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Flow chemistry: analysis of market trends

Sightseeing by skilled flow chemists

KEYWORDS: Flow chemistry, market and regulatory trends, offer width.

Abstract The recent flow chemistry market, offer, and regulatory trends are displayed in the light of experts comments. Moving demand is pushing the equipment makers to adapt themselves quickly and efficiently leading to an innovative and interactive Innovation

A MARKET/PERCOLATION MATRIX

The concept of flow chemistry has been promoted for more than one decade now, not only through the organization of specific scientific symposiums, but with an increasing and self-adapting offer of innovative equipments available on the market at various scales. A need for an up-dated picture of where this technology breakthrough stands, naturally emerged.

To more accurately figure out the current flow chemistry scene, a questionnaire was sent out to both chemical companies and equipment manufacturers. All the participants, with no exception, mentioned a positive trend in the adoption of continuous intensified processes. This trend is more visible since a couple of years.

All markets do not respond the same way. The first segment to taste the flow chemistry was obviously the pharmaceutical industry. The commissioning by GSK at the beginning of this year of a fully continuous process for API manufacturing is the result of a decade of human and technical investments said Andrew Rutter. Most of the big pharmaceutical companies have reached a well advanced point in the knowledge of flow.

This was not so visible until recently, due to internal maturation processes and, as early stage drug development is always surrounded by strict confidentiality. **Vijay Kirpalani**, Ceo at Pi - Process Intensification Experts LLP, adds: "Key drivers for Pharma have been cost savings, robust steady-state manufacture and access to non-infringing routes via hitherto considered forbidden-chemistries. Fine, Speciality and Agro chemicals are driven by cost, safety and the stricter environmental laws".

This was confirmed at the last CHEMSPEC Europe in Basel, by Jörg Schrickel, who explained the benefits of flow vs batch approaches for chlorinations and sulfonations. **Sebastian Rieth** from Roche adds: "The pharma production is under an increasing pressure of costs, so the industry looks for more economic ways of production. In chemistry, where more and more dangerous chemicals are used, it is a big advantage if I can synthesize them in a small flow-device, and do not have to store or transport them".

Charlotte Wiles of Chemtrix® said: "Whilst the recent publicity cases relating to the use of continuous manufacturing are largely related to the technologies use within the pharmaceutical industry, the trend of the past

two years is that uptake is fastest within the fine chemical and specialty sectors."

Indeed, the speciality chemical sector remains a good target, especially in Europe where a need for new investments is more pregnant to accompany continuous market growth.

This is one of the reasons why equipments providers are launching larger capacity continuous reactors. These bigger tools are used for dedicated productions on the speciality chemicals segment, while the fine chemicals sector is using those as multi-purpose continuous productions tools. The introduction of new materials like the silicon carbide, first developed on flow chemistry by MEPI® in 2008, are rendering possible, a large variety of chemistries in the same equipment, due to exceptional heat exchange and corrosion proof performances. **Robert Tinder** of Proteaf Technologies confirms: "With new technologies emerging every day, it is hard to imagine flow chemistry not gaining greater acceptance as a tool for accomplishing chemical transformations".



"We see a rather small percentage of processes in flow today but that is certainly increasing" states **Jeffrey C. Raber**, President of KinetiChem, Inc. In Fierce Pharma Manufacturing, Feb. 19, 2013, CEO of GlaxoSmithKline Andrew Witty said: "[...] Between a third and a half of the company's current portfolio of drugs could be made using continuous processing."

In reality, the answer is a sophisticated mixture of chemistries trends, application segments and geographical zones.

Gareth Jenkins from AM Technology says: "For new products which need new plants to be built, starting out designing with continuous processing in mind will mean that all of the potential benefits can be applied. For existing products, however, it is a much more complex picture and depends on many factors. There will be examples where continuous processing could be used tactically to debottleneck an operation or part of a plant."

SIGNS OF HOPE

More recently, new investments were disclosed in Europe in the fine chemical sector (PCAS in Couterne, Dottikon ES in Aargau...). These are building encouraging signals for the flow chemistry in Europe after nearly two decades of a really quiet period on the investments side.

These first signs of changes could be propelled by a higher desire of China & India to improve the eco impacts of their local chemical industries, and associated closures of out of international standards factories.

At the same time, and logically, the adoption of flow chemistry in Asia has been by far the quickest since few years, while cash flow, quick decision processes, need for up-grade & innovation are common. The recent growth in Europe is adding on the world demand.

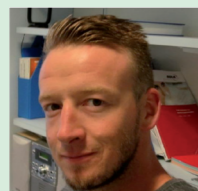
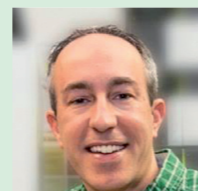
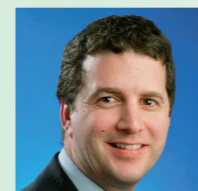
When it comes to predict the future market share of continuous over batch processes, the answers are all leading to a double digit figure, but it is harsh to predict it in a more accurate way.

