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On the scale-up of micro-reactors for liquid–liquid reactions

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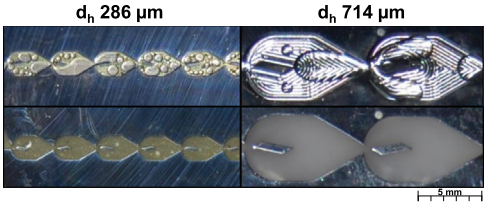
HIGHLIGHTS

- A constant energy dissipation approach was used to scale-up micro-reactors.
- Two different sizes were tested using a liquid–liquid reactive extraction.
- Their energy dissipation rates and $K_c a$ were similar at designed flow rates.
- Different reactor sizes and commercial mixers are compared for scale-up.

GRAPHICAL ABSTRACT



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ABSTRACT

The scale-up of a micro-reactor with a mixer designed for liquid–liquid reactions is investigated using a 3/7th approach that scales the hydraulic diameter at increased flow rates and keeps constant the average rate of energy dissipation. Smaller (d_h 283 µm) and larger-scale (d_h 714 µm) mixers are compared using single phase pressure drop measurements and a liquid–liquid reactive extraction. The single phase tests demonstrate that the energy dissipation rate of the larger scale mixer is comparable to the smaller scale mixer at flow rates ~8.5 times greater. The overall volumetric mass transfer coefficients of the reactive extraction, $K_c a$, of both scale mixers were also similar at equal energy dissipation rate in the drop flow regime. Finally, the upper limit of the sizing approach is discussed and compared with commercially available static mixers.

1. Introduction

Micro-reactors have sub-millimeter characteristic lengths that enable reaction control over harsh process conditions difficult to reach with conventionally sized reactors. At relatively small flow rates, they have become essential tools for process development in flow (Pastre et al., 2013). By using them modularly (Plouffe et al., 2014a), micro-reactors allow novel and intensified process conditions, and scale-up (Hessel et al., 2013). As a result, they have been an attractive technology for process development and intensification in the fine chemical and pharmaceutical industries, which remain traditionally dominated by batch and semi-batch synthesis (Roberge et al., 2008, 2005). Additionally, it is advantageous to use a continuous process early on, i.e. to use micro-reactors, in order to establish a manufacturing process in flow.

For this technology to be a viable alternative to batch synthesis, it needs to be versatile and scalable over several orders of magnitude. During the development of a new medicine (Kockmann et al., 2008; Malet-Sanz and Susanne, 2012), milligrams of the diverse candidates will be required for toxicological and kinetics studies. Some of these molecules may then proceed to the next development stages where an increased amount of material will

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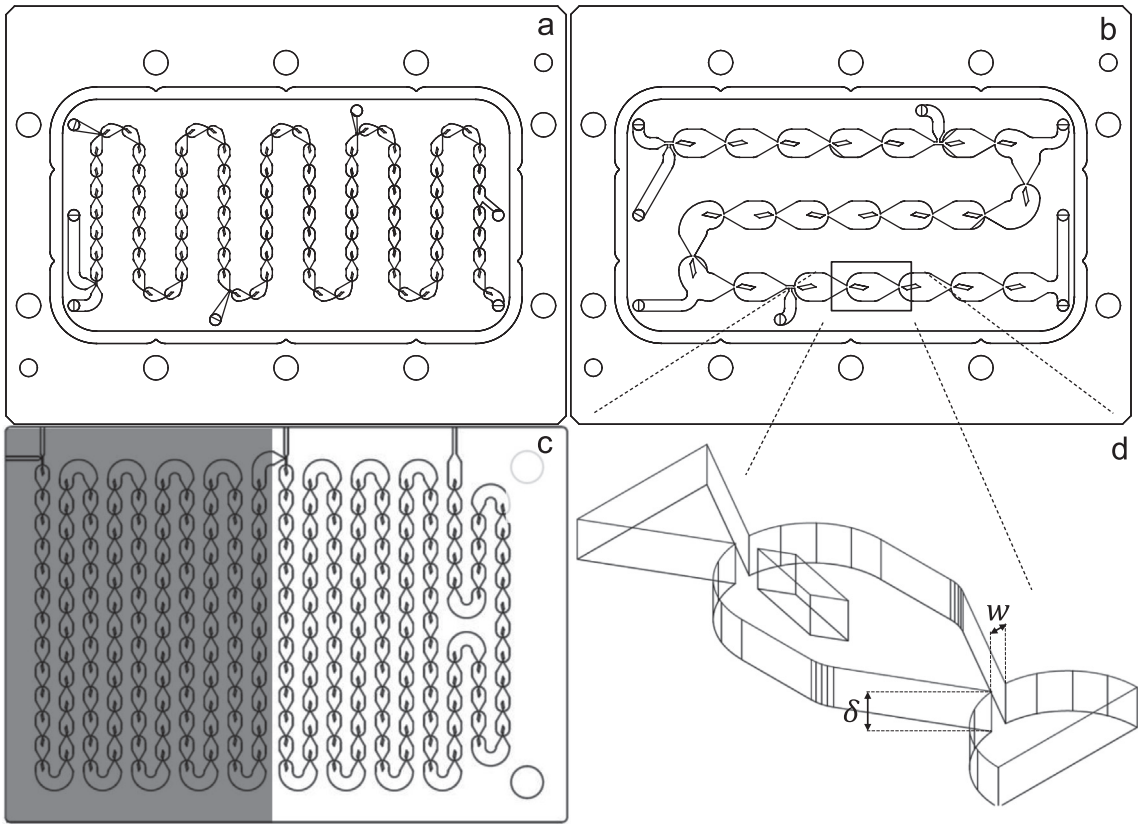

