Supplementary Information (SI) for Reaction Chemistry & Engineering.

Supplementary Information

Advances in Continuous Manufacturing of Albuterol Sulfate: Optimization of an Amination Reaction in Flow

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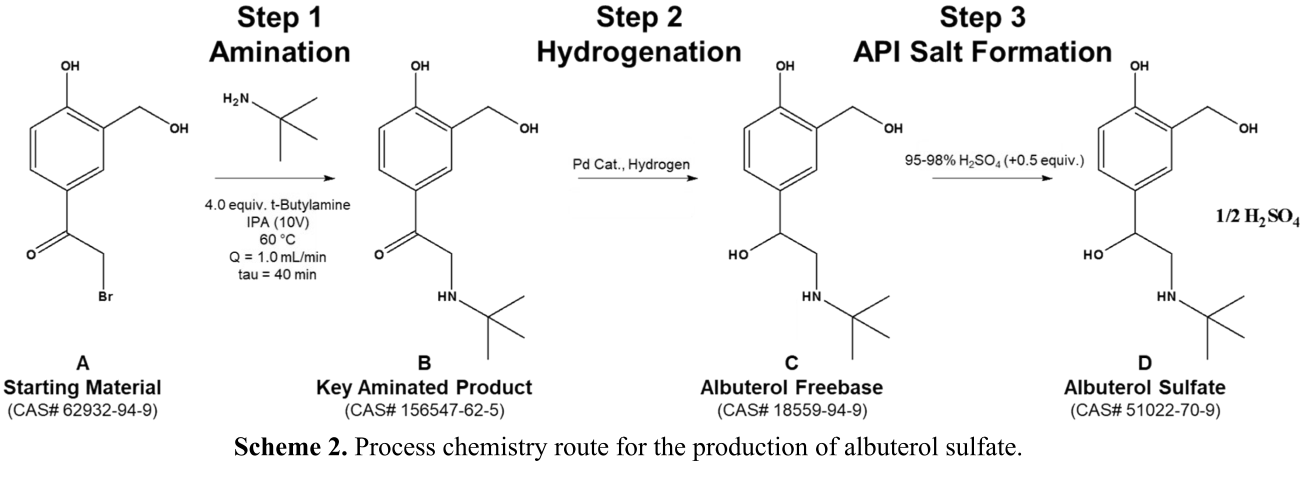


Scheme 2. Process chemistry route for the production of albuterol sulfate.

