Electronic Supplementary Material (ESI) for Polymer Chemistry.

Supporting Information: Design rules for performing water-sensitive polymerizations in an aqueous dispersion

*Danielle D. Harrier & Damien Guironnet**

Department of Chemical and Biological Engineering, University of Illinois, Urbana-Champaign, Illinois, 61801.

*corresponding author: (D.G). Email: guironne@illinois.edu

Materials and reactant preparation and storage

ROP of delta-valerolactone. The reactants δ-valerolactone (VL), 1,3 diphenylurea, and potassium methoxide (KOMe) were purchased from Sigma Aldrich. Proper monomer preparation is vital to ensure that the monomer solutions are free of impurities and completely dry. The δ-valerolactone (VL) was distilled and stored at 4˚C under anhydrous conditions. All preparation materials (syringes, vials, needles, etc.), and solvents (THF and toluene) were dry and stored under anhydrous conditions. All batch polymerizations were performed inside the glovebox. While all subsequent solutions used during the fast quench and droplet generation experiments were prepared inside the glovebox, loaded onto the appropriate glass syringes, and the capped syringes were brought out of the glovebox and attached to the microfluidic device.

ROP of propylene oxide. The reactants propylene oxide, tributylborane, phosphazene base P2-Et, and octanol were purchased from Sigma Aldrich. All reactants were stored under inert atmosphere. The octanol was distilled before storage and subsequent use. All solutions were prepared inside the glovebox, loaded onto appropriate glass syringes, and the capped syringes were brought out of the glovebox and attached to the microfluidic device.

Amphiphilic block copolymers. The Pluronic (14600 g mol^{-1}) and all reactants needed for the synthesis of the amphiphilic block copolymers (PEG-PVL, PEG-PLA, and PEG-PCL) including methoxy poly(ethylene glycol), 3,6-dimethyl-1,4-dioxane-2,5-dione, ε-caprolactone, triazabicyclodecene, and tin(II) 2-ethylhexanoatemethoxypolyethylene glycol, δ-valerolactone, were purchased from Sigma Aldrich. All synthesis were performed under inert atmosphere.

Droplet-based microfluidic device

Fast quench vs droplet configuration. The off-the-shelf droplet-based microfluidic device can be operated in two configurations.[1] The first is the fast quench configuration where the hypodermic tubing dispersed phase outlet tip can be inserted into the quench solution. This configuration allows us to precisely determine the conversion and molecular weight at each specific flow rate before droplet formation. The second configuration is the droplet generating configuration where the hypodermic tubing is threaded through a secondary cross tee where the continuous aqueous phase is being supplied. On the opposite end of the tee the hypodermic tubing is centered inside the glass capillary allowing water to completely sheath the hypodermic tubing and shear the dispersed phase off into droplets continuously, ***Figure S1***.

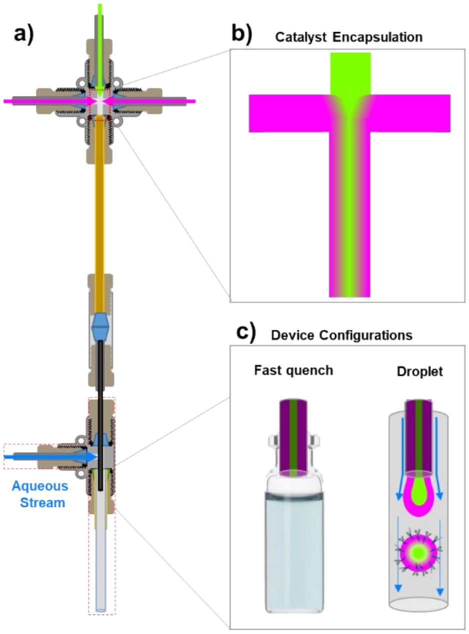


Figure S1: a) Off-the-shelf droplet-based microfluidic device. b) The water-sensitive catalyst is sheathed between two streams of monomer solutions c) Graphic showing the fast quench configuration and droplet generating configuration that the device can be operated in.

