percent Error (accuracy)	Percent error (precision)
Water	50	4.26%	7.44%
Water	30	0.67%	12.68%
nBA monomer	30	3.73%	11.65%

3.3 Results

Not every reaction polymerized. 22 out of 30 reactions showed some amount of polymerization occurred while the remaining 8 reactions showed little to no visible polymerization for a 73.33% success rate.

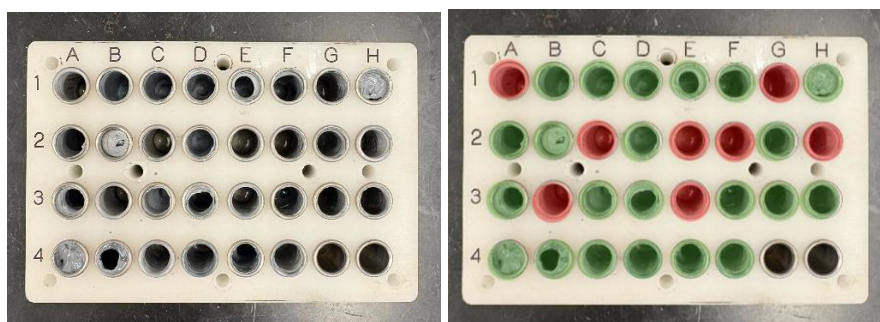


Figure 23. Reaction vials after processing in the ball mill for 4.5 hours (left). Green circles indicate visual polymerization while red circles indicate no visual polymerization (right).

The reaction vials that did not polymerize seem to be random, indicating that the position of the reaction vials in the holder and the components of the formulations are not the cause of a lack of polymerization.

A possible reason for a mechanoredox reaction to not polymerize after ball mill processing is that air could have entered the sealed reaction vial through the injection site. It is been theorized that during the milling process, the oxygen is “scrubbed” from the environment within the reaction vial¹³. Any additional oxygen to the environment during the milling process could hinder this process leading to incomplete polymerization. Another possibility could be that the increased processing time of 4.5 hours is not sufficient to achieve polymerization. More impacts could be necessary to ensure total polymerization across all reaction vials.

3.3.1 Conversion Rate

Since the filtering and extraction of polymers is a manual process in this workflow, only one reaction from each successful formulation was characterized. Notably, the formulation containing 55% TFEA (column D) was the only copolymerization in which all three reactions were successfully polymerized, and all three resulting polymers were characterized.

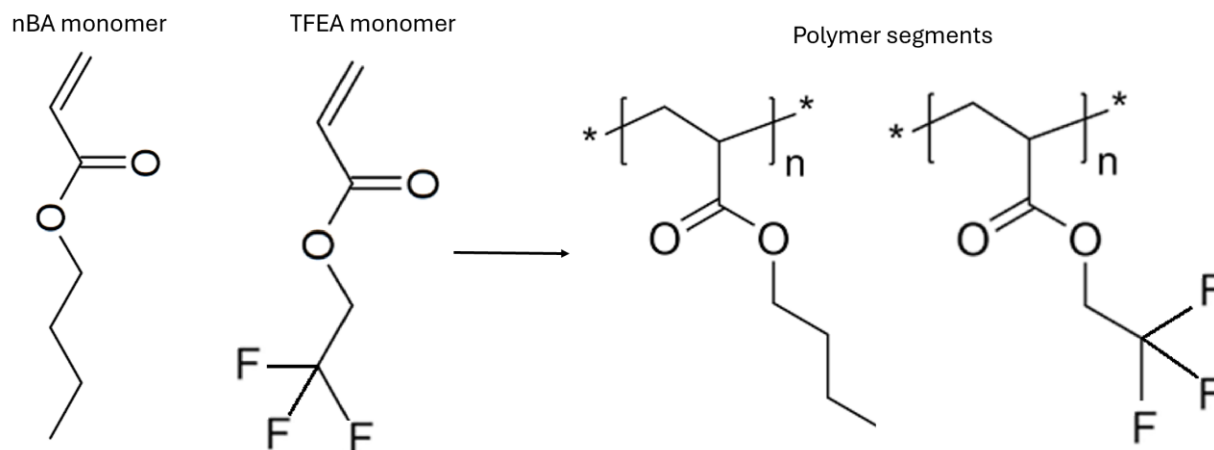


Figure 24. The structure of the nBA and TFEA monomers added to the reaction (left). The structures of the polymer chain segments of the synthesized copolymers (right).