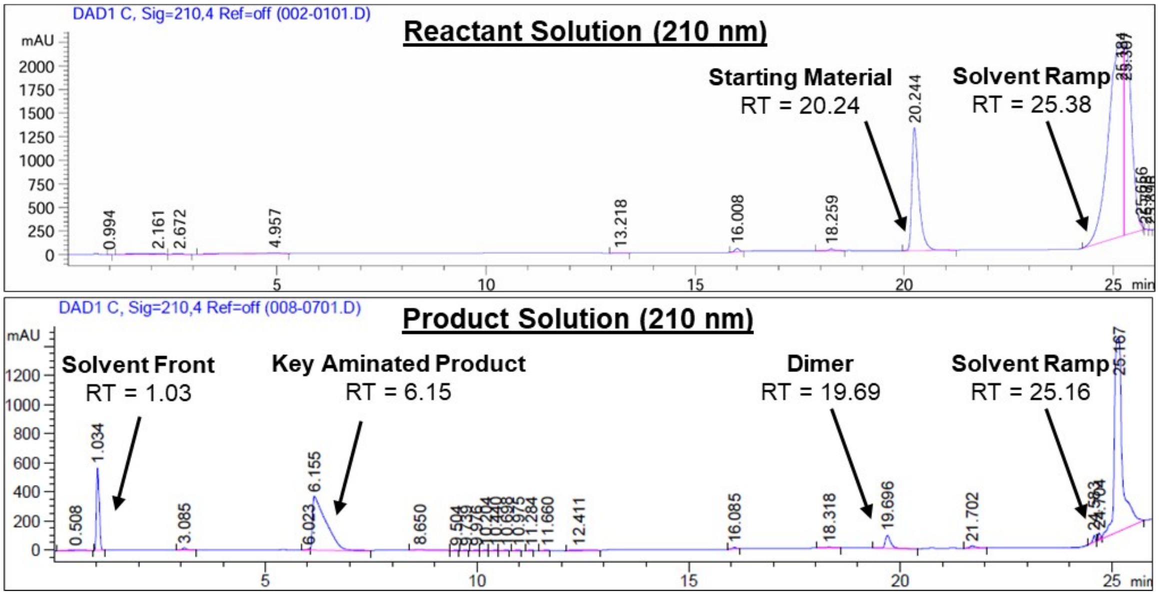


Fig. S1. Representative High Performance Liquid Chromatograms for Amination Species Quantification.

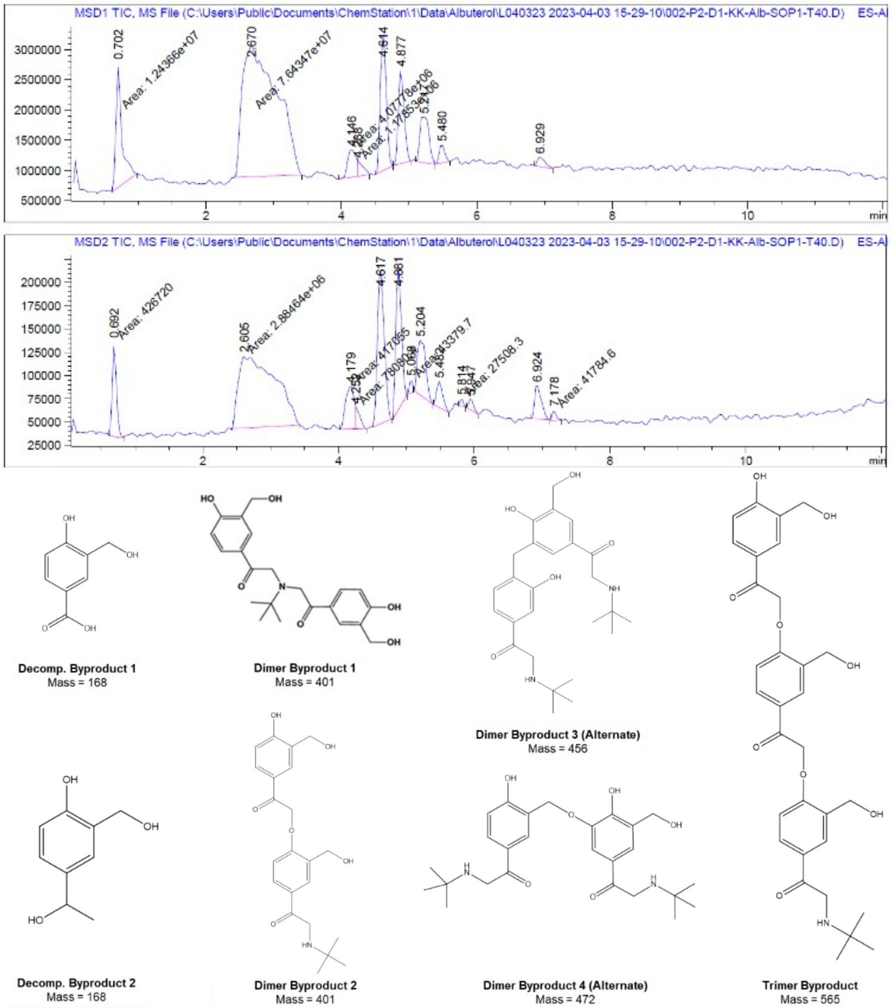


Fig. S2. Example liquid chromatography mass spectrometry analysis for species identification from early batch study.

Table S1. Example liquid chromatography mass spectrometry analysis for species identification from early batch study.

