Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Development of a Continuous Melt Reactor for an Acid-Mediated Decarboxylation

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Contents

S1. Initial plate reactor feasibility studies

The first plate prototype contained four heating cartridges and had an S-shaped flow path (Figure S1). Heating tests were performed prior to any reaction studies to ensure that the plate could reach the reaction temperature, and to evaluate the temperature gradient from the heating cartridges to the plate surface. Figure S2 shows the heating cartridge internal temperature profiles for the four heaters, indicating good control of the heater temperatures at the setpoint of 250 °C using proportional-integral-derivative (PID) control of the pulse width modulation (PWM) duty cycle for the solid-state relays used to modulate power delivered to the heaters.

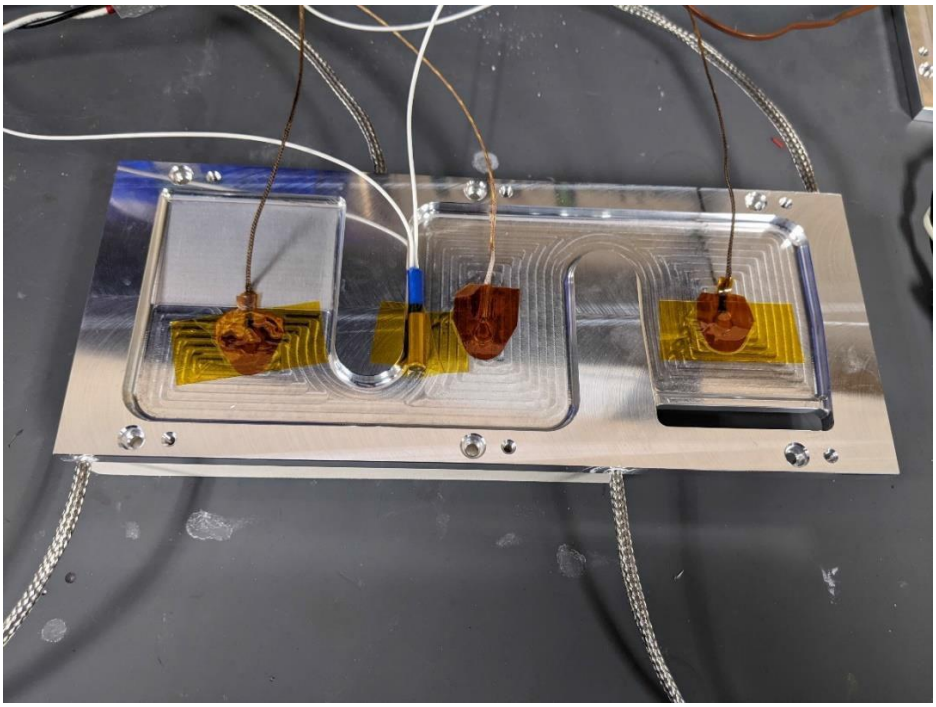

Figure S1. Heating testing setup of the first plate prototype

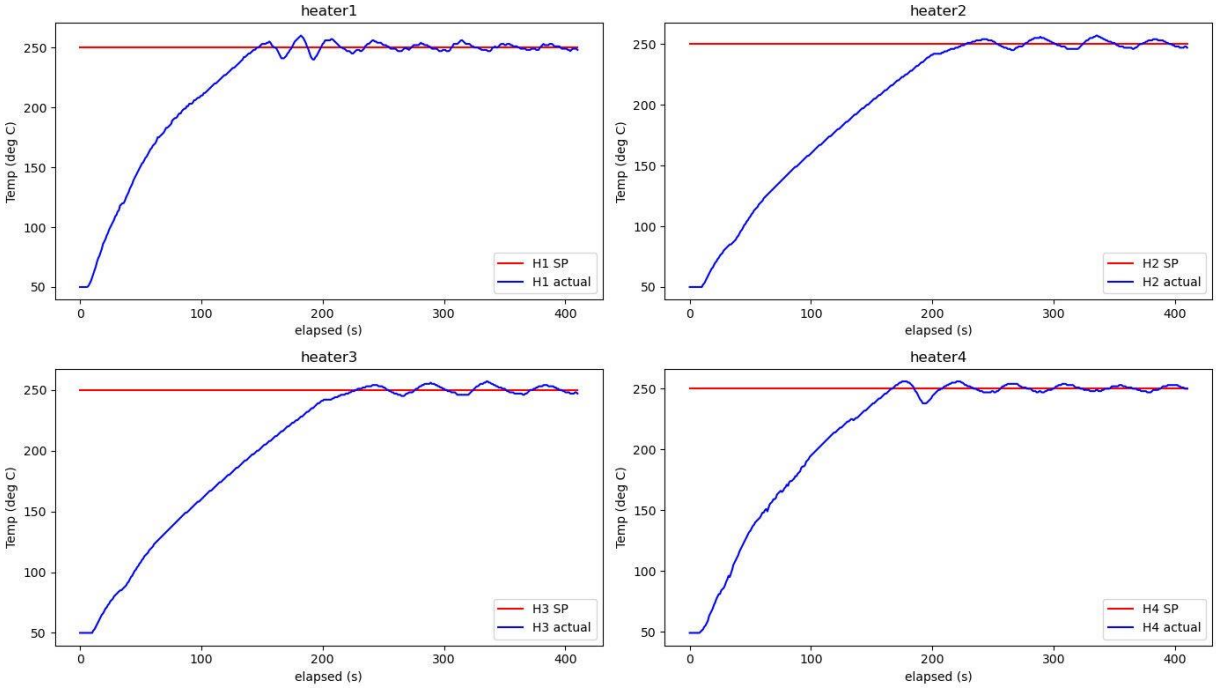

Figure S2. Heater temperature profiles during initial heating testing of the first plate prototype

Figure S3 shows the plate surface temperatures during the heating test, measured with surface thermocouples. The surface eventually reached a temperature of ~ 200 °C, about 50 °C below the heater temperatures, suggesting that the reaction temperature of 230 °C can be achieved without excessively high heater temperatures.