Device design materials and assembly specifications. The microfluidic device we designed is made from all commercially available components. **Figure S2** shows a cross-section of both intersecting flow points the co-flow droplet generating microreactor. The microreactor consists of one PEEK 0.02” thru hole cross assembly and one PEEK 0.02” thru hole tee fitting purchased from IDEX Health & Science. Input flow was supplied by three syringe pumps with glass syringes connected to $^{1}/_{16}$” OD, 0.02” (177.8 μm) ID PEEK tubing, which was also purchased from IDEX. Connecting the two fittings is a 3” piece of 25G thin wall stainless steel hypodermic tubing with a 0.02 OD, 0.012 ID purchased from Component Supply. One end of the metal tubing was inserted into a piece of the $^{1}/_{16}$” PEEK tubing to seal an end on both fittings, while the other end of the metal tubing was entirely threaded through the tee. The glass capillary was inserted into 1/8” PEEK tubing and positioned at the opposite end of the tee. This allowed enough space for the water to flow through the gap around the metal tubing to shear off the droplets.

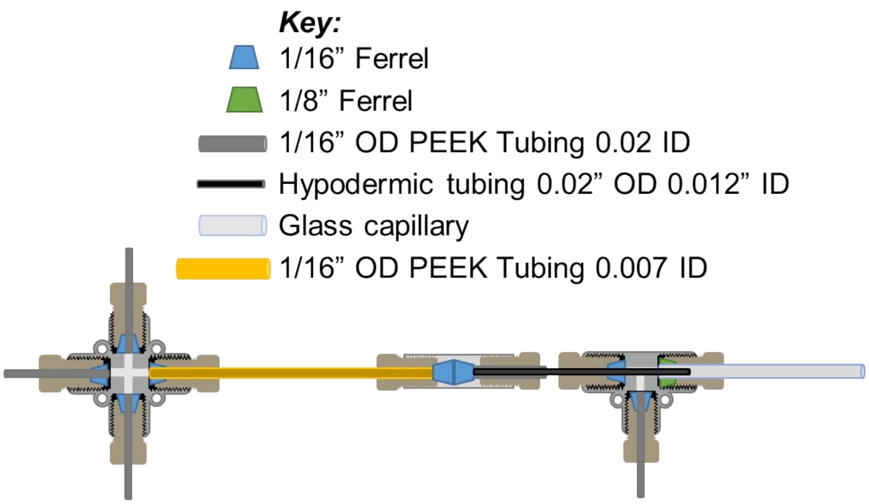


Figure S2: Droplet generating co-flow microfluidic device with all components listed

Dripping Flow Regime. To successfully encapsulate the catalyst within the center of the droplet and allow the catalyst the longest amount of time for polymerization we must operate in the dripping regime. In the dripping regime the droplets are formed close to the tip of the tube with strict periodicity.[2] Whereas the jetting regime has droplet formation at the end of a jet, ***Figure S3a.*** In the jetting regime there is a larger surface area being exposed to the aqueous phase before droplet formation, which leads to faster quenching of the catalyst.

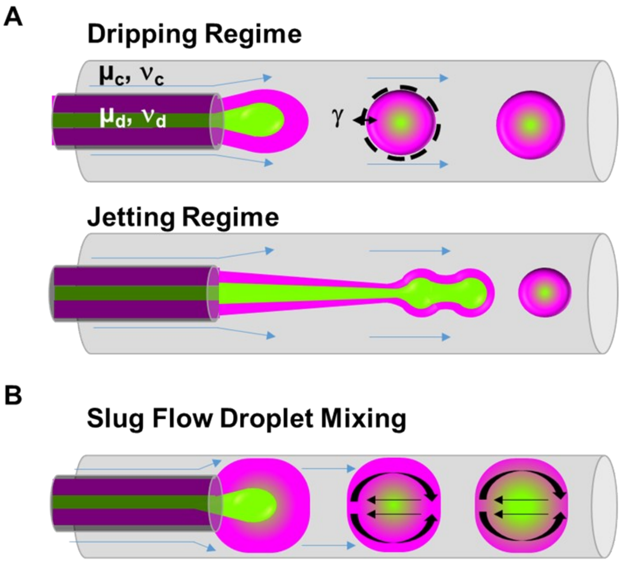


Figure S3: A)Undesired jetting regime versus desired dripping regime B) Droplet mixing induced from slug flow

