

5. Supplementary Information

5.1 Analytical Information

5.1.1 HPLC Method 1 Details: Run 2 and Batch Experiments

Column: Agilent Eclipse XDB-C18 (4.6 x 250 mm; 5 µm)

Mobile Phase A: 0.1% Phosphoric acid in Water (1 mL HPLC-grade H₃PO₄ in 1000 mL HPLC-grade water)

Mobile Phase B: Acetonitrile

Injection volume: 1 µL

Column temp.: 30 °C

Flowrate: 1.5 mL/min isocratic at 40% B for 12 min

Detector wavelength(s): 255 nm (primary), 210 nm (for information only)

Retention time of Sulfonyl Chloride: ~9.6 min

Retention time of Sulfonic Acid: ~1.5 min

5.1.2 HPLC Method 2 Details: Runs 3 and 4

Column: Agilent Eclipse XDB-C18 (4.6 x 250 mm; 5 µm)

Mobile Phase A: 0.1% Phosphoric acid in Water (1 mL HPLC-grade H₃PO₄ in 1000 mL HPLC-grade water)

Mobile Phase B: Methanol

Gradient: 25% Methanol increased linearly to 75 % over 15 min; hold at 75% for 5 min; 4 min post time

Injection volume: 1 µL

Column temp.: 30 °C

Flowrate: 1.5 mL/min

Detector wavelength(s): 235 nm (primary), 275, 210 nm (for information only)

Retention time of Sulfonyl Chloride: 15.8 min

Retention time of Starting Material: 14.7 min

Retention time of Sulfonic Acid: 4.5 min

5.1.3 Number of HPLC Mass Assay Sampling Procedures

Run 2–10 Samples (Average)

Run 3–1 Sample

Run 4–3 Samples (Mass-weighted average)