RT (min)	260 nm Area %	m/z	Comments
0.702	Not Detected	227 (ESI+); 232 (ESI-)	1 Br; 2 Br
2.670	76%	238 (M+H); 236 (M-H)	Key Intermediate
4.146	1.00%	457 (ESI+); 455 (ESI-)	Dimer
4.238	1.40%	457 (ESI+); 455 (ESI-)	Dimer
4.614	11.80%	402 (ESI+); 400 (ESI-)	Dimer
4.877	4.40%	402 (ESI+); 400 (ESI-)	Dimer
5.068	0.90%	199 (ESI-)	1 Cl
5.217	2.00%	238 (ESI+); 236 (ESI-)	Decomposed
5.480	0.80%	566 (ESI+); 564 (ESI-)	Trimer
5.947	0.20%	363 (ESI-)	1 Cl
6.929	0.09%	453 (ESI-)	1 Br
7.178	0.08%	617 (ESI-)	1 Br

Response Factor Scaling:

- **Methodology:** Approximate the concentration of dimer. Relate chromophore count to the response factor of known standards, extrapolate response factor of dimer and create an approximate calibration curve.

Chemical Species	Lone Pair Count	Double Bond Count	Chromophore Count	Response Factor
Starting Material (1)	9	4	13	1079.6
Aminated Product (3)	7	4	11	846.2
Dimer Byproduct (4)	13	8	21	2012.9

Chromophore Absorbance

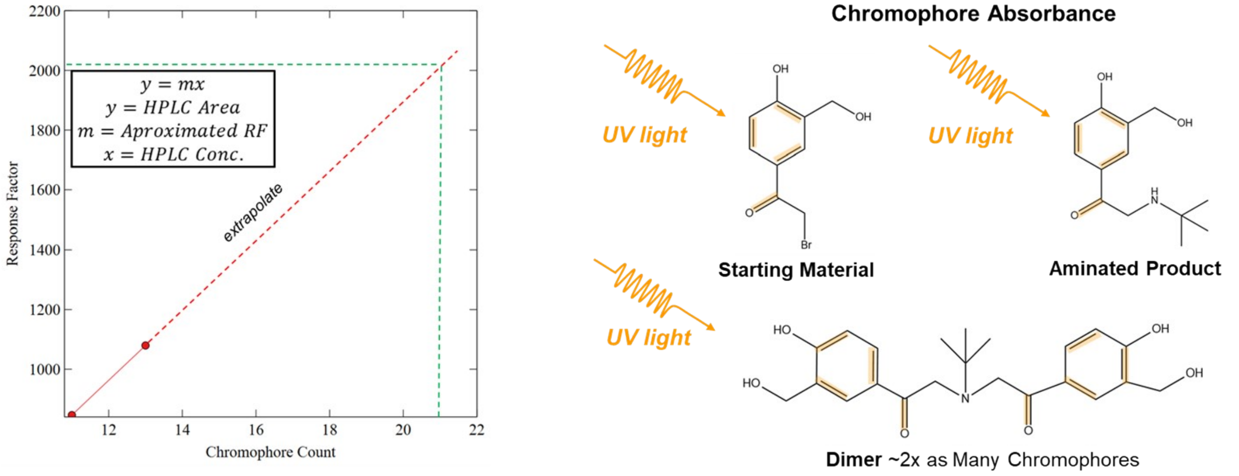


Fig. S3. Response Factor Estimation *via* Chromophore Analysis for Quantification of the Dimer.

Batch Amination Kinetics

- **Methodology:** Determine the kinetic rate constants (**k**) and reaction rates **(r)** *via* batch laboratory studies.
- **Arrhenius Equation**
  - Calculates the rate constant
  - Relates reaction rate to Temp.