It is also undesirable for the regime to switch into the slug flow regime, where the droplets fill the cross-section of the glass capillary tube. In this regime the slug’s internal fluid circulates very effectively due to high shear interactions with the glass capillary wall. The faster mixing owing to the twirling effect and recirculating flow would lead to faster quenching of the catalyst within the droplet, ***Figure S3b.***[3,4]

General synthesis of Amphiphilic Block Copolymers (ABC)

PEG-PLA. A solution of the catalyst DBU (0.069 mmol 1eq) and 3000 g mol^{-1} mPEG (1eq) in 3mL of DCM was prepared in a glovebox in a 20 mL vial. A separate solution of the lactide (100eq) in 5 mL of DCM was also prepared in a separate vial. The two solutions were mixed and quenched after 15 min with benzoic acid.[5] The ABC is then precipitated in diethyl ether and hexane (1:1) and dried via high vacuum.

PEG-PVL. Similarly a solution of the 1,3 diphenylurea (3eq), potassium methoxide (0.142 mmol 1eq) and 2000 g mol^{-1} mPEG (1eq) were dissolved in THF in a glovebox. A separate solution of δ-valerolactone in THF was also prepared. The two solutions were mixed and quenched after 60s with benzoic acid. The ABC is then precipitated in diethyl ether and hexane (1:1) and dried via high vacuum.

PEG-PCL. A solution of the tin(II) 2-ethylhexanoate(0.098mmol 1eq), 5000 g mol^{-1} mPEG (1eq), and ε-caprolactone were added to a round bottom flask with a stirbar and sealed with a septum. The round bottom flast was taken out of the glovebox, attached to a Schlenk line under N_2, and the temperature was brought to 120˚C for 6hrs. The reaction was quenched with benzoic acid.[6] The ABC is then precipitated in diethyl ether and hexane (1:1) and dried via high vacuum.

Table S1: Amphiphilic block copolymer composition and block molecular weights

Composition	PEG wt%	Mw_{total}	Mw_{blockA_PEG}	Mw_{blockB}	HLB
Pluronic[a]	82.5	14600	12000	2600	16.5
PEG-PCL	35.4	13300	5000	8300	7.08
PEG-PVL	33.1	6500	2000	4500	6.12
PEG-PLA	43.1	7300	3000	4300	8.6

Polymer product analysis and characterization

To measure the success of the catalyst encapsulation and protection from the aqueous phase, we analyzed both the fast quench and droplet samples with gel permeation chromatography (GPC) for the molecular weight and gas chromatography (GC) for monomer conversion. The GC analysis of conversion is a powerful tool to monitor the decrease in monomer with respect to an internal standard. The validity of this method relies on an accurate determination of the initial monomer-to-internal standard ratio,[3] which we obtained by taking a preliminary sample of the solution before starting the polymerization. For our system, we employed decane as our internal standard as it is stable during the polymerization and analysis. It is important to note that the internal standard was added to the monomer phase so the initial monomer-to-internal standard ratio sample would be taken from the same solution. Additionally, the quantity of the internal standard was shown to be an important factor, as too small of a quantity of internal standard does not allow sufficient precision for the accurate determination of conversion over time.

GPC Data Processing and Dispersity: We utilize the EcoSEC software associated with our GPC to perform the data processing associated with obtaining molecular weight and dispersity. We do not rely on the automatic integration of each peak, instead we edit every peak individually to ensure we include the entirety of the peak and any peak tailing. We draw a straight baseline from the furthest left bound of the peak to the furthest right bound of the peak. Care is taken to make sure that our baseline is not is not higher than the original baseline or sloping.