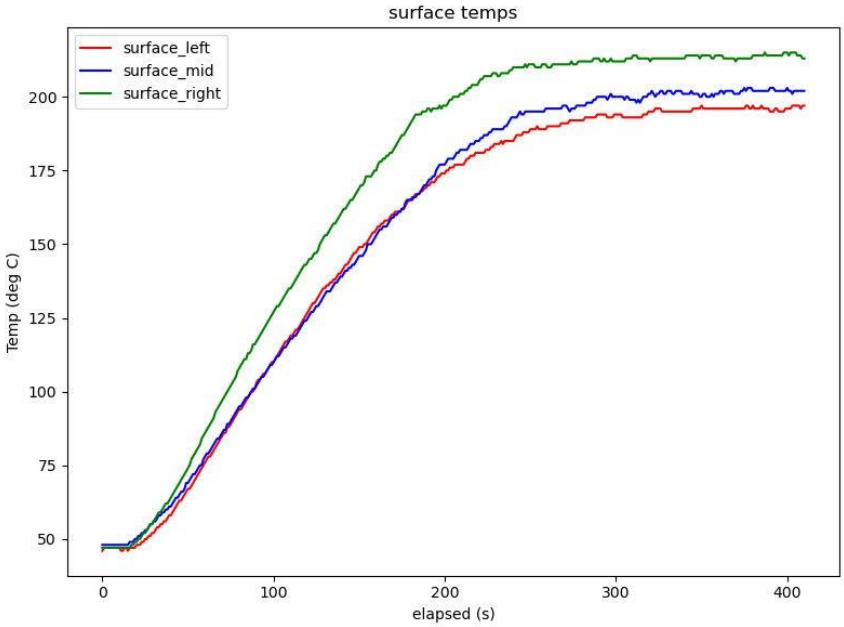

Figure S3. Surface temperature profiles of the plate during initial heating testing

After successful testing of the heating capabilities of the plate, we next investigated the ability of the plate to carry out the midazolam synthesis reaction. The plate was heated to an internal heater temperature of 275 °C and premixed PTSA (5.8 equiv.) and TCA powder was manually added to the plate (Figure S4).

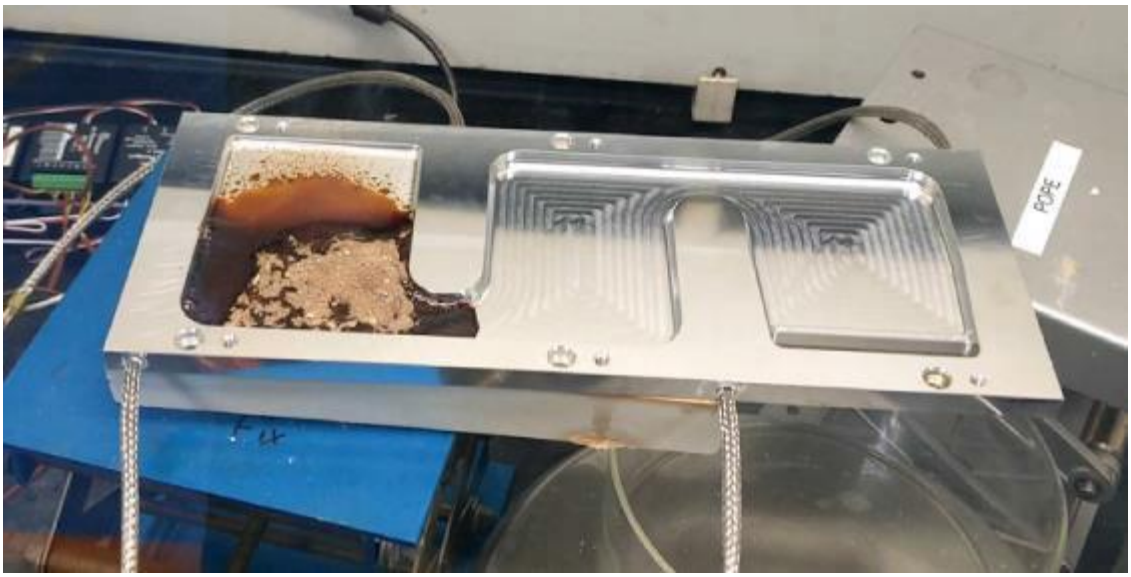

Figure S4. TCA/PTSA powder mixture after being added to the plate heated to an internal temperature of 275 °C.

After several minutes, the powder completely melted and began flowing through the plate channel (Figure S5). Significant bubbling and off-gassing was observed, suggesting that the decarboxylation reaction was occurring. The melt temperature was measured at approximately 220 °C.

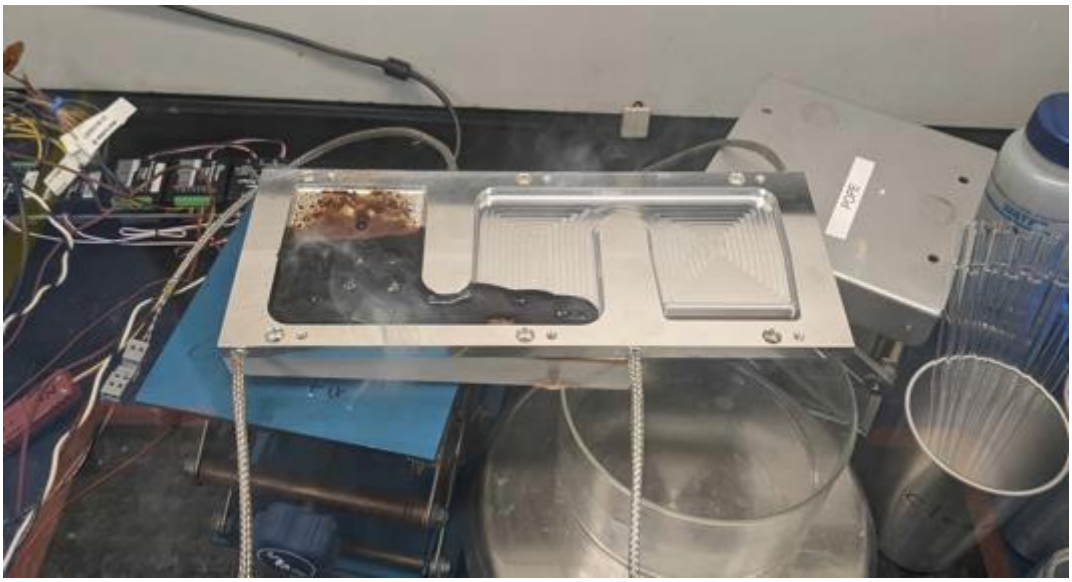

Figure S5. Fully melted TCA/PTSA mixture flowing through heated plate.

Figure S6 shows chromatograms from melt samples collected over time from the plate. The four primary peaks in order from left to right are ring-open midazolam, ring-open TCA, ring-closed midazolam, and ring-closed TCA. The ring-open and ring-closed peak areas are summed to get the total midazolam and TCA concentrations, from which the conversion and yield are calculated. After 38 minutes, the TCA conversion was 90% and the midazolam liquid chromatography area percent (LCAP) was 88%, indicating that the plate reactor has the potential to produce midazolam at reasonably high yield.

