Follow the pharma flow

Speciality chemicals manufacturers can benefit from Big Pharma's growing interest in flow chemistry, says **Duncan Guthrie** of **Vapourtec**

Continuous - or flow - chemistry has been an important process arrangement for the full-scale production of both industrial chemical products and pharmaceutical compounds for some time, but more recently interest has focused on using flow chemistry much earlier in the development process. If a reaction can be proven and optimised at a small and economical scale, the logic goes, then scale-up to pilot production will be rapid and low-risk.

In both industry sectors, early participants in this area were somewhat pioneering, creating their own systems from basic components. Now, vendor support for flow chemistry is growing, such that users can get started with a relatively inexpensive 'meso-scale' system off-the-shelf and be running reactions immediately. The risks are far less and systems can often be loaned or rented for short periods to help the would-be user get some experience.

Recent investment

Much of the vendors' recent product development has been focused on the pharmaceuticals industry, but these systems offer a readily available method for other sectors. The chemicals industry can ultimately benefit from the huge investments in research that have been made recently by the pharmaceuticals companies.

In late 2007, Novartis and MIT announced a €50 million, ten-year collaboration called the Centre for Continuous Manufacturing, with the aim of replacing batch processes 'from start to finish'. In 2008 in the UK, the Engineering & Physical Sciences Research Council, along with Pfizer and GSK, awarded €6 million in grants to academic/industrial collaboration projects aimed at increasing the volume of research and training in flow chemistry.

The winning proposals included systems for continuous ozonolysis, online electrochemistry for oxidation and catalyst nanoparticles held static in the flow by magnets, as well as new sensing technologies for online measurement and characterisation of reaction products.

In some ways, the needs of pharmaceuticals (especially drug discovery) users are different from those in other industries. The medicinal chemist initially developing a small scale synthesis route may have somewhat less interest in yield or purity, provided that the molecule of interest can be reliably made and purified later, since the costs of ingredients have less impact on the bottom line than in the chemicals industry.

For this reason, the main benefits touted initially for flow chemistry were reproducibility, the speed with which pressurised, superheated reactions could facilitate the exploration of parameter workspace and the way even the most exothermic reactions (or multi-step reactions with unstable intermediates) could be safely attempted without first obtaining calorimetry data. It is now also becoming apparent that using flow chemistry early on at small scale does offer a rapid route to very efficient manufacture.

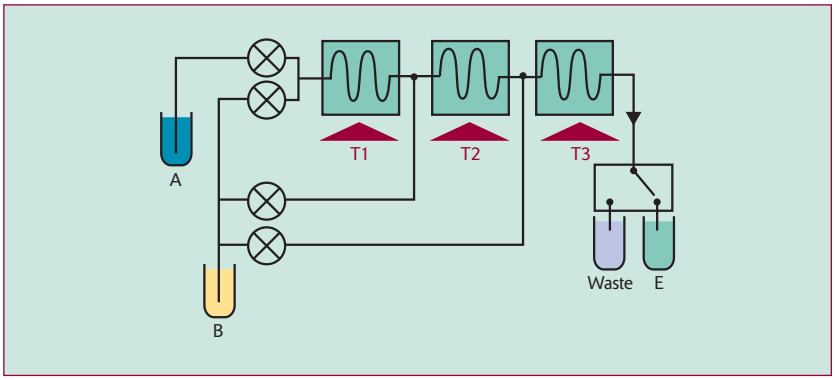


Figure 1 - Partial addition in flow

The rise of automation

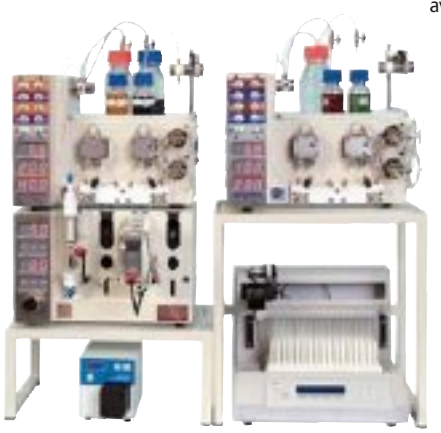
As off-the-shelf systems have developed to support more automation over the past two years, chemists have become able to use flow systems as fully integrated reaction optimisation platforms.

The exploration of different permutations of concentration, stoichimetric ratio, reactor residence time and reaction temperatures can be fully automated, with each result captured in a separate fraction collector vial. Because modern systems can detect leaks or blockages and handle even extreme exotherms comfortably, they are safe to run completely unattended.

At least one currently available system, Vapourtec's R Series Modular Flow Chemistry System, supports the use of an autosampler to feed different reagents or catalysts into the system for each consecutive queued reaction. This makes the system incredibly flexible, with all parameter measurements logged and saved for analysis later.

Since scale-up can be predicted reliably, most optimisation experiments can be carried out on a tiny scale, using the absolute minimum amount of reagents necessary. Each reaction can be run as a discrete 'plug' through the reactor system. The Vapourtec system can even model the dispersion that occurs throughout the pipes and reactors, thus predicting which portion of the output stream represents true steady state and using the absolute minimum amount of reagent to produce the requested amount of product.

As users' confidence with flow chemistry has grown, so have the demands on - and hence the capabilities of - the available systems. Systems are readily available now with capacity for four separate pumped reagent channels and up to four separate temperature controlled reactor stages. This allows the small-scale bench-top user to simulate more fully larger-scale manufacturing processes, such as the modular meso-scale system, with four pumped channels and a fraction collector (*pictured left*).



Reactor developments

Much of the trade press coverage of flow chemistry focuses on reactor design. In the majority of liquid phase reactions, reactor design is primarily of importance for mixing. With very fast reactions that take part in few seconds, the speed of mixing (i.e. whether mixing is mostly complete in one sec-

ond or one tenth of a second) can represent a very significant variable, with a huge impact on scale-up.