We have found that the dispersity of the polymers obtained from the microfluidic droplet-based system are higher than in batch. Additionally, when comparing the fast quench configuration samples to their droplet configuration counterparts we also see an increase in dispersity of the polmer produced, ***Figure S4.*** We attribute the increase in dispersity to the initiation of small polymer chains by the water after droplet formation, and nonhomogeneous quenching of the catalyst within the particle due to water diffusion.

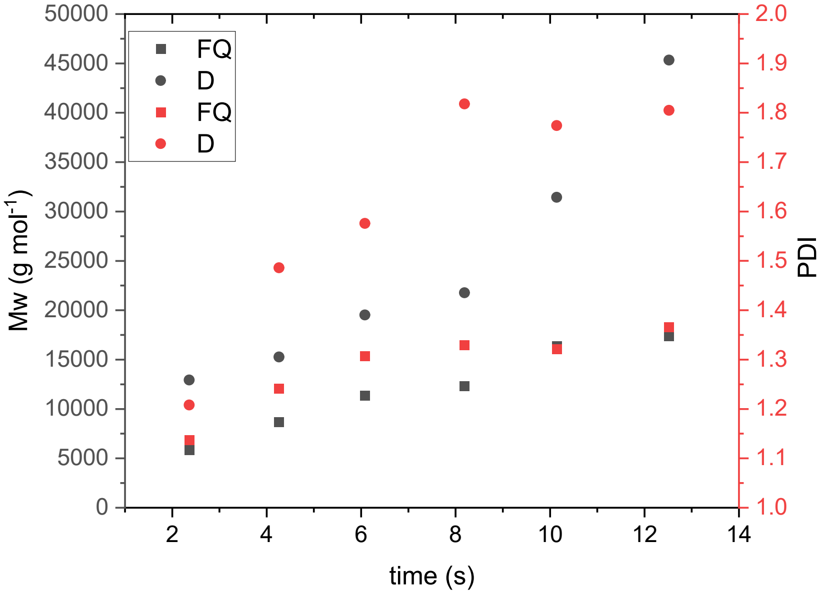


Figure S4: Fast quench and droplet molecular weight and dispersity (PDI) obtained from the GPC. The droplet configuration produces more dispersed polymer than the fast quench due to small polymer chain initiation and nonhomogenous quenching of the catalyst.

We start our polymerization with a living system, but because the initiation and quenched are occurring in a non-homogeneous mixture we observe tailing in the MWD. The dispersity is indicative of this tailing but the visual of the GPC traces is more insightful. ***Figure S5.*** In this figure you can see broadening of the peaks with increase in rt within the reactor.

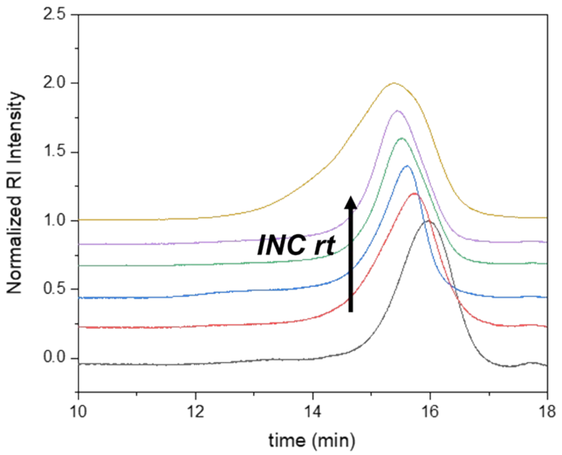


Figure S5: A series of GPC traces showing the molecular weight distribution broadening an tailing due to the initiation and quenching happening simultaneously in the non-homogeneous disperse phase.