5.2 Supporting Figures and Tables

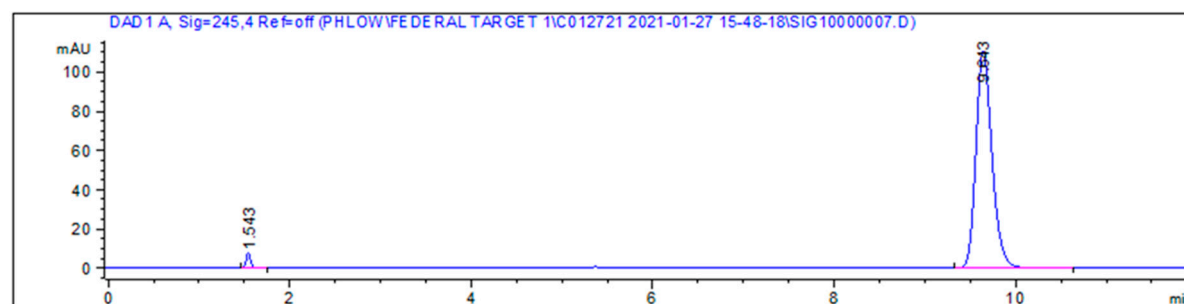


Figure S1. Chromatograph, HPLC Method 1: Run 2

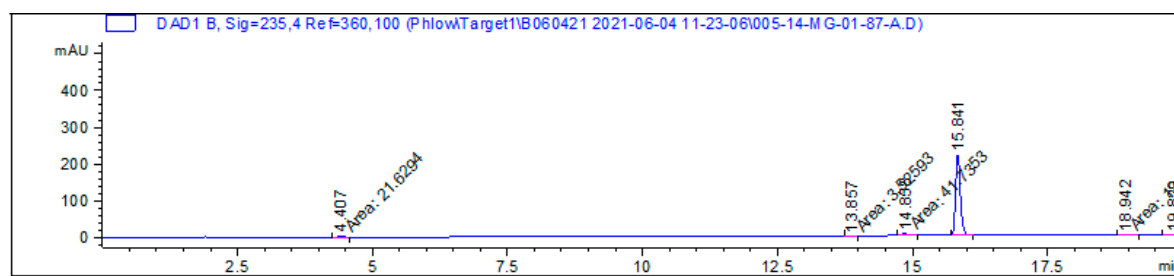


Figure S2. Chromatograph, HPLC Method 2: Run 3

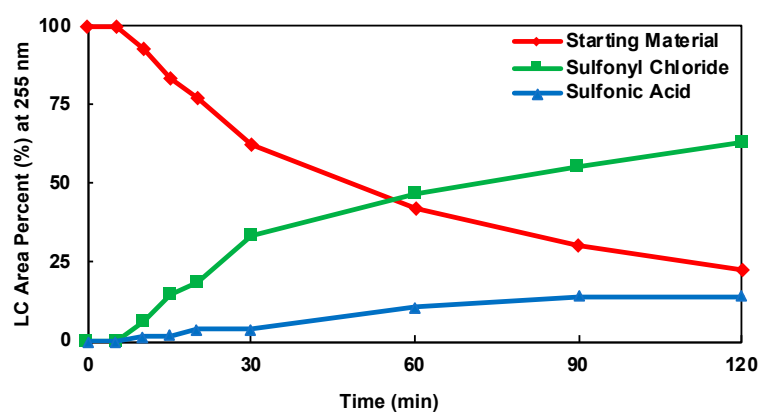


Figure S3. Kinetic Plot of DOE Batch Experiment 1

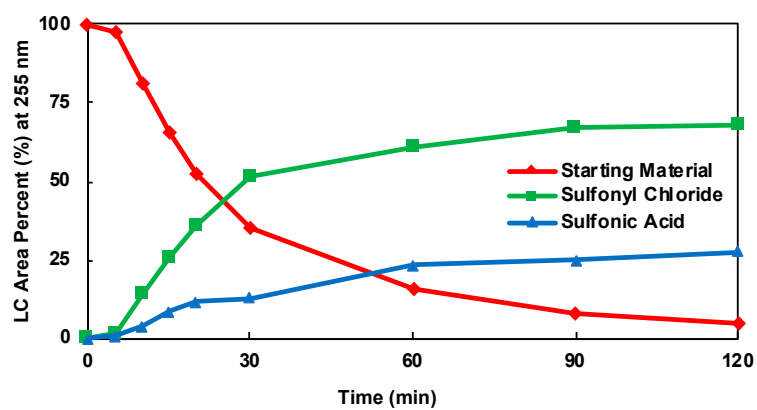


Figure S4. Kinetic Plot of DOE Batch Experiment 4

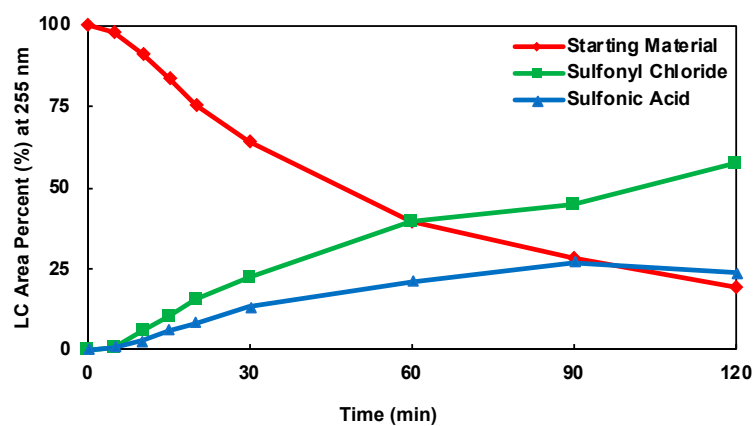


Figure S5. Kinetic Plot of DOE Batch Experiment 5

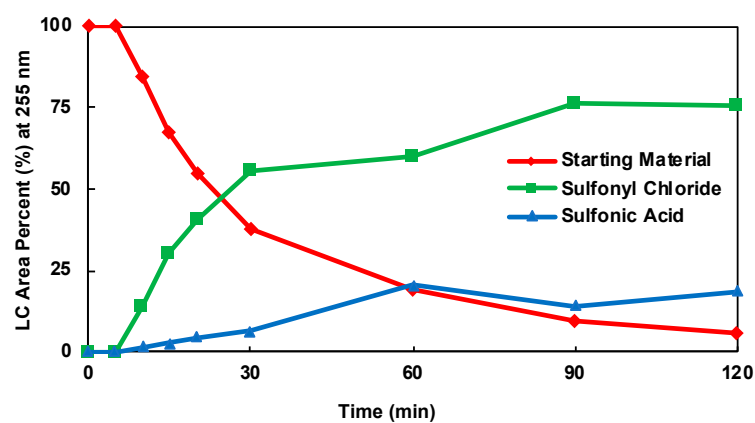


Figure S6. Kinetic Plot of DOE Batch Experiment 6