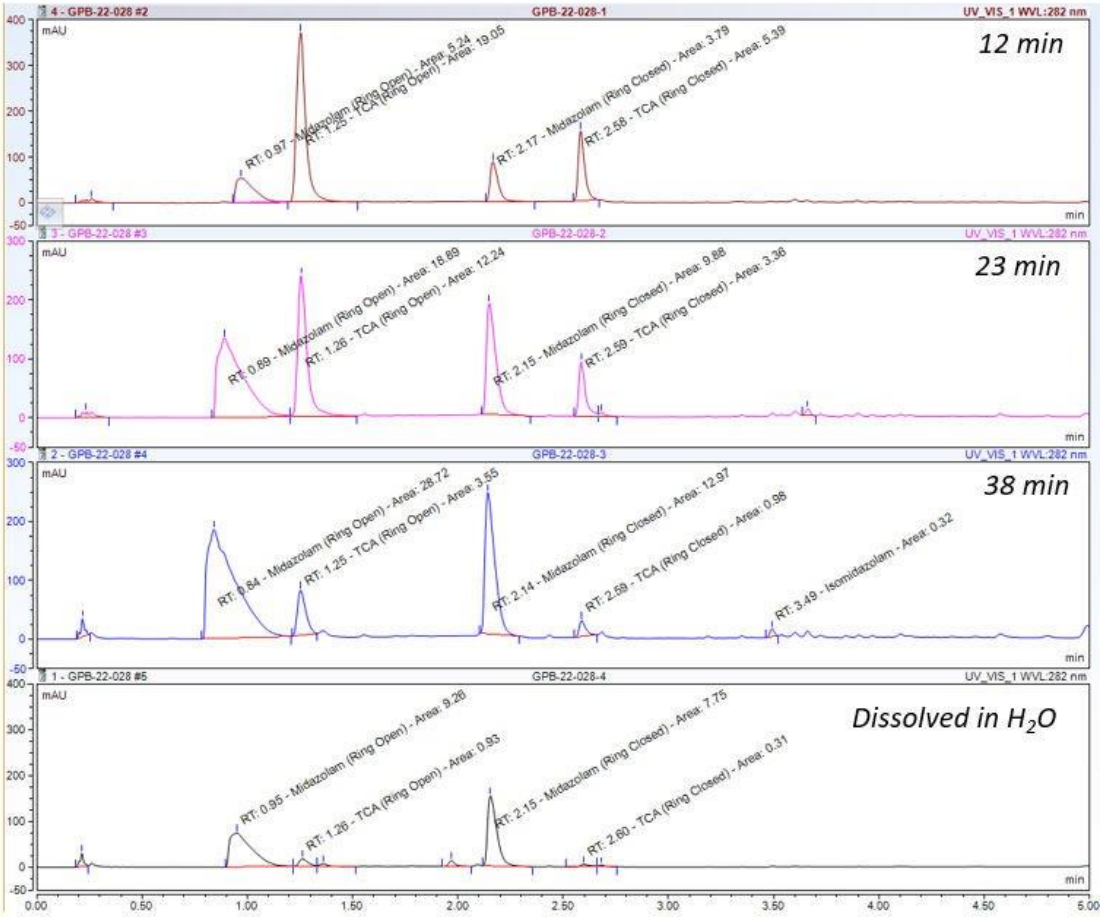

Figure S6. Chromatograms from initial melt reaction testing on the heated plate.

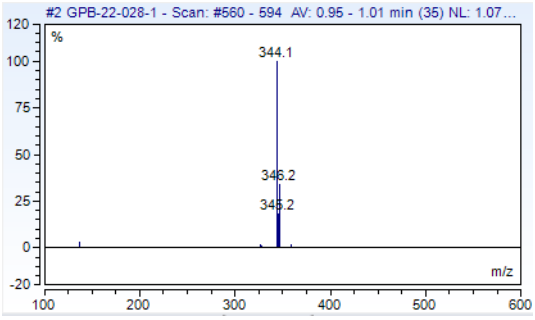

Figure S7. Mass spectrum associated with ring-open midazolam at 1 minute in the top chromatogram in Figure S6.

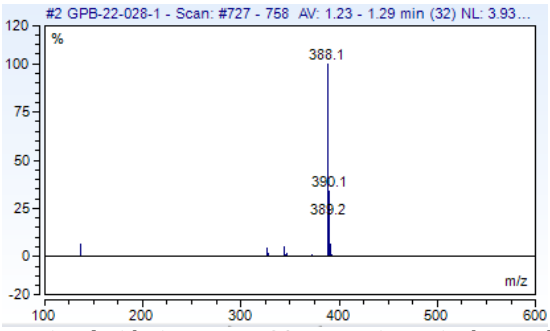

Figure S8. Mass spectrum associated with ring-open TCA at 1.3 minutes in the top chromatogram in Figure S6.

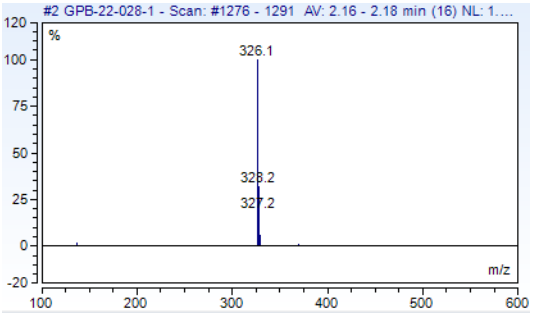

Figure S9. Mass spectrum associated with ring-closed midazolam at 2.2 minutes in the top chromatogram in Figure S6.

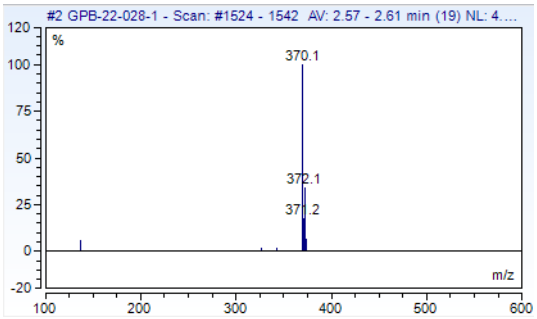

Figure S10. Mass spectrum associated with ring-closed TCA at 2.6 minutes in the top chromatogram in Figure S6.

S2. Plate flow dynamics testing and optimization

As discussed in the main text, early plate prototypes produced highly intermittent flow because of surface tension. Figure S11 shows the flow profile test setup and results for an early plate prototype. Water is fed to the plate at a constant rate *via* an addition funnel, and the flow rate out of the plate is measured by a scale placed under the plate outlet. As can be seen in the measured flow profile, liquid flow periodically stops until the liquid level builds up above the dam to the point that gravity overcomes surface tension and the water spills over the dam. Eventually the flow stops, and the process repeats.

