FLOW CHEMISTRY IS STARTING TO FLOW

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TNO innovation for life

"One good thing about this symposium on flow chemistry is that at least half of the papers was on actual applications", summarized one member of the audience of the IPIT symposium in Rotterdam, 25 May 2012. This remark can be viewed as a compliment to the organizer, TNO, a Dutch contract research organization. More importantly, it shows that flow chemistry is, slowly but steadily, being accepted in the production of fine chemicals and pharmaceutics.

In order to get flow chemistry accepted in the fine chemicals industry, one should not called it so. This industry is so used to working with batches in a tank reactor, that the simple mentioning of flow chemistry, or continuous production of chemicals in tubular or plate like reactors, does not go down well, according to several authors at the IPIT 2012 symposium in Rotterdam. But is not the only factor that is causing flow chemistry's slow progress in the industry.

One big point is that Capex is always higher than the tank reactor, if only because large numbers of tank reactors are standing idle in the current downturn. Added development cost and cost for certification of pharmaceuticals, fear of reactor clogging and the huge gap in experience on scaling up are also important factors counteracting the use of flow chemistry. But one may question whether this really outweighs the advantages of flow chemistry: its inherent safety and the relatively low consumption of energy and feed stock. These factors make it more sustainable and on the long run cheaper.

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DISINVESTING

Frederik van Oene believes that the problem may be even more fundamental to the chemical industry. Van Oene, a well experienced partner of Arthur D. Little specializing in innovation management, argues that chemical companies are very good at debottlenecking, or optimizing current solutions, but have little attention for what is needed in more than five years. Indeed, the industry does not view itself as innovative. Van Oene asked the audience which percentage of chemical production processes has seen breakthrough innovations in the past 25 years. About 20-30 percent, guessed most. In fact, it is 70 percent.

Innovation, by the way, is not limited to the processes, but can also involve new business models, new service and new products. As an example, companies that used to license out a certain production process, now also supply the equipment and even the operators on the site of their customer. So, chemical companies are innovating their business and they need to do so to face the challenges like globalization and sustainability. Already, companies are now disinvesting in processes that are not sustainable. Sustainability is becoming as important as financial factors in decision making.

For effective innovation one needs partnership between R&D and business developers, says Van Oene. Create special incubator labs, separate from the usual business, he advices. Put the creative pressure on. Van Oene: “Big ideas come up when the need is at its highest.” Cooperation is also essential: ecosystems are now competing with ecosystems, rather than individual companies. In this way, one can attract the best ideas from a region, if not the whole world.

But breakthrough innovation is a high risk, high gain game. Consequently, many of the executives in the industry have burned their fingers on innovation during their long careers. Obviously, this leaves a taste. Yet, the time is ready for flow chemistry as a sustainable solution, now more than ever. So let us see how different tactics are used to deal with the blockades against flow chemistry in different industrial branches: pharma; fine chemicals and biochemicals.

PHARMA

The approach of Alain Merschaert, associate director at UCB Pharma SA, is to try to use flow chemistry for a new process. “One of our products is an enantiomer of a complex amine. Large amounts of the unwanted enantiomer was lost in the resolution process.” Thus, the search was on for an effective racemization process. A free radical method at high temperature appeared to be most suitable. Batch processing required charcoal treatment to obtain constant results, causing 5-7 percent production loss. Also, it was unsafe as a large amount of unreacted, explosive reagent was brought to high temperature. Additionally, impurity levels remained lower in the continuous process. Finally, ROI for the continuous process is reached after 2 ton of production, versus 5 ton in the case of a batch process. Merschaert: “Still, discussion on this investment are going on because of the need of an additional reactor and questions were raised on waste of this process.”

“One should remember that not all processes are suitable for flow chemistry”, remarks Merschaert. Products that have low solubility and processes requiring many purification steps, as is often the case for pharmaceuticals, are not suitable. Also, production cost are only a small factor in total drug cost and cost of reassessment for regulatory purposes easily counteract any reduction in production cost. Thus, one should do both the product development in the lab as well as the actual production in flow reactors.