Conversion rates can be calculated using ^1H NMR. ^1H NMR measures how the hydrogen nuclei in molecules respond to a high magnetic field. This provides information on the location and number of hydrogens in a molecule's structure. By comparing the ^1H NMR spectra of the monomers before processing (time 0) and the polymer after processing, the conversion rate of polymerization can be calculated. A time 0 spectra will show a set of triplicate peaks corresponding to the alkene hydrogens of the monomer. Though the alkene peaks are not distinguishable between the nBA and TFEA monomers, their total integration across 6.7-5.8 ppm will capture the total number of alkene hydrogens present before processing. Once the monomers polymerize, the alkene bonds are broken to form the polymer chain. Conversion rate can be calculated by comparing the difference in intensities of the alkene peaks before and after processing. Peak integration is calculated relative to a reference peak seen in both the time 0 and polymer ^1H NMR spectra. The number of methyl hydrogens from the nBA remains constant before and after polymerization. This peak located at 0.95 ppm is used as the relative peak for integration.

$$\text{Conversion}\% = \frac{\text{Time 0 alkene integration} - \text{Polymer alkene integration}}{\text{Time 0 alkene integration}} * 100\%$$

A small aliquot from each reaction vial was diluted in 2mL of chloroform-D and centrifuged. The supernatant was then filtered through neutral alumina into an NMR tube. The ^1H NMR spectra were run on a AV301 using a PABBI-ATMA ^1H {X-BB} probe.

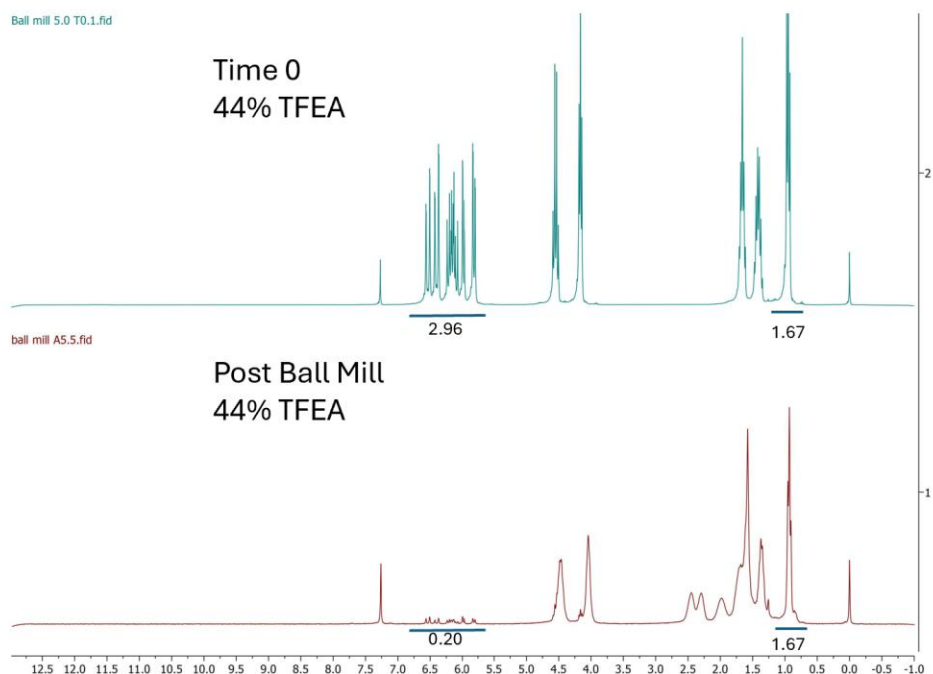


Figure 25. ^1H NMR spectra for conversion analysis: top, formulation 5 at time 0 (55% TFEA monomer); bottom, polymerized formulation 5.

The integration of the methyl peak for both spectra at 0.95ppm is set to 1.67. This was determined by comparing the number of methyl hydrogen compared to the total number of alkene hydrogens present in the formulation.

$$\text{Conversion}\% = \frac{2.96 - 0.20}{2.95} * 100\% = 93.24\%$$

Table 4. Formulation numbers, TFEA content, and resulting polymer conversion for the parametric copolymerization study.