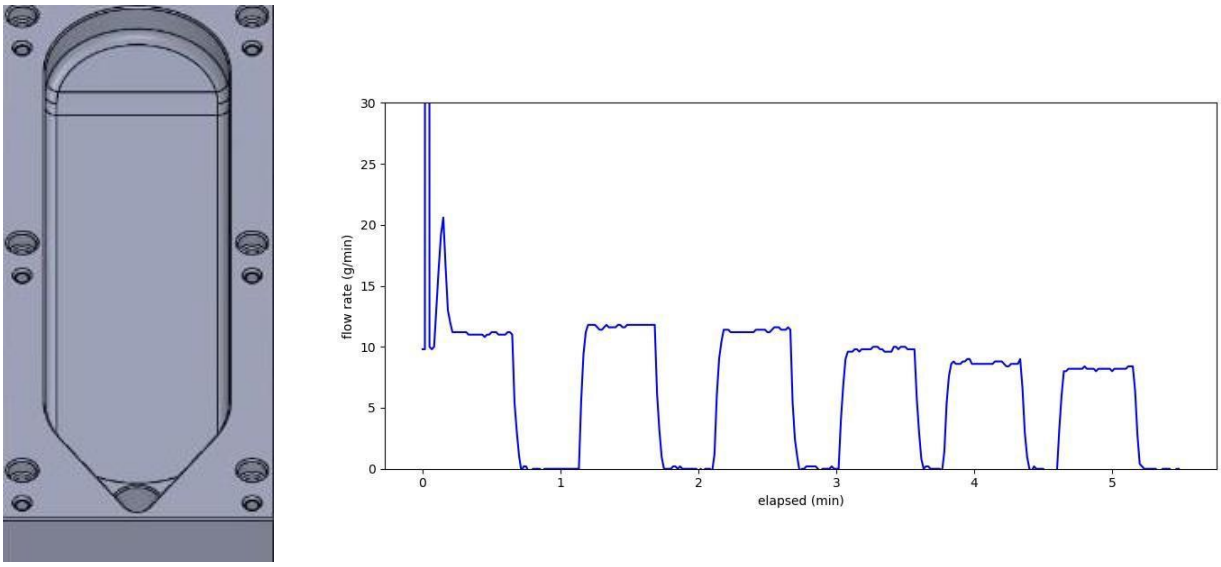

Figure S11. Intermittent flow profile of water in an early plate prototype

We tested numerous variations of outlet shape (both machined and 3D printed plates), some examples of which are shown in Figure S12. Overall, we found that the key to maintaining steady flow is to provide a gradual, smooth transition over the dam, and to funnel the liquid into a narrow channel as it exits the outlet so that a constant stream is always maintained. If at any point the liquid stream breaks, the liquid front pulls back behind the dam and the flow stops.

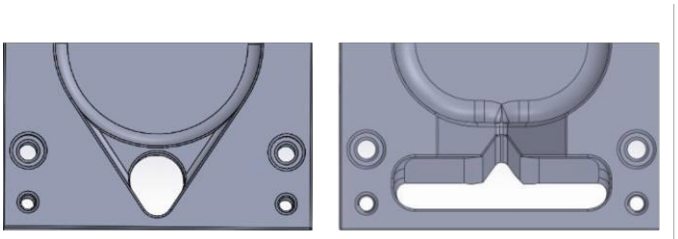

Figure S12. Examples of plate outlet prototypes tested to optimize the liquid flow dynamics.

Figure S13 shows the flow profile that was eventually achieved after optimizing the outlet shape. Even with three stacked plates, a consistent flow rate of approximately 5 g/min is maintained over a period of about 1 hour.

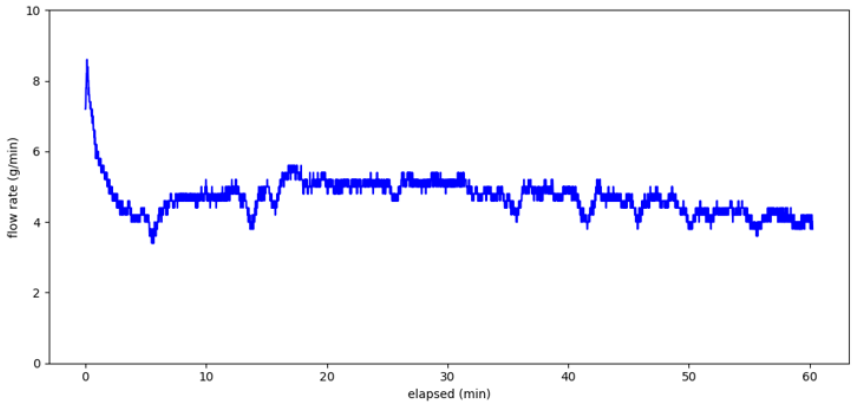

Figure S13. Flow profile of three stacked plates with optimized outlet shape.

After initial testing with water, the flow dynamics of the melt were tested as the plate outlet shape was being optimized to ensure that the melt exhibited similar flow characteristics to water with respect to the outlet shape on the flow rate consistency.

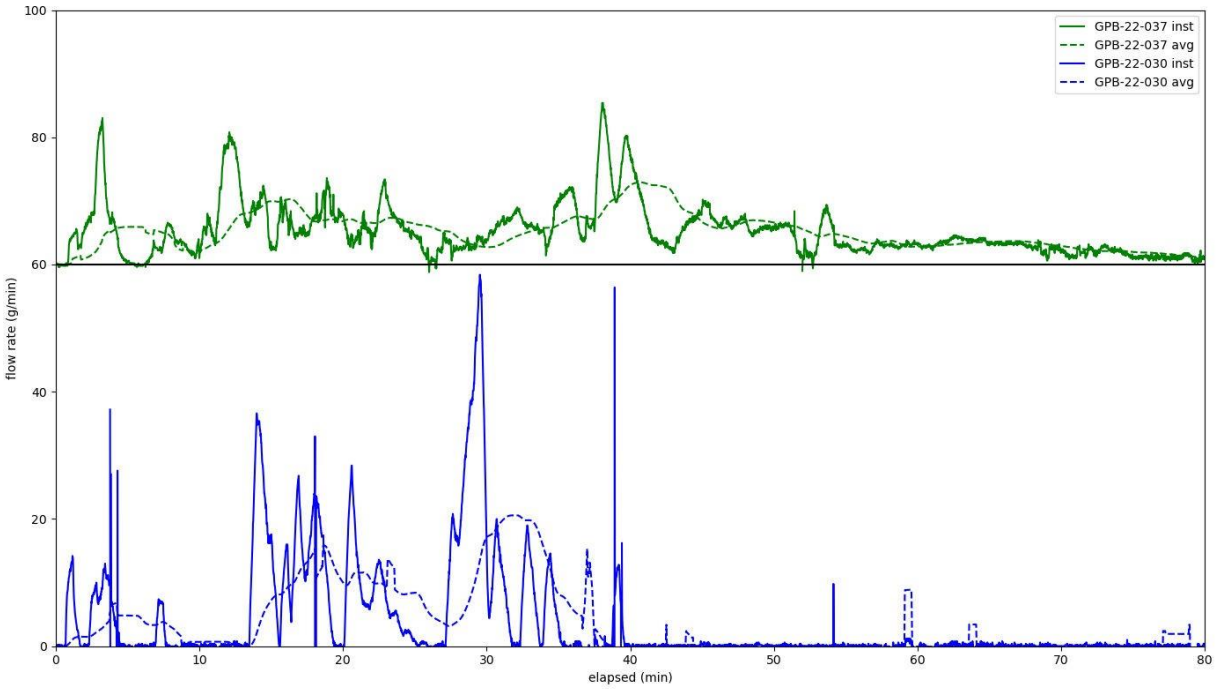

Figure S14. Comparison of the melt flow profile with optimized (top) vs. not yet optimized (bottom) plate outlet shape. Solid lines denote the instantaneous measured flow rate, and dashed lines represent the flow rate averaged over five minutes. Green curves are offset by 60 g/min relative to the blue curves.

