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Modeling mesoscale reactors for the production of fine chemicals

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HIGHLIGHTS

- We modeled mesoscale reactors with 1-d dispersion, 2-d colaminar feeds, and 3-d Y-junction CFD approaches.
- We extended the traditional 1-d dispersion model to include effects from sample loops and feed tubing.
- We demonstrated regions where the 1-d dispersion model applies and compared the results against batch gather kinetic results.

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ABSTRACT

Flow based synthesis at the mesoscale level allows precise control over process conditions (such as temperature and mixing), and offers advantages such as reduced processing times, higher reproducibility, and enhanced selectivity compared to batch reactors. Precise heat and mass transfer control allows for safer operations when using toxic or explosive materials or for highly exothermic reactions. We present a simple transient one-dimensional (1-d) dispersion model to analyze mesoscale reactors. The conversions predicted by the 1-d dispersion model matched well with conversions predicted by a two-dimensional (2-d) colaminar model. A computational fluid dynamics simulation (CFD) of a 120° Y-junction leads to a lower conversion at higher Damköhler numbers. Estimation of the kinetic parameters for the reaction between sodium azide and 2-phenylethylbromide demonstrated excellent agreement between the 1-d dispersion model and rates generated using a standard batch experiment.

1. Introduction

The successful commercial development of pharmaceutical and fine chemical processes benefits from high fidelity kinetic information. Historically, researchers develop kinetic rate laws in batch experiments, where the reaction progress is tracked either *in situ* with spectroscopic probes like IR or RAMAN, or it ex situ with LC, NMR, or GC methods. Batch experiments are well suited for kinetic rate law development, and simple techniques are used to extract kinetic information from composition data.

Batch experiments, however, have limitations. Fine chemical production requires the conversion of relatively complex and sometimes toxic materials. As batch sizes reach 100 mL to 1 L scale, the handling, disposal, and potential exposure concerns may require significant capital to operate safely and sustainably. An example is the Hofmann rearrangement to form (−)-Oseltamivir (Tamiflu) [1]. In this reaction, the toxic brominating species can be difficult and problematic to handle. Recently, Ley et al. [2] demonstrated the use of flow chemistry to produce relatively high yields of several Hofmann rearrangement products, which minimized toxic material on-hand. An equally toxic chemistry is the nitration and bromination of imidazo[1,2-α]-pyrazole demonstrated in a flow system by Pelleter [3].

Available heat exchange is another potential limitation of batch systems. The relatively small surface area to volume ratios make isothermal performance problematic. Better temperature control is the reason why some researchers have switched to flow-based platforms over batch experiments [4–6]. Other situations, such as lithiation reactions, require cryogenic operation to prevent side-product formation [7]. Cryogenic batch processes with larger volumes require significant pre-experiment time for the reactor to achieve set point temperature, and the cooling process must be repeated with each batch experiment. High surface area to volume ratios may also be utilized in photovoltaic reactors for applications such as photooxidation [8]. Hou et al. demonstrated improved reactivity and selectivity over a fixed bed catalytic reactor using microreactors [9].

Flow systems can be operated in a regime sometimes called segmented flow, where plugs of reactants are introduced through

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Nomenclature

C	concentration (mol/L)
$\overline{C}$	average mixed-cup concentration (mol/L)
Ca_o	initial concentration of primary reactant (mol/L)
$\overline{C}_{i,wall}$	wall-averaged concentration (mol/L)
CoV	coefficient of variance (n/a)
Da	Damköhler number (unitless)
De	dispersion coefficient $\left(\frac{cm^2}{s}\right)$
D_m	diffusivity coefficient $\left(\frac{cm^2}{s}\right)$
Ea	activation energy $\left(\frac{Kcal}{mol}\right)$
k	reaction rate constant (appropriate units)
k_r	reactivity ratio reaction 2 : reaction 1 (unitless)
k_v	feed velocity ratio stream 2 : stream 1 (unitless)
L	total system length (cm)
L_m	mixing-length as a fraction of reactor length (unitless)
Lv	inverse vessel dispersion number (unitless)
N	total number of feed components (n/a)
r	radial position (cm)
r'	dimensionless radial position (unitless)
R	tube overall radius (cm)
Re	Reynolds number (unitless)
r_b	dimensionless radius of inner tube for colaminar simulation (unitless)
R_1	radius of inner tube for colaminar simulation (cm)
$\mathcal{R}$	reaction rate $\left(\frac{mol}{L^{-3}}\right)$
t	time (s)
t'	dimensionless time (unitless)
u	mean velocity (cm/s)
$u(r)$	velocity as a function of radial position (cm/s)
X_i	dimensionless concentration (unitless)
z	axial position (cm)
z'	dimensionless axial position (unitless)