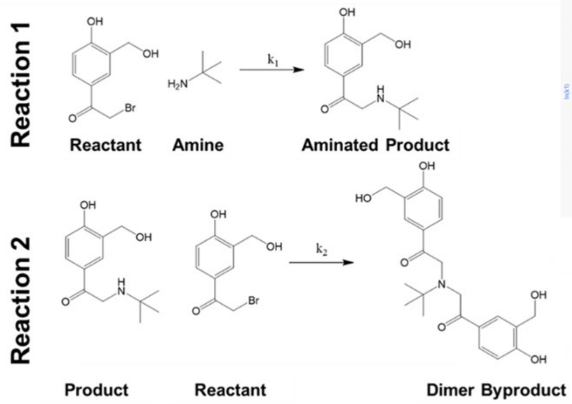
$$k = Ae^{-E_a/(RT)}$$

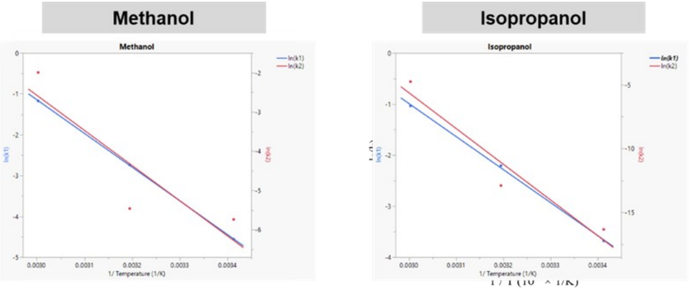
k = Rate Constant
A = Pre-exponential Factor
E_a = Activation Energy
R = Gas Constant
T = Temperature

$$\ln k = \frac{-E_a}{R}\left(\frac{1}{T}\right) + \ln A$$

$$\ln k = \ln A - \frac{E_a}{R}\frac{1}{T}$$

$$y = mx + b$$





Parameter	Methanol		Isopropanol	
Temperature (°C)	k_1 $(M^{-1}min^{-1})$	k_2 $(M^{-1}min^{-1})$	k_1 $(M^{-1}min^{-1})$	k_2 $(M^{-1}min^{-1})$
20	0.0105	0.0032	0.0252	8.00×10^{-8}
40	0.0646	0.0043	0.1102 (0.0801)	2.51×10^{-6}
60	0.3098	0.1364	0.3557	0.0087
E_A (kJ/mol)	68.79	74.56	53.77	233.14
A $(M^{-1}min^{-1})$	1.90×10^{10}	3.64×10^{10}	9.82×10^{7}	1.19×10^{34}

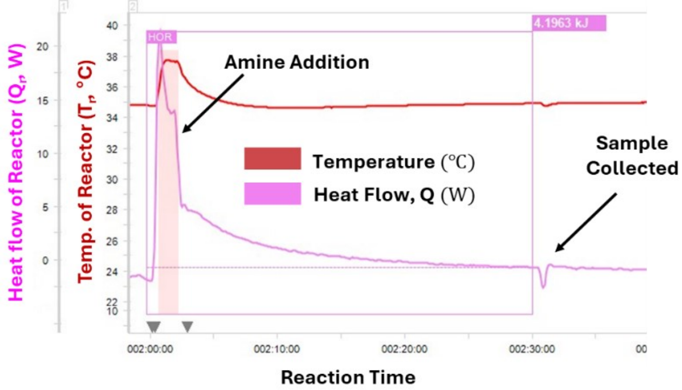
Figure S4. Kinetic Modeling and Arrhenius Plots.

Calorimetry

- **Heat of Reaction Study (ΔH_{Rxn})**
  - Quantify the Heat of Reaction through calorimetry.
  - System: EasyMax 102 Reactor from Mettler Toledo
- **Overview:**
  - **Conditions:** 3 Hr Reaction in MeOH vs. IPA, $T_{internal} = 35°C$
  - **Measurements:** $C_p, \Delta T$, and Q

$$\Delta H_{rxn} = \int_{t_0}^{t_f} Q\, dQ$$

$$\Delta\widehat{H}_{rxn} = \frac{\Delta H_{rxn}}{moles\ reacted}$$



Solvent	ΔH_r (kJ/mol)	95% CI
IPA	179.08	1.43
MeOH	265.74	5.05

Fig. S5. Representative Batch Amination Reaction Calorimetry Data.