Figure S14 shows a comparison of the melt flow rate exiting the reactor for the optimized plate outlet geometry (green) and one of the earlier plate prototypes (blue), with the final optimized geometry exhibiting a much steadier flow profile.

After optimizing the plate outlet geometry, we performed several experiments to determine the optimum top plate melting temperature required to achieve > 95% conversion. Figure S15 shows an example of data collected from one of these experiments, with the top plate temperature of ~135 °C resulting in a melting rate that is too high, and a residence time that is too low, as exhibited by the midazolam LCAP of ≤ 80%.

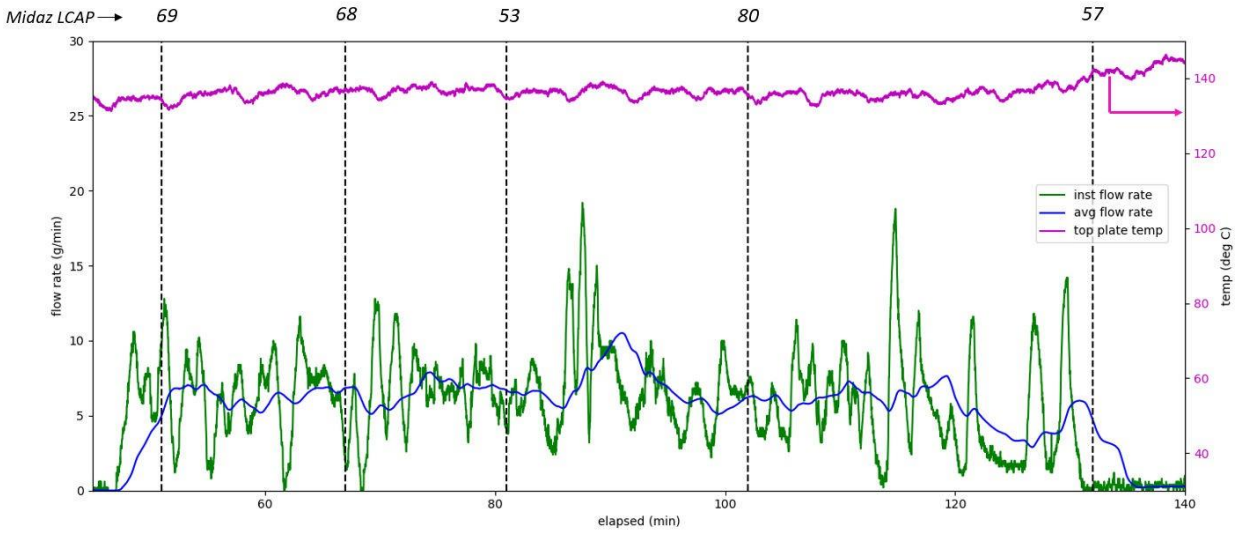

Figure S15. Top plate temperature (pink), instantaneous melt flow rate exiting the reactor (green), and melt flow rate exiting the reactor averaged over five minutes (blue) for one of the melting temperature optimization experiments. The midazolam LCAP is shown for samples collected at times denoted by the dashed lines.

Figure S16 shows the melt being collected on a scale as it exits the reactor.

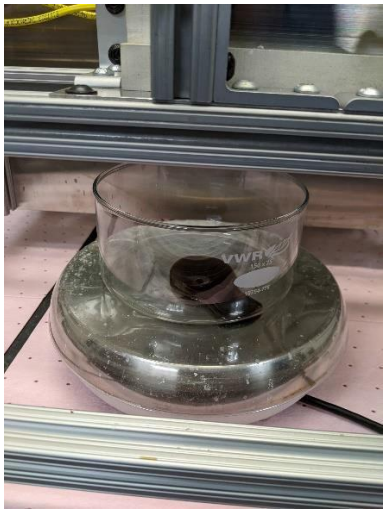

Figure S16. Melt as it exits the plate reactor and is collected on a scale for flow rate measurement and top plate temperature optimization.

S3. Additional detail of top plate and melting section designs

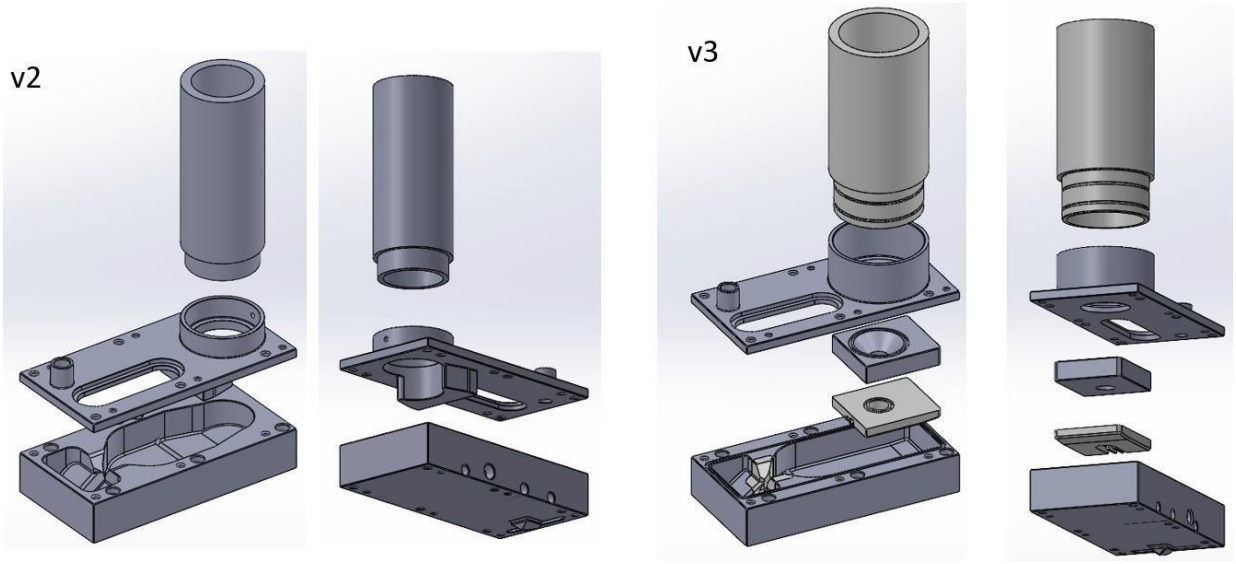

Figure S17. Exploded view of the v2 and v3 top plate and melting zone designs.

