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Citation: Nagy, Kevin D. et al. "Mixing and Dispersion in Small-Scale Flow Systems." *Organic Process Research & Development* 16.5 (2012): 976–981.

As Published: <http://dx.doi.org/10.1021/op200349f>

Publisher: American Chemical Society (ACS)

Persistent URL: <http://hdl.handle.net/1721.1/76275>

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

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Mixing and Dispersion in Small-Scale Flow Systems

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ABSTRACT: Continuous flow chemistry is being used increasingly; however, without detailed knowledge of reaction engineering, it can be difficult to judge whether dispersion and mixing are important factors on reaction outcome. Understanding these effects can result in improved choices of reactor dimensions and give insight for reactor scale-up. We provide an overview of both dispersive and mixing effects in flow systems and present simple relationships for determining whether mixing or dispersion is important for a given flow system. These results are summarized in convenient charts to enable the experimentalist to identify conditions with potential mixing or dispersion problems. The information also expedites design changes, such as inclusion or changes of mixers and changes in reaction tube diameters. As a case study, application of the principles to a glycosylation reaction results in increased throughput and cleaner product profiles compared to previously reported results.

■ INTRODUCTION

Flow reactors are gaining increasing interest for chemical transformations for their advantages,¹ including the ability to work at elevated temperatures^{2–4} and pressures,^{5–7} and scalable processing conditions. Micro- and minireactors^{8–10} represent an important subset of continuous flow reactors that can vary in complexity from simple capillary tubing^{11–13} to complex devices with integrated separators,^{14–17} valves,^{18–20} pumps,^{21,22} or even piezoelectric elements^{23–25} to enable specific applications. A common question experimentalists face is: does a simple T provide sufficient mixing or is a special micromixer warranted. In addition to mixing, experimentalists must decide whether steps should be taken to mitigate dispersion effects resulting from the flow in the center of the tube moving faster than that near the walls in laminar flow. The ensuing difference in reaction conditions can adversely affect yield and selectivity.

Also of interest in process development is the ability to translate results from a single microreactor to production levels since production rates from a single microreactor are typically too small to be industrially relevant. The so-called “scaling out” technique of running large numbers of microreactors in parallel is rarely practical because of the significant challenges of realizing and maintaining uniform fluid distribution to each reactor. An alternate, more feasible approach to larger production rates is to change reactor geometry, in particular, to increase the tube diameter^{3,26–28} as far as possible without losing the heat transfer advantages inherent in the flow systems. Further increases then have to be realized by scaling out with the now smaller number of units, which mitigates the fluid distribution problems. Since changes to reactor geometry, such as increasing tube diameter, affect the quality of initial mixing and dispersion characteristics of a system, understanding these effects becomes important to process development.

A wealth of literature exists in the chemical engineering field dating back to the 1950s^{29,30} on both mixing^{31–36} and dispersion^{37–41} in continuous flow systems, but general guidelines describing when either effect is important can be

challenging to extract for experimentalists. Herein we provide charts based on reactor dimensions (tube diameter) and flow characteristics (residence time) for evaluating when either mixing or dispersion effects are important on the basis of only a single experimental data point and an approximate kinetic model. As a case study, the performance of a glycosylation reaction⁴² is considered, and the resulting enhanced mixing and reduced dispersion result in nearly a 3-fold increase in throughput and improvement of selectivity.

■ WHEN IS MIXING IMPORTANT?

The lack of turbulence and recirculation eddies in microreactors means that radial mixing is strictly due to diffusion. The solution to Fick's law (eq 1) is frequently cited as a characteristic mixing time, τ_{mix} , where d_t is either the tube diameter or channel width and D is the diffusion coefficient.

$$\tau_{\text{mix}} = \frac{d_t^2}{4D} \quad (1)$$

However, this mixing time does not take into account the effect of chemical reactions occurring when mixing two reactive streams. A more accurate analysis relies on the Damköhler number (Da), which describes the relative rates of reaction and mass transfer by diffusion (eq 2). When the Damköhler number is greater than one, the rate of reaction is faster than the rate of mass transfer, implying that concentration gradients exist within a system. These gradients are normally detrimental to ideal reactor performance and could result in increased byproduct formation. Thus, evaluation of the system Damköhler number provides an estimate of whether enhanced mixing techniques are required. Accurately assessing the Damköhler number can be difficult, as knowledge of both the rate constant and the kinetic model is needed.