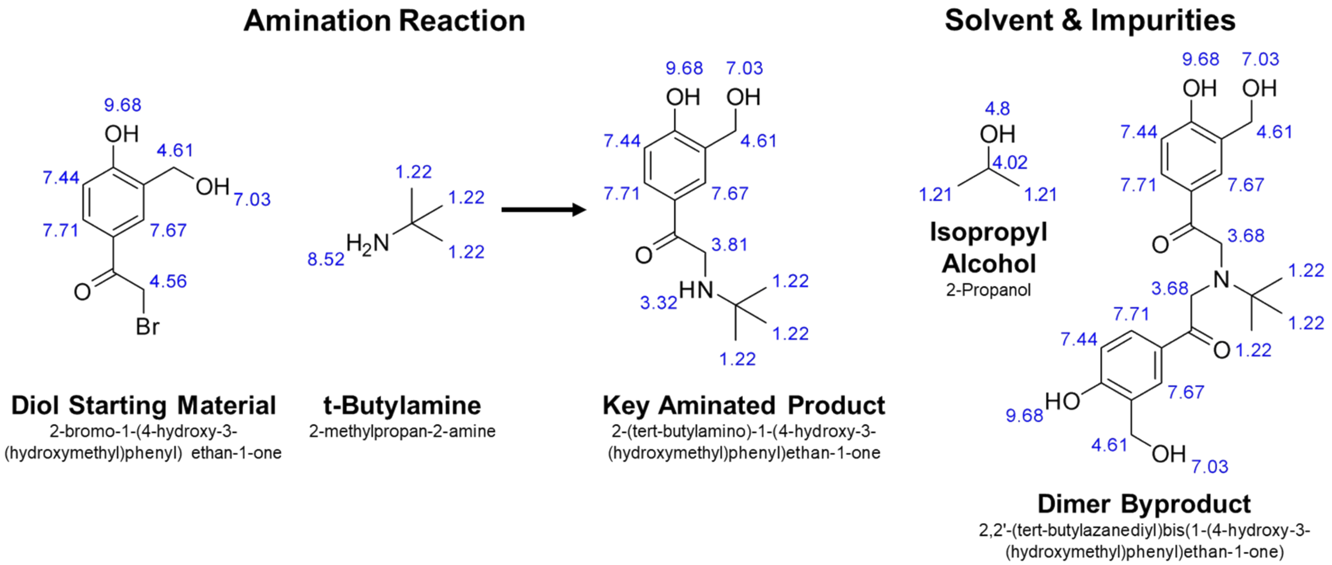


Fig. S6. ^{1}H NMR simulation of key protons as predicted by ChemDraw.

Table S2. Solubility limits of albuterol sulfate in key solvent mediums.

Solute	Solvent	Weight % Solute
Albuterol Sulfate	Deionized Water	16.7 ± 1.0
Albuterol Sulfate	Methanol	0.85 ± 0.01
Albuterol Sulfate	Ethanol	0.175 ± 0.025
Albuterol Sulfate	Isopropyl Alcohol	0.0225 ± 0.0025

Table S3. Solubility limits of the Bromo-Diol Starting Material in key solvent mediums.

Solute	Solvent	Temp.	Concentration	Weight % Solute
Bromo-Diol SM	Methanol	RT	120 mg/mL	13.2 wt%
Bromo-Diol SM	Methanol	40°C	190 mg/mL	19.4 wt%
Bromo-Diol SM	IPA	RT	50 mg/mL	5.9 wt%
Bromo-Diol SM	IPA	40°C	120 mg/mL	13.2 wt%