S4. Powder plug vial preparation

To prepare the mixed TCA/PTSA powder plugs that were fed to the plate reactor feed hopper, PTSA was fed by a food-grade auger device and TCA was fed by a vibratory feeder bowl into a weigh boat placed on a scale. PTSA was supplied first, followed by TCA. The scale logged the amount of PTSA added, and the feeder subsequently supplied TCA until the correct ratio was reached. The scale, auger feeder, and bowl feeder were controlled and automated *via* a LabVIEW interface. After both powders were dispensed, the mixture was added to vials, allowed to age overnight, then placed in a 4 °C freezer if not used within one day.

Figure S18. Mixed TCA/PTSA powder plugs.

S5. Production campaign data

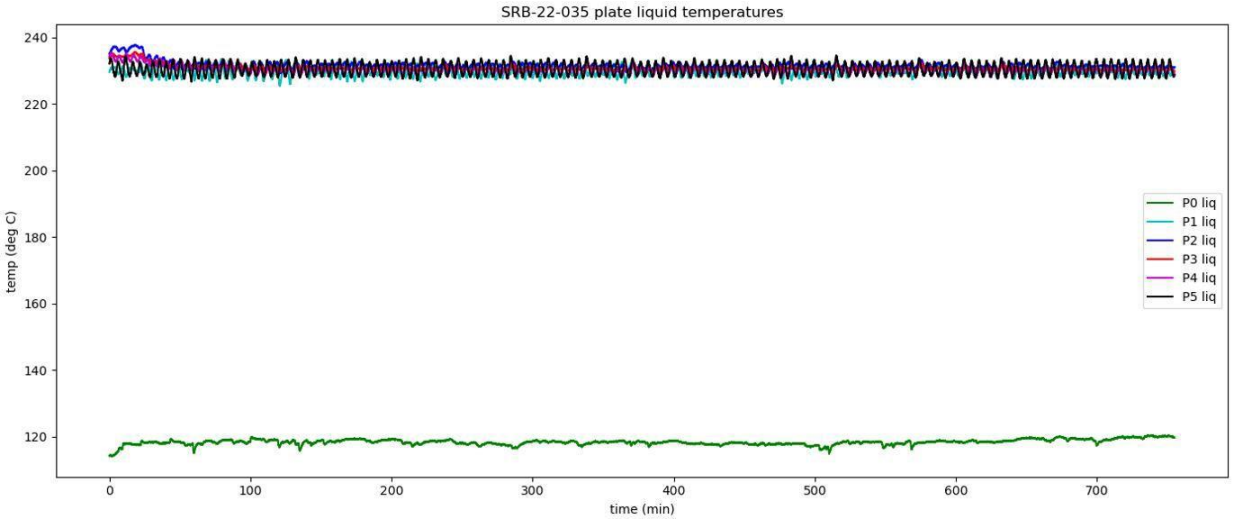

Figure S19. Example reactor temperature data collected during the plate reactor production campaign, showing a top plate melting temperature of 120 °C and tight control of the lower plate liquid temperatures at the set point of 230 °C.

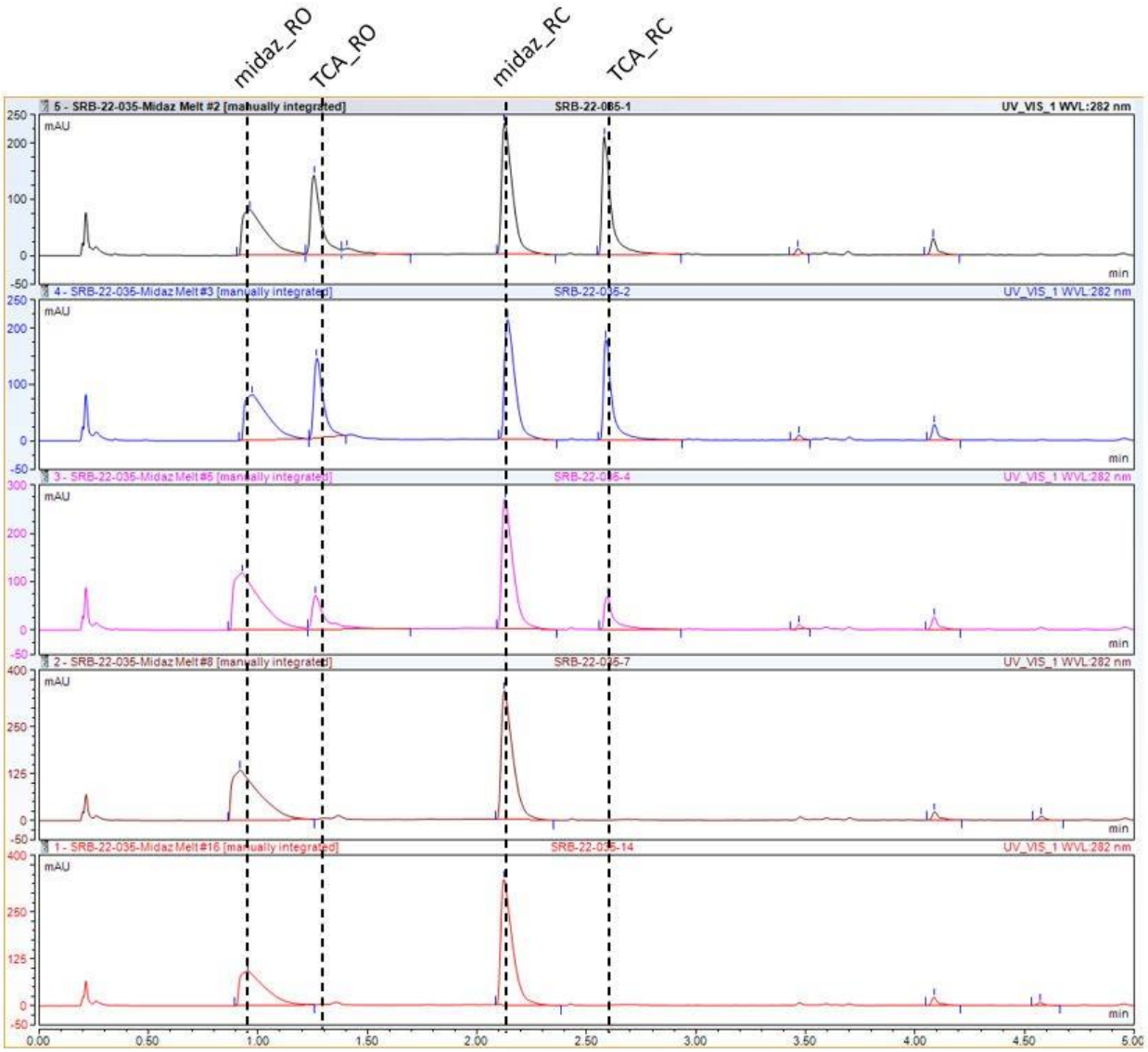

*Figure S20. Example chromatograms of samples collected directly from the **reactor outlet** during the plate reactor production campaign, showing a gradual decrease in the TCA peaks and a corresponding increase in the midazolam peaks from top to bottom as the reactor reaches steady state. The RO and RC modifiers denote the ring-open and ring-closed forms of TCA and midazolam.*