ROP of δ-valerolatone with the addition of ABCs and hydrophobes

To ensure that the addition of amphiphilic block copolymers (ABC)s did not negatively affect the ring opening polymerization kinetics we first tested the formulation in batch. With a 1 wt% loading of ABC we saw that the PEG-PVL, PEG-PCL, and Pluronic all reached high molecular weight (20 kg mol^{-1}) and high conversion (X>90%) in 20 seconds, ***Figure S6***. The only ABC that showed a negative impact on the ROP kinetics was PEG-PLA where the maximum molecular weight was around 6 kg mol^{-1} and the maximum conversion attainable was around 30%.

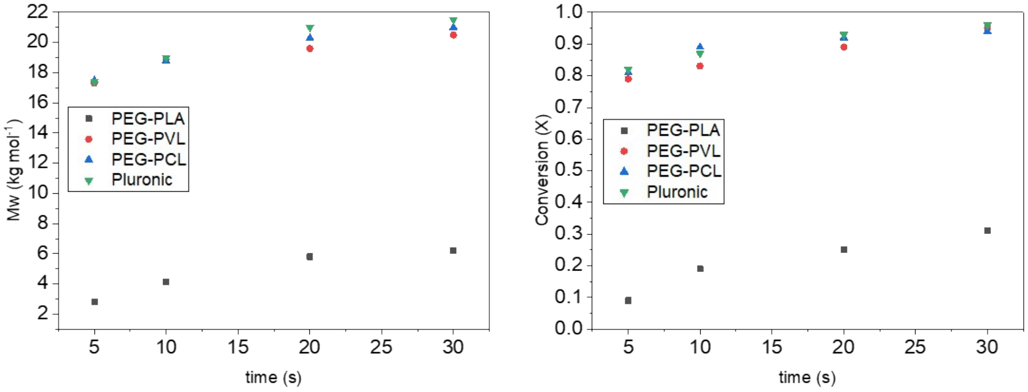


Figure S6: Batch polymerization results from the ROP of delta-valerolactone with 1,3 diphenylurea with the addition of the amphiphilic block copolymers

Similarly the addition of hydrophobes was tested in batch. The hydrophobe that showed the least negative impact to the ROP kinetics was hexadecane. We saw that with the addition of 0.4M hexadecane the batch polymerization was still able to reach high molecular weight (20 kg mol^{-1}) and high conversion (X>90%) in 20 seconds, ***Figure S7***.

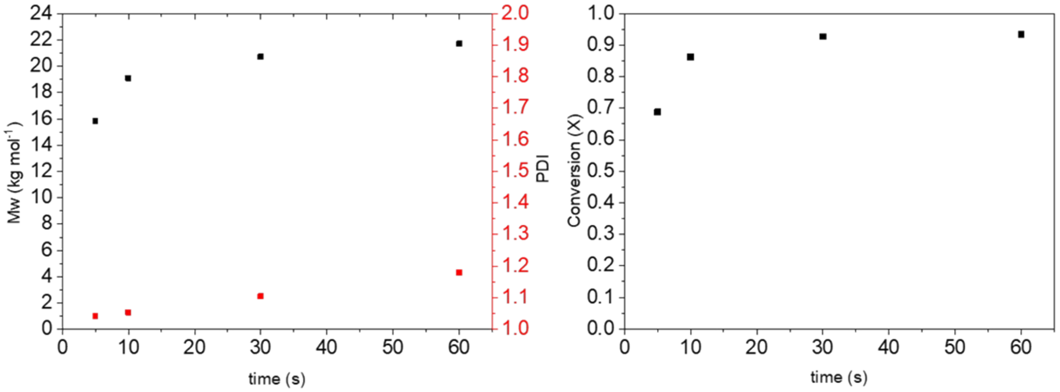
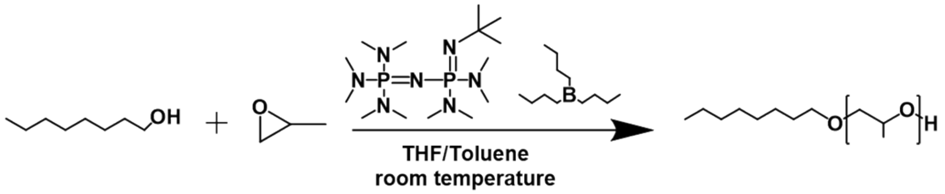


Figure S7: Batch polymerization results from the ROP of delta-valerolactone with 1,3 diphenylurea with the addition of the amphiphilic block copolymers and hexadecane.