Special Issue: Continuous Processing 2012

Received: December 2, 2011

$$Da = \frac{\text{rate of reaction}}{\text{rate of diffusion}} \quad (2)$$

In order to address this difficulty, we propose that the Damköhler number can be estimated using the ratio of the residence time, τ , to the time to diffuse halfway across a channel (represented as a Fourier number, Fo) and a coefficient, χ , that depends on the system kinetics and feed ratios (eq 3 and 4). The characteristic length of a half channel comes from the assumption that volumetric feed ratios into a mixing junction are approximately equal.

$$Fo = \frac{\text{residence time}}{\text{transverse diffusion time}} = \frac{4D\tau}{d_t^2} \quad (3)$$

$$Da = \frac{\chi d_t^2}{4\tau D} = \frac{\chi}{Fo} \quad (4)$$

It is then possible to plot lines where $Da = 1$ for different values of χ for different tube diameters and residence times (Figure 1).

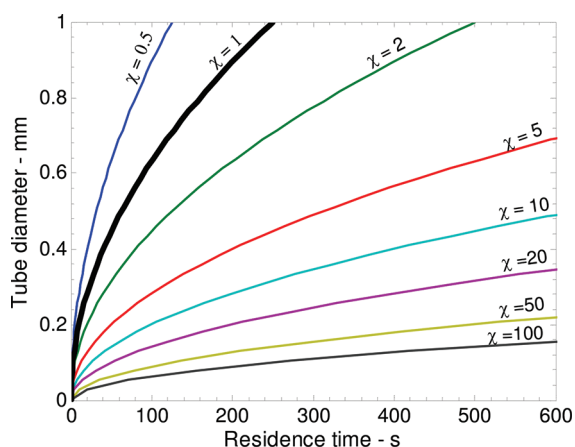


Figure 1. Curves corresponding to $Da = 1$ for different values of χ . Combinations of tube diameters and residence times falling above $Da = 1$ represent reactor dimensions and flow conditions requiring the use of mixing units.

When $\chi = 1$, the expression reduces to the diffusion based mixing time predicted by eq 1. Operating conditions above the curves warrant the use of mixing techniques,⁸ such as the use of interdigitated multilaminating devices,¹³ the use of a second phase,⁴³ or premixing at low temperatures for thermally initiated reactions.²

We have derived the functional form of χ for several kinetic models, which are available in the electronic Supporting Information (SI); most values of χ were found to be between 2 and 19. The procedure used to obtain χ is illustrated by the following example..

If the reaction $A \rightarrow B$ follows first-order kinetics, the conversion of A as a function of time is given by eq 5.

$$kt = -\ln(1 - X_A), \quad kt_{95\%} = 3 \quad (5)$$

Here k is the first-order rate constant, and t is the reaction time to conversion X_A . For a residence time to achieve 95% conversion under flow conditions, this equation simplifies to $k\tau = 3$, which upon rearrangement yields an estimate of the rate constant as $3/\tau$. Inserting this rate constant into the expression of the Damköhler number for a first-order reaction (eq 6), substituting the Fourier number definition (eq 3), and

comparing with the previous Damköhler number reveal that, for a first-order system at 95% conversion, the parameter χ is equal to 3.

$$Da_{95\%} = \frac{kL^2}{D} = \frac{3d_t^2}{4\tau D} = \frac{3}{Fo} \quad (6)$$

By using analogous derivations for common kinetic models, the parameter χ was determined, and selected values are summarized in Table 1; 95% conversion was chosen as a

