

Supplementary Information

Abbreviations

CBZ: Carbamazepine (5H-dibenzo[b,f]azepine-5-carboxamide)

CBZ-A: 10,11-Dihydro-5H-dibenz[b,f]azepine-5-carboxamide

CS: Continuous Synthesis

CSTR: Continuous Stirred Tank Reactor

FDA: Food and Drug Administration

HPLC: High Performance Liquid Chromatography

ISB: Iminostilbene (5H-Dibenz[b,f]azepine)

PAT: Process Analytical Technologies

RBF: Round Bottom Flask

WHO: World Health Organization

HPLC Method and Method Validation

Instrument: Agilent 1260

Analytical Column: Waters Cortex C18, 2.7 µm particle size, 2.1 x 100mm

Guard Column: Waters Cortex C18, 2.7 µm particle size, 2.1 x 5 mm

Detector: Diode array detector 230 nm

Injection Volume: 2 µL

Flow Rate: 0.4 mL/min

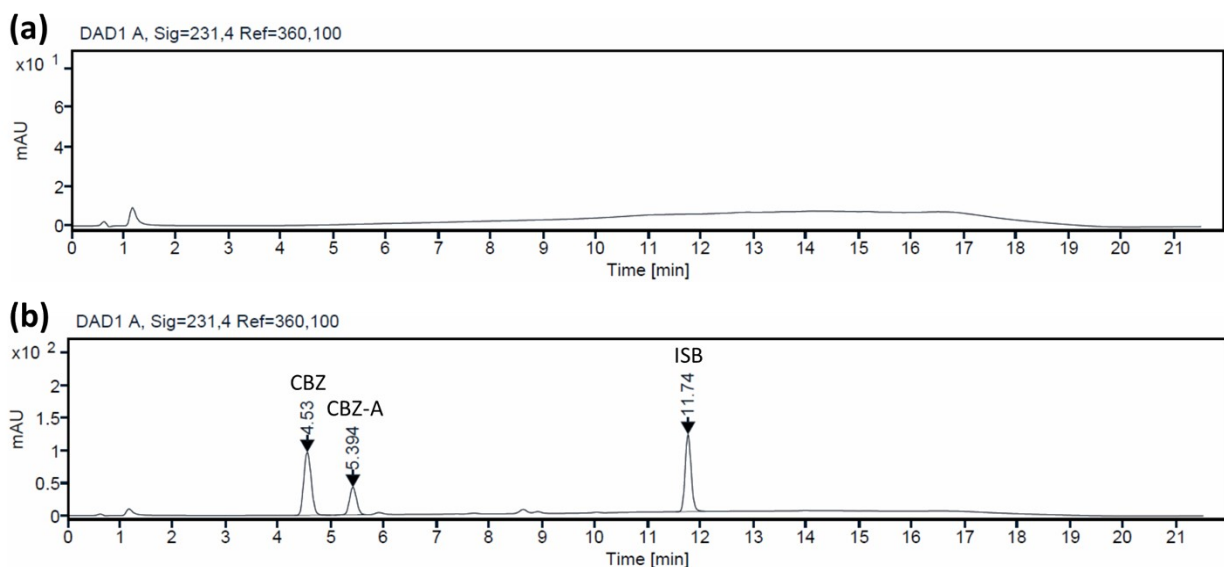
Column Temperature: 30 °C

Stop Time: 24 min

Table S1: HPLC Method Gradient

Time (min)	Milli-Q water (%)	Methanol (%)	Acetonitrile (%)
0	57	40	3
1	57	40	3
11	38	60	2
14	38	60	2
16.5	57	40	3

Figure S1: HPLC chromatogram of blank injection (a) and system suitability (b) at 10.0 µg/mL of CBZ, CBZ-A and ISB.



Batch Kinetic Data

Table S2: CBZ in Solution Yield (%) of Batch Reaction Timepoints. HPLC measurements and fitted model predictions are shown.

Time (sec)	30°C		40°C		45°C		50°C		60°C		70°C	
	HPLC	Model	HPLC	Model	HPLC	Model	HPLC	Model	HPLC	Model	HPLC	Model
30	4.2	1.9	7	3.1	6.4	3.9	7.2	4.9	9.6	7.4	10	10.7
60	8	3.7	9.7	6	10	7.5	10.8	9.3	14.4	13.7	17.7	19.2
90	9.5	5.5	17.7	8.8	12.9	10.8	14.8	13.3	19.3	19.1	25.1	26
120	17.2	7.2	15.1	11.3	15.4	13.9	17.6	16.9	25.5	23.8	31	31.6
300	20	16.2	26.7	24.1	28.6	28.6	33.4	33.3	42.7	42.7	50.3	51
600	28.6	27.8	39.4	38.4	42.3	43.8	48.8	48.9	57.3	57.4	62.4	63
900	35.5	36.5	47.4	47.9	51	53.1	57.1	57.7	64.4	64.4	66.5	67.6
1800	49.9	52.9	61.8	63.1	65	66.8	69.4	69.5	72.4	71.9	69.9	71
2700	58.6	62	69.3	70.1	71.5	72.5	74.7	73.9	74.8	73.8	70.5	71.5
3600	63.6	67.7	73.9	73.9	75.3	75.4	76.8	75.8	75.5	74.4	70.6	71.5
5400	70.9	74.3	80.3	77.7	78.9	77.9	79	77.3	76	74.6	70.7	71.5
7200	75.1	77.8	81	79.4	80.5	78.8	79.7	77.7	76	74.7	70.7	71.5

Raman Method and Method Validation

Table S3: In-line Raman Method Validation procedure. The sample 'calibration curve 0' is for informational purposes and the model should be considered only semi-quantitative outside of the ranges ISB [0.50-2.50 mg/mL] and CBZ [0.70-7.50 mg/mL].