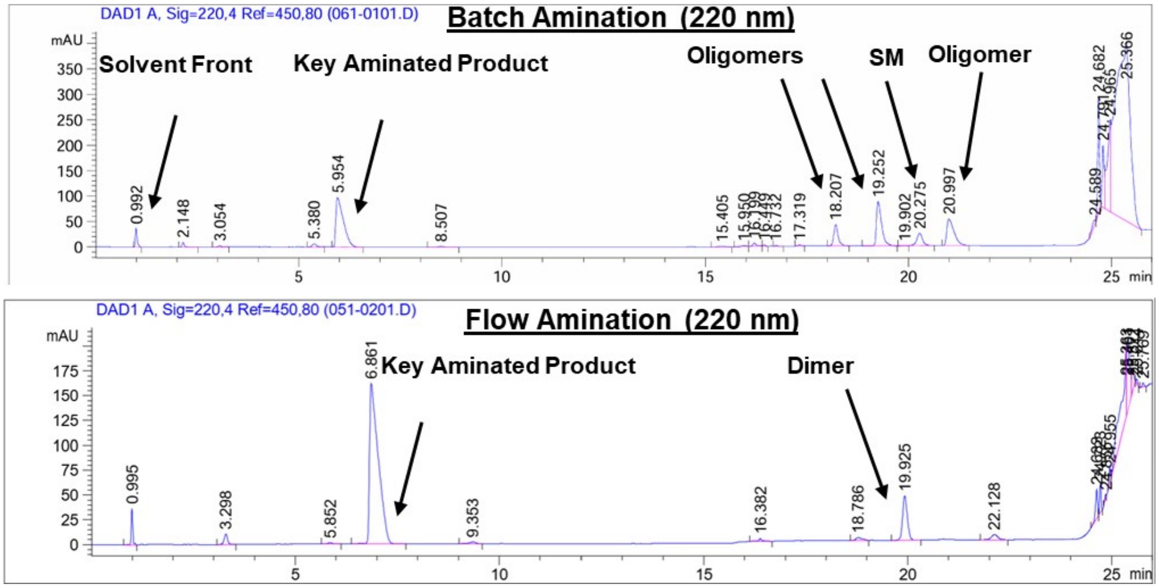


Fig. S7. Representative HPLC Chromatograms of a batch versus flow amination reaction

Table S4. A representative comparison of HPLC peak areas for a batch versus flow study.

Species	Rt	Flow		Batch	
		Peak Area	Area %	Peak Area	Area %
Solvent Front	0.9	105.0	3.7%	119.5	3.6%
Product	5.9-6.0	2384.9	83.6%	1262.2	37.7%
Oligomerized Byproduct	18.2	-	-	305.4	9.1%
Dimerized Byproduct	19.2	362.5	12.7%	775.7	23.2%
Starting Material	20.2	-	-	244.9	7.3%
Oligomerized Byproduct	20.9	-	-	636.0	19.0%

Section 2. Kinetic Rate Laws.

Coupled ordinary differential equations (ODEs) used as rate laws to model the amination reaction as shown in Scheme 1:

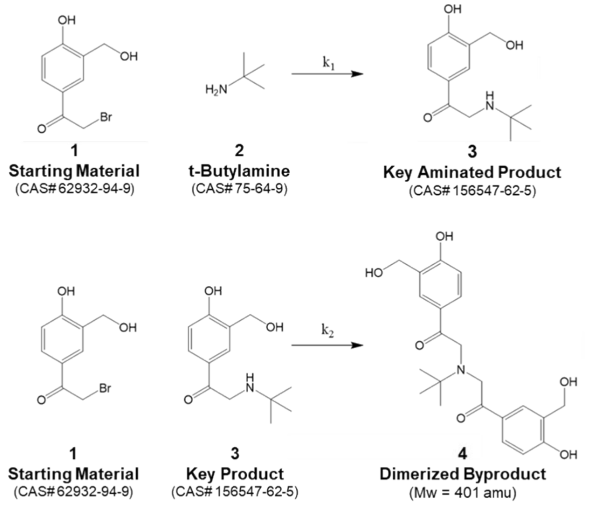
$$r_{Starting\ Material} = \frac{dC_{SM}}{dt} = -k_1 C_{SM} C_{TBA} - k_2 C_{SM} C_{Prod}$$

