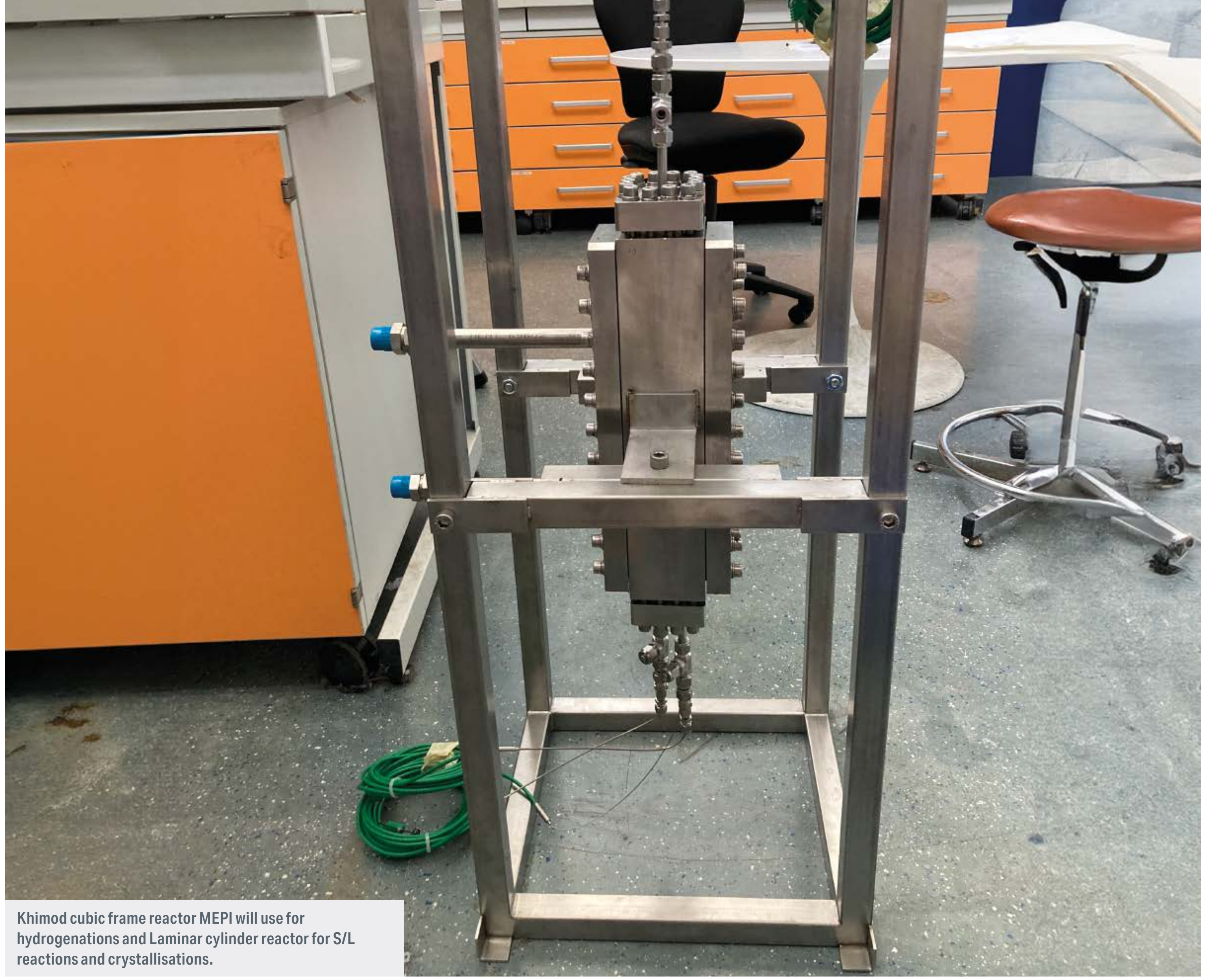
What's next for **flow?**

Enlarging flow chemistry technology offer can better answer market requirements, says **Laurent Pichon**, president of **MEPI**



Khimod cubic frame reactor MEPI will use for hydrogenations and Laminar cylinder reactor for S/L reactions and crystallisations.

Flow chemistry, which is now one of the best-known tools for industry to adopt the 12 Principles of Green Chemistry, first appeared on the market about 20 years ago. At the outset, most of the activity took place among academic entities and big pharmaceutical companies at laboratory scale.

Development at industrial scale has been relatively slow until recently. However, the recommendation by the FDA to adopt continuous processes, coupled with inline analysis to better manage and control the quality of API production, has helped to move things further.