FINE

Domique Roberge is head of the continuous flow/microreactor department at Lonza AG. This mere fact goes to show that Lonza is more experienced in flow chemistry. Indeed, fosgene, a very hazardous chemical, has been produced for more than 20 years in continuous flow, along a range of other special chemicals. At Lonza, the use of small plate reactors is preferred as they have a much better heat transfer than tubular reactors. Roberge: “Tubular reactors are by no means isothermal, as often is assumed. Plate reactors usually are”. But sometimes even in plate reactors hot spots are observed. Roberge advices to use multi-injection ports in such cases.

Small or even microreactors are used in parallel to scale-up production. This is not as easy as it sounds, due to pressure differences that result in significant flow differences. “We prefer to use a separate pumps for each reactor. The potential problem of plugging in microreactors can be controlled by using glass reactors, so that early set on of deposition can be tackled, for instance using ultrasonic systems”.

Another problem often encountered is variability in the feed stock, which results in variation of the optimum residence time. Modular systems, or overdesigned systems may solve this. For this purpose, Lonza developed a range of flow plate reactors sized A5, A6 and A7 (as in the paper sizes). This allows very easy scale-up. “In fact, we bring the lab into the fab, although we must use others terms to get it accepted”, summarizes Roberge.

BIO

Biochemical production is often much more sustainable than traditional chemical production. Henk Noorman, corporate scientist bioprocess technology of DSM, showed examples of the production of an antibiotic, where 13 fine chemical productions steps were replaced successfully by one fermentation and two enzymatic steps, reducing total energy and materials consumption by two third while yielding a higher purity product at considerably lower cost.

The reactor concept used by DSM is an intermediate between batch and continuous operation. A 250 l tank reactor is fitted with a continuous feed and a membrane filtering system that separates spent medium but retains the cells and the product. It is parallelized to scale-up production. Noorman: “That reduces total Capex with a factor five. Also, it allows us to delay decisions, and thus makes our business model more agile”. A final neat trick is that the reactions are performed in disposable bags in the tank reactors, reducing cleaning time and expenditure considerably.

Noorman sees many other potential applications for biochemical processing, although the infamous valley of death looms as for any invention. On the process side, for instance the use of pure oxygen to speed up processes. New feedstock, biomass that has no food value, can be used for lignocellulose production. “It is essential, however, that a good use is found for each side product”, says Noorman. New products include bio-succinic, that has many potential uses that still need developing, as well as bio-caprolactam, which is used to make nylon. The principle of biological production of caprolactam is proven, greenhouse gas production may be reduced by a factor 8. The outlook for many of these processes is that smaller, cleaner and greener production sites make valuable products using a mix of biochemistry and chemistry.

NEW ROUTES

Another new route for flow chemistry was shown by Pascal Buskens, TNO. He argues that nanomaterials are not a hype but a new line of products, with very special optical, thermal, electronic and magnetic properties. These properties are due to the small and special dimensions of nanomaterials. To guarantee these properties, nNanoparticle dimensions must be extremely well controlled during production, while the cost price has to be reduced considerably to open up the market. A typical case for flow chemistry. Volker Hessel of the TU Eindhoven pleads for a holistic view on (flow) chemistry, integrating smart design of the synthetic route and micro process technologies, combined with new catalyst concepts and the development of in silico technologies. He has a multitude of examples to support his case.

Another new route for innovation is cooperation, argues Jan Willem Sluikoord of TNO. An example is the HOLST centre, founded by TNO, IMEC and Philips, with currently more than 30 partners cooperating in the development of organic solar cells and organic LED’s.

Laurent Pichon actually works at such a cooperative innovation center, MEPI in Toulouse, which is aimed at ‘alternative chemistry’. A recent survey performed by MEPI shows that three out of four fine chemical producers are currently using flow chemistry; most started to do so quite recently and typically for less than ten percent of the total production of a site. But all companies are interested in applying flow chemistry (more often) in the near future.

In conclusion: flow chemistry is slowly starting to flow and this flow will steadily grow.