ROP of propylene oxide with organobase and tributylborane

To illustrate the versatility of our system we expanded to another water-sensitive ROP chemistry, ***Scheme S1***. The ROP of propylene oxide via an organobase and tributylborane with octanol as an initiator was chosen for two reasons: firstly, this chemistry is also known for being able to reach high molecular weight polymer with low dispersity, and secondly, the reaction is highly reactive and exothermic. By choosing a very reactive chemistry we could show the benefit of using a small reaction volume flow system such as our droplet-based microfluidic device. We can safely increase the co-catalyst loading within our device to levels that in batch would be unsafe and highly exothermic.

Scheme S1: Ring-opening polymerization of propylene oxide



Device design modification for the ROP of epoxides

Small modifications were made to the droplet generating microfluidic device to allow the implementation of the epoxide ROP chemistry, ***Figure S8***. The possibility of clogging the device due to the high reaction rate and quick increase in viscosity combined with the high exothermicity of the polymerization of propylene oxide prompted us to optimize the device. Firstly, we moved the flow system into a chemical reaction hood as the first safety measure. Secondly, we increased the length of the tubing entering the main cross-tee to 3ft coils. Increasing these portions of tubing would ensure that if the device did clog there would not be any backflow into the syringes leading to a runaway reaction.

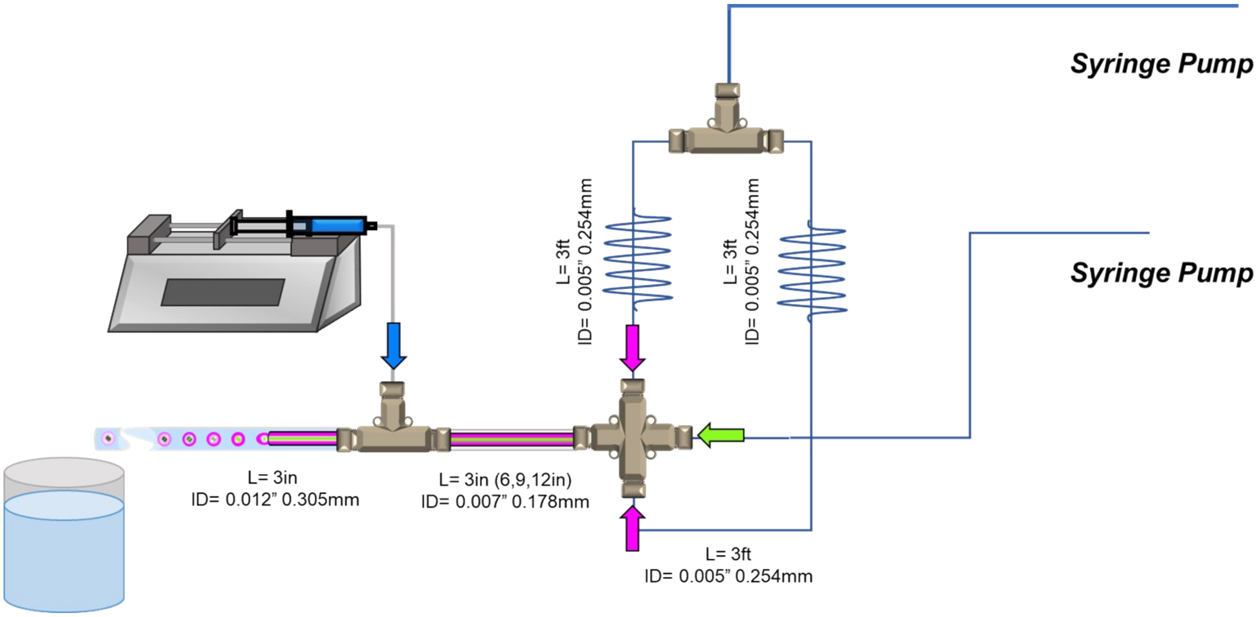


Figure S8. Modified device design, removing small diameter tubing after the cross tee.

