Scale-up of continuous process

Dr Gilda Gasparini of **AM Technology** and **Dr Pietro Delogu** of **Serichim**, explain the scale-up strategy for the continuous production of two APIs*

Despite their obvious performance advantages, the uptake of flow reactors in the pharmaceuticals and fine chemical industries has been held back by perceived drawbacks in terms of flexibility and development complexity.

By virtue of their size and geometry, flow reactors can deliver substantially better heat transfer conditions than batch reactors. They operate under steady state conditions, which is the key to simpler control and more consistent product quality.

Plug flow is also an important feature of some - though not all - flow reactors. This optimises the spatial concentration distribution of reagents and products, thereby maximising reaction rates in strict analogy, a condition analogous to a perfect batch reaction. Unlike batch reactors, flow systems avoid transient states, such as feeding, heating, cooling and discharge, giving more accurate and uniform control of the reaction conditions.

In the development of manufacturing processes for APIs and intermediates, reaction conditions are usually optimised at the laboratory scale and checked at the pilot and industrial scale, without passing through a fundamental kinetic and thermodynamic analysis. That means that scaling up is based on analogy criteria between laboratory and industrial reactors.

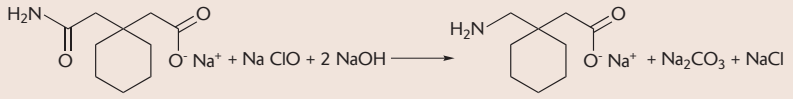
The performance of flow reactors, however, can be very size-sensitive. Small differences in reactor geometry can have a major impact on mixing, plug flow and heat transfer.

Tubular v. CSTRs

Flow reactors can be classified into two broad categories. **Static mixing devices** rely on diffusion or motion of fluid through the reactor for mixing. The most common type in this category is the tubular reactor. **Continuous stirred tank reactors** (CSTRs), by contrast, carry out mixing via the use of mechanical stirrers.

CSTRs are characterised by their size, shape and speed of mixing. From a mixing perspective, scale-up is relatively straightforward, since the mixing efficiency is independent of the residence time and the user has the freedom to vary agitator speed to generate the required mixing energy.

Table 1 - Hofmann rearrangement test results



	Fed batch	ACR	Tubular reactor
Temperature (°C)	25	40	40
Conversion (%)	99	99	99
Yield (%)	93	93	93
Reactor volume (ml)	2,000	60	250
Reaction time (hours)	4	0.5	0.5
Experimental conditions: Sodium hypochlorite concentration 5%, hypochlorite/amide molar ratio 1.2, sodium hydroxide/amide molar ratio 3.2			

Table 2 - Results of API 2 intermediate synthesis at 20°C

	Fed-batch	Fed-batch	ACR
Volume (ml)	20	2,000	60
Reaction time (minutes)	5	10	5
Yield (%)	90	64	94

The Coflore ACR

The disadvantage with the single-stage CSTR is that it is not a plug flow system and the reactants entering the system are diluted by the vessel's contents. This has undesirable implications for selectivity, reaction rates and the control of reaction time.

The tubular reactor can deliver plug flow but presents a variety of scale-up problems. Above the micro scale, tubular reactors become very sensitive to the geometry of the flow channel and the velocity of the process fluid. Insufficient velocity in large channels leads to problems with mixing, plug flow and heat transfer. High velocities imply reactors with long channels and high pressure drops, especially for slower reactions.

Combining the flexibility and performance of the CSTR with the benefits of plug flow represents the ideal solution for this problem. An established technique for achieving plug flow in a CSTR is to combine a number of vessels (typically five or more) in series.[1] In each CSTR, mixing is substantially independent of reactor size and the concentration profile associated with plug flow can be reproduced at different scales without difficulty.

The additional benefits of CSTRs include very low pressure drops and their ability to handle difficult process materials such as immiscible liquids, slurries and gas-liquid mixtures. The key to exploiting them better is to find a simpler way of building small-scale systems.

AM Technology's Coflore ACR (*pictured*) is a dynamically mixed, multi-stage continuous reactor. Ten stages are obtained from a single compact block, interconnected by small channels. All of the reaction cells are of similar size and contain a loose, uncoupled agitator element.

The reactor block is mounted on a shaking platform, whose sideways movement generates differential movement between the process fluid and the agitator element. This generates efficient random mixing within the reaction cell without the need for seals, shafts or baffles.

Different sizes and types of agitator element are used within the reactor block to optimise mixing conditions and cell

ses using multistage CSTRs

capacity at different points within the reactor. This allows the user to adapt the reactor geometry to suit different reaction types.[2]

Pharmagen project

A Coflore flow reactor was used to study continuous reactions in the Pharmagen project, which sought to check and quantify the advantages given by flow processes in the industrial synthesis of pharmaceutical compounds. It was co-ordinated by Serichim and AM Technology was one of six European partners, along with Flamma, Apotecnia, Carbopharm, PSE and LD&T. The work was funded by the EC's DG Research within the Seventh Framework Programme for R&D.