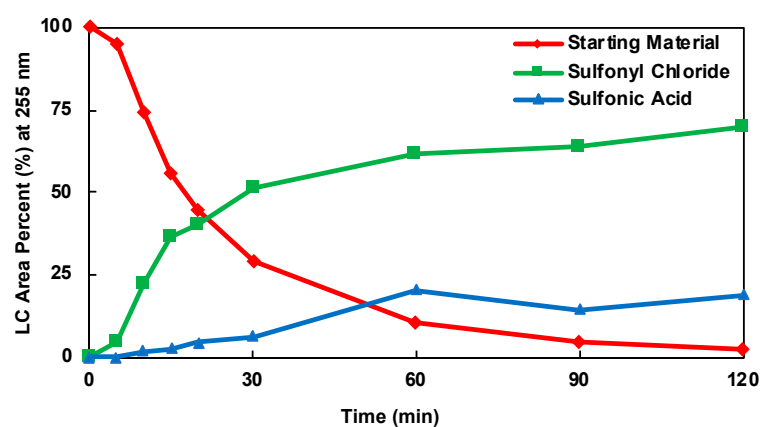


Figure S7. Kinetic Plot of DOE Batch Experiment 7

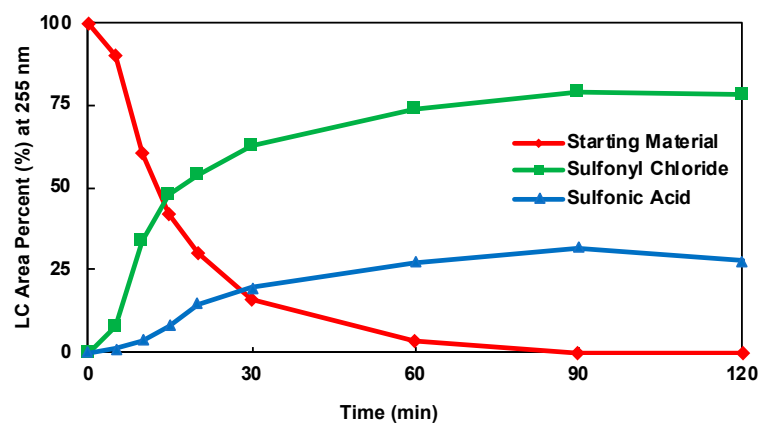


Figure S8. Kinetic Plot of DOE Batch Experiment 8

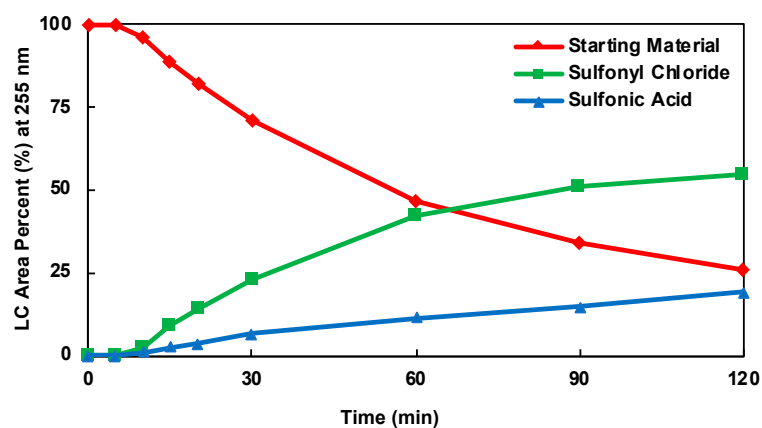


Figure S9. Kinetic Plot of DOE Batch Experiment 9

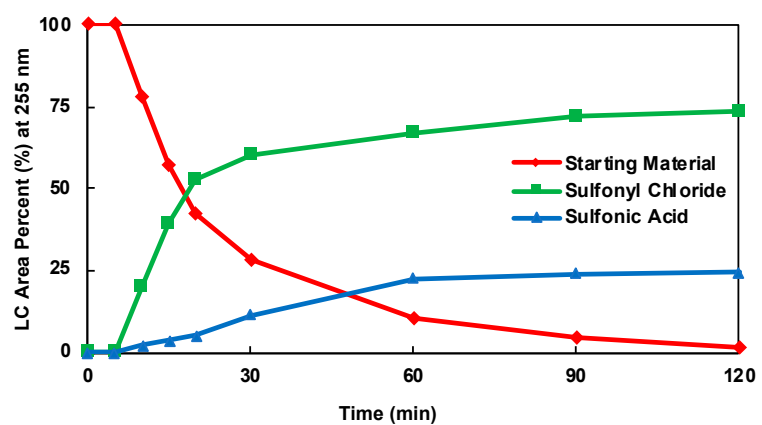


Figure S10. Kinetic Plot of DOE Batch Experiment 11

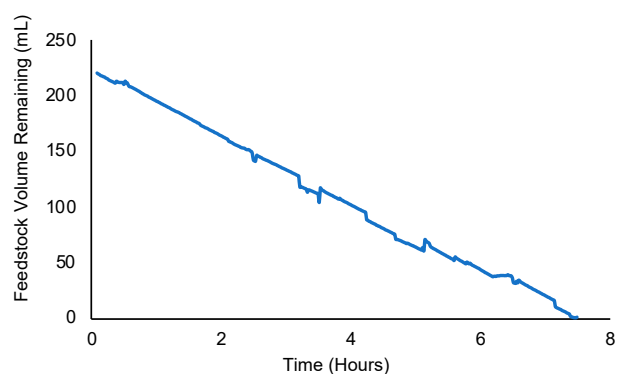


Figure S11. Process Monitoring Data from Run 1



Figure S12. Fume Hood Setup for Run 3. PTFE pump heads and PTFE tube sets were purchased and implemented without the use of C-Flex tubing.