Table 1. Values of χ for various kinetic models at 95% conversion^a

| A | B | B_0/A_0 | χ , 95% | A | B | B_0/A_0 | χ , 95% |
|---|----------------|-----------|--------------|---|----------------|-----------|--------------|
| 0 | N/A | N/A | 0.95/ A_0 | 1 | 1 [#] | 2 | 1.1 |
| 1 | 0 | N/A | 3 | 1 | 1 [#] | 4 | 0.6 |
| 2 | 0 | N/A | 19 | 2 | 1 | 1 | 200 |
| 3 | 0 | N/A | 200 | 2 | 1 | 1.1 | 90 |
| 1 | 1 | 1 | 19 | 2 | 1 | 2 | 16.6 |
| 1 | 1 | 1.1 | 10 | 2 | 1 | 4 | 6 |
| 1 | 1 | 2 | 4.7 | 1 | -1 | 1 | 0.95 |
| 1 | 1 | 4 | 3.6 | 1 | -1 | 2 | 2.0 |
| 1 | 1 [#] | 1 | 1.8 | 1 | -1 | 4 | 2.5 |
| 1 | 1 [#] | 1.1 | 1.7 | | | | |

^aThe columns correspond to the reaction order for a given species. A_0 and B_0 represent initial concentrations. (#) Autocatalytic in B .

representative value for the examples in this paper. If χ needs to correspond to a different conversion, it can be easily calculated using the analytical forms of χ for different rate expressions given in the Supporting Information. For reactions displaying dependencies on multiple species, the feed ratio is also important. The higher the conversion required, the more stringent the mixing requirements will become.

■ WHEN DOES DISPERSION MATTER?

Most small-scale liquid-phase flow systems have Reynolds numbers significantly less than 2000, which means these systems exhibit laminar flow and thus have a parabolic flow profile. Fluid at the center of the channel spends half as much time in the reactor compared to fluid at the walls, yet microreactors are frequently ascribed as displaying plug flow behavior. Reconciling a parabolic flow profile with plug flow behavior is only possible if radial diffusion across a channel is much faster than convective mass transfer down the channel. The dispersion model, derived by Taylor and Aris in the early 1950s,^{29,30} provides a general framework to estimate when a plug flow model is appropriate, as well as how to account for systems that deviate from plug flow.

An important necessary condition to apply the plug flow model with dispersion is that the tube length, L , is sufficiently long for fully developed flow to be achieved.³⁹ For very fast reactions flowing through short tubing lengths, a convection model should be used. Details of convection models are available in standard textbooks.^{38,44} The guideline for when to use a plug flow model with dispersion is represented by eq 7,

$$\frac{L}{d_t} > 0.04 \frac{\bar{u}d_t}{D} \quad (7)$$

This inequality can be expressed in terms of the Fourier (Fo) number by noting that the mean residence time equals the reactor length divided by the average flow velocity (i.e., $\tau = L/$

\bar{u}),

$$Fo > 0.16 \quad (8)$$

The Taylor dispersion coefficient, D , incorporates the effect of both diffusion, D , and convection^{30,38} (eq 9). Convection dominates most small-scale flow systems, except when a system has an extremely small volumetric flow rate. As a result, the diffusive portion of the Taylor dispersion coefficient can be neglected.

$$D = D + \frac{\bar{u}^2 d_t^2}{4\beta D} \cong \frac{\bar{u}^2 d_t^2}{4\beta D} \quad (9)$$

Here, the parameter β depends on the channel geometry and is 48 for circular tubes and approximately 30 for square channels.⁴⁰ The ratio of convection to dispersion is an important parameter in estimating deviation from plug flow, and this ratio is often measured in terms of the Bodenstein number (Bo):

$$Bo = \frac{\bar{u}L}{D} \quad (10)$$

The Peclet (Pe) number is also used to characterize this ratio, but here we define it as the ratio of convection to diffusion:

$$Pe = \frac{\bar{u}L}{D} \quad (11)$$

Combining eq 9 and eq 10 produces a simple estimate of the effect of dispersion as a function of the system Fourier number,

$$Bo = \frac{4\beta D\tau}{d_t^2} = Fo\beta \quad (12)$$

The largest source of uncertainty in using this expression likely comes from estimating the diffusion coefficient, though several correlations exist.^{45,46} We assume a typical liquid-phase diffusion coefficient of 10^{-9} m²/s in all calculations and diagrams herein.