Hence much discussion focuses on scale-up of reactions that are initially carried out in expensive micro-machined cavities and hence the impression is often given that flow chemistry is only accessible to those with large budgets. Not all reactions fall into this category, however.

Reactions requiring residence times of a few minutes or more can be carried out within simple small bore tube reactors (several metres of PFA or stainless steel tubing), with mixing occurring in simple small-bore 'T' pipe junctions. Mixing is complete in a few seconds and is barely significant as a variable compared to the overall reaction time of several minutes or more. The costs of these reactors are small and they are often included in the system price.

Some reactions, when carried out in batch, necessarily involve careful incremental addition of reagents or catalysts. This might be to control highly exothermic reactions or to achieve better selectivity. Though thermal control is rarely an issue with flow chemistry, incremental addition has been investigated recently in flow (Figure 1) specifically to achieve better selectivity in certain reactions.

Most of the value in a good off-the-shelf system, compared to a self-build system, is in the development lessons that have already been learned. Modern systems include features to make life easier, such as provision for easy pump priming, continuous pump monitoring for air bubbles, the detection of leaks or blockages to allow for safe unattended operation and fail-safe heater controls.

They also mostly come with a ready supply of information (application notes and publications) showing how to use the system for given types of reaction. This not only allows the user to get up to speed quickly, it also assists pre-purchase evaluation of system capabilities. Loans or rental agreements may be available for those still hesitating.

Areas of interest

One of flow chemistry's greatest benefits is in the safe execution of reactions which are either highly exothermic or which generate unstable intermediates. A recent publication by the Innovative Technology Centre in Cambridge, UK, demonstrated the safe synthesis of a number of compounds using the Curtius rearrangement route, synthesising 25 grams at a time. A batch reaction at this scale would be forbidden on safety grounds in most research labs.[2]

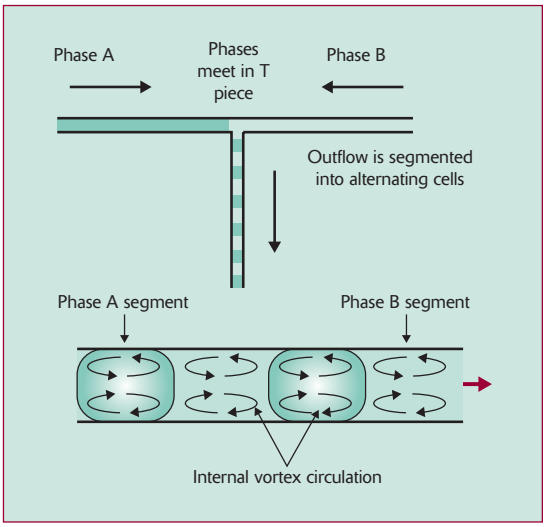
Another publication by ETH Zürich demonstrated safe Weinreb amidation in flow, which would also tend to be avoided in batch due to pyrophoric reagents and the risk of thermal runaway. Both of these publications detail work carried out on commercially available equipment.[3]

Biphasic reactions are particularly useful where they offer the prospect of an easily separated two-phase product in which one phase contains predominantly desirable compounds and the other contains the waste. In batch chemistry, this might require the use of an emulsion, maintained by aggressive stirring.

In flow, however, things can be much simpler. When immiscible reagents are brought together in similar proportions in a small bore T piece junction, the resulting combined flow is segmented (referred to as Taylor Flow, Figure 2).[3]

The alternating segments roll along the tube, exchanging reagents across the boundary between segments, and resulting in extremely efficient mixing. The size of the segments is independent of flow and temperature and depends mostly on the geometry of the T piece used and the reagents' relative surface tension properties. Application notes are freely available employing this approach to carry out phase transfer catalysis (alkylation of esters), using standard off-the-shelf equipment.

Figure 2 - Segmented bi-phasic flow



The same principles apply to aqueous work-up. The emerging product stream after the main reaction is joined with an aqueous flow and then allowed to interact for a controlled time - and at a controlled temperature, if required - before final collection and separation.

Another area of growing interest is **solid supported catalysts**. Various encapsulated metal catalysts are now readily available, for example those supplied by Phosphonics, which are based on functionalised silicas. These are quick and easy to employ in small columns for heterogeneous reactions such as Suzuki or Heck couplings at meso-scale.

Silica-based products need no pre-swelling and have broad solvent compatibility. Products are available for metal-mediated oxidations, acid-promoted reactions and metal-mediated cross coupling reactions. There is little or no metal leaching from them.

Finally, recent work, mainly in Japan, has demonstrated the suitability of capilliary flow micro reactors for producing monodispersed **nanoparticles**.[4] In one study, $LiCoO_2$ and $LiMnO_2$ particles were synthesised by the hydrolysis of the metal alkoxide, which was intended for high performance lithium ion battery electrodes.

Pre-reactor mixing was achieved by simply combining two near laminar flows concentrically, so that the particles formed at the interface did not impinge onto the tube reactor walls. Close control and uniformity of time and temperature conditions in the reactor resulted in a far more regular particle distribution that could be achieved in a similar batch reaction. Other studies include Mn_2+ incorporated ZnS particles for use in luminescent displays.

The equipment used in each case is cheap and simple, so such approaches might be regarded as fairly standard in a few years time.

Conclusion

With affordable equipment and abundant application documentation, meso-scale flow chemistry is now easily accessible to the small producer. It is also clear that with the research funding mentioned above, new process routes for flow will continue to be explored.

If the past few years are anything to go by, manufacturers of integrated bench-top equipment will continue to add capabilities to enable these new approaches. There has never been an easier time to get into meso-scale flow chemistry.

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