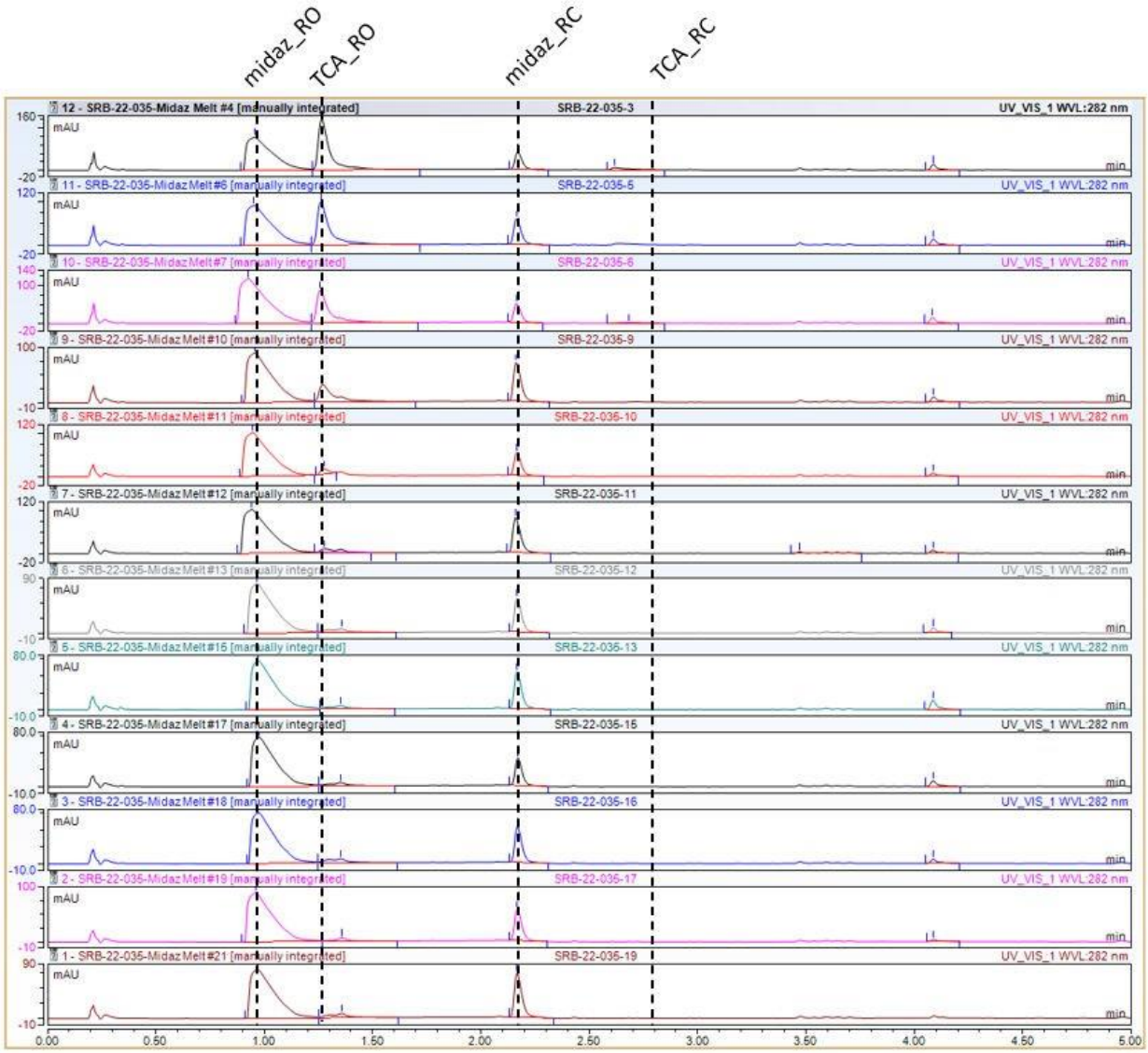

*Figure S21. Example chromatograms of samples collected directly from the **dissolution vessel outlet** during the plate reactor production campaign, showing a gradual decrease in the TCA peaks and a corresponding increase in the midazolam peaks from top to bottom as the reactor reaches steady state. The _RO and _RC modifiers denote the ring-open and ring-closed forms of TCA and midazolam.*