In an attempt to further increase the molecular weight attainable with the PO ROP we added in a crosslinker, 1,4-butanediol diglycidyl ether. With a 1wt% addition of the crosslinker we saw a dramatic increase in viscosity of the solution compared to the formulation without the crosslinker. This increase in viscosity could very easily clog the system at longer residence times, therefore we only operated the system with flow rates that resulted in less than 10 second residence times within the device. With the addition of the crosslinker we saw an increase at rt = 9.5s from 26% to 41%, ***Figure S9.***

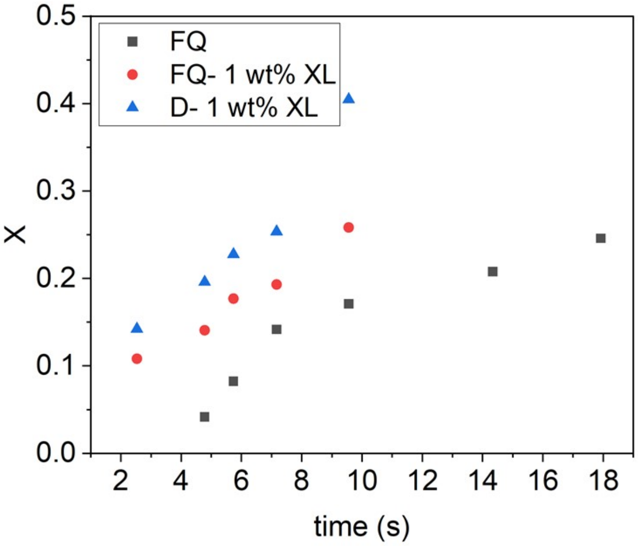


Figure S9. Ring opening polymerization of propylene oxide with the addition of 1wt% 1,4-butanediol diglycidyl ether as a crosslinker

References:

(1) Harrier, D. D.; Kenis, P. J. A.; Guironnet, D. Ring-Opening Polymerization of Cyclic Esters in an Aqueous Dispersion. *Macromolecules* **2020**, *53* (18), 7767–7773.

(2) Shen, C.; Liu, F.; Wu, L.; Yu, C.; Yu, W. Dripping, Jetting and Regime Transition of Droplet Formation in a Buoyancy-Assisted Microfluidic Device. *Micromachines* **2020**, *11* (11), 962.

(3) Tanthapanichakoon, W.; Aoki, N.; Matsuyama, K.; Mae, K. Design of Mixing in Microfluidic Liquid Slugs Based on a New Dimensionless Number for Precise Reaction and Mixing Operations. *Chem. Eng. Sci.* **2006**, *61* (13), 4220–4232.

(4) Li, Y.; Reddy, R. K.; Kumar, C. S. S. R.; Nandakumar, K. Computational Investigations of the Mixing Performance inside Liquid Slugs Generated by a Microfluidic T-Junction. *Biomicrofluidics* **2014**, *8* (5), 054125.

(5) Maikawa, C. L.; Sevit, A.; Lin, B.; Wallstrom, R. J.; Mann, J. L.; Yu, A. C.; Waymouth, R. M.; Appel, E. A. Block Copolymer Composition Drives Function of Self-Assembled Nanoparticles for Delivery of Small-Molecule Cargo. *J. Polym. Sci. Part A Polym. Chem.* **2019**, *57* (12), 1322–1332.

(6) Gupta, M. K.; Walthall, J. M.; Venkataraman, R.; Crowder, S. W.; Jung, D. K.; Yu, S. S.; Feaster, T. K.; Wang, X.; Giorgio, T. D.; Hong, C. C.; et al. Combinatorial Polymer Electrospun Matrices Promote Physiologically-Relevant Cardiomyogenic Stem Cell Differentiation. *PLoS One* **2011**, *6* (12), e28935.