Systems with a $Bo > 100$ have small deviations from plug flow, and systems with $Bo < 100$ display large deviations from plug flow.³⁸ Systems with $Bo > 1000$ can be approximated as having plug flow behavior. Regions of different flow behavior can be represented in terms of reactor dimension by plotting the above expressions as functions of the residence time at constant Bodenstein numbers (Figure 2). Dispersion effects are more pronounced in square channels as compared to circular tubes⁴⁰ due to the increased liquid holdup in the corners. Both 500- μ m diameter capillary tubes and 400- μ m square channel reactors show plug flow characteristics at residence times >20 min. Large deviations from plug flow are expected for reactions with residence times less than 120 s in capillary reactors and 150 s in 400- μ m square channels.

Figure 2 provides an estimate of whether increasing tube diameter will result in significantly increased dispersion effects. For cases where these transitions result in moving from a region of plug flow or near plug flow to a region where significant dispersion effects are expected, incorporation of an appropriate residence time distribution model for simple kinetic models is possible to predict performance in a reactive flow system.^{3,38,47} Possible steps to mitigate increased dispersion characteristics include incorporation of static mixers or a second phase to disrupt the laminar flow profile.^{41,48} Alternatively, use of coiled tubes with Dean numbers greater

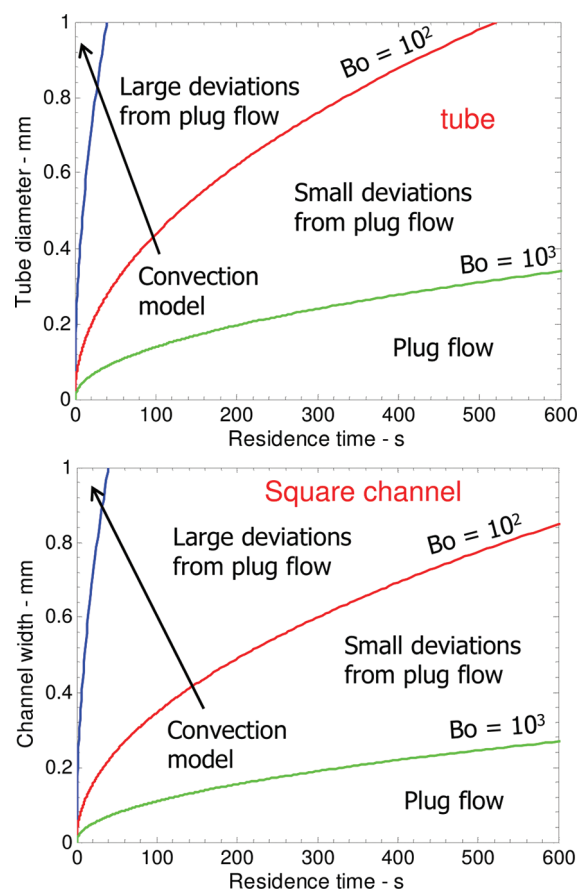


Figure 2. Magnitude of dispersion effects and the corresponding flow characteristics in circular tubes and channels with square cross section.

than ~ 10 can reduce dispersion effects due to outward radial flow.³²

The above criteria for mixing and dispersion effects are summarized in Table 2. The Fourier number can be calculated