Greek

$\alpha_{j,k}$	power of species j in reaction k rate law (unitless)
β	integer (0, 1) to indicate if the reactivity ratio should be included (N/A)
ν	reaction stoichiometric coefficient (unitless)
τ	residence time (s)
Θ	angle between feed tubes (degrees)
ψ_1	fractional conversion by 1-d dispersion model (unitless)
ψ_2	fractional conversion by colaminar model (unitless)
ψ_3	fractional conversion by CFD Y-junction model (unitless)

Subscripts and superscripts

i	species and corresponding feed index
j	reaction index
k	species index for reactions
n	index referring to the reactor
$-$	prior to interface
$+$	after interface

sample loops. At set intervals, switching valves oscillate between bypassing and loading mode. The continual reactor purging allows the system to remain at reaction conditions throughout multiple experiments, potentially increasing laboratory testing capabilities [10,11]. Additionally, operating in segmented flow may reduce raw material usage, which is critically important for high valued pharmaceutical applications.

One flow chemistry drawback is the ability to measure concentrations *in situ* without disrupting the system. Batch processes typically have enough volume and reactor space to insert a concentration probe. The small diameters (or channels) that provide an advantage of flow chemistry preclude the use of traditional composition probes. However, several researchers are developing flow cells capable of interfacing with the small diameters and lower flow system volumes [11–13]. The IR flow cells are used to track product elution and to ensure that multiple feeds combine at the proper time and sequence. Additionally, reactant dispersion effects are tracked by IR flow cells. The results obtained from IR flow cells can be compared to post-reactor system analysis. However, researchers must account for potential sampling differences between through-the-wall and mixed-cup analysis, particularly for sample-loop injected reagents [14,15].

Several papers discuss challenges and benefits of transitioning to flow-based chemistry [16,17]. Valera et al. [17] present a road map on deciding whether to use micro-flow reactors based on the information desired. Valera indicates that flow chemistry may be used for rapid screening, medicinal chemistry, or high throughput goals. However, Valera suggests that detailed kinetics are best studied in a simple flask with a probe. In contrast, Hartman et al. [16] present mathematically based criteria to decide when flow systems would be appropriate. Hartman proposed that when the Damköhler number is significantly larger than one, or when the ratio of heat generation to heat removal in a flask is greater than one, or when the inverse vessel dispersion (referred to as Bodenstein) and Peclet numbers are less than one, flow chemistry systems are an appropriate means to generate reasonable data.

Mixing is a critical aspect in mesoreactor (or flow chemistry) applications. Several researchers fabricate and multiple companies offer mixing devices with numerous turns, channel widths of less than 100 μm, and volumes on the order of 100 μL [18,19]. Interdigital mixers, where alternating micron sized feed channels are used to facilitate fast mixing, are typical [3,20–24]. These ultra small devices serve to minimize both heat and mass transport limitations by shortening the total diffusion length across the cell. The mixing capability of several interdigital mixers has been evaluated experimentally [25], and micro-channel mixing characterization research continues [26]. Many researchers have focused on improved mixing devices [20,24,27] and modeling efforts [26,28–31] to understand the best and most efficient means for mixing chemicals entering micro-channel devices. The application of herringbone structures on the micro-channel floor has been shown to enhance mass transfer in falling film microreactors through experiment [32] and modeling [33] via application of eddy diffusivity to capture transverse flow effects. Improved mixing, caused by extremely short diffusion lengths, in micro-channel mixers and reactors may eliminate dispersion effects and modeling those systems may be approximated with the plug flow assumption [34].

However, not all researchers use interdigital or ultra small devices to mix reagents. Researchers interested in gram quantities or exploratory chemistries, will simply combine streams at a tee intersection [2,5,6,35–40]. DeAngelis [35] demonstrated the safe production of several arylhydrazines via Pd-catalyzed cross-coupling reactions. Baumann [36] cited the convenience and safety benefits of flow chemistry for the fluorination of numerous compounds. Brocklehurst [6] commented that simple tee-piece mixers are sufficient for efficient mixing and high conversions for nitration chemistry in flow reactor systems. Aoki et al. [41] discuss the role