Experimental and computational investigation of fluid flow and solid transport in split-and-recombine oscillatory flow reactors for organic chemistry in water

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Highlights

- Novel insight into fluid dynamics and solid transport in oscillatory flow reactors
- Split-and-Recombine principle enables transport up to 10 wt% solid loading in H_2O
- Novel particle tracing method in oscillatory flow resulted in 80% reduction in computational time
- Oscillatory flow reactor enables scalable and fast reactions in HPMC/H_2O solutions as solvent.

1. Introduction

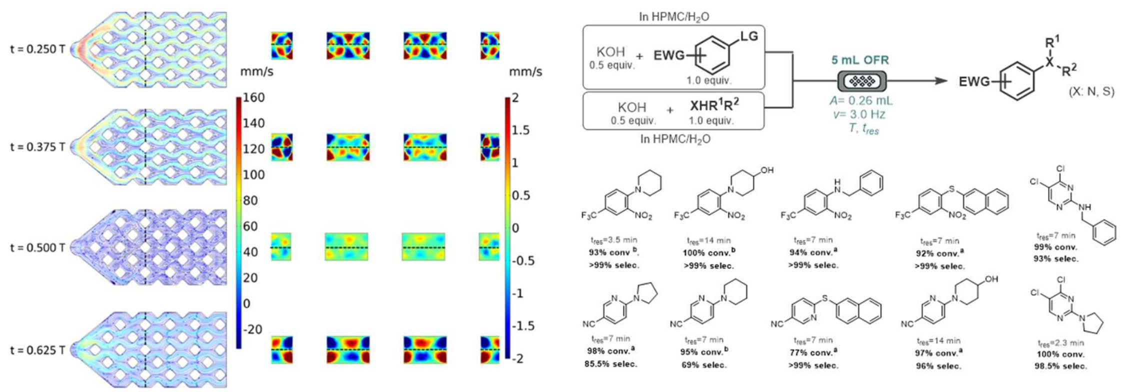
Oscillatory flow reactors (OFRs) have been used for process intensification in various fields, including polymerization, crystallization, and multiphase reactions. Among different fields of application, this technology has gained a lot of momentum in the pharmaceutical industry, given the rapid rise in interest regarding flow chemistry in recent years [1]. In an oscillatory flow reactor, a steady flow rate is coupled with an oscillating one. This configuration effectively decouples the long residence times needed for organic synthesis from the mixing phenomena in the reactor. In addition to this, the significant capability of OFRs in maintaining a homogeneous solid suspension within fluid flow holds crucial importance, as it offers a potential solution to overcome key challenges for small-scale and micro-reactors, such as fouling and clogging, expanding the applicability of flow chemistry [2]. The most common strategy to enhance resuspension of solid particles in OFRs is the installation of several baffles inside a cylindrical reactor (the so-called continuous oscillatory baffled reactors). Recently, another mixing strategy involving the coupling of pulsation with static mixing structures has been found effective in processing pharmaceutically relevant chemical reactions that involve solid phases under continuous flow. This strategy has been used primarily in the commercially available HANU flow reactor line, which exploit the beneficial combination of active and passive mixing resulting in a split-and-recombine mixing effect [3,4] . This work analyzes fluid dynamics and solid transport in split-and-recombine oscillatory flow reactors, to improve the understanding of the mechanisms behind the resuspension capacity of solids in flow driven by their efficacy in the processing of multiphase reactions. The reactor was then used to scale-up reactions characterized by solid precipitation in water as solvent, in the presence of a biomass-based polymeric additive (HPMC).

2. Methods

To achieve this, a combination of experimental analysis using the commercially available HANU 2X 5 reactor and CFD simulations with Lagrangian solid particle tracking has been exploited. The experimental campaign, aided by a DoE approach, focused on examining the impact of oscillation parameters and flow rate on solid handling performance. Slurries of SiO_2 in H_2O were utilized as a model system. Using nucleophilic aromatic substitutions (S_NAr) as valuable model reactions, reaction parameters optimization was then performed first in a small-scale reactor for 10 different substrates. The optimal conditions were then directly transferred to a larger reactor.

3. Results and discussion

Experiments in the HANU 2X 5 flow reactor reveal a six-fold reduction in particle deposition under oscillatory flow compared to constant flow. A DoE approach investigated the influence of oscillation parameters and flow rate, revealing the importance of tuning parameters to achieve homogeneous suspension and prevent clogging. Quantitative transport of up to 10 wt% SiO_2 slurries under optimized conditions was achieved. A CFD model revealed the presence of large recirculation regions and remarkable positive upward velocities near the static mixers under oscillatory flow, which facilitate particle resuspension, up to five times compared to stationary flow (Figure 1 (a)). Lagrangian particle tracing simulations were efficiently implemented through an original procedure, allowing reduced computational time by 82% under oscillatory flow conditions. The simulation validated the benefits of oscillations in sustaining particle suspension, explaining the mechanism that limits the particle deposition at the reactor bottom, compared to constant flow.



(a) (b)

Figure 1 (a) CFD model of HANU reactor, generation of positive upwards velocities during the oscillation cycle (b) Substrate scope for S_NAr reaction performed in lab scale reactor

S_NAr reactions between various nucleophiles and electrophiles were selected to study process scalability. Initially, reaction parameters optimization was performed by using a lab-scale instrument having an internal channel volume of 5 mL. Quantitative conversion and high selectivity were found with short residence times ($\tau = 2.5$-15 min) under mild reaction conditions (max. 60 °C) (see Figure 1(b)). Fine-tuning of frequency and amplitude of oscillations proved particularly useful in reaching an optimal homogeneous suspension. Ultimately, the optimal conditions from the small-scale experiments were directly transferred to a 15 mL OFR, achieving a three-fold scale-up by just adjusting the constant flow rate. Comparable isolated yields were obtained at the 2 scales.

4. Conclusions

The combination of experimental and computational approaches provides valuable insights for optimizing oscillatory flow reactor design, further advancing their utilization in chemical reactions. The numerical model developed offers a detailed understanding of fluid flow and particle trajectories within the reactor and also provides a novel methodology to reduce simulation times under oscillatory conditions. The scale-up protocol ensured the production of approx. 5.6 g of pure product per hour, which translates to around 130 grams per day using a small-footprint reactor system and water as a sustainable reaction medium.

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