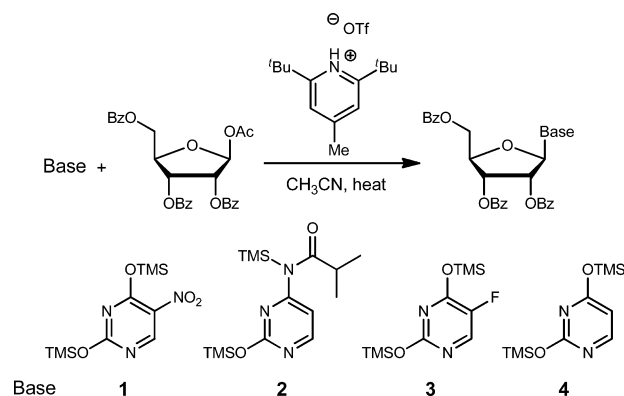
Table 2. Critical values of the Fourier number and χ for evaluating the impact of dispersion and mixing on a flow system

| Fo_{tubes} | Fo_{square} | action |
|---------------------|----------------------|---------------------------------|
| | <0.16 | use laminar flow reactor model |
| <2.1 | <3.3 | large deviations from plug flow |
| <21 | <33 | small deviations from plug flow |
| >21 | >33 | plug flow behavior |
| | $\chi < Fo$ | no premixing necessary |
| | $\chi > Fo$ | premixing advised |

from system dimensions, average flow rate, and estimates of the diffusion coefficient. Some preliminary understanding of the reaction mechanisms is necessary to estimate the χ parameter. For researchers with preliminary results from a flow system, calculation of Fo and estimation of χ provide insight into what modifications in reactor, mixer, or operating conditions could improve performance.

■ A CASE STUDY

As an example of using the above guidelines to increase understanding and mitigate effects of mixing and dispersion, we consider a glycosylation reaction⁴² (Scheme 1).

Scheme 1. Glycosylation reaction scheme from Sniady et al.^{42a}

^a Base 1 was used in the experimental study. The major byproduct corresponded to bisalkylation of the base at the 3 position.

The initial studies were performed with a stainless steel T mixer (ID \approx 1.5 mm) in conjunction with a PTFE capillary reactor. The kinetic model was predicted to be second order overall on the basis of the proposed mechanism. With a molar feed ratio of 1.1, a value of χ of 10.4 was used to estimate the Damköhler number, which in all but one case exceeds unity (Table 3). For base 1 and base 2, application of the above

Table 3. Comparison of glycosylation reactor performance based on data from Sniady et al.⁴² (P = product, BP = byproduct)

| base | d_t (μm) | τ (s) | P | BP | Bo | Da | Fo |
|------|-------------------------|------------|----|----|------|------|------|
| 1 | 500 | 30 | 99 | 0 | 23 | 22 | 0.48 |
| 2 | 500 | 300 | 80 | 6 | 230 | 2.2 | 4.8 |
| 3 | 500 | 600 | 87 | 9 | 461 | 1.1 | 9.6 |
| 4 | 500 | 1200 | 88 | 11 | 922 | 0.54 | 19.2 |
| 1 | 750 | 30 | 91 | 8 | 10 | 50 | 0.21 |
| 2 | 750 | 300 | 70 | 11 | 102 | 4.8 | 2.1 |
| 3 | 750 | 600 | 80 | 17 | 204 | 2.4 | 4.3 |
| 4 | 750 | 1200 | 78 | 13 | 409 | 1.2 | 8.5 |

analysis reveals that large deviations from plug flow existed and dispersion effects are potentially important. Base 1 was investigated further to demonstrate whether the previously described engineering principles could be used to enhance the performance of the system.

With the large Damköhler number and large deviations from plug flow, it is not clear whether the bisalkylation byproduct is caused by initial concentration gradients or from axial dispersion. In order to provide insight into the effect of mixing, three types of mixers were investigated, (1) the stainless steel T (SS T) used in the initial study (Swagelok, ID \approx 1.5 mm), (2) a PEEK T mixer (Idex Health and Science, ID = 0.5 mm), and (3) a custom silicon multilaminating micromixer³ (channel width = 50 μm). Three tubing diameters were investigated (500, 750, and 1000 μm). As expected, use of an improved mixer resulted in faster initial rates and higher conversions (Figure 3). Nearly complete conversion was achieved after 30 s in all cases, which can be understood in terms of "earliness of mixing."³⁸ In systems with poor initial mixing, the reaction rate is higher later in the reaction compared to that of a well-mixed system. This rate enhancement is due to the bulk concentration of the substrate in the poorly mixed case being higher later in the