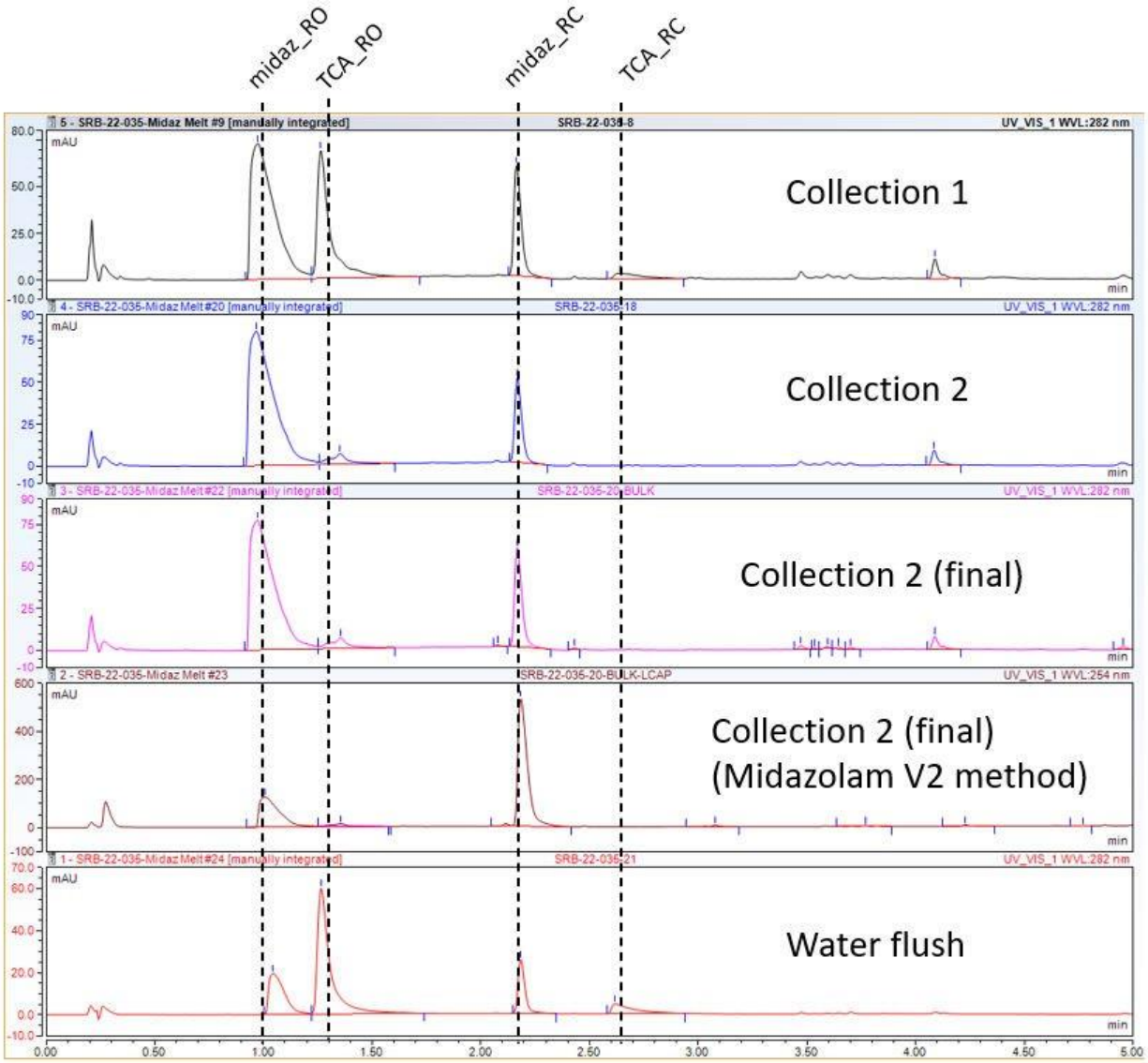

Figure S22. Chromatograms of samples collected from the bulk product collection (i.e. the final collection vessel for the dissolution outlet) during the first production run. Collection 1 is the product collected prior to steady state and has more TCA due to the lower conversion. Once steady state was reached, the collection bottles were exchanged, and Collection 2 started.

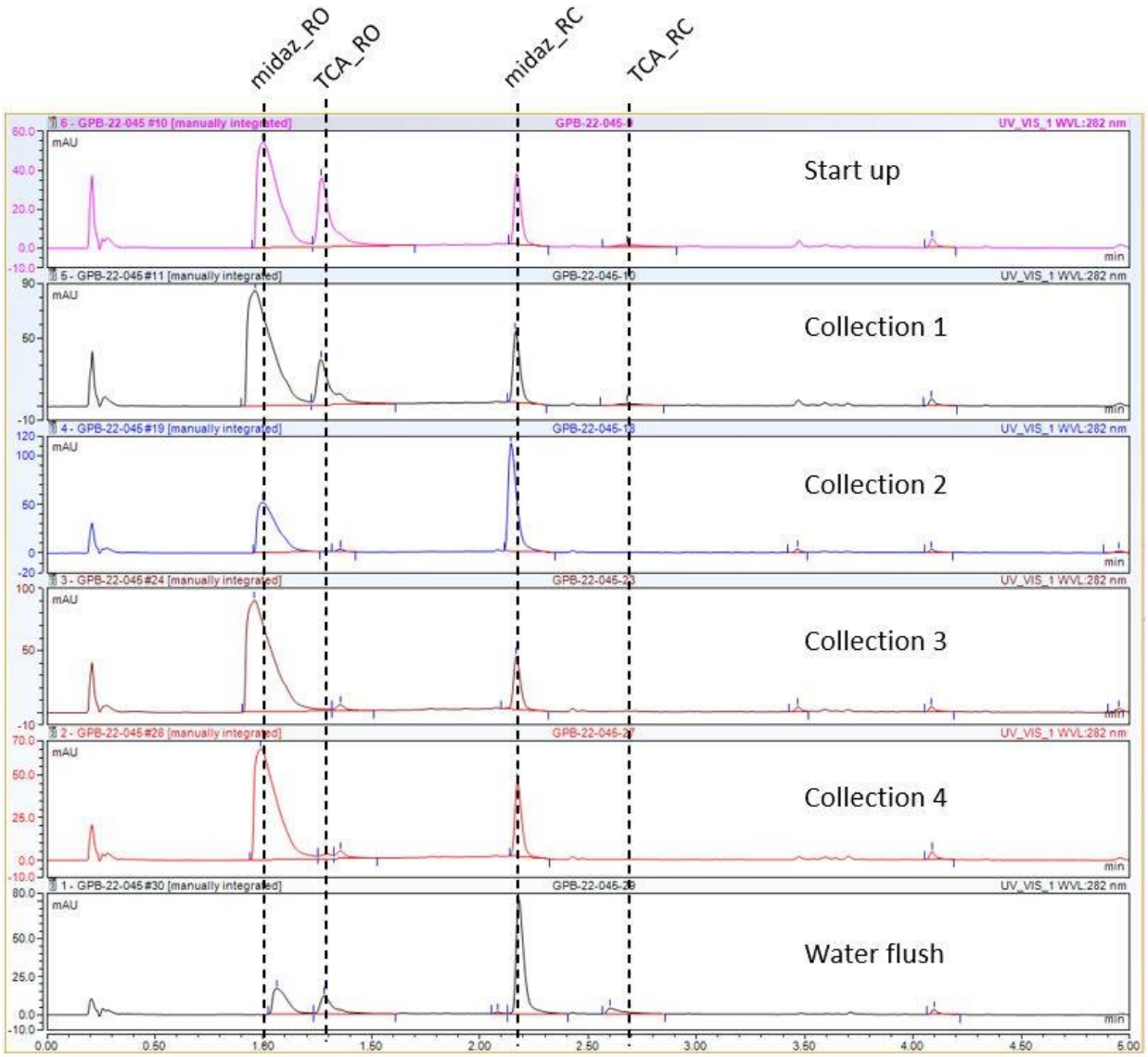

Figure S23. Chromatograms of samples collected from the bulk product collection (i.e. the final collection vessel for the dissolution outlet) during the second production run. Start Up and Collection 1 are the products collected prior to steady state and have more TCA due to the lower conversion. Once steady state was reached, the collection bottles were switched, and Collection 2 started. As each bottle was filled, it was exchanged for an empty one and a new collection was started. Water flush denotes a sample collected from the post-reaction water flush, analyzed to investigate whether the water flush could be combined with the other collections and sent to downstream extraction and purification.