Among the continuous reactions studied was one for Gabapentin, a high volume API (>1,500 tonnes in 2008) for the treatment of various types of neuralgia.[3] The last chemical step for its production is a Hofmann rearrangement of the cyclohexanediacetic acid monoamide to Gabapentin.

This reaction is fairly exothermic, -76.5 kcal/mole, and it is traditionally performed in a fed batch mode. Reported batch times range from four to eight hours to achieve yields of 65-90%.[4] A fed batch reaction carried out at 25°C gave 93% yield with a total batch time of four hours.

A continuous reaction method was first optimised using the Coflore ACR. Amide solution and sodium hypochlorite solution were injected into Cell 1, maintaining temperature at the pre-determined value. Larger agitator elements were fitted to the early reaction cells to increase the heat transfer area to volume ratio, where the rate of reaction is highest. Temperature was controlled by a heat exchanger at the back of the cells.

Different operating temperatures and residence times were tested to optimise the yield and conversion. Because the Coflore ACR uses dynamic mixing, the changes in residence time did not affect the mixing characteristics.

By operating in continuous mode and by exploiting high heat transfer area to volume ratios, it was possible to complete the reaction within 30 minutes at 40°C. These results demonstrated that, under flow conditions, a given capacity can be obtained using a much smaller reactor than in the batch mode.

The Hofmann reaction occurs in a homogeneous liquid phase and could therefore be scaled up to operate in tubular reactor or static mixers, subject to adequate heat transfer capacity. Using the data from the Coflore reactor, the experiment was repeated on a larger tubular reactor, 2.5 cm in diameter, filled with a suitable packaging. As Table 1 shows, the scale-up exercise was successful.

A second API of interest is an oral antidiabetic agent used in the management of Type II diabetes mellitus. The manufacturer of this product required a flow reactor for this process in order to reduce the scale of equipment and the quantity of in-process material.

The synthesis includes several reaction steps. One of these is relatively complex, with consecutive-parallel side reactions (Figure 2). The reaction is complete within six minutes and liberates -35 kcal/mol of heat. The reaction was initially performed in a fed batch mode, the reactant B being fed to A, with an excess of A over B at all times to prevent B from reacting with other components.

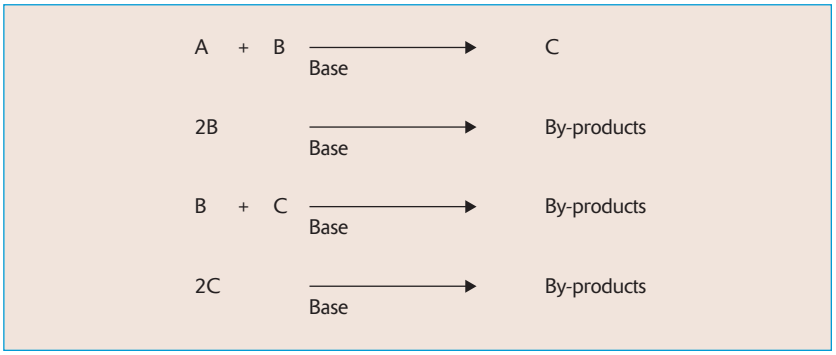


Figure 1 - API of interest synthesis with consecutive-parallel steps

When performed at tens of millilitres batch scale, a yield of 90% is achieved. At the two-litre batch scale, the yield drops to 64% (Table 2). This is a mixing-sensitive reaction. Instantaneous mixing in a 1:1 ratio will ensure that all of B is consumed only by A. Unbalanced concentrations of B, even for short periods, lead to side reactions.

This process does not lend itself to scaling up in a batch reactor, due to the difficulty in maintaining the right molar ratio between reagents under poor mixing conditions during B feeding time. In addition to this, feeding the two reactants is also ineffective, due to the side reactions between B and C, as well as those between two C molecules.

The solution to this problem is a continuous plug flow reactor. This was demonstrated by the Coflore ACR which demonstrated high yields and reproducible results.

Conclusions

Continuous reactors can deliver substantial benefits in terms of capital cost, quality, yield and operating flexibility. The key to exploiting flow solutions, however, relies on a good understanding of the processes and flexible low throughput reactors for process development.

This study has demonstrated the value of understanding the chemistry and employing equipment which matches the needs of the process. The effectiveness of using a low throughput multi-stage CSTR for determining the optimum operating conditions of a larger static mixer was also evident from these results.

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