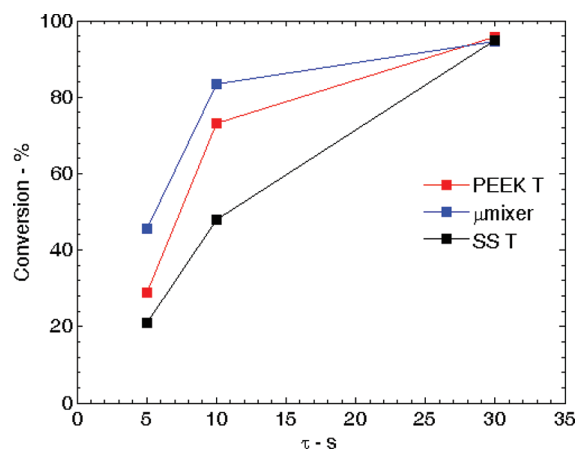


Figure 3. HPLC conversion of the ribofuranose derivative in 1-mm ID tubing using three different mixers. The other tubing sizes followed similar trends.

reaction. As the current analysis is most concerned with reactions in which byproducts can form due to concentration gradients, late mixing is considered undesirable, although this is not always the case. The ¹H NMR data showed no evidence of the bisalkylation product at 10-s residence time for any conditions examined.

Data at partial conversion at a residence time of 10 s provide insight into the effects of mixing (Table 4). Use of a micromixer

Table 4. Conversion at 10-s residence time using different mixing schemes^a

| ID (μm) | SS T | PEEK T | μmixer | $\mu\text{mixer} + \text{N}_2$ |
|----------------------|-----------------|-----------------|-------------------|--------------------------------|
| 500 | 83 \pm 2 | 89 \pm 1 | 91 \pm 1 | 94 \pm 1 |
| 750 | 76 \pm 2 (66) | 89 \pm 2 (87) | 92 \pm 1 (88) | 93 \pm 1 (90) |
| 1000 | 48 \pm 1 | 73 \pm 1 | 83 \pm 2 | 89 \pm 3 |

^aIsolated yields are in parentheses. Mixing improves going from left to right and from bottom to top.

with 500- μm tubing resulted in 91% conversion, a nearly 3-fold increase in throughput compared to the initial reported values. Going from 500- μm tubing to 1000- μm tubing with a micromixer resulted in an 8% decrease in conversion at a residence time of 10 s. This decrease can be directly attributed to the flow profile within the reactor. The Fourier number for a 10-s residence time in 1-mm tubing is 0.04, which corresponds to a convection flow model. In both cases, even at this very high conversion, no bisalkylation product was detected. The clean product purity at a 10-s residence time with high conversions, even with poor mixing, gave strong indication that the bisalkylation product was in fact due to the residence time distribution within the system and not due to concentration gradients initially present in the system.

In order to further investigate the effects of dispersion, we introduced a gas–liquid segmented flow, which is well-known to introduce cross-stream mixing by recirculation in Taylor cells.^{14,41,48,49} Addition of nitrogen in close to a 1:1 volumetric ratio created a segmented flow (Figure 4) resulting in nearly identical performance across the three tube diameters and a slight enhancement relative to the single-phase flow in the 500- and 750- μm ID tubing (Figure 5). Moreover, the ¹H NMR at 30 s with the segmented flow showed no evidence of bisalkylation product.

