Partnering with equipment makers to advance flow

Laurent Pichon describes some recent advances in solid handling and particle engineering at **MEPI**

Flow chemistry is still evolving after 25 years. Equipment makers are increasingly listening to market expectations. This is a very dynamic trend and is more than encouraging for the future of this technology. MEPI *(Maison Européenne des Procédés Innovants)*, a non-profit industry partnership organisation based at the *Institut National Polytechnique de Toulouse* in France has been working on some of these.

Flow synthesis

Even if elementary fluorinations[1,2], nitrations[3], sodium azide chemistry, lithiations, oxidations and other energetic reactions are still leading the way in flow chemistry, the demand for the downstream processes to be turned into a continuous regime is increasing.

In this respect, MEPI tested pressure differential membrane separators for liquid/liquid (L/L) or liquid/gas (L/G) separations both at laboratory and pilot scales. The expertise here lies in the chemical treatment of the membrane to render it hydrophilic or hydrophobic, and in pore sizes. These devices allow emulsions to be split promptly and swap solvent in cascading flow steps or L/L extractions.

Flow crystallisation

Extensive testing was also done on flow crystallisation using multiple technologies:

- Continuous oscillatory baffled reactor (COBR)
- Mixed suspension mixed product removal (MSMPR)
- Taylor Couette reactor (LCTR)

Unlike static mixers, these dynamic or active reactors offer excellent mixing at low flow rates, with larger channel diameters. They make solid formations possible during chemical reactions, but have so far been more used in crystallisations. Both cooling and anti-solvent crystallisations were tested for organic and inorganic chemistries, with various results upon the type of reactor and configurations.

COBR and MSMPR reactors use pulsation devices for their agitation. Various parameters like flow rates, temperature ramp and the amplitude and frequency of the pulsations can be set up. By contrast, LCTR reactors use rotation and the possible parameters include flow rates, temperature ramp, rotation speed and the gap in between the two cylinders.

With proper fine-tuning of these parameters, it is possible to control the size and distribution of the particles, as well as their morphology. This gives access to a 'two in one' flow strategy to match a client's specifications directly, while batch crystallisation is often followed by batch micronisation to meet the targeted granulometry.

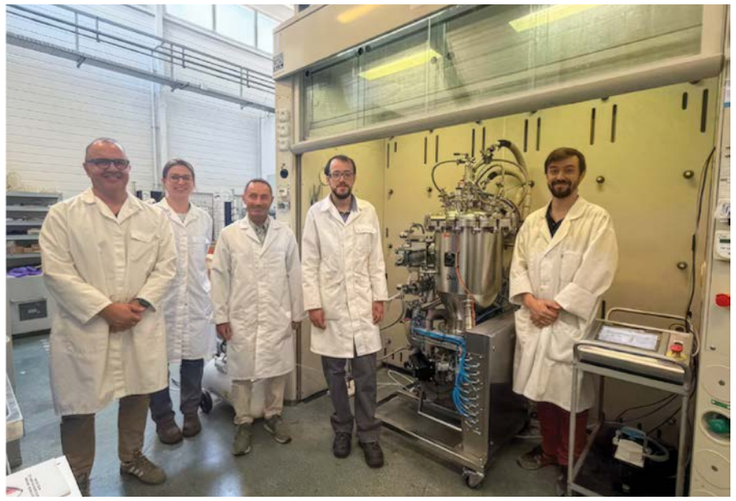
We were able to deliver two different crystal sizes, starting from the same crude solution. This means that several final applications can be served at the same time. For example, in pharmaceuticals, it becomes possible to make larger crystals for caps and smaller one for inhalation products. In addition, flow crystallisations may be five to 20 times faster than the same in batch mode, allowing interesting capex and opex savings.

This new area of particle size engineering via flow crystallisation is attracting the attention of many application markets including pharmaceuticals and energetic materials for defence and aerospace.

Continuous filtration & drying

After flow synthesis and flow crystallisations, a logical next step was to test new technologies for continuous filtration, washing and drying. That was investigated





using technologies from DEC Continuous Processing, using a DN50 Inverted Pocket Filter* to screen parameters before scaling up via a DN110 Astro Filter*.

The technology enables fast filtration followed by washing steps and hot air or nitrogen drying. We managed to speed up the process by a factor of ten compared to the current batch processes.

Continuous hydrogenations

An additional area of interest for MEPI is related to gas/liquid (G/L) reactions. In addition to elementary fluorinations run in silicon carbide plate heat exchange flow reactors, which we pioneered in 2009, MEPI started to investigate flow hydrogenations in 2019.

The first idea was to use heat exchange reactors, but having free flowing traditional palladium-carbon catalysis led to clogging issues. So, when we discovered that our neighbours, the LHFA laboratory from Toulouse University, had patented some liquid catalysts using precious and non-precious metal nanoparticles in glycerol-based stabilised collodions, we ran new flow experiments.[4]

We started using plate exchange reactors, but faced issues with a proper feeding of the hydrogen through the system, often creating flushing effects, which is detrimental to an efficient G/L quality and time contacts.

We then tested tube-in-tube technology, with hydrogen feeding through a membrane tube where the reaction media is flowing. That gave excellent results but there were still the challenges of recycling the catalyst and scaling up the technology.

Recently, we began a cooperation with the French flow reactor manufacturer Khimod. This tubular technology offers seamless scale-up. The tubes can be fed with catalytic static mixers or filled with catalysts in a packed-bed approach. The catalytic system stays in the reactor during production and can be recycled or regenerated when its efficiency starts to decline.

MEPI is currently investing in a new line, and associated safety devices, that will be able to supply hydrogen pressures up to 50 bar, rendering possible harsher hydrogenations.

A complementary approach is to use the membrane tower hydrogenator from Zaiput offering huge catalyst density per unit of reaction volume,. This enables the reaction to run in flow at lower pressures and lower temperatures, harsher conditions that are compulsory in a traditional batch strategy.



An initial Raney Nickel hydrogenation run in batch over 24 hours at 30 bar and 200°C was transposed to flow at 50°C and 5 bars in few minutes. These milder conditions offer improved safety and economic conditions. ●

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** - Khimod K1 is a registered trademark of Khimod

References:
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