Formulation #	% TFEA	Conversion %
TFEA only	100	91.92
1	88	98.10
2	77	98.06
3	66	99.63
4A	55	91.04
4B	55	96.77
4C	55	95.70
5	44	93.24
6	33	91.35
7	22	96.43
8	11	99.64
nBA only	0	99.32

All tested reactions achieved conversion percentages exceeding 90%, consistent with the results reported by Zeitler ¹³.

3.3.2 GPC-MALS

Gel Permeation Chromatography with Multi-Angle Light Scattering (GPC-MALS) is a characterization method used to determine the molecular weight and size of polymers. In GPC, polymer chains are separated by hydrodynamic volume, with larger molecules eluting first. As the separated polymers pass through the MALS detector, the intensity of scattered light at multiple angles is measured. This allows the calculation of molecular weight (MW) and molecular weight distribution ($\bar{M}_w/\bar{M}_n$) without relying on calibration standards.

A small aliquot from each reaction vial was diluted in 2mL of GPC chloroform and centrifuged. The supernatant was then filtered through neutral alumina further filtered through a 0.22 μ m PTFE chromatography syringe filter into a 1.5mL GPC vial.

While running the samples from this campaign, the GPC-MALS experienced a clog. This caused unusual artifacts in the chromatogram and light scattering (LS) spectra which made calculating accurate molecular weight distribution and molecular weights unobtainable. Due to time constraints these tests could not be run again.

The LS spectra were still able to provide some useful observational data. The spectra below is the LS data from 6 different formulations with varying concentration of TFEA.

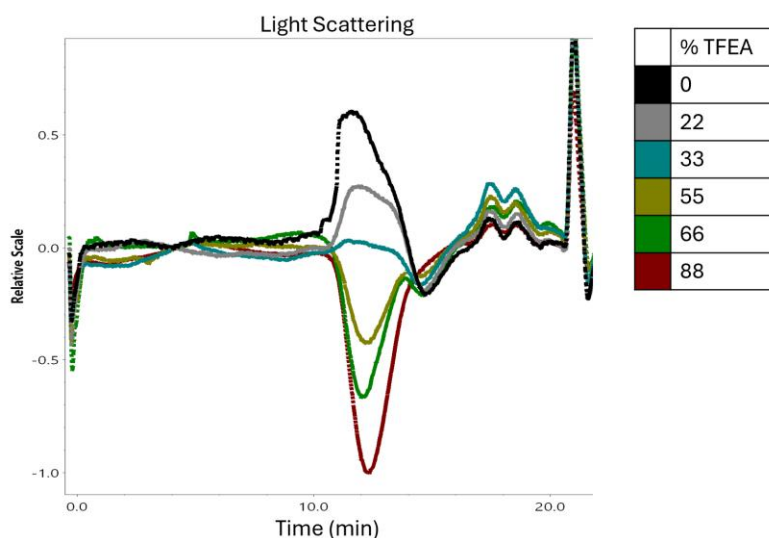


Figure 26. Light scattering (LS) spectra for six formulations from the parametric campaign. Formulations contained 0, 22, 33, 55, 66, and 88% TFEA.

The consistent negative peak around 14 minutes is thought to be an artifact of a clog in the internal tubing of the GPC-MALS. Since each formulation shows a singular peak, it is confirmed that copolymerization occurred for each reaction rather than the formation of 2 homopolymers.

The location of the peaks indicates that the copolymers that were synthesized are in the mega Dalton size range. In MALS, fluorinated polymers can show negative light scattering peaks because their refractive index difference with the solvent (dn/dc) is very low or slightly negative, which reduces the measured scattering intensity.

$$\frac{dn}{dc} = \frac{\text{change in refractive index } (n)}{\text{change in polymer concentration } (c)}$$

The sign and size of the peaks shown in Figure #. show that the polymers that have a higher TFEA concentration have a larger negative peak. As the concentration of TFEA decreases, the peak intensity lessens and eventually flips when the nBA concentration is higher than TFEA.

Chapter 4: Conclusion and Future Work

4.1 Workflow Efficiency

A high throughput workflow aims to perform a high quantity of formulations in an efficient amount of time. This workflow is able to produce 64 different reactions in 6 hours excluding overnight evaporation and manual filtration and extraction. For 64 formulations, dispensing the PNP suspension required 40.02 minutes, dispensing the three liquid components required 50.18 minutes, and processing in the ball mill required 4.5 hours. This is a fraction of the time it would take an individual to create the same 64 formulations manually.