STRATEGIES ARE SELF-DESIGNING

In fact we see three emerging strategies for flow chemistry industrial implementations:

1. The "container factory" which consists in building your intensified plant within a mobile box, that can move from one workshop to another, or one site to another. This strategy has been pushed by companies like Ehrfeld Mikrotechnik BTS within the INVITE programs.
2. The "hood factory" consisting of placing the reactive parts of the milli-plant in a hood, as innovation platforms do, but also industrial actors like Merck, confirmed John Naber at the last RSC Symposium in Cambridge.
3. The "squatter factory" is a hybrid solution consisting of placing flow chemistry mobile components (reactors, pumps, thermal exchange device, data acquisition) in an existing batch workshop. The former batch reactors are temporarily connected to the flow unit and used as feeding or receiving stations. This remains an excellent option at reasonable cost for some flow eligible chemistry candidates. MEDICHEM revealed the implementation of such a strategy on their Girona site with a Corning® reactor at the last Chemistry Today Symposium in Delft, on September 2015.

The availability of flow chemistry equipment with improved cost and performance are a boosting factor. "Innovative manufacturing techniques for industrial flow reactors, like 3D metal printing (selective laser melting) recently developed and launched by DSM", says **André H.M. de Vries** Business Manager Innosyn®, "will certainly reinforce the attraction to the flow offer".

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Intensification ExpertsSebastian Rieth
RocheCharlotte Wiles
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Andrea Adamo
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Nuno Matos
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FUTURE TRENDS

Few barriers are however regularly mentioned. When it comes to regulatory affairs, and especially for the pharmaceuticals sector, flow is certainly challenging a batch minded community. However, the learning curve is now playing in favor of continuous processes. In April this year, the continuous production of Janssen HIV drug Prezista® at their Porto Rico Gurabo site was greenlighted by the FDA, which is encouraging other pharmaceutical companies to engage similar moves.

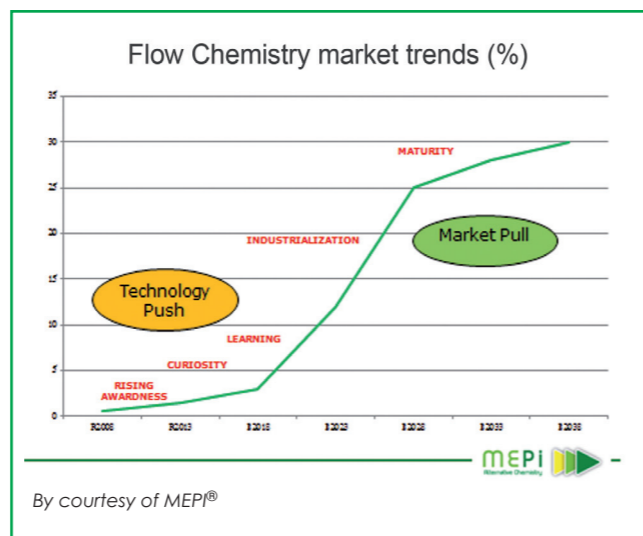
Pharmaceutical companies, or CMO working for the pharmaceutical sector, like Novartis, Ely Lilly, AstraZeneca, SK Chemicals... are more and more presenting achievements on continuous processes at various Flow Chemistry Symposiums.

Another concern is the switch to continuous for the downstream steps.

Andrea Adamo from Zaiput Flow Technologies says: "We think the land scape of equipment offer is quite populated, especially in terms of reactor units. We hope our in line work-up technology will experience wider adoption and lead to higher level of process integrations. Probably more solutions are needed in some aspects of downstream processing".

But here again, the technology is evolving quickly to fill the existing gaps.

Nuno Matos, Head of Continuous Manufacturing at Hovione, said: "We are optimistic that in the next 5 years important technology developments will occur allowing to extend to other unit operations what was already achieved with flow reaction. For instance, at Hovione, besides Spray-Drying, we are currently testing and developing



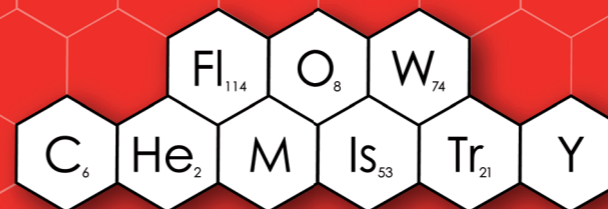
several technologies that will allow us to isolate our products in a continuous fashion, outputting particles with chemical and physical attributes tightly controlled".

Dirk Kirschneck, Managing Director of Microinnova Engineering® is adding: "In the last two years we have done more and more activities in downstream processing like crystallization and extraction as well as in continuous liquid formulation. Furthermore we realized a high demand of modular flow systems which can deal with different types of technologies including one for high viscosities and for continuous processing of solids."

"However the market is still working in a conservative way and breaking the pattern is possible only with the increase of successful number of installations in continuous and time, as any "disruptive" technology adoption in conservative market" confirms **Alessandra Vizza** Abrial, Regional Commercial Manager EMEA & NSA Corning Reactor Technologies, at Corning SAS.

The percolation of continuous processes on the traditionally batch set industrial grounds remains challenging, but positive signs are now definitively on. Cultural changes, growing demand, regulatory pushes, need for more eco-efficient processes, and offer agility are now paving the way to a bright flow chemistry spread out.

TRENDS



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