$$r_{TBA} = \frac{dC_{TBA}}{dt} = -k_1 C_{SM} C_{TBA}$$

$$r_{Product} = \frac{dC_{Prod}}{dt} = k_1 C_{SM} C_{TBA} - k_2 C_{SM} C_{Prod}$$

$$r_{Dimer} = \frac{dC_D}{dt} = k_2 C_{SM} C_{Prod}$$

$$r_{Net} = \frac{dC_{Net}}{dt} = k_1 C_{SM} C_{TBA} + k_2 C_{SM} C_{Prod}$$



Section 3. Model Development for Laminar Flow Reactor.

For a reaction being performed in a continuous operation that is flowing through a tubular system with a high Reynold's number (Re > 4,000), plug flow is the expected fluid behavior. Meanwhile, for that same system with a low Reynold's number (Re < 2,100), laminar flow is the expected fluid behavior. Additionally, both plug and laminar flow conversion models depend on the order of the reaction. For a first or second order reaction with plug flow behavior, the design equation for predicting conversion is already analytically solved,[1] however the derivation for a conversion model in laminar flow is as so:[2]

For a Newtonian fluid flowing with a fully developed laminar flow in a cylindrical pipe of length L and radius R, the following velocity profile is obtained:

$$u = 2\bar{u}(1 - ({}^{r}/_{R})^2) \tag{1}$$

Where $\bar{u} = {}^{u_{max}}/_{2}$. By performing a mass balance on species A, the following is obtained:

$$D\frac{\partial^2 C_A}{\partial z^2} - u\frac{\partial C_A}{\partial z} + \frac{D\,\partial}{r\partial r}\left(r\frac{\partial C_A}{\partial r}\right) - r_A = \frac{\partial C_A}{\partial t} \tag{2}$$

For non-dimensionalization, the following expressions can be made:

$$\xi = \frac{z}{L}; \eta = \frac{r}{R}; \theta = \frac{t}{\bar{t}}; c = \frac{C_A}{C_{A_0}}$$

Where $\bar{t} = L/\bar{u}$, the mean residence time, and C_{A_0} is the initial concentration of species A. Therefore, for an n^{th} order reaction, the following can be obtained:

$$\frac{D\,\partial^2 c}{\bar{u}L\partial\xi^2} - 2(1 - \eta^2)\frac{\partial c}{\partial\xi} + \frac{D}{\bar{u}R}(\frac{L}{R})\frac{1\,\partial}{\eta\partial\eta}\left(\eta\frac{\partial c}{\partial\eta}\right) - kC^{n-1}_{A_0}\bar{t}c^n = \frac{\partial c}{\partial\theta} \tag{3}$$

Assuming that the ratio between axial diffusion time to overall process time is significantly larger than 1 and that the system is operating at steady-state, then a simplified version of Equation 11 can be obtained:

$$-2(1 - \eta^2)\frac{\partial c}{\partial\xi} - Da_n c^n = 0 \tag{4}$$

Where $Da_n = kC^{n-1}_{A_0}\bar{t}$ and is known as the Damkohler number. Therefore, the following conversion models can be obtained for a reaction under laminar flow:

$$c_{exit} = C_{A_0}[\left(1 - \frac{Da}{2}\right)\exp\left(\frac{-Da}{2}\right) + \frac{Da}{4}E_1\left(\frac{Da}{2}\right)] \tag{5}$$

$$c_{exit} = C_{A_0}[\frac{Da^2\log(-Da)}{2} + \frac{Da^2\log(-Da-2)}{2} - Da + 1] \tag{6}$$

Here Equation 5 models a 1st order reaction and Equation 6 models a 2nd order reaction. E_1 is known as an exponential integral.

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[1] Levenspiel, O. Chemical Reaction Engineering. *Ind Eng Chem Res* **1999**, *38* (11), 4140–4143. https://doi.org/10.1021/ie990488g.

[2] Fogler, S. *Elements of Chemical Reaction Engineering*, 6th ed.; Pearson Education Ltd., 2022.