Lonza's advances in flow chemistry

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The concept of a Mini-Mono-Plant for the synthesis of fine chemicals[1,2] is a quite appealing approach in order to substantially reduce production costs, increase product consistency and, strengthen process robustness. The concept could lead to a revolutionary transformation of the pharmaceutical manufacturing industry. A Mini-Mono-Plant can be defined with following attributes:

- Continuous manufacturing to enable high process intensification
- Intermittent batch reactors to fill/empty where needed;
- Use of "best in class" reactor technology or unit operations;
- High degree of automation resulting in minimal manpower;
- Small factory footprint; and
- Production scenario over time rather than batch cycle times / campaigns

Needless to say there also remains important technical limitations/challenges that have to be addressed and solved. Two major challenges are (i) the control of multi-phase applications such as with liquid-liquid or solid-liquid systems and (ii) the mastering of scale-up. In this respect, it is of prime importance to enable broad applications of flow technology not only in reactions but also for extraction, crystallization, and drying.

For liquid-liquid reactions, Figure 1 nicely depicts a novel structure that answers the liquid-liquid challenge via a simple methodology but based on a deep understanding of reactor design and fluid mechanics:[3,4]

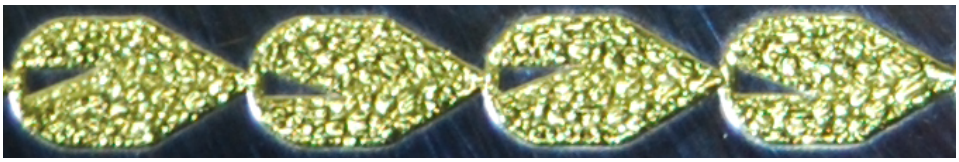

Figure 1. FlowPlate® LL-Triangle-Structure that shows a desirable drop-flow regime.

During the development of a basic reactor structure for multi-phase applications, it was quickly realized that curvature is detrimental to mass transfer and, as a result, needs to be minimized as much as possible.[3] As seen in Figure 2, curvatures generate centrifugal forces which tend to separate phases, not mix them. Despite this fact, many microreactors or static mixers are designed using curvatures. This is a pitfall that needs to be avoided when dealing with multi-phase applications of different densities.

Figure 2. A typical unwanted Parallel-Flow pattern where the denser phase remains close to the wall due to centrifugal forces.

The scale-up challenges can be solved when a process is operated in a pseudo-turbulent flow regime even at low flow rates (which is the main challenge). For liquid-liquid reactions this would mean operating with a proper flow pattern such as Drop /Dispersed-Flow (Figure 1). The scale-up is ensured by adjustment of the hydraulic diameter via the so-called "3/7 power rule".[4] Equivalent results are obtained when constant energy dissipation rate is maintained in the reactor (Figure 3).[5]

A- B-

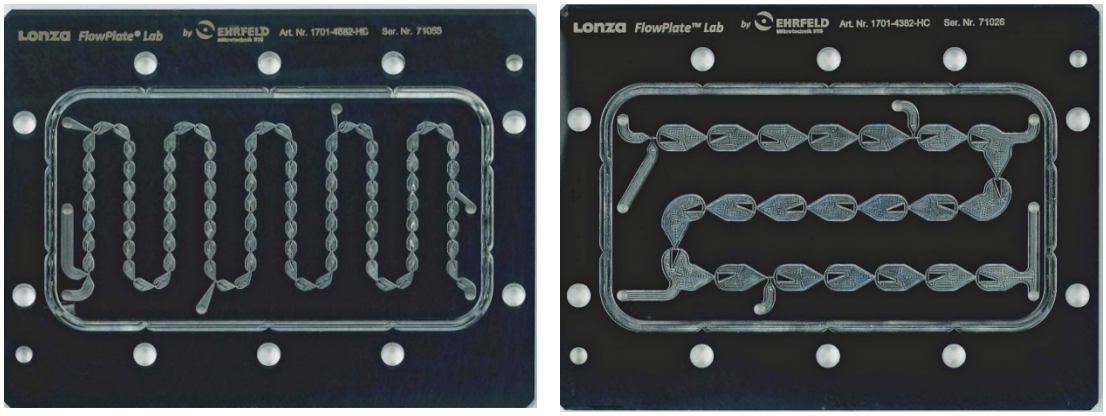

Figure 3. FlowPlate® Lab with LL-Triangle-Structure for small flow rate applications (A-; 1-15 mL/min) and a scalable version at ten times this basic flow rate (B-; 15-150 mL/min).

Finally, this presentation also shows a complete and operating Mini-Mono-plant where the main reaction is a multi-phases system. It will also show a cascaded process to a 2nd reaction at high temperature and pressure. The process output then proceeds to a continuous crystallization which is enabled by a novel suspension transfer unit. The process is completed via an automated filter-dryer unit that is operated in an intermittent-batch methodology but with complete automation.

References

1. Adamo et al., *Science* **2016** (*352*) 61.
2. Cole et al., *Science* **2017** (*356*) 1144.
3. P. Plouffe et al., *Chemical Engineering Journal* **2016** (*300*) 9.
4. P. Plouffe et al., *Chemical Engineering and Sciences* **2016** (*143*), 216.
5. E. Mielke et al., *Journal of Flow Chemistry* **2016** (*6*) 279.