Sample	ISB [mg/mL]	CBZ [mg/mL]	Spectra Collected
Blank	0	0	10
System Suitability	0.75	1.25	10
*Calibration Curve 0	0.25	0.4	1
Calibration Curve 1	0.5	0.7	1
Calibration Curve 2	0.75	1.25	1
Calibration Curve 3	1	2.5	1
Calibration Curve 4	1.5	4.5	1
Calibration Curve 5	2	6	1
Calibration Curve 6	2.5	7.5	1
Low-Level Quality Control	0.7	1	5
Mid-Level Quality Control	1.25	3.25	5
High-Level Quality Control	2	6	5

Table S4: Accuracy and precision of quality controls and system suitability during method validation.

Samples	Validation 1	Validation 2	Validation 3
ISB System Suitability	98.3 ± 0.9%	102.3 ± 1.3%	101.3 ± 0.5%
ISB Low-Level	99.1 ± 1.4%	99.8 ± 0.8%	102.4 ± 0.6%
ISB Mid-Level	98.2 ± 0.8 %	99.7 ± 0.3%	98.7 ± 0.3%
ISB High-Level	97.6 ± 0.5%	100.9 ± 0.4%	100.8 ± 0.4%
CBZ System Suitability	101.2 ± 0.9%	105.1 ± 1.7%	101.3 ± 1.6%
CBZ Low-Level	103.8 ± 2.1%	104.2 ± 1.5%	101.6 ± 1.7%
CBZ Mid-Level	97.1 ± 0.2%	102.0 ± 0.4%	101.8 ± 0.6%
CBZ High-Level	98.7 ± 0.5%	101.0 ± 0.3%	100.4 ± 0.3%

Table S5: Intermediate repeatability results for quality control measurements over a period of 7 days.

Quality Control Samples	Day 0	Day 1	Day 2	Day 3	Day 7
ISB Low-Level	102.2 ± 0.6%	104.6 ± 0.7%	105.1 ± 0.7%	103.2 ± 0.6%	102.2 ± 0.4%
ISB Mid-Level	98.2 ± 0.3%	98.8 ± 1.1%	98.1 ± 0.3%	98.3 ± 0.5%	97.2 ± 0.6%
ISB High-Level	98.1 ± 0.4%	100.0 ± 0.3%	98.5 ± 0.4%	99.4 ± 0.2%	98.0 ± 0.5%
CBZ Low-Level	100.5 ± 1.5%	101.7 ± 2.5%	102.4 ± 3.3%	103.9 ± 1.9%	102.1 ± 1.2%
CBZ Mid-Level	99.9 ± 0.6%	97.3 ± 0.7%	100.2 ± 0.8%	100.6 ± 0.6%	97.5 ± 0.6%
CBZ High-Level	97.0 ± 0.3%	98.5 ± 0.5%	99.3 ± 0.3%	98.3 ± 0.5%	96.3 ± 0.7%

Discretized Batch Equations

$$S1) [CBZ] = [CBZ]_0 + \lim_{\Delta t \rightarrow 0} \sum_{t=0}^t A_1 e^{-\frac{E_{A,1}}{8.314 \times T}} [ISB_i] [HOCN_i] \Delta t$$

$$S2) [ISB] = [ISB]_0 + \lim_{\Delta t \rightarrow 0} \sum_{t=0}^t -A_1 e^{-\frac{E_{A,1}}{8.314 \times T}} [ISB_i] [HOCN_i] \Delta t$$

$$S3) [KOCN] = [KOCN]_0 + \lim_{\Delta t \rightarrow 0} \sum_{t=0}^t \left\{ -A_1 e^{-\frac{E_{A,1}}{8.314 \times T}} [ISB_i] [HOCN_i] - A_2 e^{-\frac{E_{A,2}}{8.314 \times T}} [HOCN_i] \right\} \Delta t$$

Discretized Continuous Equations

$$S4) [CBZ] = [CBZ]_0 + \lim_{\Delta t \rightarrow 0} \sum_{t=0}^t \left\{ A_1 e^{\frac{-E_{A,1}}{8.314 \times T}} [ISB_i] [HOCN_i] - \frac{[U_1 + U_2][CBZ_i]}{V} \right\} \Delta t$$

$$S5) [ISB] = [ISB]_0 + \lim_{\Delta t \rightarrow 0} \sum_{t=0}^t \left\{ -A_1 e^{\frac{-E_{A,1}}{8.314 \times T}} [ISB_i] [HOCN_i] + \frac{[U_1][ISB_{inlet}]}{V} - \frac{[U_1 + U_2][ISB_i]}{V} \right\} \Delta t$$

$$S6) [KOCN] = [KOCN]_0 + \lim_{\Delta t \rightarrow 0} \sum_{t=0}^t \left\{ -A_1 e^{\frac{-E_{A,1}}{8.314 \times T}} [ISB_i] [HOCN_i] - A_2 e^{\frac{-E_{A,2}}{8.314 \times T}} [HOCN_i] + \frac{[U_2][KOCN_{inlet}]}{V} - \frac{[U_1 + U_2][KOCN_i]}{V} \right\} \Delta t$$

Raman Spectra used for Peak Assignment

Figure S2: Raman Spectra Used for Peak Assignment