Table S1. Pumping Flowrates

| Table | ISO-CSTR Setpoint (mL) | Jacket Set-point | P-1/P-2/P-3 (mL/min) | P-4 (mL/min) | P-5 On/Off (min:sec) | P-5 On (mL/min) |
|-------|------------------------|------------------|----------------------|--------------|----------------------|-----------------|
| 1 | 400 | -5°C | 0.5 | 12.5 | 0:25/2:35 | 98.3 mL/min |
| 2 | 10000 | -5°C | 2.5 | 100 | 1:00/3:00 | 410 mL/min |
| 3 | 500 | -10°C | 0.67 | 6.7 | 0:30/4:30 | 73.7 mL/min |
| 4 | 7500 | -5°C | 2.5 | 7 | 0:10/1:02 | 200 mL/min |

Table S2. ANOVA of Product (R1)

| Source | Sum of Squares | df | Mean Square | F-value | p-value |
|------------------|----------------|----|-------------|---------|---------|
| Model | 2057.35 | 7 | 293.91 | 41.34 | 0.0056 |
| A-Temp. | 803.59 | 1 | 803.59 | 113.03 | 0.0018 |
| B-Eq. | 260.53 | 1 | 260.53 | 36.65 | 0.009 |
| AB | 53.06 | 1 | 53.06 | 7.46 | 0.0718 |
| A ² | 49.87 | 1 | 49.87 | 7.01 | 0.0771 |
| B ² | 104.93 | 1 | 104.93 | 14.76 | 0.0311 |
| A ² B | 126.97 | 1 | 126.97 | 17.86 | 0.0242 |
| AB ² | 1.14 | 1 | 1.14 | 0.1605 | 0.7155 |
| Residual | 21.33 | 3 | 7.11 | | |

| | | | | | |
|-------------|---------|----|--------|--------|--------|
| Lack of Fit | 0.7919 | 1 | 0.7919 | 0.0771 | 0.8073 |
| Pure Error | 20.54 | 2 | 10.27 | | |
| Cor. Total | 2078.68 | 10 | | | |

Table S3. ANOVA of Starting Material (R2)

| Source | Sum of Squares | df | Mean Square | F-value | p-value |
|----------------|----------------|----|-------------|---------|----------|
| Model | 2397.11 | 5 | 479.42 | 29.53 | 0.001 |
| A-Temp. | 2185.97 | 1 | 2185.97 | 134.64 | < 0.0001 |
| B-Eq. | 37.62 | 1 | 37.62 | 2.32 | 0.1884 |
| AB | 8.56 | 1 | 8.56 | 0.5274 | 0.5003 |
| A ² | 158.7 | 1 | 158.7 | 9.78 | 0.0261 |
| B ² | 20.88 | 1 | 20.88 | 1.29 | 0.3082 |
| Residual | 81.18 | 5 | 16.24 | | |
| Lack of Fit | 47.54 | 3 | 15.85 | 0.942 | 0.5519 |
| Pure Error | 33.64 | 2 | 16.82 | | |
| Cor. Total | 2478.29 | 10 | | | |

Table S4. ANOVA of Sulfonic Acid (R3)

| Source | Sum of Squares | df | Mean Square | F-value | p-value |
|----------------|----------------|----|-------------|---------|---------|
| Model | 0.0046 | 5 | 0.0009 | 26.38 | 0.0013 |
| A-Temp. | 0.0008 | 1 | 0.0008 | 24.18 | 0.0044 |
| B-Eq. | 0.0009 | 1 | 0.0009 | 26.6 | 0.0036 |
| AB | 0.0004 | 1 | 0.0004 | 12.48 | 0.0167 |
| A ² | 0.0019 | 1 | 0.0019 | 54.51 | 0.0007 |
| B ² | 3.93E-09 | 1 | 3.93E-09 | 0.0001 | 0.992 |
| Residual | 0.0002 | 5 | 0 | | |
| Lack of Fit | 0.0002 | 3 | 0.0001 | 5.53 | 0.1571 |
| Pure Error | 0 | 2 | 9.45E-06 | | |
| Cor. Total | 0.0048 | 10 | | | |