Fig. 1. Micro-reactor plates A7 Size 600 (a) and Size 300 (b), A5 Size 300 (c), and Micro-Mixer (d).

Table 1
Micro-reactors properties.

Scale	Contraction size (μm)	Plate size (mm)	Number of mixers	Total volume (mL)
Size 600	w: 200, δ: 500, d_h: 286	A7 (74 × 105)	88	0.241
Size 300	w: 500, δ: 1250, d_h: 714	A7 (74 × 105)	21	0.949
		A5 (148 × 210)	113	5.638

be synthesized for the pre-clinical trials (grams), clinical trials (kilograms) and productions (tons).

Scale-up of the production rate can be performed generally via one of two methods: numbering-up of micro-reactors, or sizing-up of the constituting channels and mixers. With numbering-up, micro-reactors are added in parallel and the flow of reactants is divided amongst them. This method of scale-up can maintain the advantages of the smaller scales, but is difficult to apply in practice. The difficulty arises mainly with the dosing of the reactants; the equal and stoichiometric subdivision of the different reactant feeds into amounts greater than two or three can be challenging especially for multi-phase reactions (Kashid et al., 2010). The sizing-up approach is not similarly limited in practice, but the sized-up dimensions have to be carefully engineered to carry the advantages of miniaturization at larger production rates.

This research group has previously described a mathematical approach to the conservation of mass transfer performance for the sizing-up of micro-reactors as well as provided some supporting evidence for single phase reactions (Holvey et al., 2011; Kockmann et al., 2011). The fundamental approach is derived from the scale-up of turbulent static mixer for mixing in pipes (for examples, see Etchells and Meyer (Chapter 7 of (Paul et al., 2004))). An article by (Woitalka et al., 2014) successfully matched the extraction efficiency and mass transfer coefficient of different sized liquid–liquid micro-reactors as a function of residence time. However, no detail is provided on the approach used for scale-up and the basis of comparison, residence time, is insufficient without more information since adding mixing elements would increase time spent in the reactor for a given flow rate, but not the mass transfer coefficient. The purpose of this work is to test an energy dissipation derived sizing-up approach with a liquid–liquid system and to evaluate its impact on the inter-phase mass in a micro-reactor. Additionally, a comparison is made with traditionally sized static mixers and reactors to determine the operational boundary of both types of reactors.

2. Derivation of the scale-up rule and sizes

The size and velocity of eddies in a fluid as well as the thickness of the boundary layer at the interface with another fluid vary with the energy dissipation rate and impact mixing and mass transfer. The sizing-up approach assumes that the mass transfer performance of a sized-up reactor will stay the same if the average rate of energy dissipation is kept constant during scale-up. The average rate of energy dissipation is calculated from the total flow rate, pressure drop and volume of the reactor as shown in Eq. (1).

$$\varepsilon = \frac{\Delta P Q}{\rho V_R} \propto f \frac{Q^3}{d_h^7} \tag{1}$$

From Eq. (1), it is possible to calculate the required reactor size at a scaled flow rate such to keep the energy dissipation constant, as shown in Eq. (2). In a straight channel, the friction factor would be proportional to the inverse of the Reynolds' number for laminar flow and constant for turbulent flow. In the first case, the hydraulic diameter would scale with the ratio of the design flow rates to the