The total amount of polymer produced per formulation varied from 0.15 to 0.25g. Producing polymers at this scale enables the use of multiple characterization techniques per reaction. The larger sample volume also permits mechanical and chemical testing, including chemical resistance, conductivity, and rheological analysis, which traditional high-throughput polymer workflows could not accommodate.

4.2 Future work

The workflow has room for further improvements, optimization and additional steps to make it a more accurate and higher throughput workflow.

Not every reaction polymerized during the campaign. Optimizing the reaction time in the ball mill and conducting further tests on the vial seals would help guarantee complete polymerization in all reaction vials.

An example of potential workflow improvements is illustrated below.

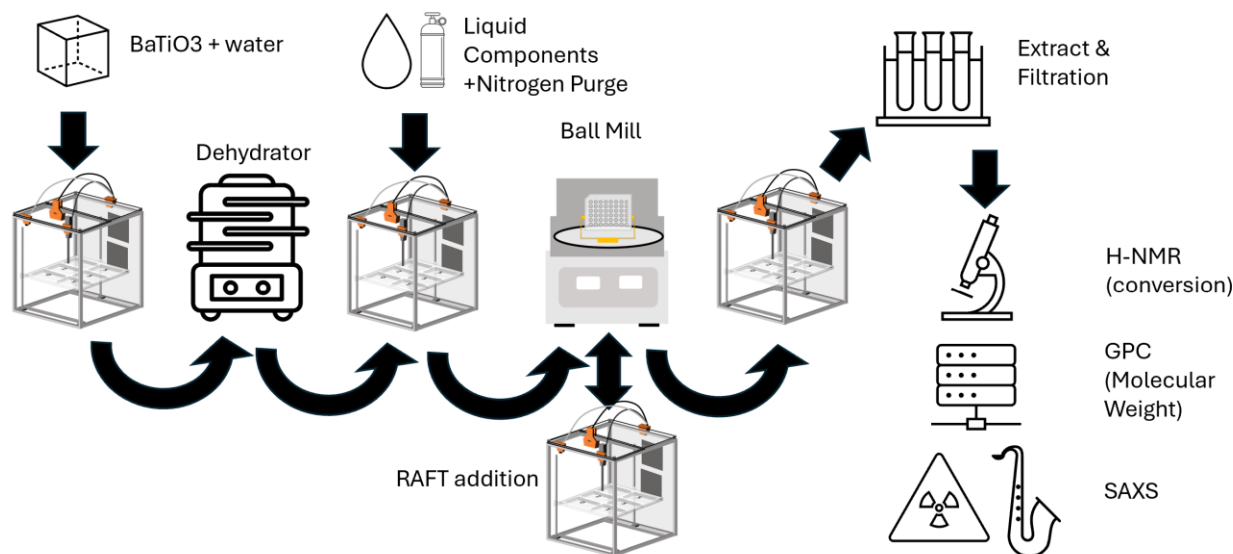


Figure 27. An improved HTP mechanoredox polymerization workflow.

This workflow, in its current state is only capable of synthesizing oxygen tolerant FRP reactions. Oxygen sensitivity remains the primary limitation preventing this workflow from being applied in advanced research, such as RAFT block copolymerization. To accommodate RAFT chemistry, the environment inside the reaction vials must be replaced with an inert gas, mimicking glovebox synthesis. This was a driving factor for the design choice creating an access point where fluids can be added into sealed reaction vials. Using this same access point, a purging tool could be integrated into this workflow. By using a nitrogen tank and a coaxial needle, a researcher could replace the air inside the reaction vials with nitrogen. This would mimic synthesis in a glovebox and could lead to more controlled and advanced polymerizations.

The most time consuming and manual step in this workflow was filtering and extracting the polymers after they had been processed in the ball mill. Science Jubilee has the ability to handle the liquid solvents so theoretically some of the manual aspects of this process could be replaced. Integrating this step into the workflow to some degree would greatly improve the high throughput nature of this workflow.

If this workflow is improved to accommodate more complex chemistries and polymer architecture, the addition of more advanced characterization techniques can be utilized. Small-Angle X-ray Scattering (SAXS) is a common characterization method used to quantify the structure of block copolymers ⁷. This technique has been utilized in a or the fully automated synthesis and characterization of colloidal mesoporous silicas using Science Jubilee ¹⁴.

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