Unexpected events like industrial disasters causing supply chain shortages, and more recently the COVID-19 pandemic and the war in Ukraine, have prompted awareness of the need for countries to be more self-sufficient and catalysed the reshoring of strategic industries like the chemical industry, especially in Europe. The resumption of paracetamol production in France is one example among many others.

Countries where double-digit inflation is raging are also considering local production to better control finances. As these projects often involve the construction of greenfield plants, it makes sense to consider implementing new and innovative technologies when building them.

Who is adopting?

However, the adoption rate of flow chemistry varies a lot from one country to another. In some cases, it is the result of 'pull' by government initiatives, like France 2030, subsidising decisions to invest in novel technologies in order to reduce the associated financial risk companies might take.

Meanwhile, China has established a rating of the 15 most dangerous chemical reactions and it is compulsory by law for the top five to be run in a flow system in the first instance. For this reason among others, China has by far the highest number of industrial scale flow set-ups, well ahead of the rest of the world.

The dissemination of flow technologies is also related to the potential application markets. Indeed, the first available industrial tools had flow rates capacities around 10 L/h, limiting a high return on investment to high added-value segments.

After the initial numbering-up strategies were replaced by economically more attractive 'light and seamless' scale-up (up to 100 times) options, flow was able to enter the speciality chemicals arena. The first commercial successes were in large nitrations or ethoxylations. This boosted interest from other segments, including pharmaceuticals, in adopting a cheaper, multi-purpose approach, using one reactor to run several flow campaigns with proper changeover procedures in place.

Initial focus

Initial demand mainly focused on chemical reactions, with the idea of achieving safer, cheaper, purer, greener synthesis. The ideal candidate would be an energetic, fast and exothermic reaction, if possible, with a liquid/liquid (L/L) biphasic reaction media, which would fit nicely into static mixers with efficient heat exchange and mass transfer capacities.

Common chemistries were nitrations, fluorinations, azidations and oxidations.[1,2] Biphasic enzyme-catalysed reactions were also investigated, with enhanced mixing playing a significant role.[3] More recently, the need appeared to enlarge the field towards more efficient liquid/gas and liquid/solid flow reactors to accompany the growth of flow.

In this field, MEPI (***M****aison* ***E****uropéenne des* ***P****rocédés* ***I****nnovants*) a Toulouse-based academic-industrial partnership that promotes eco-friendly and cost-competitive processes to cut traditional sourcing routes short and encourage the return of local manufacture, started a partnership with a French flow reactor company, Khimod, focusing on continuous scalable hydrogenations.

Here the technology not only involves reactor design, but also specific catalysis know-how, delivered via several options, including catalytic static mixers or trickle-bed options. In collaboration with Toulouse University, MEPI has also developed a specific metal-based catalytic solution using a liquid matrix, avoiding deadly clogging issues in flow reactors.[4]

Issues with solids

If the introduction of solids into a flow reactor remains very challenging, the need to address solid generation in flow reactors without causing clogging issues is definitively there. A common way of achieving this is to use continuous stirred tank reactors. However, these involve larger reaction volumes and poorer heat exchange control, which could lead to some limitations. For this reason, MEPI formed a collaboration with the South Korean flow reactor maker Laminar and developed a specific Taylor Couette active reactor for chemical purposes.

It should be noted that this technology allows solid formation inside the reactor and slower chemistries, thus potentially opening doors to reactions that have not been eligible for flow synthesis so far. We may also think of running L/L reaction in less diluted conditions to increase concentration and cost-efficiency. Reactions with several temperature zones and multi-injection strategies are also possible.

The equipment also shows interesting performances in crystallisation with specific narrow particle size distributions. In addition, other crystallization tools, and continuous filtration, washing and drying units, from AWL DEC Group, among others, are now available offering a wide panel of technologies to address downstream processing steps.

Last but not least, the intrinsic reactor volume reduction gained when switching from batch to flow makes it particularly attractive to photochemistry and electrochemistry options.[5] This not only makes it possible to revive old chemistries, but also opens our minds towards reaching targeted structures through alternative synthetic pathways. The flexibility and the inventive DNA of the flow chemistry players are definitively paving the way to a promising eco-friendly chemical future. ●

Laurent Pichon
PRESIDENT
MEPI
l.pichon@mepi.fr
www.mepi.fr

References
1: *A. Harsanyi et al., Org. Process Res. Dev. 2017, 21, 2, 273–276*
2: *S. Elgue, A. Conté et al., Chimica Oggi, July/August 2012, 30(4)*
3: *A. Conté et al., Chimica Oggi November/December 2013, 31(6)*
4: *A. Reina et al., AIChE Journal, 2019; e16752.*
5: *S. Elgue, et al., Chimica Oggi, 2015, 33(5), 58-62. ISSN 0392-839X*