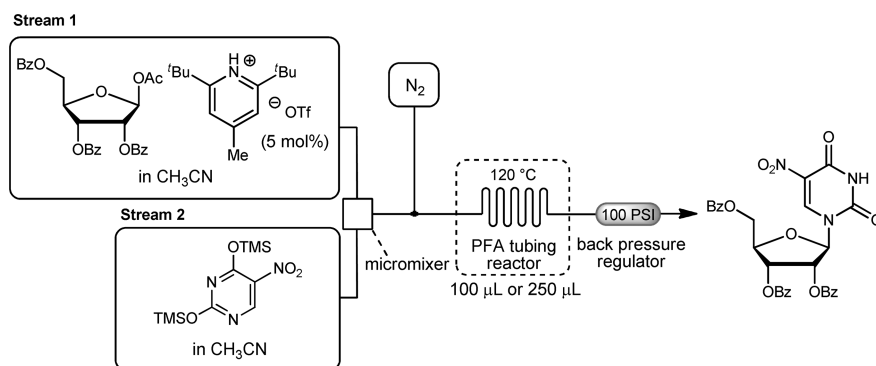


Figure 4. Schematic of experimental setup for creating a gas–liquid flow to reduce dispersion effects. A reactor volume of 100 μL was used for 5- and 10-s residence times, and a reactor volume of 250 μL was used for the 30-s residence time experiments.

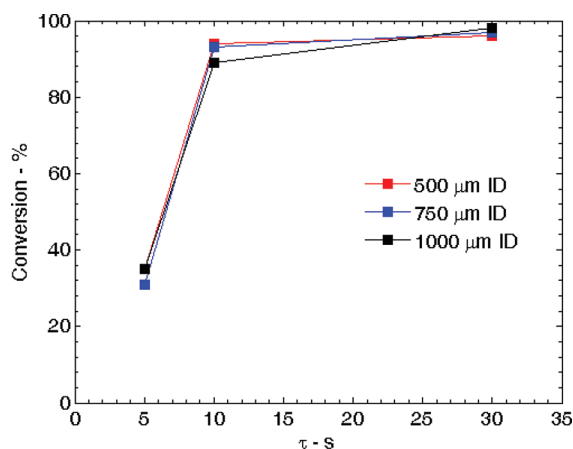


Figure 5. Experimental conversions using gas–liquid segmented flow. Results are nearly independent of tube diameter.

Finally as a check of the initial estimate of χ , the three data points obtained from the 500 μm tubing with a micromixer were fit to a second-order model produced an estimate of the rate constant of $3.6 \pm 1.1 \text{ s}^{-1} \text{ M}^{-1}$ (Figure S1 in the SI). The Damköhler number calculated using the experimental rate constant is $Da = 23 \pm 7$, which compares very favorably with the estimated value of $Da = 22$ based an estimate of χ of 10.4 for a second-order reaction with a 1.1 feed ratio.

CONCLUSION

Dispersion and mixing are important factors in understanding behavior in continuous flow reactors, especially for reactions where byproducts or degradation can occur. We have derived easily calculable relationships that serve as references for when either mixing or dispersion are important in a flow system. For very fast reactions, a laminar flow reactor model may be necessary to fully understand the reactor system, but mixing is likely the most important factor. For most microchemical systems, only small deviations from plug flow are expected due to the ability of radial diffusion to compensate for a parabolic flow profile. However, scale-up by increasing tube diameters will likely require incorporation of a dispersion model to accurately predict performance. A glycosylation reaction case study served to demonstrate the usefulness of these techniques in understanding and improving conditions with the result of increased throughput by enhanced initial mixing and cleaner product profile by eliminating dispersion. Furthermore, the proposed method for estimating the Damköhler number was

found to give an excellent match to subsequent estimates of the rate constant from experimental data.

EXPERIMENTAL SECTION

Samples were collected in triplicate at 5, 10, and 30 s and were analyzed by HPLC. Conversion of the sugar was calculated on the basis of consumption relative to an internal standard. The mixer and tubing were heated by submersion in an oil bath, although the cartridge back-pressure regulator was not immersed. Nitrogen was introduced in a 1:1 volumetric ratio using a mass flow controller that was calibrated immediately prior to use. All other conditions were identical to those previously reported.⁴² Isolated yields were obtained by flash chromatography on a Biotage Isolera purification system.

ASSOCIATED CONTENT

Supporting Information

Further details regarding the experimental conditions and χ parameter derivations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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ACKNOWLEDGMENTS

We thank Novartis MIT Center for Continuous Manufacturing for financial support.

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